Resting-State, Responsivity, and Circadian Rhythmicity:

Three Different Functional Components of Autonomic Nervous System Activity in the Context of Developmental Psychopathology

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Study 1

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Study 2

Sigrist, C., Reichl, C., Schmidt, S. J., Brunner, R., Kaess, M., Koenig, J. (*under review*). Cardiac Autonomic Functioning and Clinical Outcome in Adolescent Borderline Personality Disorder over Two Years. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *111*, *110336*. doi: 10.1016/j.pnpbp.2021.110336.

Study 3

Sigrist, C., Jakob, H., Beeretz, C. J., Schmidt, S. J., Kaess, M., Koenig, J. (*under review*). Circadian Variation of Cardiac Autonomic Activity in Non-Suicidal Self-Injury. *Research on Child and Adolescent Psychopathology*.

Abstract

First onset of psychiatric symptoms and disorders usually occurs in childhood or adolescence, presenting a significant portion of the burden of disease in young individuals. The disruption of physiological regulatory systems may present one patho-mechanism underlying the development of psychiatric symptoms and disorders in this age group. Altered autonomic nervous system (ANS) function has been shown to occur prior to observable clinical symptoms, and is typically characterized by an imbalance between its two branches, the sympathetic and parasympathetic nervous systems. Dysfunction of the ANS is frequently indexed by reduced vagally-mediated resting-state heart rate variability (vmHRV), reflecting parasympathetic (vagal) activity. Substantial neurophysiological evidence suggests a relationship between reduced vmHRV and psychiatric disorders characterized by impaired emotion regulation (ER). Alongside resting-state ANS activity, measures of ANS responsivity to challenge (i.e., cardiac reactivity and recovery in response and subsequent to psychological stress exposure) have been suggested as markers of ER, while existing findings on the respective relationships are mixed. Markers of cardiac vagal activity follow rhythmic pattern of circadian variation (circadian variation patterns, CVP), reaching peak levels during nighttime. Indices of CVP of ANS activity may quantify restorative physiological processes, and may be linked with the restoration of autonomic balance. CVP of ANS activity may therefore present further indices of socio-emotional regulatory capacity.

The aim of the present thesis was to investigate different markers of cardiac autonomic activity indexing different functional components of ANS activity (i.e., resting-state, responsivity, and circadian rhythmicity) in developmental psychopathology. First, potential associations between experiences of severe adversity early in life (early life maltreatment, ELM), typically associated with deficient ER, and resting-state vmHRV were investigated in a comprehensive meta-analysis. Second, cardiac responsivity to a standardized stress task was assessed as potential predictor of treatment outcome over two years in a preliminary experimental psychotherapy study. Here, heart-rate (HR) and vmHRV responsivity were used as ANS markers. In a third study, CVP of cardiac autonomic activity was analyzed in female adolescents engaging in non-suicidal self-injury (NSSI). The meta-analytic study suggested no general association between resting-state vmHRV and ELM exposure, while accompanying meta-regression analyses revealed potential patterns of association between exposure to ELM and resting-state vmHRV as a function of several moderators, including mean age of and presence of psychopathology in the respective study sample. In the second study, resting-state and vmHRV recovery following stress exposure were identified as potential predictors of clinical improvement over the time course of two years in adolescent females with higher and lower dimensional manifestations of BPD. The third study revealed altered CVP of ANS activity in NSSI disorder compared to healthy controls, and in association with more severe ELM exposure, and critical confounders of the respective associations were identified. The present synopsis aims to integrate these findings into a psychophysiological framework of ER in development, and discuss methodological considerations, limitations, and potential future directions resulting from the studies that constitute the thesis at hand.

Contents

1. Conceptual Framework

1.1 The Neurovisceral Integration Model

The Neurovisceral Integration Model (*NIM*; Thayer & Lane, 2000, 2009) provides a conceptual framework that also allows the investigation of different aspects and processes of self-regulation, including the regulation of emotion, from a psychophysiological perspective. The *NIM* adopts a dynamical systems perspective when considering the human organism, meaning that specific phenomena, such as processes of self-regulation, are interpreted as complete, self-organizing and self-regulating entities that emerge from reciprocal interactions among lower order constituents (Lewis & Douglas, 1988). From a neuroscientific viewpoint, the NIM integrates various sub-systems of the central nervous system (CNS) regulating autonomic, attentional, and affective processes into a network of functional and structural units.

According to the NIM, the central autonomic network (*CAN*; Benarroch, 1993; 1997) is one important network within the CNS underlying the "flexible adaptation of the organism to changing environmental demands" (Thayer & Lane, 2000; pp. 202). The CAN comprises *structural units* within cortical and sub-cortical structures, including the anterior cingulate, insular, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary medulla, and the medullary tegmental field (Thayer & Lane, 2000). These structures form a common reciprocal inhibitory neural circuit, where subcortical regions support defensive behaviors, and prefrontal cortical regions exert tonic inhibitory control over these subcortical structures (Thayer & Brosschot, 2005; Thayer & Lane, 2009). The CAN is therefore assumed to present an integrated component of an internal regulation system, controlling visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior and adaptability (Benarroch, 1993; Thayer & Lane, 2000). As a central element of self-regulatory processes, in the NIM, the concept of emotion is interpreted as “organismic response to an environmental event that allows for the rapid mobilization of multiple subsystems for action” (Thayer & Lane, 2000; pp. 202). Thus, emotion is conceptualized as to present an integrative index of an internal monitoring system, signaling momentary adjustment to a constantly changing environment. Emotional responses are seen as to support the selection of an appropriate behavioral response (sub-)system, as well as the inhibition of less appropriate responses, from a pre-existing behavioral repertoire (Thayer & Lane, 2000).

As central components of the NIM, through sympathetic and parasympathetic nerves that form parts of the ANS, (preganglionic) sympathetic and parasympathetic neurons present two different inputs which dually innervate most organs of the human body (Wulsin et al., 2018). In any organ system, these two branches of the ANS may function in a complex relationship, including antagonistic, complementary, or cooperative functions, and their relative balance may be set by genetic and largely modified by environmental influences, as well as aging and circadian rhythms. Considering the human

physiological system in its complexity, the ANS, by producing patterns of dynamic variability, contributes to the organismic aim of minimizing energy expenditure (Kok et al., 2013; Thayer et al., 2010; Van der Kolk, 2015; Wulsin et al., 2018). Critically, besides most other organs, the ANS also innervates the heart, via the stellate ganglia and the vagus nerve (VN). The interplay of these nerves at the sino-atrial node of the heart produces a complex variability in the heart rate time series, termed heart rate variability (HRV; Saul, 1990; Thayer & Lane, 2000). If optimally high, HRV is assumed to characterize a healthy and adaptive organism. As a measure of cardiac autonomic activity, HRV presents an indirect output of the CAN regulating the interplay of sympathetic and parasympathetic (vagal) influences on the activity of the heart. Of note, autonomic control of the heart is highly complex, but autonomic neural control via the sympathetic and parasympathetic nervous systems have been identified as predominant factors (Nolte et al., 2017; Smith et al., 2017).

Important for the present conceptual framework, peripheral end-organs including the heart, propagate sensory information back to the CAN; therefore, HRV is seen as an "index of central-peripheral neural feedback and CNS-ANS integration" (Thayer & Lane, 2000; pp. 205). As stated above, within a reciprocal inhibitory neural circuit, prefrontal cortical regions exert tonic inhibitory control over subcortical regions. Importantly, in the event of threat or stress exposure, the prefrontal cortex (PFC) is assumed to be rendered hypoactive, resulting in vagal (parasympathetic) withdrawal and disinhibition of sympatho-excitatory circuits, which may lead to an organismic response to the respective stressor or threat being faced. Inhibitory neural circuits are assumed to maintain an important role in both stress and emotion regulation, while a disruption of neural inhibitory processes may result in pathological outcomes in both physiological and affective domains. Based on this premise, the NIM proposes measures of cardiac autonomic activity to index the inhibitory activity of the PFC, further reflecting the capacity of adaptive emotion regulation, as well as executive control functions more in general (Beauchaine, 2015). Deficient top-down control (e.g., by the medial PFC) of limbic structures (e.g., of the amygdala), and reductions in the functional connectivity between limbic and prefrontal structures, are assumed to be linked with deficient self-regulation, and in particular, deficient ER (Beauchaine, 2015; Churchwell et al., 2009; Hilt et al., 2011). Based on the NIM, numerous psychophysiological studies concerned with the identification of physiological markers of ER and respective deficiencies have been conducted.

To summarize, the NIM assumes that complex co-existing physiological, behavioral, emotional, and cognitive processes, which rely on a common functional and structural neural basis (i.e., the CAN) are linked with processes of response organization and selection, serving to modulate psychophysiological resources in attention and emotion (Friedman & Thayer, 1998; Thayer & Friedman, 1997) and thus are involved in self-regulation and adaptability. The NIM highlights the importance of dynamic adjustments of physiological arousal to situational and environmental demands (Appelhans & Luecken, 2006; Friedman, 2007; Friedman & Thayer, 1998), and relies on markers of vagal regulation at the level of the heart. The NIM suggests a role for individual differences in HRV in

physiological, affective, and cognitive regulation, while the critical role of inhibition for effective functioning in a complex environment is emphasized (Thayer & Lane, 2009). The NIM conceives vagal regulation of heart rate as a marker of prefrontal control over subcortical activity, and thus of the functional integrity of self-regulatory systems (Thayer & Lane, 2000; Thayer & Lane, 2009).

On grounds of this neurovisceral perspective, it had been outlined that in order to arrive at a complete model, the complex variety of pathways that ultimately cause a specific disorder of interest should be accounted for (Brosschot et al., 2006). Indeed, several important elaborations of the NIM exist, adding further complexity to the suggested mechanistic pathways involved in the development of different kinds of pathology. Recently, a conceptual outline (Koenig, 2020) has been provided that is concerned with the integration of the neurovisceral perspective into a developmental psychopathology framework, which, as a central conceptualization underlying the present thesis, will be presented in the following section.

1.2 Further elaboration of the NIM: Neurovisceral Integration in Development

As a commonly held view in the field of developmental psychopathology, and based on findings that the majority of mental disorders have their onset during childhood or adolescence (e.g., Merikangas et al., 2009, 2010; Meyer & Lee, 2019), psychiatric disorders are seen as developmental disorders (Koenig, 2020). Aiming to arrive at a model providing a conceptual understanding of the etiology of psychiatric disease, while assuming that psychiatric disorders are in fact developmental disorders, the *NIM* has been elaborated towards an explanatory model of developmental psychopathology, considering neurodevelopmental aspects and sensitive periods of early human development from a neurovisceral perspective. This *dynamic model of neurovisceral development* (Koenig, 2020) considers important developmental trajectories underlying the dynamic CNS-ANS co-regulation assumed to be associated with affective regulation and psychopathology. Importantly, while the CNS needs input from the environment to develop normally, particularly during sensitive periods of development, environmental experiences have lasting effects on brain function and behavior. *Sensitive developmental periods* have recently been defined as developmental learning mechanisms of neurobiological encoding of particular expectable environmental experiences (including, e.g., a variety of inputs pertaining to sensory, cognitive, and affective domains), which are necessary for an adaptive development of the human organism across a variety of capacities (Gabard-Durnam & McLaughlin, 2020), also including the regulation of affect. One primary aim of the *dynamic model of neurovisceral development* is the conduct of psychophysiological research from a neurodevelopmental perspective, in order to enhance the current understanding of developmental trajectories in association with psychological functioning, which would allow early identification of those at risk for psychopathological outcomes, as presenting a prerequisite for early intervention (Koenig, 2020). What is more, the respective model considers the NIM within the context of the Research Domain Criteria (RDoc) initiative (Kozak & Cuthbert, 2016), aiming to integrate

different physiological systems and their complex interactions to form a profound understanding of psychiatric disorders.

The *dynamic model of neurovisceral integration in development* is based on the NIM premise that the functional overlap between arousal of the ANS and emotion regulation relies on shared neural circuits involved in the regulation of both the ANS and emotion. As mentioned above, the NIM assumes a flexible network of neural structures that is dynamically organized in response to environmental challenges (Thayer & Lane, 2009), and it is suggested that a common reciprocal inhibitory cortico-subcortical neural circuit allows the PFC to exert inhibitory control over subcortical structures associated with the stress response (Thayer & Siegle, 2002). Critically, in the present elaboration, the functional interaction of the ANS and CNS is assumed to be shaped early in the course of life, while adolescence is assumed to present the most sensitive period of development in this circuitry, forming the foundation for adaptive neurovisceral regulation throughout the lifespan (Koenig, 2020). By paradigmatically considering studies regarding the normative development of cardiac autonomic function and its association with emotion regulation, it is outlined that vagal (parasympathetic) influence over cardiac autonomic activity increases early in the course of life, and that this increase is important in shaping emotional development (Koenig, 2020). The assumed normative increase in vagal parasympathetic influence (reflected by an increase in HRV levels) over the course of early childhood and adolescence is further assumed to reflect neurodevelopmental processes of cortical thinning in prefrontal and subcortical brain regions. Cortical thinning, in turn, is linked with better neuropsychological performance (i.e., verbal learning and memory, visuospatial functioning, and spatial planning and problem solving), and might be linked with more adaptive emotion regulation (Squeglia et al., 2013; Vijayakumar et al., 2014; as cited in Koenig, 2020). Based on several lines of previous research, including findings that connections between the PFC and limbic structures are fine-tuned during adolescence, and that these processes may underlie characteristic instabilities of affect and behavior in this developmental period (Ahmed et al., 2015; Casey et al., 2008; see further Koenig, 2020), it is proposed that the development of the ANS (i.e., the normative increase in vagal activity in sensitive developmental periods such as the transition from adolescence to early adulthood) is critical for patterns of PFC maturation and associated psychological regulatory capacities to emerge (particularly, ER). Consequently, it is suggested that decreased ANS activity, widely observed over the spectrum of psychiatric disorders (e.g., Alvares et al., 2016; Chalmers et al., 2014; Clamor et al., 2016; Kemp et al., 2010; Koenig et al., 2016a; Koenig et al., 2016b), might not present a decrease per se, but rather the absence of normative developmental increase (Koenig, 2020). Altered ANS functioning during adolescence (i.e., the absence of normative increase in vagal activity) is supposed to lead to heightened sensitivity to stressors and stress vulnerability, and increased risk of psychopathology.

Considering potential antecedent factors, based on assumptions that can be drawn from research focusing on dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, the second major stress-response system in the human body, in the dynamic model of neurovisceral integration, it is suggested

that ANS dys-maturation might be mediated by early environmental factors and the caregiving environment. Early life stress (ELS) has been discussed as one potential antecedent factor, while it has been outlined that several other factors are likely to contribute to the absence of normative ANS maturation (see e.g., Mulkey & du Plessis, 2019; as cited in Koenig, 2020). Indeed, substantial evidence has been accumulated that ELS, and in particular highly severe forms of EMS, leave unequivocal neurophysiological marks (Heim et al., 2019) including alterations in the major stress axes (i.e., ANS and HPA-axis). Potential mechanisms and pathways effecting such neurophysiological changes are discussed in several influential and partly competing neurobiological models. Among these, a more recent model (Agorastos et al., 2019; Daskalakis et al., 2013; Nederhof & Schmidt, 2012) providing an explanatory basis well-aligned with the ideas put forth in the *dynamic model of neurovisceral integration in development* (Koenig, 2020) is the "three-hit concept of vulnerability and resilience". This model puts emphasis on the high degree of cerebral plasticity, and suggests that an interaction of the individual genetic background (hit-1) with ELS exposure (hit-2) results in an evolving phenotype characterized by altered stress-axis regulation and sensitivity due to early developmental programming, further interacting with later-life challenges (hit-3) to result in a higher (or lower) vulnerability, depending also on the type of challenge experienced (Agorastos et al., 2019). Importantly, this model can be distinguished from cumulative models of stress-exposure such as the highly influential diathesis-stress model (e.g., McEwen, 1998) in critical ways, that is, it is assumed that ELS exposure can also have advantageous effects, that is, by representing a possible source of adaptation, potentially even promoting resilience (Agorastos et al., 2019). In the diathesis-stress model, it had simply been suggested that if the accumulation of stressors along the life span exceeds a certain threshold, this enhances disease risk in individuals with high stress exposure – thus neglecting the aspects of coping and adaptation. Importantly, the aspect of resilience is highlighted also in the dynamic model of neurovisceral integration in development, where cardiac vagal activity is assumed to present a marker of increased risk when decreased, but a marker of better resilience when increased (Koenig, 2020).

To recap, the psychophysiological perspective towards a *dynamic model of neurovisceral integration in development*, developed based on the NIM, provides a conceptual basis for the conduct of thee empirical studies that constitute the present thesis.

1.3 Theoretical Considerations of Emotion Regulation and Dysregulation

There are various contemporary theories of emotion and its regulation, while in most theories, physiological reactivity is considered as one of the main response domains to be investigated (Balzarotti et al., 2017; Kreibig, 2010; Mauss & Robinson, 2009). Of note, the definition of emotion itself has been under long-standing scientific debate (Gross & Feldman Barrett, 2011), and while the amount of research studies focusing on ER steeply increased in the last two decades or so, considerable theoretical fragmentations also extended to the definition of ER (Koole, 2009). Among the different existing

theories, one definition of ER includes the ability of an individual to modulate the experience and expression of positive and negative emotions, according to the respective situational context in which they unfold (Balzarotti et al., 2016; Gross, 2001; Gross & Thompson, 2007), and ER is assumed to be critical in terms of psychological and social functioning (Balzarotti et al., 2016; English et al., 2013; Gross, 2007; Gross & John, 2003; Haga et al., 2009). Difficulties in ER have been associated with a wide spectrum of psychopathology (Berking & Wupperman, 2012; Sheppes et al., 2015), and in contrast to the adaptive nature of ER, emotional dysregulation has been described as patterns of emotional experience and expression that interfere with appropriate goal-directed behavior (Beauchaine, 2015a,b; Beauchaine & Gatzke-Kopp, 2012). It has been suggested that in both internalizing and externalizing mental disorders, one or more negative emotions (i.e., sadness, panic, anxiety, and anger) are experienced either too intensely or too enduringly to be adaptive (Beauchaine et al., 2007). While the fragmentation of research concerned with emotion and its regulation complicates the investigation of ER from a developmental perspective, and impedes the development of a comprehensive, mechanism-based framework of the development of ER (Lewis et al., 2010), most existing theories agree on the presumption that emotions are multi-faceted, whole-body phenomena (Gross, 2001), and that their regulation includes aspects of central and peripheral physiology. In developmental research concerned with the study of ER, it has been pointed out that "only by looking to the biological constituents underlying psychological phenomena can one find the precision required for a detailed model" (Lewis et al., 2010; pp. 55). Consequently, an explanatory model of emotion regulation and dysregulation in development might indeed be approached best by taking a psychophysiological stance, as provided in the thesis at hand.

2. Present Thesis

Situated in between clinical and physiological research, the present thesis is concerned with specific aspects of ER in the context of socio-emotional and neurobiological development, and based on the psychophysiological framework presented above. In the studies that constitute the thesis at hand, physiological correlates of potential precursors and disorders of ER are investigated, while focus is laid on the developmental periods of early childhood and adolescence. In the following, the three studies constituting this thesis are presented in manuscript form.

2.1 Manuscript

Early Life Maltreatment and Resting-State Heart Rate Variability: A Systematic Review and Meta-Analysis

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Abstract

Recent focus on the consequences of early life adversity (ELA) in neurobiological research led to a variety of findings suggesting alterations in several physiological systems, such as the cardiovascular system. In this systematic review and meta-analysis, we focused on the relationship between early life maltreatment (ELM), one form of ELA, and resting vagal activity indexed by resting-state heart rate variability (HRV). A systematic search of the literature yielded 1′264 hits, of which 32 studies reporting data for group comparisons or correlations were included. By quantitative synthesis of existing studies using random-effect models, we found no evidence for a relationship between ELM exposure and resting vagal activity in principal. Conducting meta-regression analyses, however, we found the relationship between ELM and resting vagal activity to significantly vary as a function of both *age* and the *presence of psychopathology*. In light of the current multitude of vastly unclear pathways linking ELM to the onset of disease, we emphasize the need for further research and outline several aspects to consider in future studies.

Keywords: *Early life maltreatment*; *Early life adversity*; *Heart rate variability*; *Vagal activity*; *Psychopathology*

1. Introduction

1.1. Early life adversity: Lasting changes in regulatory biological systems

Early life adversity (ELA) encompasses exposure to various forms of adverse experiences in childhood (Heim et al., 2019), and is considered a profound and non-specific risk factor for the development of a wide range of physical and mental health disorders later in life (Felitti et al., 1998; Gilbert et al., 2015; Gilbert et al., 2009; Kalmakis & Chandler, 2015; Krugers et al., 2017; Nemeroff, 2016). The exact mechanisms underlying this association are not yet fully understood. Childhood is a highly sensitive period for the developing brain, and exposure to ELA during this critical time may result in long-lasting consequences (Anda et al., 2006; Bellis et al., 1999; Lupien et al., 2009; Maniglio, 2009; Pirkola et al., 2005; Spataro et al., 2004) affecting both neuromaturation and mental health. Health consequences related to ELA often manifest or aggravate in response to acute stress, and ELA may lower the threshold to develop symptoms of psychopathology by the occurrence of acute stressors during adulthood (Hammen et al., 2000). Exposure to ELA during sensitive periods of developmental plasticity may provoke core dysfunctions at the level of stress-regulatory systems, promoting the pathophysiology of various stress-related disorders (Heim et al., 2019). Alongside neuro-structural and functional alterations affecting brain regions critically involved in stress, homeostasis, and emotion regulation, ELA may affect key-regulatory capacities of the autonomic nervous, endocrine, metabolic, and immune system (Anacker et al., 2014; Lupien et al., 2009; Nemeroff, 2016; Provençal & Binder, 2015). Increasing evidence suggests epigenetic mechanisms to play an important role in the biological embedding of long-term effects of ELA exposure, as ELA could affect gene function by modulating gene expression via epigenetic mechanisms (including DNA methylation and histone modification of chromatin; for a review see e.g., Kundakovic & Champagne, 2015). Epigenetic changes in neural activity and stress hormone receptors might lead to long-term changes in the brain and peripheral tissue, which could partly explain the effects of ELA on different biological regulatory systems (Provençal & Binder, 2015).

Despite the substantial body of research investigating the developmental consequences of ELA, there has been surprising heterogeneity between research studies with respect to types, severity, frequency, or co-occurrence of ELA examined (McLaughlin et al., 2015). Due to this lack of consistency regarding the definition and measurement of the construct (McLaughlin et al., 2019), ELA has been operationalized in manifold ways: from parental illness, to the death of close relatives, to sociodemographic events (e.g., financial problems, moving, parental unemployment, natural disasters, loss of home), to intra-familial events (e.g., birth, foster care, family arguments, and the divorce of parents), to – and this will present the focus of the current meta-analysis - early life maltreatment (ELM). ELM has increasingly been the focus of investigation in a large number of studies and efforts to reach a consensus definition have been made: A recent definition of ELM encompasses experiences of threat and deprivation, either chronic or severe in nature, that represent a deviation from the expectable environment of an average child, requiring psychological or neurobiological adaptation (McLaughlin,

2016). In the context of ELM, deprivation encompasses a series of acts of omission, while threat could be defined as any act of commission resulting in harm, a potential for harm, or threat of harm to a child (Leeb et al., 2008). Experiences of deprivation, such as physical or emotional neglect, are by definition chronic in nature, while acts of commission (i.e. physical, emotional, or sexual abuse) can include single severe or chronically occurring harmful acts perpetrated towards minors (Barnett et al., 1993; Manly et al., 2001). Estimates of the frequency of occurrence of ELM are problematic, also due to inconsistencies arising from current methodological challenges (Baldwin et al., 2019; Norman et al., 2012). However, estimated rates in high-income countries range from 4 to 16 % for childhood physical abuse, and are reported at 10 % for both childhood emotional abuse and neglect. Furthermore, meta-analytic evidence suggests the worldwide prevalence rate for child sexual abuse among females to be as high as 24 % (Gilbert et al., 2009; Y. Pan et al., 2019).

Emerging evidence suggests a link between ELM exposure and altered trajectories of brain development (Teicher et al., 2016), as ELM seems to particularly affect the development of brain regions that show ongoing development postnatally (Teicher et al., 2003). Specifically, studies examined how ELM might be linked with aberrations in the structure and function of brain regions involved in central autonomic control and stress response. For example, childhood physical and emotional abuse might affect hypothalamic, limbic and forebrain regions that constitute stress-related visceral neural circuits (Banihashemi et al., 2015; Card et al., 1993; Herman et al., 2002; Koenig, 2020). In one study (Banihashemi et al., 2015), four specific regions that are important regulators of stress responses have been examined (i.e. the paraventricular nucleus of the hypothalamus, bed nucleus of the stria terminalis, central nucleus of the amygdala, and subgenual anterior cingulate cortex). While a negative correlation between childhood physical abuse and stressor-evoked activity (as induced by a multi-source interference task and the Stroop task) within all of these regions has been identified, childhood emotional abuse correlated negatively with activity within both the subgenual anterior cingulate cortex and the amygdala (Banihashemi et al., 2015). The authors concluded that childhood physical and emotional abuse may influence stressor-evoked responses within visceral brain regions integral to the control of stress responses. Interestingly, further studies on ELM exposure (i.e. exposure to childhood physical abuse and violence at home) found increased stressor-evoked activity within the anterior insula and the amygdala in response to a biologically salient threat cue (i.e., angry but not sad faces; McCrory et al., 2011), as well as elevated activation within the right amygdala when processing (pre-attentive) emotional cues including angry and happy faces (McCrory et al., 2013). In another study, examining a presupposed shift in activity balance from the human bed nucleus of the stria terminalis (BNST) to the amygdala when moving from threat anticipation to actual threat confrontation, ELM exposure (and especially emotional abuse and neglect) was associated with a hyper-activation of the amygdala during threat anticipation (Klumpers et al., 2017). Available studies thus suggest that ELM exposure might be associated with atypical patterns of neural adaptation specifically in regions involved in autonomic and neuroendocrine control and the subsequent stress response.

Brain regions undergoing specific growth spurts concurrent with ELM exposure seem to be particularly affected by developmental alterations (Teicher, 2006; Teicher et al., 2016). Besides the importance of the time-point of exposure, different experiences of ELM seem to exert differential effects on the developing brain: While experiences of threat have been associated with accelerated pubertal timing and development, cellular aging, and cortical thinning of the ventromedial prefrontal cortex (PFC), deprivation was found to be linked with thinning in frontoparietal, default, and visual networks (Colich et al., 2019). Findings further suggest that different forms of ELM (i.e., abuse, neglect, and food insecurity) distinctively affect biobehavioral indices of reward processing, conferring risk to develop psychopathology such as depression (Dennison et al., 2019). Beyond timing, the impact of ELM might also vary depending on exposure severity and chronicity, and studies often ignore that many individuals affected by ELM report multiple forms of maltreatment, rendering the approach to consider subtypes in isolation without excluding or controlling for other adversities (Glaser, 2000). On the other hand, many studies combine diverse experiences into a cumulative risk index and further associate that index with outcomes and underlying pathways, combining experiences that might have a highly diverse impact on neurobiological and psychological development (Bush et al., 2016). Even though the relevance to consider these factors in the investigation of ELM exposure seems crucial – not only with regard to brain-developmental aspects but in general - many studies failed to do so.

As shown previously in this section, the biological mechanisms linking ELM with physical and mental health outcomes remain an ever growing area of research. Psychophysiological measures, including biomarkers of the cardiovascular system, have been of prime importance in understanding how experiences can influence health and disease (Steptoe, 1998). Thus, given their great potential to broaden our understanding of the processes linking experiences of ELM with altered neuromaturation and disease risk they are increasingly investigated in the context of ELM.

1.2. Heart rate variability: A marker of cardiac autonomic regulation

Heart rate variability (HRV), the naturally occurring variability in time intervals between succeeding heart beats over time, has been widely adopted as a non-invasive index of cardiac control through the autonomic nervous system (ANS, Berntson et al., 1997). Measures of HRV can be divided into time-domain, frequency-domain, and non-linear measurements (Shaffer and Ginsberg, 2017), with the high-frequency (HF) power component of HRV as well as specific time-domain measures, including the root mean of the square successive differences (RMSSD), reflecting parasympathetic vagal activity (Appelhans & Luecken, 2006; Thayer et al., 2010, 2012; Thayer & Lane, 2000). Respiratory sinus arrhythmia (RSA), a cardiorespiratory phenomenon characterized by heart rate (HR) fluctuations that are in phase with inhalation and exhalation, is similarly considered a peripheral marker of cardiac-linked vagal (parasympathetic) regulation, especially if recorded during stable conditions without changes in physical activity, respiratory rate, and tidal volume (Grossman et al., 2004; Grossman & Taylor, 2007).

In a prominent bio-behavioral framework termed the *Neurovisceral Integration Model* (NIM) (Thayer & Lane, 2000), HRV is emphasized as a marker of vagal inhibition of the heart, reflecting the primary output of the central autonomic network (CAN) responsible for controlling psychophysiological resources and appropriate responses to environmental change (Kemp et al., 2017). According to this framework, relatively higher HRV is characteristic of a healthy and adaptive organism and indexes higher self-regulation abilities associated with greater behavioral flexibility and adaptability in a changing environment (Thayer & Lane, 2000). Reductions in resting-state HRV, in turn, index vagal impairment linked with prefrontal hypoactivity, amygdala hyperactivity, a predisposition to threat perception and inflated negativity biases (Kemp et al., 2017), linked with higher levels of stress and increased stress vulnerability. The *NIM* emphasizes the role of the CAN responsible for the inhibition of medullary cardioacceleratory circuits, reflecting the inhibitory capacity of the PFC, controlling psychophysiological resources and appropriate responses to environmental challenge (Kemp et al., 2017). Within this framework, HRV indexes the functional integrity of the CAN. The NIM highlights the importance of prefrontal inhibition over lower subcortical pathways in shaping brain activity and subsequent autonomic responses, and suggests HRV as a transdiagnostic biomarker of psychiatric illness: This view is supported by findings that link higher resting-state HRV with a wide range of positive psychological outcomes, while lower resting-state HRV is linked with symptoms of internalizing and externalizing psychopathology (Beauchaine & Thayer, 2015).

A meta-analysis including any psychiatric disorder investigated in association with HRV found a substantial reduction in resting-state HRV for an overall patient pool (including mood, anxiety, psychotic, and substance-dependence disorders), while the significance of these results was not affected by medication status (Alvares et al., 2016). A number of meta-analytic studies found resting-state HRV to be reduced in specific psychiatric disorders, i.e. major depressive disorder (Kemp et al., 2010; Koenig et al., 2016a), anxiety disorders (Chalmers et al., 2014), schizophrenia (Clamor et al., 2016), and borderline personality disorder (Koenig et al., 2016b). Evidently, reduced HRV is significantly associated with a wide range of psychiatric illnesses, and might index autonomic and emotion dysregulation as seen in many psychiatric disorders (Beauchaine & Thayer, 2015; Thayer & Lane, 2000). While an interpretation of the association between reductions in resting-state HRV and psychopathology crucially depends on the assumed temporal direction of this relationship, longitudinal studies are as of yet very scarce in this area of research. In a study examining the relationship between resting-state HRV and depressive symptoms over a 10-year period, higher HRV measures at baseline (including RMSSD and HF-HRV) predicted a lower likelihood to develop depressive symptoms at follow-up measurements in men (but not women) without depressive symptoms at baseline, whereby confounders including sociodemographic and lifestyle factors as well as cardio-metabolic conditions and medications did not alter these trajectories (Jandackova et al., 2016). Importantly, there was no inverse relationship between depressive symptoms at baseline and resting-state HRV at follow-up in either men or women, favoring the assumption that reductions in resting-state HRV represent a risk-

marker for the development of psychopathology rather than a consequence thereof. Another study examining the longitudinal temporal pattern of association between HRV and depressive symptoms in male twin pairs found lower HRV at baseline (across all frequency bands; for an overview of HRV metrics see e.g., Shaffer & Ginsberg, 2017) to be associated with elevated depressive symptoms (measured using self-reports) at follow-up (on average 6.6 years later), independently of health-related factors and medication use (Huang et al., 2018). In this study, an opposite longitudinal association between depressive symptoms at baseline and lower HRV at follow-up was also found, although less consistently so. When taking medication use into account, depressive symptoms at baseline were significantly related to HRV at follow-up only in one frequency-domain (HF-HRV). The authors acknowledged that there might be a bidirectional inverse association between HRV and depression, while assuming the pathway linking lower HRV to future depression or increasing severity of depressive symptoms to be stronger than the opposite, similarly suggesting ANS dysfunction as indexed by reduced resting-state HRV to be a risk factor for the development of depression rather than a consequence.

1.3. Hypothesized associations between ELM and HRV

ELM may induce fundamental changes in stress regulatory systems at an early point in development, programing these systems for life (Heim et al., 2019). Resulting disruptions in the functioning of stress response systems are then thought to be a central mechanism by which ELM exposure can affect human development (McLaughlin et al., 2015). While growing evidence points towards long-lasting consequences of ELM exposure on the structure and functioning of various brain areas, many of these areas are implicated in the regulation of the ANS, particularly the parasympathetic branch (Beissner et al., 2013). Autonomic control over stress responses may be altered in individuals exposed to ELM (McEwen & Gianaros, 2011), leading to alterations in physiological, behavioral and cognitive processes, maladaptive health behaviors, and altered reactivity to stress (Carroll et al., 2011). Alterations in ANS regulation caused by ELM could lead to more frequent, prolonged, and exaggerated responses to subsequent psychosocial stressors, which over time could result in a dysregulated ANS response. In support of such mechanism, studies have shown that ELM exposure predisposes adults to develop post-traumatic stress disorder (PTSD) following traumatic experiences in adulthood (Yehuda et al., 1995), and was associated with a higher incidence of PTSD in Vietnam War veterans (Bremner et al., 1993). Another line of research supports the assumption of a direct effect of the exposure to a specific form of ELM (i.e., early deprivation) on altered stress response system functioning indexed by altered cortisol levels and RSA reactivity (McLaughlin et al., 2015), providing further evidence of a sensitive period in human development during which environmental factors might be particularly influential.

Given that the exact developmental mechanisms underlying the association between ELM and lifelong elevated risk outcomes are unknown, how such mechanisms could be buffered or reversed is equally unclear (McLaughlin et al., 2015). The question of whether early identification of highly adverse

stressors such as ELM improves outcomes has been controversially debated (Barnes et al., 2019), but currently, there seems no diagnostic biomarker of risk to be available that would allow to predict, prevent, or even reverse the negative physical and mental health outcomes as caused by ELM exposure (Heim et al., 2019). Resting-state HRV has previously been identified as a potential moderator of the association between exposure to ELM and adolescent psychopathology: A significant positive association between ELM exposure and internalizing problems was found only for adolescents with low but not high resting-state RSA (McLaughlin et al., 2014). Consequently, low resting-state HRV might be inherent to individuals exposed to ELM who are particularly prone to mental illness. We think that resting-state HRV provides a potential risk marker of autonomic dysregulation in individuals exposed to ELM, indicating an increased lifelong risk to develop physical and/or mental health problems.

If this assumption holds true, we would expect studies investigating indices of resting-state vagal activity with respect to ELM exposure to find a negative relationship between these two factors. Concretely, we would expect HRV markers of resting-state vagal activity to be reduced in ELM-exposed as compared to non-exposed individuals, and, under dimensional considerations, would assume a negative correlation between resting-state vagal activity and the severity of ELM exposure. Furthermore, we would expect these associations to be linked with the development of psychopathology. Considering the current literature on the relationship between resting state vagal activity and exposure to ELM, there is no clear indication regarding the magnitude or direction of such effects, as existing studies provide inconsistent results. While some report results that would clearly speak in favor of our assumptions (e.g., Winzeler et al., 2017), others find no (e.g., Lynch et al., 2015) or even an opposite than expected relationship (e.g., Shenk et al., 2014) between ELM and resting-state HRV.

1.4. Purpose and hypotheses of the present study

Attempting to resolve existing inconsistencies and clarifying the relationship between ELM exposure and resting-state HRV as a marker of vagal function, we aimed to address this relationship in a systematic review and meta-analysis. We thereby hope to contribute to a better understanding of how ELM exposure could be linked with elevated risk across the life span through altered functioning in stress regulatory systems. In the current synthesis, we tested the following hypotheses and explorative research question. Hypothesis 1: HRV markers of vagal activity at rest are decreased in individuals who experienced ELM relative to non-exposed individuals. Hypothesis 2: Reported severity of experienced ELM correlates inversely with HRV markers of resting-state vagal activity. In exploratory analyses, we aimed to address potential moderators of the association between ELM and HRV (e.g., the population from which the sample was drawn, the definition and measurement of ELM, measurement of HRV, sample demographics, and study-level characteristics (i.e., quality or risk of bias). We addressed hypotheses 1 and 2 by conducting group comparison and correlational meta-analyses, respectively. To address potential moderators of presumed relationships between ELM and HRV, we aimed to conduct meta-regression analyses and subgroup meta-analyses on predefined potential moderators identified in

the literature.

2. Method

This systematic review and meta-analysis was pre-registered through a web-based protocol on the International Prospective Register of Systematic Reviews (PROSPERO; Booth et al., 2012) at the stage of study selection (registration number: CRD42019124083). Updates to the current review will be posted to the protocol. Throughout the meta-analytic process, we followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Liberati et al., 2009; Moher et al., 2009) statement, and consulted the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011), providing gold-standard advice in conducting systematic reviews on the effects of healthcare interventions.

2.1. Literature search

The goal of the literature search was to identify studies reporting on ELM exposure in association with vagally-mediated resting-state HRV. A broad search term was formulated (CS, SP, MK, JK) and employed a combination of keywords pertaining to ELM ("childhood", "early life", "trauma", "adverse", "stress", "maltreatment", "neglect", "emotional abuse", "sexual abuse", and "physical abuse") in combination with keywords associated with HRV ("heart rate variability", "HRV", "respiratory sinus arrhythmia", and "vagal"; full search strategy provided in *Supplementary Table 1* in the Supplementary Material). We refrained from inclusion of "deprivation" as a keyword in our search term, to minimize the number of false positive search results (e.g. non-human studies, studies focusing on institutionalized rearing; see also *Section 2.2*). Our aim was to identify potentially eligible studies from a broad range of research fields (i.e., neuropsychological, clinical, and psychophysiological studies). We conducted a literature search of published articles in a number of databases: PsycINFO, PubMED, Embase, Web of Science, and the Cumulative Index of Nursing and Allied Health (CINAHL). Identical search terms were employed in all database searches. In addition, we screened reference lists of publications identified through database searches as well as relevant articles in the literature for potentially pertinent studies not identified in the initial systematic literature search.

2.2. Study selection

We included two types of studies in the current systematic review and meta-analysis: Case-control and correlational studies. To be included in the current group-comparison meta-analysis, case-control studies needed to compare vagally-mediated resting-state HRV (i.e., RMSSD, RSA, or HF-HRV) in individuals exposed to ELM with a non-exposed control group. For a candidate study to be included, ELM and non-exposed control group were required to be similar (not to differ significantly) in terms of characteristics known to influence resting-state HRV (such as, e.g., age or psychopathology). A case-control study was considered for inclusion as soon as inter-beat interval (IBI) data collection in

ELM-exposed and non-exposed individuals was reported, irrespective of the primary aims of the respective study. If group assignment of participants rested on criteria different from ELM exposure (e.g., to fulfill or not to fulfill criteria for a certain disorder), study authors were contacted and requested to re-allocate their sample into an ELM-exposed and a non-exposed control group. If study authors did not respond, but significant differences in ELM exposure measures were reported between two study groups, eligibility for inclusion was judged based on whether or not the present grouping factor was expected to significantly alter resting-state HRV measures (see section 2.6.6). Correlational studies were included if they reported a correlation coefficient between the severity of ELM exposure and vagally-mediated resting-state HRV, or if a respective measure of association was provided by study authors upon request.

Studies were excluded if they (1) were published in a language other than English or German, (2) included non-human subjects, (3) were comprised of a systematic review or meta-analysis, (4) were not a peer-reviewed study, (5) did not study ELM exposure, (6) did not report measurements of any indices of vagally mediated HRV or (7) if not enough information was published for the study to be included in the current meta-analyses, and could not be retrieved by contacting the corresponding author. Prior to a full-text review, the titles, abstracts and, if necessary, methods sections of the articles identified through database searches were screened by two independent reviewers (CS, SP) for the eligibility criteria outlined above. Publications were included in the quantitative syntheses if information regarding all inclusion criteria was reported or provided after contacting corresponding authors. In the case of overlapping samples between studies, the study with the largest sample size was chosen. If samples were identical between studies, we chose the study with the most complete extractable data or earliest publication date for inclusion.

2.3. Variables of interest

This systematic review and meta-analysis examined the effects of ELM exposure on vagal activity as indexed by vagally-mediated resting-state HRV. In order to reduce variance between primary studies due to highly heterogeneous conceptualizations of ELM exposure, we decided to narrow our definition of ELM to inform study inclusion.

2.3.1. Early life maltreatment

We restricted our definition of ELA to experiences of acts of ELM: any series of acts of omission/deprivation (i.e., physical and emotional neglect) and/or severe act or series of acts of commission/threat (i.e., sexual, physical, and emotional abuse) experienced by individuals before the age of 18 years. Studies that employed any measure capturing ELM exposure, including self-reports, clinical interviews, or agency records, were considered for inclusion. In some of the studies we identified, exposure to domestic violence (DVE) had been investigated as a subtype of ELM. Potentially eligible studies examining the influence of DVE on resting-state HRV mostly employed measures

questioning parents, typically marital dyads, about dyadic physical or verbal conflicts, without measuring actual exposure of the child to such conflicts. Given that most of the studies investigating domestic violence did not consider actual exposure of the child (with notable exceptions, i.e., El-Sheikh et al., 2011), and because DVE was not included in our definition of ELM experiences, studies examining the effects of potential DVE on child HRV were excluded. The independence of meta-analytic results from this arbitrary decision undertaken was subsequently tested in corresponding sensitivity analyses (see section 2.6.6).

2.3.2. Outcome measure

We defined resting-state HRV as any measure calculated from IBI derived from short-term recordings (e.g., 5-min resting-state recordings) collected by electrocardiogram (ECG) or photoplethysmogram (PPG), measuring parasympathetic function at rest (Alvares et al., 2016; Camm et al., 1996). Only studies that used time- or frequency-domain measures or RSA to extract vagally-mediated HRV were included. Where publications reported multiple indices of HRV, to prevent conflation of effect-size estimates, only a single HRV measure was extracted, following a hierarchical order: RMSSD was selected for analysis if available, followed by RSA and HF-HRV (both absolute and normalized values), with these measures being highly correlated (Goedhart et al., 2007). RMSSD was preferred over RSA and HF-HRV because time-domain measures are less affected by respiration (Hill et al., 2009; Penttila et al., 2001) and can be estimated with less bias and considerably smaller error than measures derived from the frequency-domain (Kuss et al., 2008). Furthermore, RMSSD can be estimated with more accuracy at lower sampling rates (Ellis et al., 2015). Absolute values were preferably included in the calculation of effect size (ES) estimates, and transformed values were included if no absolute values were reported.

2.4. Data extraction

A digital data extraction sheet was developed and refined during the data extraction process. Data from included studies were independently extracted by the first author and a student research assistant not otherwise involved in this study. Any inconsistencies in extracted study details were resolved via discussion until consensus. The following data were extracted if available: General information and identifying features of the study (full reference, region of study origin, and year of publication), descriptive information and demographics (sample population and size, age, sex, and ethnicity distributions), measures of ELM (methods of measurement and respective scales, subtypes, severity, time-point of exposure), HRV measurement (hardware used to assess IBI data, raw sampling rate, length of data collection, time of day when the measurement took place, posture of participants during resting-state, measurement of respiration rate), results (means and standard deviations of HRV measures per group, correlation coefficients between resting-state HRV and severity of ELM exposure), and potential confounders relevant to risk of bias assessment (methodological quality) of individual studies (as further detailed in section 2.5 below). Where data were reported for subgroups of study

participants (e.g. for both males and females separately), aggregated means, standard deviations (SDs) and ES estimates were calculated using the formulas provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). If data were reported at multiple time points (i.e., longitudinal data), we always extracted data from the first wave as most likely inherent of the lowest attrition rate and the largest sample size possible (Borenstein, 2009).

2.5. Study quality

For case-control studies, we defined risk of bias as a measure of risk for a biased estimation of the true difference in vagal activity as indexed by resting-state HRV between ELM-exposed and non-exposed groups of individuals. With regard to correlational studies, risk of bias was defined as a measure of risk for a biased estimation of the association between the severity of ELM exposure and resting-state HRV. Since there was no reliable and validated tool available to appropriately assess risk of bias of included studies, we composed a risk of bias tool for the purpose of this meta-analytic study, based on the "Guidelines for Reporting Articles on Psychiatry and Heart Rate Variability (GRAPH)" (Quintana et al., 2016), extended by a section of criteria for the evaluation of how ELM had been assessed (the respective tool is provided in *Supplementary Table 2* in the *Supplementary Material*). The GRAPH guidelines provide criteria for various domains of reporting HRV in the field of psychiatry, and these were adopted where appropriate. Three criteria were combined to define our key domain *Selection of Participants*, and this key domain was applied to case-control studies only. Here we considered important that the exposure and control groups, (1) except from ELM exposure were based on identical in- and exclusion criteria, (2) were defined ensuring that all participants in the exposure group were actually exposed to ELM while none of the participants in the control group were, and (3) were recruited by matching (at least for age and sex). To formulate the key domain *Measurement of ELM*, we combined 7 criteria: Whether (1) the authors used an established measure of ELM previously used in the literature, (2) ELM exposure was measured solely using a self-report measure, (3) ELM was measured at the time it occurred (and not retrospectively), (4) the authors reported age at ELM exposure, (5) the authors reported the chronicity of ELM exposure, (6) the severity of exposure was reported, and (7) if the authors took any additional effort to verify the presence and/or absence of ELM exposure in study participants. The original domains *IBI collection*, *data analysis and cleaning*, and *HRV calculation* were combined to our key domain *Measurement of Outcome*, combining 9 criteria: whether (1) the authors provided details on hardware and software used for IBI recording, extraction and analysis, (2) reported the raw sampling rate, (3) reported restrictions imposed for the participants before the measurement of resting-state HRV (e.g. concerning caffeinated beverages and alcohol consumption, smoking, or physical activity), (4) reported the time of day of the measurement, (5) reported the exact length of the measurement, (6) stated instructions given to the participants for resting-state HRV assessment, (7) reported the posture during measurements (e.g. seated or supine), (8) reported reasons for HRV data loss, and (9) if the authors reported any details on artifact identification and cleaning. A fourth key domain was formulated including 14 criteria pertaining to *Potential Confounders* of resting-state HRV

measurement: Whether (1) the authors accounted for exposure to adversities other than ELM, (2) excluded individuals with cardiovascular diseases, (3) taking medication known to interfere with cardiovascular parameters, or (4) with neurological disorders, whether (5) the authors accounted for other somatic diseases in the design or in the analysis, (6) for psychiatric disorders, (7) age, (8) sex, (9) ethnicity, (10) menstrual cycle, (11) body weight or body mass index (BMI), (12) physical activity/fitness level, (13) nicotine intake, and (14) alcohol consumption. Each item of the risk of bias tool was independently coded by the first author and a second reviewer (IML) using a binary coding scheme (0, 1), a coding of 1 reflecting that the criteria for the respective item was considered to be met, and items were coded as *n.a.* (not available/applicable) if judgement of a particular study was not possible (e.g., item 4.10: participants had not yet reached age of menarche or were males). Any inconsistencies between the two reviewers were subsequently resolved via discussion.

2.6. Statistical analyses

All statistical analyses were performed using R version 3.5.0 (R Core Team, 2018). Individual and combined ES, meta-regression, and tests for potential biases were computed and figures generated using the R-packages *metafor* (Viechtbauer, 2010), *meta* (Schwarzer, 2007) and *metaviz* (Kossmeier et al., 2019a, 2019b). A corresponding R script providing further technical details regarding the statistical analysis tools used and supporting the findings of this study is available online (https://osf.io/urxkh/; Sigrist & Koenig, 2019). Throughout statistical analyses, unless otherwise specified we considered a *p*-value less than 0.050 to indicate conventional statistical significance.

2.6.1. Group comparison meta-analysis

To examine whether there is a difference in resting-state vagal activity between individuals with and without exposure to ELM, a pooled standardized mean difference (SMD) was calculated. We first computed SMDs and 95% confidence intervals (CI) for individual case-control studies, using the bias-corrected ES estimate Hedges' *g* (Hedges & Olkin, 1985) as a weighted measure of ES. Hedges' *g* is a variation of Cohen's *d* but correcting for biases associated with small sample sizes, and might be interpreted in the same way as suggested for Cohen's *d*, that is: .2 as small, .5 as medium, and .8 as large effect, respectively (Jacob Cohen, 1988; Cooper & Hedges, 1993). Individual ES were pooled using a random-effects model (Borenstein, 2009). We used restricted maximum likelihood estimation (REML) where ES and heterogeneity estimates are achieved iteratively, as generally recommended (Raudenbush, 2009; Viechtbauer, 2005).

2.6.2. Correlational meta-analysis

To examine the relationship between severity of ELM and resting-state vagal activity, we calculated a pooled Pearson's *r*. We first applied Fisher's r-to-z transformation on all bivariate correlation coefficients extracted from correlational studies and calculated the respective 95% CI. The individual obtained values of ES were then synthesized using a random-effects model and REML

(Borenstein, 2009; Raudenbush, 2009; Viechtbauer, 2005). For better interpretability, the resulting summary ES and model statistics were back-transformed to reflect the correlation coefficient *rz'* (Silver & Dunlap, 1987). Fisher's *z* was used in quantitative syntheses because it essentially normalizes the sampling distribution of Pearson's *r* and can be used to obtain an average correlation coefficient that is less affected by sampling distribution skew, suggesting a less biased summary statistic (Corey et al., 1998).

2.6.3. Model diagnostics

Heterogeneity between primary studies was tested for significance using the Cochrane Q-statistic testing the null hypothesis that all variation in ES estimates across studies is due to sampling error. A significant Q-statistic indicates that heterogeneity of ES estimates between studies exceeds the variation that could be expected from sampling error, possibly due to variations in study samples, study methodology, or other characteristics that could introduce variance in findings at study level (Shadish & Haddock, 1994). The amount of true heterogeneity across studies was further estimated via the I^2 statistic indexing the proportion of heterogeneity across studies not due to random error. Following widely used conventions (Higgins & Thompson, 2002), we interpreted an I^2 statistic of 25% as small, 50% as moderate, and 75% as to signify high levels of heterogeneity. Next, we applied the conventional Egger's regression test (Egger et al., 1997; Sterne & Egger, 2006) to explore the likely presence (Egger's regression test: $p < 0.1$) or absence (Egger's regression test: $p \geq 0.1$) of small-study effects (Sterne et al., 2011). As further model diagnostic, variants of the funnel plot, which is the most widely used diagnostic plot in meta-analysis, were created: Funnel plots are basically scatter plots of the effect estimates from individual studies included in a meta-analysis against some measure of each study's size or precision (Egger et al., 1997; Sterne & Egger, 2001), typically including a funnel centered on the summary effect size. Here, we chose to illustrate the distribution of effect size estimates by their standard errors. Traditional funnel plots, allowing to examine whether smaller studies inherent of larger standard errors and associated lower analytic power tend to yield larger ES (examination of small-study effect), were created. Asymmetry of the funnel plot, however, can be caused by very different mechanisms, and should not be readily equated to publication bias (Peters et al., 2008). To more closely examine the distribution of studies with regard to statistical significance, we then created contour-enhanced funnel plots (Peters et al., 2008) centered on zero, and, as a graphical aid for interpretation, including contours that represent conventional levels of statistical significance (i.e., ≤ 0.01, ≤ 0.05, ≤ 0.10, and ≤ 1.00). We further examined power of the included studies to detect our effect of interest, i.e., the observed meta-analytic summary effect, by creating power-enhanced funnel plots (Kossmeier et al., 2019b). They incorporate study-level power information, by visualizing power estimates corresponding to specific standard errors with color-coded power regions on a second y-axis, and allow threefold: 1) to examine the power studies had to detect an effect of interest (i.e., observed meta-analytic summary effect), 2) whether asymmetry is driven by underpowered but significant studies, and 3) to explore and communicate the distribution of study power for an effect of interest (Kossmeier et al., 2019b, 2019a).

Meta-analytic findings suggest that low statistical power might be a problem especially in studies examining the association between biological, environmental or cognitive parameters with neurological, psychiatric and somatic diseases (Dumas-Mallet et al., 2017).

2.6.4. Subgroup analyses

To further examine potentially distinct effects of ELM exposure on vagally-mediated HRV in youths versus adults, we performed subgroup meta-analyses for age-dependent subgroups (mean age of the overall sample above or below a pre-specified age threshold of 18 years). Similarly, we examined potentially differential effects of ELM exposure on resting-state HRV in general population-based samples as compared to a clinical subpopulation by conducting subgroup meta-analyses for the respective subgroups.

2.6.5. Meta-regression

Based on theoretical considerations and current findings from the literature, we chose to include a number of potentially moderating variables in meta-regression analyses of the relationship between exposure to ELM and resting-state vagal function. Since we hypothesized that ELM exposure would cause vulnerability to alterations in ANS function reflected by reduced resting-state HRV, and as resting-state HRV consistently correlates significantly inversely with age (Fukasaki et al., 2000; O'Brien et al., 1986; Voss et al., 2012), we examined sample mean age as a potential moderator. As pointed out previously, both ELM exposure and resting-state HRV are negatively related with mental health outcomes later in life. If reduced resting-state HRV represents a risk factor for later psychopathology following ELM exposure, we would assume resting-state HRV to be more strongly reduced in clinical as compared to non-clinical samples exposed to ELM. We accordingly examined whether the relationship between ELM and resting-state HRV differed between samples with and without psychopathology. We also examined whether the relationship between ELM and HRV might vary depending on sex and ethnicity distributions in the sample, as both these factors were found to be linked with exposure to ELM (Coêlho et al., 2018; May-Chahal & Cawson, 2005; Roberts et al., 2011) as well as HRV (Hill et al., 2015; Thayer & Koenig, 2019; Voss et al., 2015). In addition to sample characteristics, we examined several features related to the study-design and measurement of ELM and HRV: These include the method used to measure ELM (Oh et al., 2018), time-point of exposure (Jaffee & Maikovich-Fong, 2011), hardware used to assess IBI data, raw sampling rate, length of data collection, time of day when HRV was measured, posture during resting-state, and measurement and control of respiration rate (Quintana et al., 2016). Finally, we examined sub-domains of study quality as assessed by our risk of bias tool as potential moderators. Summing up, continuous covariates and corresponding levels of measurement extracted were: sample-mean age (*in years*), sex *(% females*), and ethnicity *(% non-Caucasian participants*), raw sampling rate (*in Hz*), length of HRV measurement (*in min*), age when maltreatment occurred (*in years*), publication year (*in years*), and sub-domains of risk of bias assessment (*mean scores*). Bivariate covariates and corresponding levels of measurement

extracted were: population sample (*general* or *clinical* population sample), menstrual cycle controlled (*yes* or *no*), respiration rate assessed (*yes* or *no*), respiration instructively controlled for (*yes* or *no*), hardware used to measure IBI data (*ECG* or *PPG*), position during measurement of resting-state HRV (*supine* or *seated*), keeping the time of day when HRV was measured constant (*yes* or *no*), type of HRV index extracted (*time-* or *frequency-domain* (including RSA) measure), ELM measurement relying on self-report (*yes* or *no*), and the region where the study was conducted (*in* or *outside* the USA). Continuous and categorical moderators were tested using mixed-effects models. For categorical moderators (subgroup analyses using meta-regression) it was assumed that all studies within the same category of the moderator estimate a normal distribution of population ES (random-effects) with a common mean ES (fixed-effect component) within subgroups (Rubio-Aparicio et al., 2017; Viechtbauer, 2010). In line with previous meta-analyses on HRV, each moderator was tested at a time (Hill et al., 2015; Lotufo et al., 2012), by using the moderator flag in the *rma.uni* function provided in the *metafor* package. If there was no information provided regarding a specific potential moderator, the moderator was marked missing and the respective study not included in the meta-regression analyses. Following current recommendations, meta-regression was performed only when at least 10 studies within the group meta-analytic comparison or within the correlational-meta analysis reported on the potential covariate, to ensure adequate statistical power (Rao et al., 2017).

2.6.6. Sensitivity analyses

We conducted sensitivity analyses to test the robustness of our meta-analytic results against outlier studies, and to test whether results were independent from arbitrary decisions as undertaken by the authors (Higgins & Green, 2011). The visual examination of potential publication bias with the aid of funnel plots as described in section 2.6.3 might expose certain studies as outliers (hereby defining outliers as studies located outside of the corresponding traditional funnel plots), and to test the robustness of reported results against these outliers, meta-analyses were re-run whilst excluding studies located outside of the funnel (if any). Moreover, as a decision of the authors, studies focusing on DVE were excluded from current meta-analyses ($N = 3$; El-Sheikh et al., 2011; Katz, 2007; Scheeringa et al., 2004). Yet, DVE might be comparable to child neglect or abuse, and meta-analyses were conducted again while including these studies. Then, we decided to exclude studies from group-comparison meta-analysis if the comparison of resting-state HRV in groups significantly different in terms of ELM exposure was potentially confounded with the presence of psychopathology as the actual grouping factor ($N = 1$; (Tanaka et al., 2016), and comparative meta-analysis was also repeated including these studies. Finally, because the aggregation of studies investigating various forms of ELM in the same meta-analysis might not be appropriate due to differential effects of ELM subtypes, we also tested the relationship between ELM and resting-state HRV by combining correlation coefficients between ELM and HRV for ELM subtypes separately, if available.

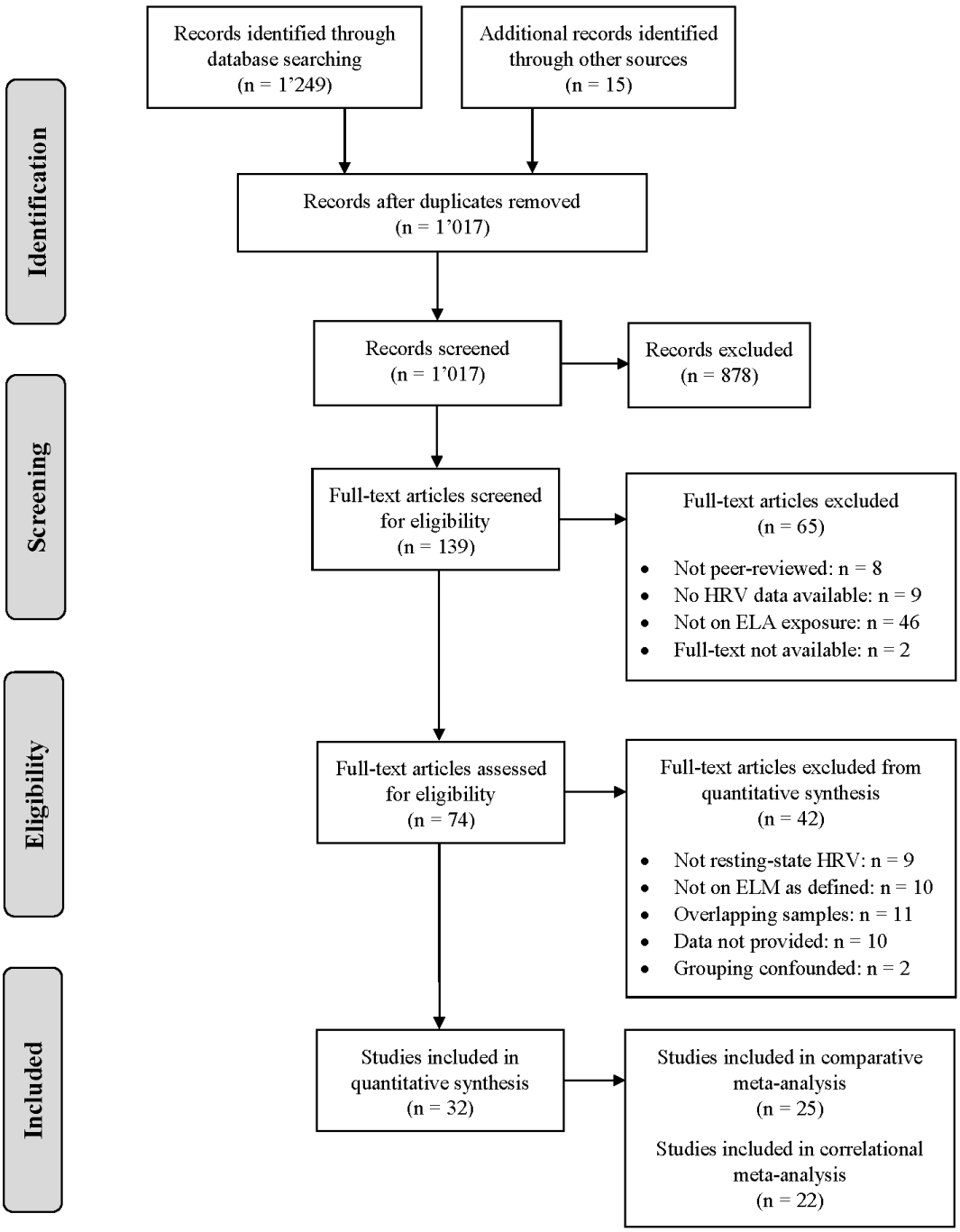

Figure 1. PRISMA Flow Diagram depicting the study selection process (adapted from Moher et al., 2009). Grouping confounded: $N = 2$ studies were excluded because the difference in resting-state HRV between ELM and control group was confounded with either age (Yachi et al., 2018) or psychopathology (Tanaka et al., 2016). HRV: Heart rate variability; ELM: Early life maltreatment.

3. Results

3.1. Search results

A first literature search was conducted on April 16th 2018, yielding 964 records (PsycINFO *N* = 149, PubMED *N* = 307, Embase *N* = 227, Web of Science *N* = 38, CINAHL *N* = 243). Search updates identical to the first search were carried out December 31st 2018 and June 30th 2019, yielding an additional 163 (PsycINFO *N* = 0, PubMED *N* = 35, Embase *N* = 70, Web of Science *N* = 13, CINAHL *N* = 45) and 122 records (PsycINFO *N* = 13, PubMED *N* = 28, Embase *N* = 10, Web of Science *N* = 55, CINAHL *N* = 16), respectively. From the 1′249 records screened for eligibility, 247 duplicates were removed. Screening of reference lists of selected records yielded an additional 15 studies. The full process of study selection (PRISMA flow diagram) is illustrated in *Figure 1* above.

3.2. Included studies

From the initial pool of potentially eligible studies, we retained 32 studies for quantitative syntheses (Aimie-Salleh et al., 2019; Ardizzi et al., 2016; Buisman et al., 2019; Cărnuţă et al., 2015; Dale et al., 2018; Dileo et al., 2017; Duprey et al., 2019; Gaebler et al., 2013; Giuliano et al., 2018; Gordis et al., 2010; Goulter et al., 2019; Hagan et al., 2017; Herzog et al., 2018; Jenness et al., 2019; Jin et al., 2018; Koenig et al., 2017a; Lovallo et al., 2012; Lunkenheimer et al., 2018; Lynch et al., 2015; McLaughlin et al., 2014; Meyer et al., 2016; Miskovic et al., 2009; Murray-Close & Rellini, 2012; Oshri et al., 2018; Patriquin et al., 2012; Reijman et al., 2014; Shenk et al., 2010, 2012; Stone et al., 2018; Tell et al., 2018; Thome et al., 2017; Waldron et al., 2015).

In total, the 32 studies identified included *N* = 3′652 participants, with a mean number of *n* = 114 (*SD* = 77) participants, a mean age of 22.82 (*SD* = 4.07) years, and on average 79.06 % females. Sample sizes ranged from *n* = 14 to *n* = 362 participants. Where age range was reported, the youngest participant was about 3 years old, while the oldest was of age 88.40 years. Sixteen studies included exclusively female samples, while the other half of the studies included mixed samples, with a percentage of female participants ranging from 40 % – 95.65 %. Eighteen studies included samples composed primarily of an ethnic majority group (>50 % of the sample belonging to an ethnic group that shows numerical dominance within the population of the respective geographical or political region), whilst in 7 studies, samples primarily comprised members of an ethnic minority group (>50 %). Seven studies did not report on ethnicity or race. Eight studies reported RMSSD as measure of resting-state HRV, while 7 and 17 studies reported HF-HRV and RSA, respectively. In 8 studies, information on ELM exposure was gathered consulting agency records, and one of these combined agency records with a self-report measure. Two studies employed an interview on ELM exposure, one of which combined the interview with a self-report measure. Twenty-two studies used self-report measures alone to assess exposure to ELM. Overall, the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1988) was the most widely employed ELM measure as implemented in 18 of the 32 studies included. Of the 32

studies identified eligible, we included 25 studies in the group comparison meta-analysis (total $N = 2'$ 921; mean $N = 117$; mean (SD) age =19.55 (10.38); 76.67 % females on average) and 22 studies were included in the correlational meta-analysis (total $N = 2'$ 512; mean $N = 114$; mean (SD) age = 23.94 (13.89); 75.43 % females on average), with 15 studies included in both meta-analyses. *Table 1* above present summary characteristics of each study included in the respective analysis.

Of the studies included in group comparison meta-analysis, 14 had explicitly recruited an ELM-exposed and a non-exposed but otherwise similar control group and resting-state HRV data for both groups were provided in respective published papers (Ardizzi et al., 2016; Dale et al., 2018; Dileo et al., 2017; Gordis et al., 2010; Goulter et al., 2019; Jenness et al., 2019; Miskovic et al., 2009; Patriquin et al., 2012; Shenk et al., 2012; Stone et al., 2018), or upon request (Giuliano et al., 2018; Lynch et al., 2015; Murray-Close and Rellini, 2012; Shenk et al., 2010). The authors of the 11 remaining studies included in comparative meta-analysis responded to our request to re-allocate their samples into an ELM-exposed and a non-exposed control group and to provide respective summary resting-state HRV data for each group (Jin et al., 2018; Koenig et al., 2017a; Lovallo et al., 2012; Lunkenheimer et al., 2018; McLaughlin et al., 2014; Oshri et al., 2018; Reijman et al., 2014; Thome et al., 2017) or provided raw data (Aimie-Salleh et al., 2019; Gaebler et al., 2013; Meyer et al., 2016).

Of the studies included in correlational meta-analysis, 10 studies reported bivariate correlation coefficients between resting-state HRV parameters and a measure of ELM exposure severity (Buisman et al., 2019; Dileo et al., 2017; Duprey et al., 2019; Goulter et al., 2019; Hagan et al., 2017; Herzog et al., 2018; Jenness et al., 2019; Meyer et al., 2016; Tell et al., 2018; Waldron et al., 2015). The authors of the 12 remaining studies included in correlational meta-analysis responded to our request to provide bivariate correlation coefficients between severity of ELM exposure and resting-state HRV (Cărnută et al., 2015; Giuliano et al., 2018, 2018; Jin et al., 2018; Koenig et al., 2017a; Lovallo et al., 2012; Lynch et al., 2015; McLaughlin et al., 2014; Miskovic et al., 2009; Oshri et al., 2018; Reijman et al., 2014; Thome et al., 2017) or provided respective raw data (Ardizzi et al., 2016).

3.3. Risk of bias assessment

Methodological quality was assessed over risk of bias of primary studies, consisting of four sub-domains: Selection of participants (assessed only for case-control studies), measurement of ELM, measurement and processing of IBI interval data, and potential confounders. *Table 2* provides a summary of average risk of bias scores over all studies included in the meta-analyses. Studies included in group comparison meta-analysis on average received a quality score of 14 (range: 8–18), with a maximum attainable value of 33. Studies included in correlational meta-analysis, where a maximum

Table 1. Summary characteristics of studies included in (1) group comparison, (2) correlational, or (3) either meta-analyses, by year of publication.

Author(s), Year	**Analysis No.**	**Total *n***	**EG *n***	**CG *n***	**Fe-males *n* (%)**	**Age M (SD)**	**Recruit-ment Source(s)**	**Matched Recruiting**	**Original Sample / Subgroups**	**Study Outcome of Interest**	**ELA Measure(s)**	**ELA Subtype(s)**	**Other Measures**	**HRV Index**	**Baseline Length**	**SMD (Var.)**	***r* (Var.)**
Gordis et al., 2009	1	362	234	128	175 (38.30)	12.10 (1.21)	CPS agencies Schools Neighborhoods	No (same or comparable census blocks)	Maltreated youth Comparison group	Aggressive behavior in maltreated youth	CPS records MCRAI (rating system)	Physical abuse Sexual Abuse Emotional Abuse Neglect	RPQ SNS activity	RSA	3 min	-0.10 (0.01)	*n.a.*
Miskovic et al., 2009	3	62	38	24	63 (100)	14.29 (1.23)	CPS agencies Existing database of children	Yes (age, gender, handedness, zip code)	Maltreated group Control group	Functional modifications of neural systems in adolescent females with child maltreatment	CPS records CTQ (self-report) CEVQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	EEG	RSA	2 min	-0.46 (0.07)	0.23 (0.02)
Shenk et al., 2010	1	123	55	68	123 (100)	18.43 (3.49)	CPS agencies Community advertisements	No (similar on age, race, SES, family constellation, zip codes)	CSA Group No CSA Group	Development of psychopathology in females with child sexual abuse	CPS records	Sexual abuse	ABF BDI-II YSR salivary cortisol	RSA	5 min	-0.02 (0.03)	*n.a.*
Lovallo et al., 2012	3	252	129	123	149 (59.13)	23.75 (2.82)	Community advertisements	No	No adverse life events One adverse life event More than one adverse life event	Stress axis reactivity to social evaluative stress in healthy young adults	C-DIS-IV (interview)	Physical abuse Sexual abuse Emotional maltreatment	SES_2 salivary cortisol	RMSSD	30 min	-0.07 (0.02)	-0.07 (0.00)
Murray et al., 2012	1	86	35	51	79 (100)	22.02 (2.71)	Community advertisements	No	CSA group No CSA group	Proactive and reactive relational aggression in women with a history of sexual abuse	CAPS (clinician administered scale)	Sexual abuse	SCI SRASBM blood pressure	RSA	6 min	-0.05 (0.05)	*n.a.*

Patriquin et al., 2012	1	123	59	64	123 (100)	18.84 (0.96)	Experimental management system for online research	No	CSA group ASV group Revictimization group No victimization group	Psychophysiological reactivity to threat in women with sexual victimization	CAS (self-report)	Sexual abuse	Emotional Stroop Paradigm SES_1	HF-HRV	3 min	0.27 (0.03)	*n.a.*
Gaebler et al., 2013	1	63	24	39	46 (73.02)	30.00 (6.81)	Self-help groups Online forums Advertisements in local out-patient treatment facilities Community advertisements University mailing lists	Yes (sex, age, handedness)	SAD group Healthy control group	Neural correspondences of physiological reactions and cardioregulatory abnormalities during emotional face processing in SAD	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	BDI-II CDS-30 DFS EHI ERQ KIMS LSAS SPF-IRI STAI-T TMT HBC	HF-HRV	5 min	-0.22 (0.07)	*n.a.*
Shenk et al., 2013	1	110	51	59	110 (100)	17.00 (1.17)	CPS agencies Local teen health center	No	Maltreated group Non-maltreated group	PTSD symptoms in adolescent females with child maltreatment	CPS records	Physical abuse Physical neglect Sexual abuse	AAQ CTI salivary cortisol	RSA	5 min	0.35 (0.04)	*n.a.*
McLaughlin et al., 2014	3	157	60	97	94 (56.00)	14.90 (1.36)	Schools After-school programs General medical clinics Community advertisements	No	Sample of adolescents (no subgroups)	Internalizing and externalizing psychopathology in adolescents with childhood adversity	CTQ (self-report)	Physical abuse Sexual abuse Emotional abuse	SAVE CBCL CIDI	RSA	10 min	-0.12 (0.03)	-0.06 (0.01)
Reijman et al., 2014	3	80	73	7	80 (100)	40.87 (7.30)	Mental health clinic	No	Maltreating mothers Non-maltreating mothers	Autonomic reactivity to infant crying in maltreating mothers	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	MCS MMCI Cry paradigm SNS activity	RMSSD	6 min	0.29 (0.16)	-0.21 (0.01)

Cărnută et al., 2015	2	62	*n.a.*	*n.a.*	62 (100)	20.97 (3.78)	University volunteer pool	*n.a.*	Sample of volunteers (no subgroups)	Potential mediator role of emotion dysregulation	CTES (self-report)	Physical abuse Sexual abuse Major parental conflicts General Trauma (death, illness, injury)	BDI-II DERS SCID salivary cortisol	RSA	5 min	*n.a.*	-0.01 (0.02)
Lynch et al., 2015	3	186	93	93	99 (53.23)	9.45 (0.28)	CPS agencies Public welfare agencies	Yes (gender, ethnicity, family constellation, history of public assistance)	Maltreated children group Non-maltreated comparison group	Multilevel prediction of physiological response to challenge in children exposed to adversity	CPS records MCS (rating system)	Physical abuse Neglect Emotional maltreatment	Crime reports DNA samples	RSA	5 min	-0.03 (0.02)	0.02 (0.01)
Waldron et al., 2015	2	14	*n.a.*	*n.a.*	14 (100)	19.15 (1.28)	Public university	*n.a.*	CSA sample (no subgroups)	Revictimization in women with sexual victimization histories	CAS (self-report)	Sexual abuse	CES-D SES_1	RMSSD	3 min	*n.a.*	-0.18 (0.09)
Ardizzi et al., 2016	3	44	24	20	23 (52.27)	7.55 (1.63)	Street-children were collected directly from the street or from schools enrolling abandoned children Private schools	Yes (age)	Maltreated group Control group	Facial mimicry and vagal regulation in children exposed to maltreatment	Question-naire on Critical Life Events (self-report)	Sexual violence Physical violence Abuse Neglect Maltreatment Mourning	BNT CPM facial EMG	RSA	2 min	-0.17 (0.09)	-0.36 (0.02)
Meyer et al., 2016	3	72	37	35	72 (100)	27.38 (5.67)	Residents registration office Community advertisements In- and out-	Yes (intelligence)	Current and lifetime PTSD group Current BPD group BPD in	HRV in patients with post-traumatic stress disorder or borderline	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional	BDI-II FDS IPDE SCID ZAN-BPD	RMSSD	5 min	-0.70 (0.06)	-0.34 (0.01)

							patient units		remission group Healthy volunteers	personality disorder		neglect Sexual abuse					
Dale et al., 2017	1	60	26	34	60 (100)	19.15 (1.12)	University psychology subject pool	No	Maltreatment No maltreatment	Physiological responses to physical and emotional stressors in women with child maltreatment	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	BSI PTSD Checklist	RSA	5 min	-0.55 (0.07)	*n.a.*
Dileo et al., 2017	3	50	20	30	20 (40.00)	8.48 (1.69)	CPS agencies Local primary schools	Yes (age, gender, socioeconomic status)	Protective care group Community control group	Development of reactive and proactive aggression in an at risk population of children	CPS records MMCS (rating system) DHQ (self-report)	Physical abuse Neglect Emotional maltreatment Sexual abuse General Trauma (accidents, natural disasters, criminal acts, chronic illness, refugee, attacked by an animal, bullying)	BRIEF CBCL ERC KBIT PCQ RPQ SCAP UPSIT	RSA	*n.a.*	0.57 (0.09)	0.05 (0.02)
Hagan et al., 2017	2	158	*n.a.*	*n.a.*	158 (100)	42.03 (4.75)	Mass mailing Schools Parenting publications Autism Clinic	*n.a.*	Healthy premenopausal women raising a child with ASD, Women raising a neurotypical child	Suppressive or avoidant coping in response to daily stress in women with exposure to a risky childhood	CTQ (self-report) PBI (self-report)	Parental over-controllingness Physical abuse, Sexual Abuse, Emotional abuse, Physical neglect, Emotional neglect,	Daily maladaptive coping responses Dot Tracking Task PSS	RSA	5 min	*n.a.*	0.03 (0.01)

												Lack of warmth					
Koenig et al., 2017a	3	60	28	32	60 (100)	15.27 (1.32)	Outpatient clinic Community advertisements	Yes (age, sex, school type)	NSSI group Healthy control group	HPA and ANS reactivity in response to acute pain in females engaging in NSSI	CECA.Q (self-report)	Sexual abuse Antipathy Neglect Physical abuse	C-GAS M.I.N.I-KID SITBI-G SCID-N/P SCID-II	RMSSD	5 min	-.09 (0.07)	0.03 (0.02)
Thome et al., 2017	3	93	49	44	63 (67.74)	35.09 (12.08)	Health services center Family physicians Mental health professionals Psychiatric clinics Community programs for traumatic-stress survivors Community advertisements	No	PTSD Group Healthy control group	Autonomic response patterns and their related neuronal patterns in individuals with PTSD at rest	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	BDI CAPS fMRI MDI RSDI SCID STAI-S	RMSSD	6 min	-0.01 (0.04)	-0.08 (0.01)
Giuliano et al., 2018	3	184	103	81	97 (54.5)	3.81 (0.76)	CPS agencies Department of public welfare agencies Database maintained on birth announcements	No	CM-Dyads Non-CM-Dyads	Inhibitory control in preschool-age children with risk for early exposure to stress	CPS records MCS (rating system)	Physical abuse Neglect Emotional maltreatment	CECV LES Shapes Stroop task Day/Night Stroop task	RSA	5 min	0.09 (0.02)	0.05 (0.01)
Herzog et al., 2018	2	75	*n.a.*	*n.a.*	75 (100)	33.10 (10.01)	Online community advertisements	*n.a.*	No child IPV group One type of child IPV group Two types of child IPV group	Baseline and task-related physiology and attention biases in women exposed to childhood	TESI-BR (self-report) CTQ (self-report)	Physical abuse Sexual abuse Emotional abuse	MDI PCL-5	RSA	2 min	*n.a.*	0.04 (0.01)

									Three types of child IPV group	interpersonal violence							
Jenness et al., 2018	3	94	38	56	46 (48.94)	13.57 (14.51)	Medical clinics Community advertisements Violent neighborhoods Clinics for low-SES clients Agencies	No	Abused Non-abused	PTSD symptoms in abused youth	CECA.I (interview) CTQ (self-report)	Physical abuse Sexual abuse Domestic violence	EDA PTSD-RI	RSA	10 min	0.04 (0.04)	0.03 (0.01)
Jin et al., 2018	3	103	59	44	63 (61.5)	28.18 (6.18)	Community advertisements	No	Non-clinical volunteers (no subgroups)	Pathway models in young and healthy adults	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	ALS BDI-I STAI-T	HF-HRV	5 min	-0.26 (0.04)	-0.07 (0.01)
Lunkenheimer et al., 2018	1	144	67	77	78 (53.42)	3.78 (0.73)	Public welfare agencies	Yes (socioeconomic status)	Maltreating families Non-maltreating families	Mother–child co-regulation	CPS records MCS (rating system)	Physical abuse Neglect Emotional maltreatment	dyadic problem-solving tasks	RSA	5 min	-0.04 (0.03)	*n.a.*
Oshri et al., 2018	3	225	115	110	122 (54.00)	21.54 (2.22)	In-person and local online community advertisements	No	Rural sample of non–college educated emerging adults (no subgroups)	Alcohol and drug use problems in emerging adults	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	AUDIT DUDIT MCQ	HF-HRV	3 min	0.16 (0.02)	-0.01 (0.00)
Stone et al., 2018	1	30	11	19	52 (100)	42.86 (5.31)	Recruited from a larger RCT	Yes (age)	MDD with EA MDD without EA Controls	Resting-state HRV in depressed women	CTQ (self-report)	Emotional abuse	SCID PROMIS QIDS	HF-HRV	6 min	-0.83 (0.15)	*n.a.*

Tell et al., 2018	2	30	*n.a.*	*n.a.*	30 (100)	52.30 (10.40)	Three breast oncology clinics	*n.a.*	Sample of breast cancer patients (no subgroups)	Stress responsivity during acute laboratory challenge in women recently diagnosed with breast cancer	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	positive affect negative affect STAI salivary cortisol	HF-HRV	10 min	*n.a.*	-0.27 (0.04)
Aimie-Salleh et al., 2019	1	23	12	11	22 (95.65)	19.4 (2.17)	Online screening of students at the University of Birmingham	Yes (age, socioeconomic status)	High-adversity group Low adversity group	Classification of stress response based on adverse childhood experiences	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	PASAT salivary cortisol	RMSSD	10 min	0.11 (0.17)	*n.a.*
Buisman et al., 2019	2	229	*n.a.*	*n.a.*	131 (57.21)	52.70 (13.19)	Participant pools of three studies	*n.a.*	Sample of parents with offspring 7.5 years or older (no subgroups)	Parental physiological regulation during conflict resolution with their offspring	CTSPC (self-report) CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect	Supportive Behaviour Task Coding Manual	RSA	2 min	*n.a.*	-0.12 (0.00)
Duprey et al., 2019	2	163	*n.a.*	*n.a.*	91 (55.80)	21.17 (2.37)	Community advertisements Word-of-mouth Flyers	*n.a.*	Non-metropolitan emerging adults	Suicidal ideation in emerging adulthood	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	RSE SIS	HF-HRV	3 min	*n.a.*	0.02 (0.01)
Goulter et al., 2019	3	101	37	64	101 (100)	19.02 (1.50)	Online prescreening of community and undergraduate women	No	Primary psychopathic variant (low maltreatment) Secondary psychopathic variant (high maltreatme	Endocrine and psychophysiological reactivity to social provocation in female psychopathic variants	CTQ (self-report)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	PANAS PPI-SV STAI-T PBI BSI PCL-5 MBPD PCS CRTT Salivary cortisol	RMSSD	5 min	0.52 (0.04)	0.14 (0.01)

nt)

Note. AAQ: Acceptance and Action Questionnaire; ABF: Antisocial Behaviours Form; ABIQ: Abbreviated Battery IQ; ALS: Affective Lability Scale; ANS: Autonomic nervous system; ASD: Autism spectrum disorder; ASV: Adult sexual victimization; AUDIT: Alcohol Use Disorders Identification Test; AVPD: Avoidant personality disorder; BDI: Beck Depression Inventory; BNT: Boston Naming Test; BPD: Borderline personality disorder; BRIEF: Behaviour Rating Inventory of Executive Dysfunction; BSI: Brief Symptom Inventory; CAPS: Clinician Administered PTSD Scale; CAS: Child Abuse Survey; CBCL: Child Behaviour Checklist; CBQ: Child Behavior Questionnaire; C-DIS-IV: computerized version of the Diagnostic Interview Schedule-IV; CECA.I: Childhood Experience of Care and Abuse Interview; CECA.Q: Childhood Experience of Care and Abuse Questionnaire; CDS: Cambridge Depersonalization Scale; CECV: Children's Exposure to Community Violence; CES: Centre for Epidemiological Studies of Depression Scale; CEVQ: Childhood Experiences of Violence Questionnaire; CG: Control group non-exposed (or significantly less exposed) to early life adversity; C-GAS: Children's Global Assessment Scale; CIDI: Composite International Diagnostic Interview; CM: Child maltreatment; CPM: Colored Progressive Matrices; CPS: Child Protective Services; CRTT: competitive reaction time task; CSA: Child sexual abuse; CTES: Childhood Traumatic Events Scale; CTI: Comprehensive Trauma Interview; CTQ: Childhood Trauma Questionnaire; CTSPC: Conflict Tactics Scales: Parent-child; DACS: Depression and Anxiety Cognition Scale; DERS: Difficulties in Emotion Regulation Scale; DFS: Questionnaire of (dys)functional self-focused attention; DHQ: Developmental history questionnaire; DNA: Deoxyribonucleic acid; DPD: depersonalization/derealisation disorder; DSD: Daily Symptoms Diary; DUDIT: Drug Use Disorders Identification Test; EA: Emotional abuse; EDA: Electrodermal activity; EEG: Electroencephalogram; EG: Study group exposed to early life adversity; EHI: Edinburgh Handedness Inventory; ELA: Early life adversity; EMG: Electromyography; ERC: Emotion Regulation Checklist; ERQ: Emotional Regulation Questionnaire; ES: Effect size (Hedge's g); FDS: German adaption of the Dissociative Experience Scale; fMRI: functional magnetic resonance imaging; FSFI: Female Sexual Function Index; HBC: Heart beat counting task to measure interoceptive sensitivity; HPA: Hypothalamic-pituitary-adrenal; HF: High-frequency; HRV: Heart rate variability; IPDE: International Personality Disorder Examination; KBIT: Kaufman Brief Intelligence Test; KIMS: Kentucky Inventory of Mindfulness Skills; LES: Life Experiences Survey; LSAS: Liebowitz Social Anxiety Scale; M: Mean; MBPD: Minnesota Borderline Personality Disorder Scale; MCQ: Monetary Choice Questionnaire; MCRAI: Maltreatment Case Record Abstraction Instrument; MCS: Maltreatment Classification System; MDD: Major depressive disorder; MDI: Multiscale Dissociation Inventory; MMCI: Maternal Maltreatment Classification Interview; MMCS: Modified Maltreatment Classification System; M.I.N.I.: Mini International Neuropsychiatry Interview; M.I.N.I.-KID: Mini-International Neuropsychiatric Interview for Children and Adolescents; NSSI: Nonsuicidal self-injury; PANAS: Positive and Negative Affect Schedule; PASAT: Paced Auditory Serial Addition Test; PBI: Parental Bonding Instrument-Care Scale; PCS: Peer Conflict Scale; PCL-5: PTSD Checklist for DSM-5; PCQ: Primary Caregiver Questionnaire; POMS: Profile of Mood State; PPI-SV: Psychopathic Personality Inventory-Short Version; PROMIS: Patient-Reported Outcomes Measurement Information System; PSG: Sleep Polysomnography; PTSD: Post traumatic stress disorder; PTSD-RI: Child version of the UCLA PTSD Reaction Index; PSQI: Pittsburgh Sleep Quality Index; QIDS: Quick Inventory of Depressive Symptomatology; RCT: Randomized controlled trial; RIA: radioimmunoassay; RMSSD: Root Mean Square of the Successive Differences; RPM: Raven's Progressive Matrices; RPQ: Reactive-Proactive Aggression Questionnaire; RSA: Respiratory sinus arrhythmia; RSE: Rosenberg Self-Esteem Scale; RSDI: Response to Script Driven Imagery Scale; sAA: salivary alpha-amylase; SAD: Social anxiety disorder; SASB: Structural Analysis of Social Behaviour; SAVE: Screen for Adolescent Violence Exposure; SB-5: Stanford Binet-Fifth Edition; SCAP: Social-Cognitive Assessment Profile; SCI: Social Competence Interview; SCID: Structured Clinical Interview for the DSM-IV Axis I Disorders; SCID-II: Structured Clinical Interview of DSM-IV-TR for Personality Disorders; SCID-N/P: Structured Clinical Interview of DSM-IV-TR, non-patient edition; SD: Standard Deviation; SES_1: Sexual Experiences Survey; SES_2: Hollingshead Four Factor Index of Socioeconomic Status; SIS: Suicide Ideation Scale; SITBI-G: German version of the self-injurious thoughts and behaviors interview; SNS: Sympathetic nervous system; SPF-IRI: Interpersonal Reactivity Index; SRASBM: Self-Report of Aggression and Social Behaviour Measure; SSS-W: Sexual Satisfaction Scale; STAI-T/S: State-Trait Anxiety Inventory; TAS: Toronto Alexithymia Scale; TESI-BR: Traumatic events screening inventory-brief report form; THQ: Trauma History Questionnaire; TMT: Trail-marking Test; TSST: Trier Social Stress Test; UPSIT: University of Pennsylvania Smell Identification Test; Var.: Sampling variance; YSR: Youth Self-Report; ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder.

score of 30 could be reached, on average received a quality score of 12 (range: 6–18). Individual scoring results of primary studies can be seen in *Supplementary Tables 3* to *6* in the online Supplementary Material. It should be noted that the studies included produced a variance of zero on two items of our risk of bias tool: Of the 32 studies included, none reported the age of participants when ELM began or occurred *(Item 2.4*), and no study explicitly accounted for exposure to adverse experiences other than ELM in the design or in the analyses (*Item 4.1*).

3.4. Statistical results

3.4.1. Group comparison meta-analysis

Pooling the results of the twenty-five studies comparing resting-state HRV in individuals with and without exposure to ELM judged eligible for the current meta-analysis, we found a small negative and non-significant pooled ES estimate (pooled SMD = -0.034, 95 % CI [-0.141; 0.072], SE = 0.054, p = 0.529), implying no overall reduction in resting-state HRV in ELM-exposed versus non-exposed individuals. A forest plot depicting individual and summary effect size estimates as observed is shown in *Figure 2*. The chi-square Q-statistic (test for heterogeneity) exceeded the level of significance (Q_{24} = 44.583, p = 0.007), suggesting the null hypothesis, assuming that variation in ES estimates was caused by sampling error alone, was to be rejected. The estimated I^2 indicated that 45.06 % of the variance in ES estimates was due to true variation among studies rather than mere sampling error, by convention regarded a small to moderate heterogeneity between studies. Corresponding traditional (A) and contour-enhanced (C) funnel plots of individual observed ES estimates against their standard errors are shown in *Figure 3*, a power-enhanced funnel plot is shown in *Supplementary Figure 1* in the online Supplementary Material. Visual inspection of the funnel plots A and C (*Figure 3*) implied absence of small-study bias, and so did Egger's regression test of funnel plot asymmetry (z = -0.944, p = 0.345). By visual inspection of funnel plot A (*Figure 3*), four clear outlier studies, two in the positive and two in the negative range, were identified and further subjected to sensitivity analyses (sections 2.6.6 and 3.4.5, respectively).

Visual inspection of funnel-plot C (*Figure 3*) revealed that the two outliers reporting a positive ES (as indicative of increased resting-state HRV in ELM-exposed individuals compared to controls) were located in the range of p-values between 0.05 and 0.10 and between 0.01 and 0.05, respectively. The two negative outliers (implying reduced resting-state HRV in ELM-exposed individuals) fell in the range of p-values between 0.01 and 0.05 below a p-value of 0.01, respectively. Finally, looking at the power-enhanced funnel plot (*Supplementary Figure 1* in the Supplementary Material) revealed a median statistical power of 12.2 % of all studies included in the group comparison meta-analysis, while only one study reached the border to the minimum statistical power of 80 % considered conventional, indicating that most studies were generally under-powered to detect our effect of interest. There was no clear indication of asymmetry driven by underpowered but significant studies.

Table 2. Summary of results of the risk of bias assessment of primary studies included in the current meta-analyses (k = 32).

Studies	*k*		Selection of Participants (*max*. = 3)	Exposure Measure (*max*. = 7)	Outcome Measure (*max*. = 9)	Potential Confounders (*max*. = 14)	Total Score (*max*. = 33; *max*. = 30)
Group Comparison	25	Average Sum Score (Range)	2 (0 – 3)	2 (0 – 4)	6 (1 – 8)	4 (1 – 9)	14 (8 – 18)
		Average Mean Score (SD)	0.59 (0.22)	0.32 (0.16)	0.67 (0.19)	0.30 (0.14)	0.43 (0.07)
Correlational	22	Average Sum Score (Range)	*n.a.*	2 (0 – 4)	6 (1 – 8)	4 (1 – 9)	12 (6 – 18)
		Average Mean Score (SD)	*n.a.*	0.31 (0.15)	0.61 (0.18)	0.33 (0.15)	0.41 (0.09)

Note. The summary results of the risk of bias assessment are separated by summary model and the respective sub-domains of the risk of bias assessment tool (the sub-domain Selection of Participants was rated only for studies included in group comparison, and numbers are not available for correlational studies, accordingly). Each item included in the current quality tool was dichotomously rated (0, 1), and higher scores mean smaller risk of bias. *k*: number of studies included in the respective meta-analysis; *max*.: maximum score; *n.a.*: not available; SD: standard deviation.

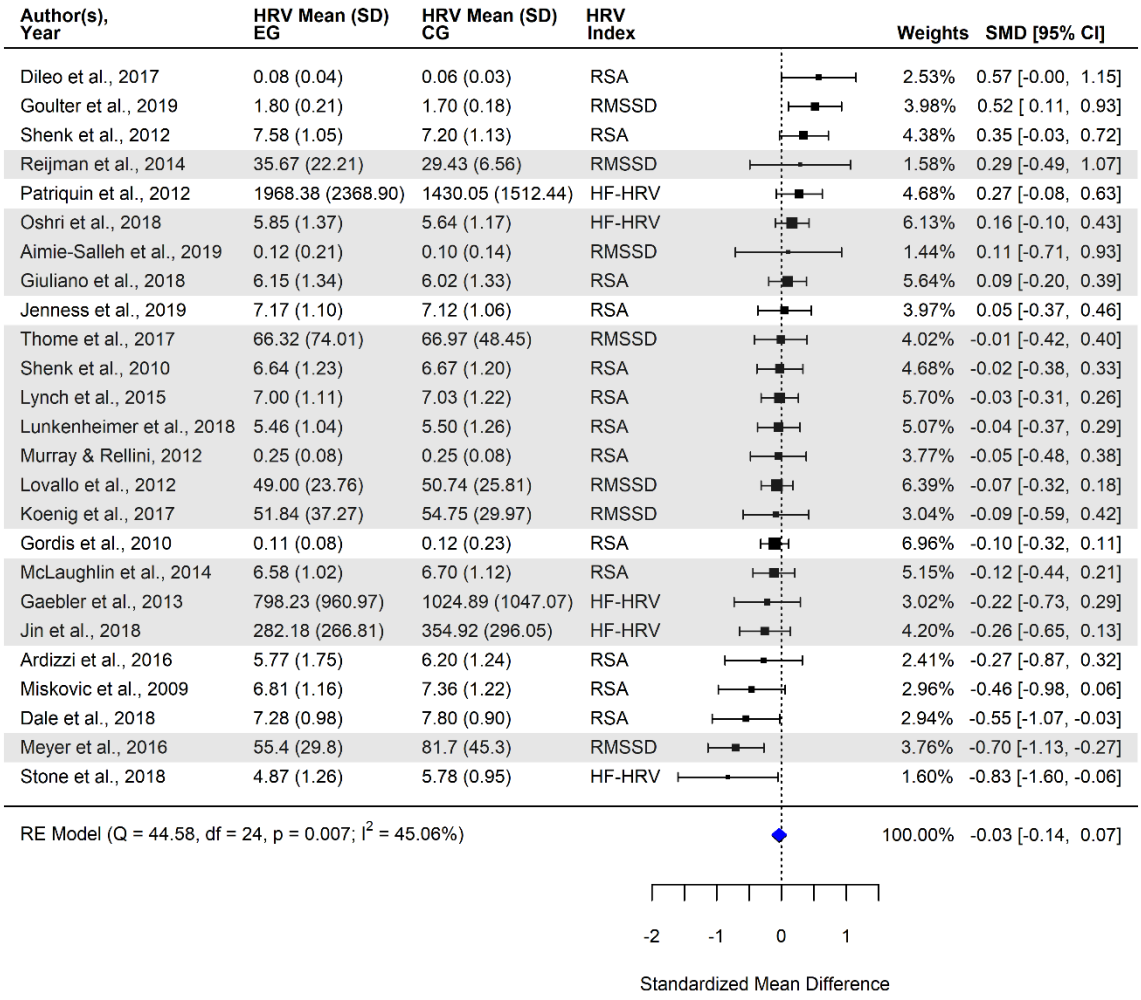

Figure 2. Forest plot of individual observed effect sizes including 95% confidence intervals, study weights, and the pooled summary model using random-effects, comparing vagally-mediated resting-state HRV in individuals with and without ELM exposure. Grey-shaded background indicates the data shown for the respective study has been provided by study authors upon request. Studies are ordered by size of the observed effects. CI: Confidence interval; CG: Control group; EG: Study group exposed to early life adversity; HF-HRV: High-frequency heart rate variability; RE: Random-effects; RMSSD: Root mean square of successive RR interval differences; RSA: Respiratory sinus arrhythmia; SD: Standard deviation; SMD: Standardized mean difference.

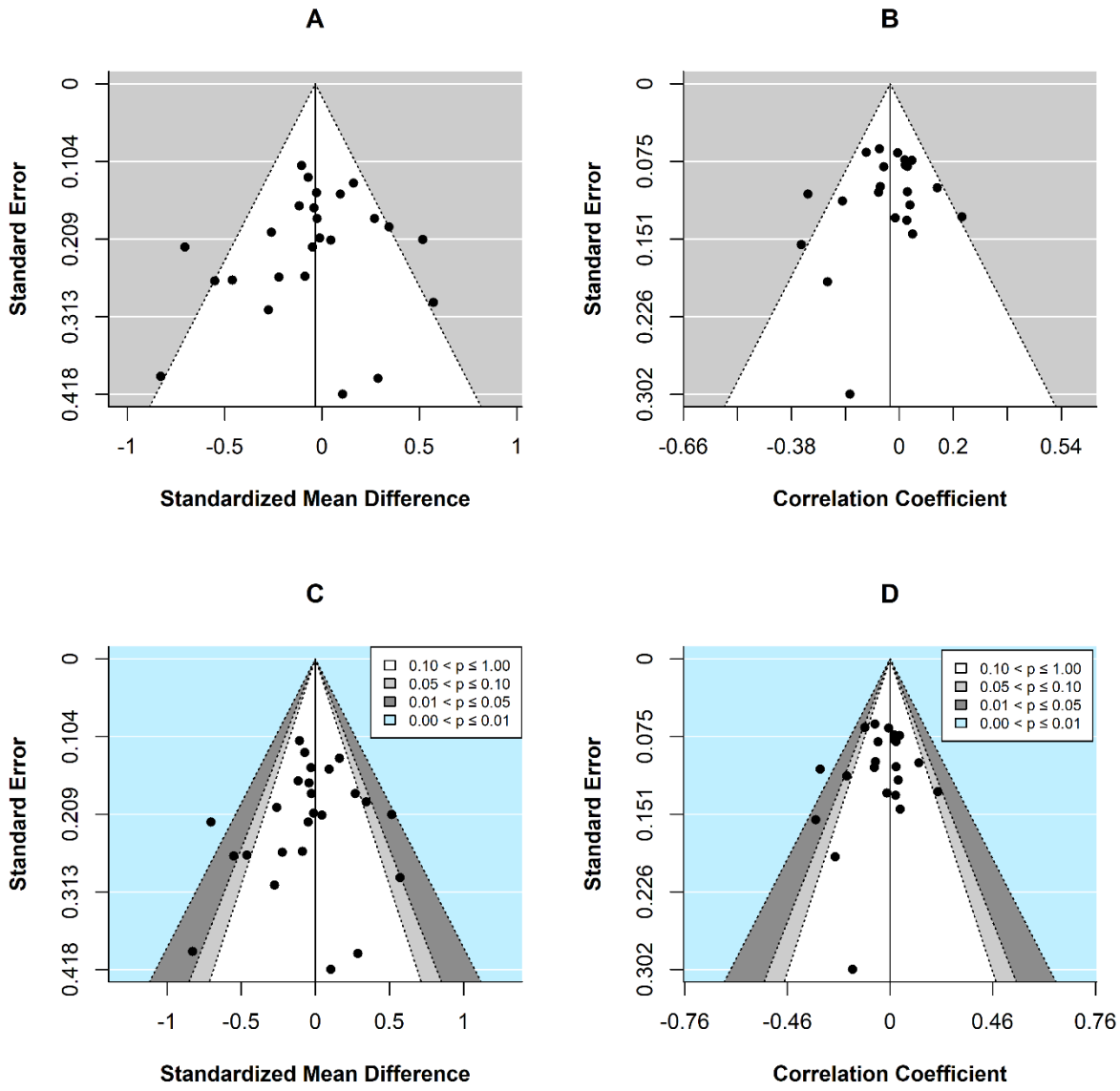

Figure 3. Funnel plots of individual observed effect sizes comparing vagally-mediated resting-state HRV in individuals with and without ELA exposure on the x-axis against the corresponding standard errors (i.e., the square root of the sampling variances) on the y-axis (group comparison meta-analysis) and of correlation coefficients between rated severity of ELA exposure and vagally-mediated resting-state HRV on the x-axis against the corresponding standard errors on the y-axis (correlational meta-analysis), to aid assessment of potential publication bias. **A, B**: Traditional funnel plots centered at the observed summary effect (group comparison and correlational meta-analysis, respectively). **C, D**: Contour-enhanced funnel plots centered at zero including grey-shaded regions that indicate various levels of statistical significance: The unshaded region in the middle of the funnel corresponds to p-values greater than .10, the dark grey-shaded region corresponds to p-values between .10 and .05, the light grey-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel (light blue) corresponds to p-values below .01 (group comparison and correlational meta-analysis, respectively).

3.4.2. Correlational meta-analysis

By pooling twenty-two independent individual observed correlation coefficients between severity of ELM exposure and resting-state HRV, we found a small and negative non-significant summary effect of association (pooled *r*: -0.034, 95 % CI [-0.081; 0.012], SE = 0.024; $p = 0.150$). A forest plot depicting individual and summary coefficients can be seen in *Figure 4*. The chi-square Q-statistic was non-significant ($Q_{20} = 30.755$, $p = 0.078$), so that the null-hypothesis that variation in ES estimates was due to sampling error was not rejected. I^2 implied that 22.79 % of the variance in ES estimates was due to true variation among studies rather than sampling error, suggesting small heterogeneity between studies. Traditional (B) and contour-enhanced (D) funnel plots are again shown in *Figure 3*, the power-enhanced funnel in *Supplementary Figure 2* in the online Supplementary Material. We found no implication of small-study bias by visual inspection of the funnels, and Egger's regression test of funnel plot asymmetry was non-significant ($z = -0.922$, $p = 0.356$), indicating absence of small-study effects. By visual inspection of funnel plot B (*Figure 3*), we identified three outlier studies, two reporting a negative and one a positive ES, and further subjected them to sensitivity analyses (sections 2.6.6 and 3.4.5). Funnel-plot D (*Figure 3*) revealed the two negative outliers were located in the ranges of p-values (one in each) between 0.01 and 0.05 and below 0.01, the positive outlier between 0.05 and 0.10. The power-enhanced funnel plot of correlation coefficients (*Supplementary Figure 2* in the Supplementary Material) suggested a median statistical power of 87.4 %, and 13 of 22 studies clearly reached or exceeded the minimum statistical power of 80 % considered conventional. Slightly less than half of the studies included were clearly under-powered to detect our effect of interest.

3.4.3. Subgroup analyses

Summary statistics resulting from subgroup analyses can be seen in *Supplementary Tables 7* and *8* and in *Supplementary Figures* 3 to *6* in the Supplementary Material. Forming subgroups of studies including youths and adults, although still considerably small, we found ES estimates for adult samples to be of larger size than for youths in both group-comparison (adult samples: $k = 14$, $\beta = -0.073$, 95 % CI [-0.256; 0.111], SE = 0.094, $p = 0.438$; youth samples: $k = 11$, $\beta = -0.015$, 95 % CI [-0.120; 0.090], SE = 0.054, $p = 0.785$) and correlational meta-analysis (adult samples: $k = 14$, $\beta = -0.058$, 95 % CI [-0.117; 0.001], SE = 0.030, $p = 0.054$; youth samples: $k = 8$, $\beta = 0.012$, 95 % CI [-0.057; 0.080], SE = 0.035, $p = 0.736$). None of the summary estimates was statistically significant, although the summary correlation coefficient for the adult subgroup fell close to the level of statistical significance. Subgroups of studies including youth samples were highly homogeneous ($I^2 = 0.00$ % in group comparison and $I^2 = 0.04$ % in correlational meta-analysis, respectively), while subgroups of adult samples were more heterogeneous ($I^2 = 61.86$ % and $I^2 = 27.60$ %).

Subgroup analyses based on study population revealed ES estimates of larger size for aggregated clinical than for general population samples in both group-comparison (general population samples:

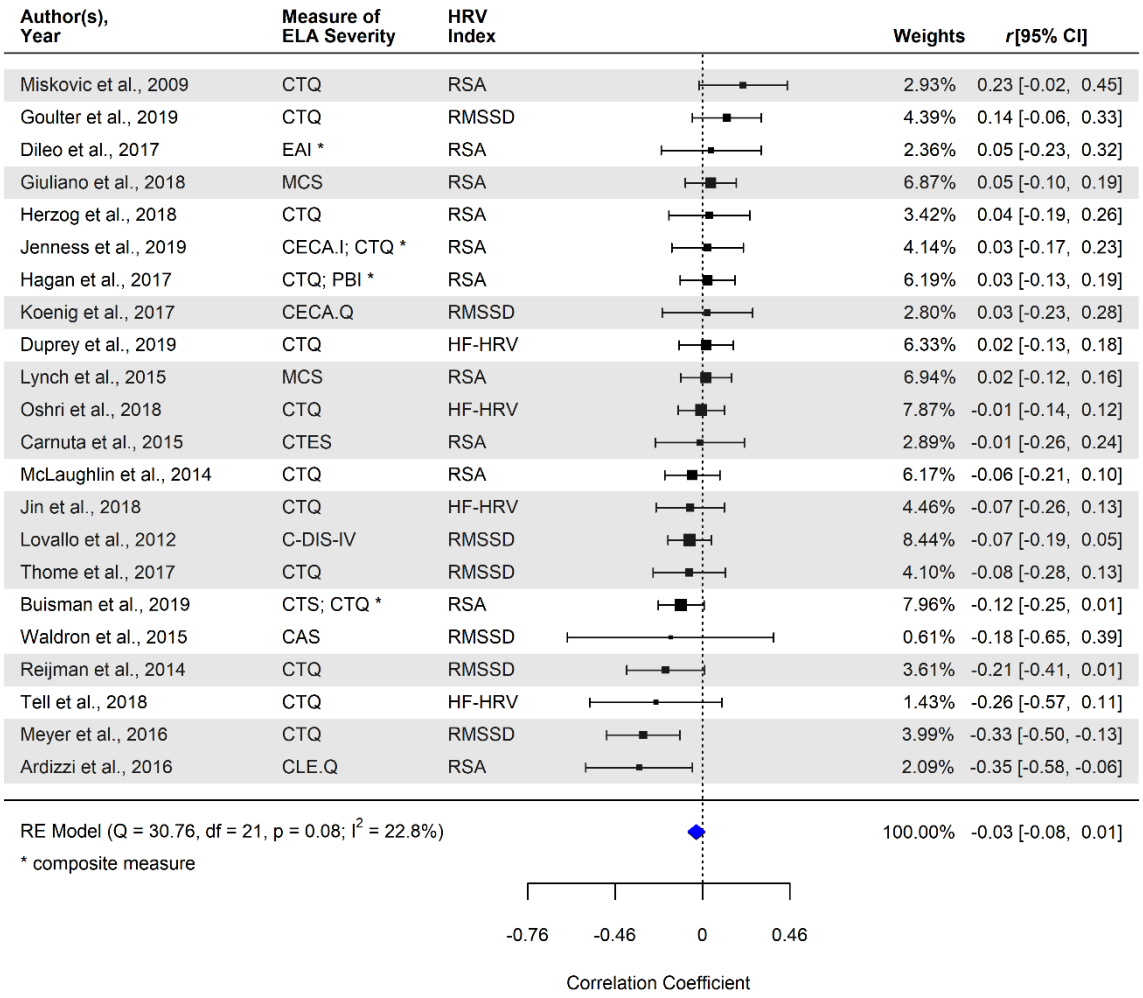

Figure 4. Forest plot of individual observed correlation coefficients including corresponding weights, 95 % confidence intervals and the pooled summary model using random-effects, examining the association between rated severity of exposure to ELA and vagally-mediated resting-state HRV. Grey-shaded background indicates the data shown for the respective study has been provided by study authors upon request. Studies are ordered by size of the observed effects. CAS: Child Abuse Survey; C-DIS-IV: Computer Version of the Diagnostic Interview Schedule - IV; CECA.I: Childhood Experience of Care and Abuse Interview; CLE.Q: Critical Life Events Questionnaire; CTES: Childhood Traumatic Events Scale; CTS: Conflict Tactics Scale; CTQ: Childhood Trauma Questionnaire; EAI: Early Adversity Index; MCS: Maltreatment Classification System; PBI: Parental Bonding Inventory; RE: Random-effects.

k =19, β = 0.013, 95 % CI [-0.086; 0.111], SE = 0.050, p = 0.804; clinical samples: k = 6, β = -0.262, 95 % CI [-0.566; 0.042], SE = 0.155, p = 0.091) and correlational meta-analysis (general population samples: k = 16, β = -0.015, 95 % CI [-0.059; 0.030], SE = 0.023, p = 0.521; clinical samples: k = 6, β = -0.124, 95 % CI [-0.250; 0.007], SE = 0.067, p = 0.064). While none of the summary estimates was statistically significant, the correlation coefficient for the clinical subgroup fell again close. General population samples showed comparatively smaller levels of heterogeneity (I^2 = 28.94 % for group comparison and I^2 = 0.01 % for correlational meta-analysis) than studies including clinical samples (I^2 = 48.07 % and I^2 = 51.01 %, respectively).

3.4.4. Meta-regression analyses

We conducted a number of pre-defined group-comparison and correlational meta-regression analyses. The number of studies included per moderator and analysis as well as the summary results for each moderator examined are shown in *Supplementary Tables 9* (group comparison) and *10* (correlational studies) in the Supplementary Material. We found one continuous moderator to significantly influence the main effect reported for both group comparison and correlational meta-analyses, while three continuous moderators were found to significantly influence the summary effect resulting from correlational meta-analysis (summarized in *Figure 5*): Sub-domain four of the study quality assessment (number of potential confounders controlled for) significantly affected the pooled SMD (β = -0.056 95 % CI [-0.106: -0.006], SE = 0.026, p = 0.028), as well as the pooled correlation coefficient (β = -0.031, 95 % CI [-0.053, -0.008], SE =0.012, p = 0.008). In studies controlling for a higher number of potentially confounding factors, firstly, reductions in resting-state HRV in the ELM versus control group were significantly greater, and secondly, a stronger association was found between the severity of ELM exposure and reductions in resting-state HRV. We further identified the mean age of study participants as a significant continuous moderator in correlational meta-analysis (β = -0.003, 95 % CI [-0.006; -0.001], SE = 0.001, p = 0.023), with studies including older-aged samples reporting greater reductions in resting-state HRV in association with more severe exposure. Equally, ethnicity significantly altered the pooled correlation coefficient (β = -0.002, 95 % CI [-0.003; -0.001], SE = 0.001, p = 0.038). In studies where a higher percentage of participants belonged to the respective ethnic majority group, severity of ELM exposure was significantly more negatively associated with resting-state HRV.

Among the binary moderators examined, one significantly influenced the pooled SMD, and two significant binary moderators were identified in correlational meta-regression. The pooled SMD was significantly reduced in clinical versus general population samples (β = -0.276, 95 % CI [-543; -0.009], SE = 0.136, p = 0.042), signifying implying significantly stronger reductions in resting-state HRV in ELM-exposed compared to non-exposed individuals from clinical as compared to non-clinical samples. The pooled correlation coefficient also significantly differed between studies that did and did not control

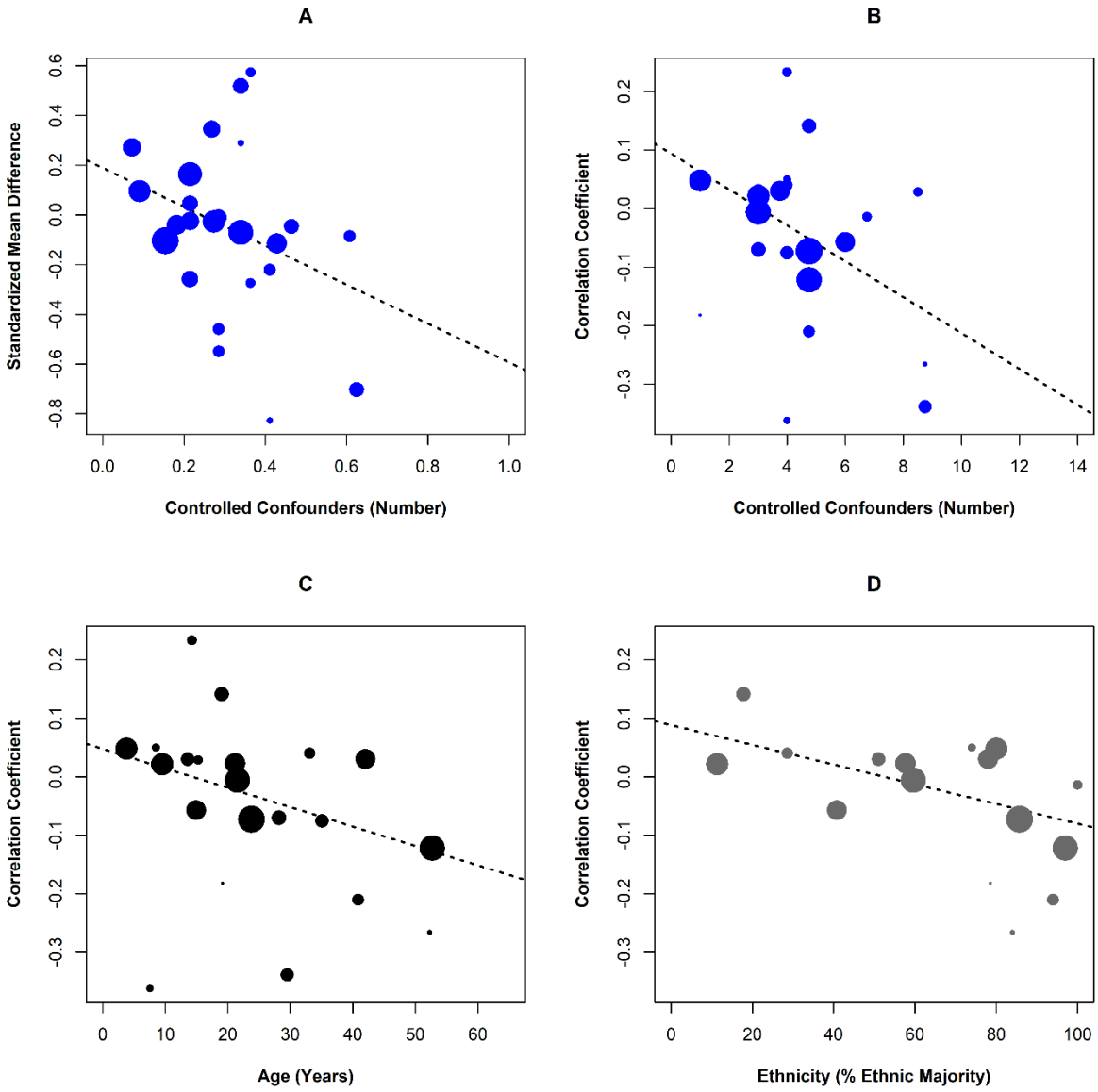

Figure 5. Meta-regression scatterplots of continuous moderators found to significantly alter the main effects reported for group comparison and correlational meta-analyses. **A**: Study quality component Number of Potential Confounders Controlled as a significant moderator of pooled SMD. **B**: Study quality component Number of Potential Confounders Controlled as a significant moderator of pooled correlation coefficient *r*. **C**: Sample mean age as a significant moderator of pooled correlation coefficient *r*. **D**: Percentage of participants of an ethnic majority group as significant moderator of the pooled correlation coefficient *r*.

for menstrual cycle in their female participants (β = -0.179, 95 % CI [-0.352; -0.006], SE = 0.088, p = 0.043). In studies where menstrual cycle had been controlled for, a significantly stronger negative association between severity of ELM exposure and resting-state HRV was found compared to studies where menstrual cycle was not controlled for. Finally, whether the study had been conducted in- or outside the USA also had a significant impact on reported correlation coefficients (β = -0.136, 95 % CI [-0.221; -0.051], SE = 0.043, p = 0.002), with studies conducted outside the USA reporting a significantly stronger negative association between severity of ELM exposure and resting-state HRV than studies conducted in the USA. Of note, sex (% females) was not found to be a statistically significant moderator in either the group-comparison or correlational meta-regression analyses.

3.4.5. Sensitivity analyses

In a first sensitivity analysis, we repeated group comparison and correlational meta-analyses excluding outlier studies identified by inspection of corresponding funnel plots (k = 4 studies excluded from group comparison, and k = 2 excluded from correlational meta-analysis). For the group comparison meta-analysis, heterogeneity decreased from I^2 = 45.06 % in the overall model to I^2 = 0.00 % in the model excluding outliers, while the remaining summary statistics including the aggregated ES estimate did not change substantially. Similarly, heterogeneity decreased from I^2 = 22.79 % in the overall correlational meta-analysis random-effects model to I^2 = 0.00 % in the model excluding outliers. Remaining summary statistics, including the aggregated ES estimate, were not considerably different after outlier exclusion. In a second sensitivity analysis, we repeated our analyses including studies focusing on DVE (k =1 in group comparison, k = 3 in correlational meta-analysis, respectively), which did not affect aggregated ES estimates in either of the two meta-analyses. For correlational meta-analysis, however, inclusion of DVE studies caused the level of heterogeneity between primary studies to increase from I^2 = 22.79 % to I^2 = 49.17 %. We conducted a third sensitivity analysis including a study previously excluded from group-comparison meta-analysis (Tanaka et al., 2016), and results remained largely identical (a summary of results from our sensitivity analyses conducted can be seen in *Supplementary Tables 7* and *8* in the online Supplementary Material). Finally, aggregation of individual observed correlation coefficients between severity of exposure to different ELM subtypes and resting-state HRV was performed. Resulting summary effects and model statistics did not remarkably deviate from the original summary model of correlational studies (*Supplementary Table 11* in the Supplementary Material).

4. Discussion

4.1. Main findings

4.1.1. Comparative and correlational meta-analysis

The systematic search and quantitative synthesis of studies reporting on resting-state vagal function and exposure to maltreatment during childhood did not reveal clear evidence for the proposed associations: Our first hypothesis of reduced resting-state HRV reflective of alterations in parasympathetic function in individuals exposed to ELM, as compared to individuals without such experiences, was not confirmed by the current meta-analytic main results. Equally, we did not find meta-analytic evidence for a relationship between the severity of ELM and resting-state HRV overall. However, and as might have been expected, we were able to identify several significant moderators. In particular, the relationship between ELM and resting-state HRV was significantly altered depending on current psychopathology and sample age.

In the two following sections, we are going to discuss these main results (section 4.1.2) as well as further exploratory findings (section 4.1.3) in more detail, attempting to integrate them within the context of other recent findings in related and emerging fields. We will also emphasize the need for more thorough scientific investigation of the relationship between ELM and HRV, highlighting important aspects concerning the interpretation and measurement of either construct. We suggest that researchers should pay closer attention to potential confounders of HRV in the planning and conduct of future studies, and will provide recommendations on how to implement these (section 4.1.3). Next, we particularly address current challenges and recommendations concerning the measurement of ELM (section 4.2). In the remainder of this discussion, we will address further challenges, as well as the limitations of our own meta-analytic study (section 4.3), which, together with current conceptual and methodological issues, might have contributed to the present main results that raise many further questions.

4.1.2. Investigating the relationship between ELM and HRV: moderating effects of current psychopathology and age

In meta-regression and subgroup meta-analyses, we found resting-state vagal activity to be more strongly reduced in individuals exposed to ELM depending on their physical and mental health status. In clinical samples drawn from a clinical population where most individuals reported psychopathology, as compared to general population samples, we found resting-state HRV to be more strongly reduced in the group that had experienced ELM. It might be that our previous assumption of a dysregulation of the ANS as caused by experiences of ELM, which further increases risk for later psychopathology, holds true for some individuals, but not for others (*differential susceptibility model*; see e.g., Albott et al., 2018). Those who are more strongly affected by the harmful consequences of ELM at the time or shortly after exposure might then also suffer more strongly from effects of adverse experiences later in life,

hypothesizing a vicious cycle ultimately leading its way to the development of psychopathology. We might find some support for this assumption in studies on ELM and structural brain development: While ELM predicts lower hippocampal volume in childhood, adolescence, and adulthood (Dahmen et al., 2018; Gorka et al., 2014; Riem et al., 2015) lower hippocampal volume seems to partly mediate the relationship between ELM and greater behavioral problems during childhood (Hanson et al., 2015) and psychopathology during early and late adolescence (Whittle et al., 2017). During adulthood, recent interpersonal stressful events seem to predict smaller hippocampal volume over and above ELM (Lawson et al., 2017). Given previous findings suggesting that ELM in fact changes the functioning of stress regulatory systems (Dedovic et al., 2009; Teicher et al., 2003), we could assume that ELM influences the threshold of stress vulnerability under certain circumstances, in interaction with factors we were not able to capture and account for in the present analyses. These factors presumably include genetic predispositions, developmental factors (e.g., pubertal status), as well as environmental factors, such as e.g. the caregiving environment and health related behavior (e.g. physical activity). Importantly, to gain a better understanding of the potential patterns of association between ELM, reduced resting-state vagally-mediated HRV, and later psychopathology, it will be crucial to address the complexity of these interacting factors, potentially confounding the present results (see further section 4.1.3).

Broadly speaking, we might find several mechanisms to be differently involved when some individuals who experienced ELM develop a psychiatric disorder, while others nonetheless manage to remain relatively healthy throughout their life course. The alterations in ANS functioning observed here could represent one such mechanism, but it could also be a mere consequence of psychopathology - or it could be both. In favor of the latter assumption, testing a mediation model of cumulative exposure to potentially traumatic events, HRV, age, and symptoms of PTSD, psychological distress and aggressive behavior in adulthood, HRV was found to be a significant mediator in the direct relationship between exposure to potentially traumatic events (PTE) and mental health outcomes, but only in combination with age (Liddell et al., 2016): Significant pathways between more severe exposure to PTE, reduced resting-state HRV, and psychopathology in this model were moderated through higher age. While the pathways to pathology following cumulative exposure to PTE should not readily be compared with pathways following ELM exposure, in our meta-regression analyses we similarly found more severe ELM exposure to be associated with reduced resting-state vagal activity depending on age. Studies including older-aged samples found significantly greater reductions in resting-state HRV in association with exposure severity than studies based on younger samples. This might suggest that, over time, ANS functioning is compromised more strongly in individuals exposed to more severe experiences of ELM.

It has been discussed previously that ELM could fundamentally influence the development of stress regulatory systems at an early point in development, influencing these systems for life (Heim et al., 2019). Arguably, the adaptive nature of stress-mediating systems during certain developmental periods might present a plausible explanation for the here examined effects of ELM on ANS functioning

(vagal activity) to become visible only at older age. It is assumed that early childhood, and essentially the first two years of life, present a critical time during which foundations for the development of stress-mediating systems like the HPA axis and the ANS are laid – these systems are thought to functionally adapt to the prevailing environmental conditions during this sensitive developmental time window (Capitanio et al., 2005; McLaughlin et al., 2015). Recent longitudinal findings now suggest that aside from this early sensitive window of adaptation, puberty might present another period during which the functional development of stress-defensive systems might be flexible enough to be critically altered based on concurrent environmental conditions. Investigating the impact of ELM, i.e., the experience of deprived upbringing in institutional care in infanthood, on HPA axis function longitudinally from ages 7–15 years, Gunnar et al. (2019) concluded that during the stage of puberty a developmental window might be reopened, during which the HPA axis might recalibrate towards a more normative stress function. While the question of whether pubertal recalibration also concerns other stress-mediating systems– like the ANS - remains to be addressed, such processes might explain our present age-related findings. Our meta-analysis did not comprise studies where samples were explicitly characterized as previously or concurrently institutionalized individuals. Thus, in contrast to the study by Gunnar et al. (2019), the majority of data included in this meta-analytic study might not originate from individuals who have experienced post-institutionalized amelioration of environmental circumstances through adoption. In fact, individuals raised in an adverse environment show an increased risk to continue their life living under adverse circumstances (Nurius et al., 2015).

Within a framework termed the *developmental history theory*, recent meta-analytic findings suggest ELM to be related to markers of biological aging, including pubertal timing and development, cellular aging, and cortical thinning (Colich et al., 2019). Accelerated biological aging is another mechanism presumably involved in the association between ELM and the development of psychopathology and pathophysiology later in life. Resting-state HRV has consistently been shown to naturally and continuously decline during adulthood (Jandackova et al., 2016; Yeragani et al., 1997; Zhang, 2007), leading us to assume that HRV might represent another potential marker of biological aging. The here observed greater reductions in resting-state HRV in older aged samples more severely affected by ELM would then support this notion. Our finding that resting-state HRV might be more strongly reduced in clinical versus non-clinical populations exposed to ELM could also be aligned within such a framework, where more strongly reduced resting-state HRV might mark accelerated biological aging further leading to the manifestation of disease.

From a neuro-structural perspective, findings from a recent longitudinal study investigating the influence of ELA on cortical thickness (CT) via psychopathology (Monninger et al., 2019) suggest that the impact of early adversity on brain alterations in young adulthood, i.e., reduced CT in the right OFC, are partly mediated through concurrent psychopathology. On a brain structural level, CT of the OFC shows strongest associations with HRV (Koenig, 2020). Given the results from our meta-regression

highlighting the importance of psychopathology, it is plausible that ELM interferes with neuromaturation of prefrontal regions via psychopathology (Monninger et al., 2019; *see also* Koenig, 2020).

As a further thought, theoretical frameworks proposing a multi-systems approach, such as those recently emerging from systems biology (e.g., the *neuroimmune network hypothesis*; Nusslock & Miller, 2016), might be interesting to consider in the current context. It is assumed that disorders may arise as a result of perturbations in biological networks and how they interact, rather than from isolated dysfunction in a single system. Growing evidence points towards the relevance of bidirectional interactions among different biological systems (Hood, 2004) and as suggested previously, we might need to shift our perspectives towards a systems-oriented generation of research, focusing more on patterns of association across different systems (Hostinar et al., 2018). In this sense, meta-analytic findings indicate that ELM exposure may significantly contribute to a pro-inflammatory state in adulthood (Baumeister et al., 2016), while a recent meta-analysis including children and adolescent samples found no such relationship (Kuhlman et al., 2019). This aligns with our own meta-regression results identifying sample age as a significant moderator of the relationship between ELM and decreased resting HRV. Given that decreased vagal activity might provoke elevated levels of inflammatory markers (Williams et al., 2019b), and that increased inflammation might contribute to the manifestation of psychopathological diseases (Uddin & Diwadkar, 2014), in the sense of interactional systems a pathway from ELM exposure to decreased vagal activity and elevated systemic inflammation might be assumed, leading to the psychopathological outcomes more frequently observed in ELM-exposed individuals (Danese & Baldwin, 2017). Recent findings that increased inflammation might mediate a potential link between ELM and altered functional cortico-limbic connectivity (Kraynak et al., 2019), a brain network involved in emotion regulation and essentially also related with later psychopathology (Peverill et al., 2019), further emphasize the importance to incorporate the investigation of interactional mechanisms of different biological systems in future research.

In summary, with regards to the age and psychopathology effects identified in our moderator analyses, considering potential patterns of association between ELM, HRV, and psychopathology, different pathways might be hypothesized. It might be assumed that (1) as a consequence of ELM, we find insufficient PFC recruitment and poor emotion regulation, further leading to psychopathology onset and consequently low HRV. However, we could also assume that (2) ELM can lead to aberrations in the development of the ANS, and specifically, to insufficient increase in vagal activity during childhood and adolescence, indexed by lower than normal HRV, leading to insufficient PFC maturation and deficiencies in affective regulation, ultimately increasing the risk for psychopathology. However, it might also be assumed that (3) a third factor exists (e.g., brain development), which, after exposure to ELM, may affect HRV and emotion regulation independently from each other (which, as we think, might be rather unlikely). Having outlined these different potential scenarios, we may find support in

favor of model (2). Nonetheless, a 'third factor' argument still remains plausible, as early development is driven by many confounders, potentially resulting in greater inter-and intra-individual variance that need to be accounted for to statistically unravel significant associations between environmental conditions and e.g. physiological function. However, future longitudinal studies addressing ELM, HRV and brain maturation are warranted to clarify the exact cascade underlying our present findings. The interested reader is referred to Koenig (2020) for a theoretical model and existing review.

4.1.3. Further exploratory results and recommendation for future research

Interestingly, our meta-regression results also suggest that the relationship between resting-state vagal activity could be associated with ELM exposure depending on sample ethnicity: In studies where a higher percentage of the sample was part of an ethnic majority group - with that being European-Americans in the majority of studies - resting-state HRV was found to be more strongly reduced in association with more severe ELM exposure. Meta-analytic findings suggest that, relatively speaking, European-Americans have lower resting HRV than the minority group of African-Americans (Hill et al., 2015), potentially supporting the plausibility of our observed results: Physiological variations underlying the variation in resting-state HRV between different ethnic groups, and higher resting-state HRV in African-Americans in particular, might make them less vulnerable to disruptions in physiological mechanisms than European-Americans. Resulting alterations of ANS functioning might more likely be a consequence of ELM exposure in the latter ethnic group. Further potential explanations might be found when combining findings from genetics with assumptions made within the *NIM* mentioned earlier: Resting-state HRV was found to carry a high degree of heritability, and estimates of heritability do not seem to differ between European-Americans and African-Americans (Wang et al., 2005, 2009). The *NIM* assumes that vagal functioning, as indexed by resting-state HRV, is important in terms of emotion regulation capacities. Presumably, members of ethnic minority groups face comparably greater adversity on average than members of otherwise similar ethnic majority groups. Framed in terms of the *NIM*, having to deal with a higher amount of daily stressful environmental demands, simply due to a dissimilar ethnic background, might require greater emotion regulation capacities from ethnic minority members. In this sense, if multiple generations of ethnic minorities face greater environmental challenges, and if resting-state HRV is highly heritable across generations, higher-resting state HRV in ethnic minority members in the face of ELM could mirror a genetically-driven adaptation mechanism, causing ethnic minority members to heritably possess more robust vagal functioning less likely affected by ELM exposure. We furthermore found that the relationship between ELM and resting vagal activity could vary depending on the region of study origin: In studies conducted outside the USA, severity of exposure was more strongly negatively related with resting-state HRV compared to studies conducted in the USA. Studies conducted in the USA more often included a higher percentage of ethnic minority members, aligning with the above assumed differences related to ethnic sample distributions.

While the World Health Organization acknowledges ELM as a global public health concern, large discrepancies exist between different parts of the world as to how this problem is currently being addressed. Disparities also manifest in research: For many countries, data on pure estimates of the frequency of ELM are still lacking, while current estimates vary greatly depending on the country and the method of research used (World Health Organization, 2016). In the current study, among the 32 primary studies included in our quantitative syntheses, 21 had been conducted in the USA. While ELM exposure had more frequently been prospectively assessed consulting Child Protective Services (CPS) records in US studies (7 out of 21 studies, or 33.4 %), consultation of official documentations of maltreatment in order to recruit study samples or assess ELM exposure was less common in studies conducted outside the USA (1 out of 11 studies, or 9.1 %). Most studies conducted outside the USA used retrospective self-reports to assess ELM exposure. In light of recent meta-analytic evidence that agreement between prospective and retrospective measures of childhood maltreatment is poor (Baldwin et al., 2019), studies conducted inside and outside the USA may therefore identify different groups of individuals, with potentially different risk pathways. Furthermore, estimates of prevalence rates of ELM from retrospective self-reports are generally much higher than rates derived from prospective measures (Fergusson et al., 2000). Since self-reports measuring ELM (which result in higher numbers) seemed to be applied more frequently in regions where study samples were more likely to belong to an ethnic majority group (potentially inherent of lower resting-state HRV as argued above), this could serve as an alternative explanation of the here observed correlational patterns. While both prospective and retrospective reports of ELM seem to have predictive validity (Tajima et al., 2004), future studies will need to pay greater attention to such measurement issues, and global consensus in the definition and measurement of ELM should be sought. Furthermore, and especially since several moderators currently identified point towards the potential importance of ethnicity in the interplay between ELM and vagal activity, future studies should not only consistently and transparently report on ethnicity distributions of their samples but they should actively investigate if and how ethnicity as well as geographical region might affect potential effects of interest.

Especially relevant for the planning of future studies, we also found that the methodological quality of included studies, when defined as the number of potentially confounding factors study authors controlled for in either the study design or in statistical analyses, had a significant impact on the individual observed ES estimates, a finding we observed for both meta-analyses. In studies where study authors more rigorously controlled for factors potentially confounded with our effect of interest, the observed ES estimates for the respective study were greater and in the expected negative direction. Considering the respective section of the risk of bias ratings of included studies in greater detail (*Supplementary Table 6*), on average, less than a third of the potential confounders judged as being influential and thus important to consider when measuring and reporting resting-state HRV, such as physical activity or medication, were actually controlled for. We observed a high variation between included studies, with the study inherent of the highest potential risk of bias controlling for only one

confounding factor, while the study with the least potential risk controlled for nine out of fourteen confounders included in our risk of bias tool. Despite the relative importance to consider participants' levels of physical activity or fitness, this factor has often been neglected in the study of HRV in association with ELM, especially in studies including youth samples. Among the 32 studies included, none of the 12 studies including youth samples ($N = 7$ studies included adolescent samples), reported to have assessed or controlled for physical activity levels. Among the 20 studies that included adult samples, only 4 studies reported to have controlled for participants' physical activity levels. It has been shown that regular exercise can modify autonomic balance (Task Force of the European Society of Cardiology, 1996), may benefit the development of autonomic function during development (Nagai & Moritani, 2004), and may increase HRV (Prado et al., 2010). On the other end of the extreme, obesity in children and adolescents was shown to be associated with autonomic dysfunction and reduced cardiac vagal activity (Chen et al., 2012; Dangardt et al., 2010; Nagai & Moritani, 2004; Rodríguez-Colón et al., 2011).

Another important aspect to consider when studying HRV is age, and when studying youth samples, additionally, pubertal status needs to be considered. It has been shown that the stage of puberty may be marked by increases in cardiac contractility, and normatively increasing blood pressure levels during puberty were found to be associated with increased sympathetic and decreased parasympathetic activity post-pubertal, but not in preadolescence (Milicević et al., 2003; Tanaka et al., 2000). While the literature on the relationship between age and vagally-mediated HRV, especially during puberty, is still growing, existing studies highlight age-related differences in vagally-mediated HRV between different developmental stages, underscoring the importance to consider these aspects when studying HRV (Koenig, 2020). However, only two studies included in this meta-analysis reported any information on the stage of pubertal development, of which only one reported to have controlled for pubertal status in statistical analyses, due to significant differences between study groups.

Where respective information was reported and could be coded, we included key confounding factors in meta-regression also separately, and we found that controlling for the menstrual cycle was a significant moderator of the association between the severity of ELM exposure and resting-state vagal activity. Studies where the menstrual cycle of female participants had been controlled for, found significantly greater reductions in resting-state HRV compared to studies where no such control had been reported. This result might be interpreted in light of very recent meta-analytic results suggesting a significant decrease in vagal activity from the follicular to luteal phase within the menstrual cycle (Schmalenberger et al., 2019) and underlines the importance of future more thorough study designs allowing to appropriately control for the physiological and psychological effects of the female hormonal cycle (Schmalenberger & Eisenlohr-Moul, 2019). In the planning of future studies, measurement of and controlling for potentially confounding factors should form a key component, as this will be key to a

better understanding of the relationship between ELM and the functioning of physiological systems such as the ANS.

So far, research in the field has missed to address some of the key confounding factors related to the current effect under investigation, potentially contributing to our observed summary effect having been levelled out to zero. To conduct a thorough psychophysiological investigation of HRV measures, however, it is of importance to consider any confounding variable that could influence HRV that can be controlled for. Available guidelines and reviews provide an overview of variables currently recommended to consider (Quintana et al., 2016; Quintana & Heathers, 2014; Task Force of the European Society of Cardiology, 1996), however, a search for most recent updates on this matter might always be advisable, given that research is ongoing.

4.2. Current challenges and further recommendations

It has been outlined that many studies examining the effects of ELM focused on only a limited range of ELM experiences, typically focusing on relatively extreme exposures such as sexual abuse or institutional rearing. Furthermore, it has been noted that many studies have utilized a cumulative-risk approach, which simply accumulates the number of distinct forms of ELM experienced to create a risk score, without considering the type, time of exposure, chronicity, or severity of ELM, and this risk score was then used as predictor of outcomes, with the assumption that all forms of ELM have equal and additive effects on developmental outcomes (Colich et al., 2019; Evans et al., 2013). By integrating correlation-coefficients between ELM subtypes (that is, physical and emotional abuse and neglect as well as sexual abuse) and resting-state HRV, we did not find evidence for a relationship between the rated severity of any of these subtypes and resting-state vagal function. Although in line with our main results, interpretation of these findings is problematic for various reason. The numbers of studies that could be included in our sub-analyses were very small, ranging from k =6 to k = 8 studies. Due to this small number of studies as well as a lack of information not reported by primary studies we were not able to control for the extent of exposure to other subtypes or adversities, rendering differential inferences difficult. Future studies examining the relationship between ELM and vagal activity should pay close attention to the co-occurrence and dimensionality of different subtypes of ELM. In order to do so, researchers need to carefully select appropriate measurement instruments.

Measurement instruments to assess ELM exposure have been reviewed repeatedly (see e.g. (Burgermeister, 2007; Hulme, 2007; Roy & Perry, 2004; Satapathy et al., 2017; Strand et al., 2005), while a recent review examined the methodological quality and measurement properties of available instruments (Saini et al., 2019). Additionally, the strength of evidence for research use of each instruments was assessed in this review, and the authors also determined which measures provide information on the developmental timing of ELM. In general, the 52 instruments examined were found to vary greatly regarding methodology, measurement, and psychometric properties, and no single instrument was superior to all others across settings and populations. Thus, as has been stated, the choice

of the most appropriate instrument will depend on the respective context in which it will be employed. The authors provide a number of instruments with moderate to strong level of evidence for methodological quality and measurement properties that may be suitable for particular research questions (please see Saini et al., 2019 for further details). In said review, it has further been stated that among the instruments examined, the CTQ, which is one of the most frequently used instruments as also reflected by the studies included in our own meta-analyses, was the only scale that has been thoroughly investigated and demonstrated a strong level of evidence with adequate internal consistency, reliability, content validity, structural validity, and convergent (hypothesis testing) validity (Saini et al., 2019). Yet, despite this seemingly strong level of evidence, we would argue that the CTQ has many shortcomings as well, e.g., this instrument lacks an assessment of maltreatment-related details (including the frequency of occurrence, chronicity, and age at onset), and choosing this questionnaire will not always be appropriate in every research context. Instruments are also available, however, that capture information on the developmental timing of ELM, and many of these instruments were shown to have a moderate to strong level of evidence as well (again, please consider Saini et al., 2019 for further details). Among these, the Abuse Chronology of Exposure Scale (MACE; Teicher & Parigger, 2015) has been highlighted as particularly interesting, as it was developed to overcome prevailing limitations by assessment of cumulative severity and number of types of recollected exposure to abuse during each year of childhood. What is more, the MACE also information on peer victimization, witnessing inter-parental physical violence, violence towards siblings, parental loss, unavailability of father, or unavailability of a mother, which could allow researchers to control for factors otherwise potentially confounding the effects of ELM exposure. A further instrument (which was not included in the above review) to provide information on the age of onset of ELM as well as the respective duration and frequency, and that has been proven useful especially in relation to brain based measurements (e.g., Boccadoro et al., 2019) is the Stressful Life Events Screening Questionnaire (SLESQ; Goodman et al., 1998). The SLESQ has originally been developed as a general traumatic event screening questionnaire and is a 13-item self-report screening measure to assess lifetime exposure to a variety of traumatic events. Besides exposure to physical, emotional, and sexual abuse, it assessed exposure to further potentially traumatic events (including, e.g., serious accident or illness, witnessing intimate partner violence) thus equally allowing to control for these potential confounders of ELM exposure. To summarize, researchers who aim to assess ELM exposure should to carefully evaluate the tools available, while several review papers are available that could potentially guide selection of the most appropriate instrument for the respective population and research question examined.

4.3. Limitations

We will now turn to methodological limitations pertaining to the present meta-analytic study, as well as some further challenges related to the nature of our included studies, putting above presented results into further perspective. First of all, although we conducted a number of sensitivity analyses to

test arbitrary decisions undertaken throughout the review process, the results of which suggested independence of our meta-analytic results, it is still conceivable that our defined inclusion criteria resulted in a choice of primary studies that was not suitable to comprehensively address the current effects of interest. Potentially problematic in particular might be that many primary studies fulfilling our inclusion criteria had a different study focus than was defined for this meta-analysis. In order to include as many studies as possible, we eventually had to send data requests to respective study authors, sometimes asking them to re-allocate their study groups. While it is very fortunate that many authors responded to our requests, by choosing this approach, we might have involuntarily introduced some special source of bias. Furthermore, we did not determine the strategy of grouping participants in maltreated and non-maltreated groups but adopted grouping-factors as provided in primary studies (or, in the case of re-allocation upon request, relied on according subsequent decisions of study authors).

Next, while we decided not to include "deprivation" as a keyword in our search term, and studies on institutional rearing were excluded from our meta-analytic synthesis, findings from studies focusing on children subjected to early socioemotional deprivation and who as a consequence typically exhibit cognitive and behavioral deficits, suggest that early deprivation may have deleterious effects on brain maturation and function. For example, altered development of limbic and paralimbic structures characterized by glucose hypo-metabolism, as well as altered functional connections in according circuits, have been identified in children subjected to early socioemotional deprivation due to early institutionalization (Chugani et al., 2001; Eluvathingal, 2006). The identified structures affected by glucose hypo-metabolism included the orbital frontal gyrus, infralimbic prefrontal cortex, hippocampus/amygdala, lateral temporal cortex, and the brainstem (Chugani et al., 2001), and in a follow-up study examining white-matter tracts that connect these brain regions, structural aberrations in the left uncinated fasciculus were identified, suggesting impairments in the function of a neural network that promotes communication between the above regions (Eluvathingal et al., 2006). These brain regions are furthermore also involved in the stress response and autonomic control, and it might be interesting for future (meta-analytic) studies focusing on the relationship between ELM and ANS activity to also consider individuals characterized by early institutionalization.

Moreover, the present meta-analytic study focused on the relationship between ELM exposure and vagal activity at resting-state, relying on a framework where resting-state vagally-mediated HRV is seen as a global measure of stress and health (*NIM*; e.g. Thayer et al., 2012). While we felt that a combination of different frameworks would be out of scope here, as we did not find evidence for an association between ELM and resting-state vagally-mediated HRV in principal, considering altered ANS function following ELM exposure using vagally-mediated HRV measures of stress response might be worthwhile. Broadly speaking, during stress exposure, ANS response might be characterized by increased sympathetic and decreased vagal (parasympathetic) activity, the latter typically reflected by a decrease in vagally-mediated HRV, indexing vagal withdrawal (however, normative changes in vagally-

mediated HRV in response to a stressor seems to be characterized by vagal increase or decrease, which might be depending on the nature of the specific stress task, task load, and vagally-mediated HRV levels at resting-state (e.g., Herbert et al., 2010; Park et al., 2014). Generally speaking, the influence of ELM on stress reactivity is still an unclear issue in the literature. Regarding vagally-mediated HRV measures of ANS response, a recent systematic review of the literature (Young-Southward et al., 2020) considering studies on the relationship between ELM exposure and ANS responsivity reported 3 studies on vagal reactivity in children exposed to ELM. These studies show large methodological differences with regard to the stress paradigms used, and results were highly mixed, highlighting that the current literature is far from conclusive. While this and other existing reviews considering the influence of factors highly similar to ELM exposure on ANS responsivity to stress (see e.g., El-Sheikh et al., 2011), who examined the influence of family conflict on child ANS function) focused on studies including samples of young children and youths, a worthwhile area of consideration in future systematic reviews (and meta-analyses as feasible) might also be potentially altered ANS responsivity to stress following ELM exposure in adult samples. A systematic review and meta-analysis examined ANS function (resting-state and stress reactivity) in adult (potential) perpetrators of ELM (i.e. either parents who maltreated their children or adults supposed to be at risk to conduct child maltreatment; Reijman et al., 2016). Although perpetrators cannot readily be compared with victims of ELM, perpetrators of ELM might be at a higher risk to have experienced ELM themselves (e.g., Pears & Capaldi, 2001), suggesting similar potential aberrations in ANS function in this particular population. The authors reviewed and meta-analyzed 3 studies on ELM perpetration and resting-state vagally-mediated HRV, while the resulting effect size was not statistically significant (N = 232, g = 0.30, 95 % CI [-0.14, 0.75]), and 2 studies on vagally-mediated HRV reactivity to stress and ELM perpetration were included and revealed no significant effect (N = 128, g = 0.06, 95 % CI [-0.49, 0.61]). Currently, there seems to be a clear paucity of studies addressing the relationship between ELM exposure and ANS responsivity to stress in children and adults, and while the distinct reactivity pattern of the ANS in the face of different stressors remain to be established, another great challenge will be to develop a stress paradigm that could be uniformly applied for different age groups, enhancing the comparability of findings and thus simplifying and increasing the conduct and credibility of meta-analytic studies in the field. Interestingly, research has recently started to investigate associations between ELM and the functioning of stress response systems in more complex ways, and recent findings promote a curve-linear relationship between ELM and both autonomic and HPA axis reactivity, where differences in stress reactivity become apparent towards the extreme ends of ELM-exposure (Shakiba et al., 2019).

Bias introduced by inclusion of studies with differing research foci could also have affected our own risk-of-bias ratings: Group-comparison studies were rated with regard to some aspects study authors might only have considered if the study were actually a case-control study comparing individuals with and without ELM exposure, which was, as already mentioned, not always the case. Consequently, interpretation of risk-of-bias of these studies was complicated, and although the two

reviewers conducting risk-of-bias ratings reached agreement regarding how such cases were to be treated, resulting judgements could still be erroneous. While it is rather unlikely that our systematic search missed to detect those studies that specifically focused on our effect of interest, the small number of such studies identified here suggests that more research on the relationship between ELM exposure and HRV indices of vagal activity is needed before we should make any concluding inferences.

Next, the results from meta-regression suggesting both health status and age as significant moderators in the relationship between ELM and resting-state HRV could simply be a by-product of methodological issues, or reflect behavioral habits impairing physical health that are more frequent in individuals exposed to ELM. Firstly, rates of ELM exposure assessed via retrospective self-reports were found to be about ten-fold higher than rates substantiated by prospective measures (Fergusson et al., 2000; MacMillan et al., 2003), and self-reports were typically applied to measure ELM exposure in adult samples included in this synthesis. Prospective ratings, in turn, were more frequently used in youth samples. This could have resulted in higher ELM scores reported in studies where participants were adults as compared to studies including children, and consequently, since HRV is inversely related with age, higher reductions in resting-state HRV in older samples with more severe ELM exposure as compared to younger samples could simply be caused by differences in assessment methods and resulting arbitrarily inflated correlation coefficients.

Also, as previously stated, exposure to ELM may coincide with higher rates of behavioral risk factors associated with reduced resting-state HRV, while most of these risk factors could not be examined in the present synthesis due to lack of reporting by primary studies. For example, such risk factors could include smoking or nicotine consumption, alcohol consumption, obesity, or sleep disturbances. While these risk factors might not yet be present or might not yet have produced alterations in resting-state HRV in younger individuals, they could have contributed to the age-effects observed here. It has also been found that the severity and resulting impact of such risk-factors might be increased with concomitant PTSD symptoms (Dennis et al., 2014), which are frequently reported after exposure to ELM. Individuals with PTSD, in turn, are also more likely to be heavy smokers (Beckham et al., 1997; Kirby et al., 2008) and obese (Pagoto et al., 2012), to abuse alcohol (Mcfarlane, 1998), and to suffer from sleep disturbances (Koffel et al., 2016) than individuals without PTSD, which could also have contributed to the observed effects of sample health-status. Either way, although the meta-regression we conducted was on pre-defined moderators, these analyses should be considered explorative, and respective results should not have a purpose other than that of hypothesis generation: Our results provide no direct evidence for a likely presence of such effects but underscore the need for future longitudinal studies inherent of rigorous in- and exclusion criteria to examine potential pathways between ELM exposure and mental health disorders via ANS functioning, allowing to also make inferences about temporal patterns.

Furthermore, and from a methodological point of view, it has been emphasized that meta-regression results are often not interpreted in an appropriate manner. While for binary moderators, interpretational limitations might be more obvious, continuous moderators in particular might have been erroneously interpreted in the past (Petkova et al., 2013). When a moderator included in meta-regression is a subject-level characteristic that has been averaged over study participants, as it is the case for several moderators included the present meta-regression analyses (e.g., age), interpretations of meta-regression results could be problematic and should be treated cautiously (Petkova et al., 2013). While we acknowledge that caution should certainly be exercised in the interpretation of the present identified moderators and that currently widely used statistical approaches to meta-regression might be overthought, we nonetheless think that the analyses conducted here provide the most accurate straightforward approach currently available in order to gain insights into the potential effects we were interested in.

Focusing on the methodological quality of our included studies, our assessment of potential confounders is not exhaustive, for example, we did not include the highly relevant aspect of pubertal development in our quality assessment tool. Future studies are advised to consider current guidelines on confounders that should be considered in studies measuring HRV (some available sources have been provided in section 4.1.3 above). Furthermore, studies showed high variation and limitations regarding a number of other aspects. In general, sample sizes of included primary studies were very small, and especially group comparison studies showed very low statistical power. Studies also differed widely regarding underlying sample populations, raising the well-known meta-analytic concern to "compare apples and oranges". A further limitation concerns the conceptualization and assessment of ELM: Only a small number of studies attempted to address the high co-occurrence of varying forms of ELM or examined differential influences of particular adversity sub-types. Moreover, while the use of unstandardized, one-sided, and bias-prone instruments to identify and quantify ELM exposure likely contributes to current inconsistencies among studies investigating ELM (Gilbert et al., 2009), this might have been aggravated in the present synthesis due to a large variety of different scales used in our included studies, which varied greatly in the quality, number, and dimensionality of included items. Furthermore, included studies used highly divergent techniques to recruit ELM-exposed samples, which may result in meaningful differences in observed effects on outcomes. While many studies typically including youth samples recruited their participants via external agencies involved in the identification of maltreatment cases, i.e. CPS agencies, many studies including adult samples solely relied on retrospective self-reports.

What is more, and particularly striking, we found included studies to have altogether missed to address two seemingly important aspects in the investigation of ELM. Firstly, none of the studies included in this synthesis addressed potential exposure of participants to adversities other than ELM during childhood or adulthood. Without controlling exposure to other adverse events that could lead to

similar alterations via study design or statistical analyses, according inferences regarding differential effects of ELM exposure are left questionable. Secondly, none of the included studies examined or reported the age of participants at ELM onset. As mentioned previously, differences in the time point of exposure might lead to differential developmental alterations: The primary developmental task a child has to fulfill at the time of exposure is thought to be the most likely to be interrupted or disrupted by ELM experiences (McLaughlin, 2016), and developmental deviations are assumed to be carried forward, affecting the ability to accomplish future developmental tasks (Cicchetti & Toth, 1998; Sroufe, 1997). The detection of sensitive time windows of neurobiological, cognitive, social, and emotional development when the individual is particularly susceptible to environmental influences thus seems a crucial future step in the investigation of ELM (McLaughlin, 2016).

To sum up, while we acknowledge that the concept of ELM is highly complex to define and its measurement might be elusive, a first and important step towards valid and sound conclusions would be the conduct of large-scale, longitudinal, and standardized thoroughly planned research studies, the results of which would have to be reported in transparent and consistent ways.

4.4. Conclusion and outlook

In this first systematic review and meta-analysis of studies reporting data on a potential link between ELM and resting vagal function, while we found no evidence for such a relationship in principle, we were able to identify several influential factors, the controlling of which uncovered resulting summary effects as expected: Controlling for the potential study-level-moderators *presence of psychopatholog*y, *age*, *ethnicity*, *region of study origin*, *methodological quality*, and *controlling for the menstrual cycle* resulted in larger observed summary effect size estimates indicating decreased resting-state HRV in ELM exposed individuals. Future research will have to examine whether these results reflect differential susceptibility to HRV alterations and whether there are specific age effects, while factors potentially confounding HRV measurements need to be addressed more rigorously in the future.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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2.2 Manuscript

Cardiac Autonomic Functioning and Clinical Outcome in Adolescent Borderline Personality Disorder Over Two Years

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Abstract

Decreased heart rate variability (HRV) is associated with maladaptive stress regulation. Non-suicidal self-injury (NSSI) in adolescents is associated with impaired stress regulation. Existing research in adolescent psychopathology mainly focused on short-term recordings of HRV under resting conditions. Evidence in adult psychiatric patients suggests alterations of circadian variation patterns (CVP) of autonomic nervous system (ANS) activity. In the present study, we examined for the first time, whether CVP of cardiac autonomic activity, indexed by heart rate (HR) and vagally-mediated HRV (vmHRV) derived from 48 hours of ambulatory ECG recording, are altered in females with adolescent NSSI disorder, compared to healthy, age- and sex-matched controls (HC; N = 30 per study group). We furthermore examined potential associations between altered CVP and NSSI frequency, as well as a range of dimensional clinical predictors, including early life maltreatment (ELM), borderline personality disorder (BPD), difficulties in emotion regulation, depressive symptoms, and sleep duration. Several confounders, including physical activity, were controlled for. Adolescents with NSSI are characterized by altered CVP of ANS activity, indexed by a greater HR Amplitude, MESOR and Acrophase, as well as a lower Amplitude, MESOR and Acrophase of vmHRV – although the later findings were not robust when adjusting for important confounds. Further, CVP of ANS activity in adolescent NSSI is characterized by a general shift in rhythmicity of about one hour, indexed by a later Acrophase in HR and vmHRV. ELM severity significantly predicted CVP of HR and vmHRV in unadjusted but not fully-adjusted models. BPD symptomatology was a significant predictor of CVP of HR but not vmHRV. While chronobiological interventions in stress- and emotion regulation disorders might be translationally relevant avenues of future research, the present results also highlight the need for more rigorous control of critical confounders in studies focusing on the interrelation of clinical variables with ANS activity and disruption of the circadian system.

Keywords: *Cardiac autonomic function*; *Borderline personality disorder*; *Non-suicidal self-injury*; *Early-life adversity*; *Adolescents*

1. Introduction

Mental disorders cause enormous personal and societal burden, accounting for around one-third of disability worldwide (Kessler et al., 2007). It is by now evident that mental disorders are rooted early in life, and often manifest already in childhood or adolescence (Meyer & Lee, 2019). Indeed, psychiatric disorders present a significant portion of the burden of disease in youth (Gore et al., 2011; Kessler et al., 2007; Merikangas et al., 2009).

Personality Disorders are common and debilitating mental disorders (Marceau et al., 2018), and it has long been substantiated that significant personality disturbances may occur even in early adolescence (Bernstein et al., 1993; Johnson et al., 1999, 2000; Kasen et al., 1999; Rey et al., 1995; Rey et al., 1997). Borderline personality disorder (BPD), characterized by emotion dysregulation, difficulties maintaining interpersonal relationships, identity disturbances, as well as impulsive and self-harm behavior (American Psychiatric Association, 2013), is estimated to affect approximately 1 – 5% of adolescents, congruent with prevalence rates reported for adults (Chanen et al., 2004; Kaess et al., 2014; Sharp et al., 2012). The clinical phenotype of BPD is heterogeneous and complex (Marceau et al., 2018), and BPD is associated with increased risk for suicide and significant functional impairment (Leichsenring et al., 2011). Accordingly, BPD presents a personality disorder associated with a particularly high burden of disease.

Despite substantial evidence that many major psychiatric disorders emerge already in young age, only half of all children and adolescents with a current mental disorder receive mental health treatment (Merikangas et al., 2009). Among those who do receive treatment, the rates of partial or no response are concerningly high (Menke, 2018). BPD in particular is associated with challenges in effective treatment provision (Grenyer et al., 2017), and approximately one-third of BPD patients fail to respond to initiated treatment (McMurran et al., 2010). Patients as a result may experience prolonged distress and impairment, and may also undergo multiple courses of treatment linked with increasing health care costs - all of which might be prevented if an effective treatment were applied initially (Kessler, 2018). More effective treatment provision in adolescent psychiatric patients might be achieved by accurately predicting individual responses to treatment, aiding the identification of most appropriate treatment options in each individual case (McMahon, 2014). In contemporary psychiatry, the diagnostic process and based thereupon the choice of a treatment is mainly based on subjective clinical judgements, which might be either inaccurate, imprecise, or unstable over time (McMahon, 2014). Moreover, many different variables are involved that may affect individual treatment outcomes (including, e.g., familial and history of adverse experiences, sociodemographic characteristics, comorbidity, treatment adherence, etc.), making prediction of treatment responses a challenging endeavor in general (Kessler, 2018; McMahon, 2014). More recent scientific endeavors, such as the research domain criteria (RDoC; (Cuthbert, 2015), suggest this kind of problem might best be addressed by focusing on dimensions of observable behavior and more objective neurobiological measures.

In line with the RDoC, as well as recent endeavors towards a personalized approach in many medicinal fields, stronger engagement of more objective predictive markers (i.e., peripheral biomarkers) in the diagnostic and process of treatment planning might allow for a more fine-tuned selection of appropriate (order of) treatments (Chang et al., 2020; Jeong et al., 2020; Ng & Weisz, 2016), positively affecting individual treatment responses. None of the various neurobiological measures so far investigated (including biomarkers retrieved from genomics, peripheral blood, or brain imaging), has yet been clinically established in the treatment of mental disorders (Menke, 2018). These current translational gaps are likely driven by high relative costs in the form of monetary and expenditure of time related to the application of most of these biomarkers, as well as pre-requirements related to their measurement and analysis, which might be difficult to provide in clinical practice. In stark contrast, ambulatory measurements of heart function, which are at the same time inexpensive, accurate, computationally straightforward, and basically possible at any place and during activities of daily routine, allowing also for long-term measurement (Heathers & Goodwin, 2017), may present a promising alternative.

Growing scientific interest in neurobiological mechanisms underlying psychiatric symptoms and disorders led to the generation of studies that highlight altered autonomic nervous system (ANS) functioning as one mechanism potentially involved in the development of mental disorders. Several meta-analytic studies found resting-state vagally-mediated heart rate variability (vmHRV), a biomarker indexing the functioning of the parasympathetic branch (PNS) of the ANS, to be reduced in many different kinds of psychiatric disorders (Alvares et al., 2016; Chalmers et al., 2014; Clamor et al., 2016; Kemp et al., 2010; Koenig, 2016a; Koenig et al., 2016b). Longitudinal studies allowing directional inferences regarding this relationship are scarce, but existing studies suggest that reductions in PNS functioning (i.e., reduced resting-state vmHRV) may not merely be a consequence, but could rather present a risk-marker for the development of psychopathology (Huang et al., 2018; Jandackova et al., 2016); also see Koenig, 2020). Of note, meta-analytic and primary studies report reduced resting-state vmHRV in both adult (Koenig, et al., 2016b) and adolescent BPD (Koenig et al., 2017b; Weise et al., 2020), furthermore suggesting that low vmHRV may present an important trait characteristic of BPD, reflected by difficulties in emotion regulation and impulsivity (Koenig et al., 2016b).

There is increasing neurobiological evidence supporting biomarkers of ANS activity as predictors of treatment effects in adult psychiatric populations. In several studies, ANS activity measured at pre-treatment was found to be predictive of psychotherapeutic and pharmacological treatment outcomes, e.g. in adult major depressive disorder (MDD) (Bär et al., 2004; Kircanski et al., 2019). Furthermore, higher resting-state vmHRV predicted greater symptom reductions following CBT and specialized treatment in patients affected by post-traumatic stress disorder (PTSD; Soder et al., 2019). Vice versa, positive treatment outcome has been associated with improved autonomic activity indicated by re-increases in vmHRV post-treatment, again in adult MDD (Hartmann et al., 2019).

Existing studies in adults report promising results, encouraging the conduct of equivalent studies in adolescents. One previous study examined ANS activity in association with treatment outcome in adolescent BPD (Weise et al., 2020), and this study found greater pre-treatment ANS activity indexed by resting-state vmHRV to predict greater reductions in BPD symptoms and improvement in global functioning over time, while pre-treatment resting HR was not related with treatment outcome. Changes in BPD symptomatology were furthermore associated with changes in ANS activity over the course of treatment, such that increases in resting-state vmHRV and decreases in HR over time were associated with a decrease in BPD symptoms and increased global functioning. Exposure to early life maltreatment (ELM; i.e., the exposure to experiences of different forms of neglect and abuse in childhood or adolescence; (McLaughlin, 2016) was included as a potential covariate in the respective study, given that ELM presents a strong risk factor for BPD in both adolescence and adulthood (Porter et al., 2020; Winsper et al., 2016; Zanarini & Wedig, 2014), and has previously been shown to be linked with ANS functioning (Weise et al., 2020). ELM exposure showed no association with pre-treatment ANS activity or the course of BPD symptoms and ANS measures; however, lower ELM scores predicted better improvement in global functioning over time (Weise et al., 2020).

In the present study, we aimed to expand on these findings by examining pre-treatment ANS functioning over a continuum from HR and vmHRV resting-state to reactivity and recovery from psychosocial stress exposure as predictor of clinical outcome after 2 years in adolescent BPD, while controlling for important confounders of ANS functioning and clinical outcome. Furthermore, as it has been suggested that a lack of consideration for the spectrum of disorder severity may lead to sub-optimal treatment outcomes (Lesnewich et al., 2019), and as adolescent BPD is more frequently seen as a dimensional construct along a continuum of severity (Kaess et al., 2017a; Michonski et al., 2013; Sharp et al., 2012; Zimmerman, 2011), we aimed to examine our effects of interest in an adolescent youth psychiatric sample characterized by low to high dimensional BPD traits. Approximately half of our included sample fulfilled full-syndrome BPD (5 or more BPD traits), as compared to the other half characterized by a lower (subthreshold or lower) number of BPD traits. In the present study, we were also interested in further exploration of potential effects of experiences of ELM, and thus examined whether ELM exposure might modulate ANS functioning during psychosocial stress exposure, and whether it affected the predictive value of pre-treatment ANS functioning regarding clinical outcome.

2. Materials and Methods

2.1 Participants

Data used for the present analyses were acquired by merging two existing data-sets drawn from a long-term clinical cohort study aimed at the evaluation of a specialized outpatient clinic for adolescent risk-taking and self-harm behavior (AtR!Sk; “Ambulanz für Risikoverhalten & Selbstschädigung”, University Hospital Heidelberg, Germany), a subsample of which at the time of baseline assessments

also participated in a cross-sectional experimental neuroimaging study. The latter focused on neurobiological alterations in adolescents engaging in non-suicidal self-injury (NSSI), employing structural and functional magnetic resonance imaging (MRI). Study protocols of the longitudinal (Study ID: S-449/2013) and experimental (Study ID: 983 6087 8915) studies were approved by the institutional ethics committee of the Medical Faculty, University of Heidelberg, Germany, and conducted in accordance with the Declaration of Helsinki ("World Medical Association Declaration of Helsinki," 2013).

Exclusion criteria for either study were acute psychotic symptoms, acute suicidality, pregnancy, endocrine disorders, prescription of glucocorticoid medication, and poor understanding of the German language. Additional exclusion criteria for the cross-sectional experimental study were pathology that may influence brain function (vascular and neurological diseases), claustrophobia, metal implants, and a history of brain injury. Written informed consent was obtained from participants and their primary caregivers prior to study participation. The final dataset included data drawn from a total of N = 27 participants at baseline (T0).

As part of the long-term clinical cohort study, each participant underwent a structured clinical baseline interview session performed by trained clinicians in child and adolescent psychiatry. Eligible participants were then invited to participate in the cross-sectional experimental neuroimaging study, where an MRI scanning session was conducted. As part of the long-term clinical cohort study, all participants included in the present analyses received psychotherapeutic treatment either at inpatient units of the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany, or at a specialized outpatient clinic for adolescent risk-taking and self-harm behavior. Each participant received treatment specifically tailored to risk-taking and self-harm behavior in children and adolescents from an experienced clinician. Participants underwent follow-up assessments at 12 months (N = 18) and 24 months (N = 16) after the baseline assessment. At the time of the first follow-up assessment, N = 8 participants had received inpatient treatment for 31.22 days (SD = 41.76; range: 0 – 113) on average, and N = 16 participants had received outpatient treatment, on average 25.89 sessions (SD = 19.11; range: 0 – 57), while N = 8 participants had received both in- and outpatient treatment and N = 2 participants had not yet received any documented in- or outpatient treatment. At the second follow-up assessment (N = 16), N = 10 participants had received inpatient treatment for 29.38 days (SD = 47.31; range: 0 – 153) on average, and N = 9 had received outpatient treatment for 17 sessions (SD = 21.59; range: 0 – 64) on average, while N = 4 participants had received both in and outpatient treatment and N = 5 patients had not received documented in- or outpatient treatment between the first and second follow-up assessments.

2.2 Experimental stress paradigm

At the MRI scanning session, the MRT compatible Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) was performed to assess cardiac autonomic reactivity and recovery to and after

social evaluative stress. The MIST is one of the most commonly used tasks for inducing social evaluative stress in functional MRI settings, and comprises a series of computerized mental arithmetic tasks including an induced failure component. The MIST protocol has been developed to fit the constraints of an imaging environment (i.e., considering the content and duration of presented stimuli). It includes a training session (without instruction) conducted outside the imaging unit, and a test session during which functional images are acquired. The components incorporating social evaluative stress are automated within the program and brought on by the investigator. A detailed description of the MIST protocol can be found in the *Supplementary Materials*.

2.3 Clinical outcome measures and covariates

To assess BPD pathology, the German version of the Structured Clinical Interview for DSM-IV-Axis II (SKID-II; Fydrich et al., 1997) developed for the assessment of DSM-IV-TR Personality Disorders and shown to reliably assess personality disorder also in adolescents (Salbach-Andrae et al., 2008), was used. To that end, the SKID-II module designed to assess borderline-personality disorder (BPD) traits was conducted at all time-points. Potentially comorbid psychiatric diagnoses were furthermore assessed at all time-points using the German version of the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I.-KID 6.0, (Sheehan et al., 1997; Sheehan et al., 2010), a short and structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders in children and adolescents. The M.I.N.I.-KID has been demonstrated to generate reliable and valid psychiatric diagnoses (Sheehan et al., 2010). Clinical assessments further included the Clinical Global Impressions Scale (CGI; Guy, 1976) providing a clinician-determined summary measure including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function (Busner & Targum, 2007). The CGI comprises a one-item measure to evaluate the severity of psychopathology (CGI-S), which was used in the present study to quantify the severity of psychopathology during the past 7 days (CGI-S; state marker) at all time-points. The Global Assessment of Functioning (GAF) Scale was furthermore used to obtain information for Axis V of the DSM-IV (*American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, 1994), providing a standard method to estimate global psychosocial functioning (Moos et al., 2000) and demonstrating ICCs between 0.72 and 0.85 (Beitchman et al., 2001; Manassis & Hood, 1998; Smith et al., 1992). In the present study, clinicians were required to make an overall judgement about a participant's current level of psychological, social, and occupational functioning based on a 1 – 100 rating scale at all time-points. The clinical baseline interview also included the assessment of subjective experiences of ELM using the German version of the Childhood Experience of Care and Abuse (CECA) schedule, a semi-structures interview inquiring about adversities experienced during childhood or adolescence within the family environment (Bifulco et al., 1994; Kaess et al., 2011). The CECA has previously been shown to have a high degree of inter-rater reliability and reasonable levels of validity, and is seen by some as "gold standard" for the

assessment of childhood adversities (Bifulco et al., 1994, 1997; Thabrew et al., 2011). The subscales psychological, physical, and sexual abuse, and antipathy and neglect were rated for severity on a 4-point scale (1 – 4; none, some, moderate, and marked).

At the baseline assessment (T0), before diagnostic interviews were conducted and online questionnaires completed, data on variables with potential influence on ANS parameters and on the relationship between ANS parameters and clinical outcome were recorded (Quintana et al., 2016). Besides age, these included participants' body mass index (BMI: height/ weight²), state of menstrual cycle (day within current cycle) at the day of cardiac assessments, intake of cardio-active medication potentially affecting ANS functioning (yes or no), oral (hormonal) contraceptives (yes or no), smoking behavior (days of smoking per month during the past 3 months; 1 = never, 2 = 1 – 2 days, 3 = on 3 – 5 days, 4 = on 6 – 9 days, 5 = on 10 – 19 days, 6 = on 20 – 29 days, 7 = on 30 days), alcohol consumption (days of alcohol consumption per month during the past 3 months, 1 = never, 2 = on 1 – 2 days, 3 = on 3 – 5 days, 4 = on 6 – 9 days, 5 = on 10 – 19 days, 6 = on 20 – 29 days, 7 = on 30 days), drug consumption (drug consumption during the past 3 months: 1 = never, 2 = on 1 – 2 days, 3 = on 3 – 9 days, 4 = on 10 – 19 days, 5 = on 20 or more days), physical activity level (frequency of physical exercise during the past 3 months: 1 = never, 2 = 1 – 3 times a month, 3 = once a week, 4 = 2 times a week, 5 = at least 3 times a week), and illness (i.e. having a cold) during the three months preceding the collection of cardiac data (yes or no).

2.4 Measurement of Cardiac Autonomic Function

We report recording and analyses of cardiac data in line with Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH; Quintana et al., 2016). A built-in Siemens MRI-compatible photoplethysmograph (PPG) was placed on the right index finger, and recorded at a sampling rate of 50 Hz for 8 min during an initial resting-state scan where participants were instructed to lie still in the scanner. This was followed by 10 min of recording during a stress-paradigm (MIST). Readout of pulse oximetry data was automated in Stata (Version 14; StataCorp LP, College Station, TX). Pulse-to-pulse intervals were derived as a proxy for cardiac interbeat intervals (IBIs (Gil et al., 2010; Lu et al., 2009; Selvaraj et al., 2008). Mean heart rate (HR) in beats per minute (bpm), and the root mean square of successive IBIs (RMSSD) in milliseconds (ms) obtained by calculating each successive time difference between heartbeats in milliseconds after which each of the values was squared and the result averaged before the square root of the total was obtained, were calculated for each phase of the stress-paradigm. IBIs < 400 ms and > 1,500 ms corresponding to a mean HR < 40 or > 150 bpm were excluded from the analysis. On average and during resting-state, RMSSD and HR were determined across 562 IBIs (*SD* = 90.60, range: 401 – 743), and across 658 IBIs (*SD* = 124.73, range: 334 - 877) and 569 IBIs (*SD* = 83.48, range: 428 – 725) during stress exposure and subsequent recovery, respectively.

2.5 Statistical Analyses

For the present analyses, we followed an exploratory analytical approach. First, descriptive statistics were calculated and data explored visually. Next, observed difference (delta) scores were calculated to quantify HR and vmHRV (RMSSD) responses during the MIST (Burt & Obradović, 2013; Llabre et al., 1991), resulting in resting-state, reactivity, and recovery measures. Responses of HR and vmHRV measures during the MIST were tested using mixed-effects linear regression models with repeated measurements nested within participants, which allowed us to model inter-individual differences in rates of change over the different conditions of the MIST. We included potential confounders (i.e., age, BMI, menstrual cycle, cardio-active medication, oral contraceptives, smoking behavior, alcohol and drug consumption, physical activity level, and illness during the three months preceding the collection of cardiac data) in the respective models, and subsequently examined the effect of ELM exposure on ANS functioning. Clinical outcome (i.e., the number of BPD symptoms met, CGI-S and GAF scores) over time (from baseline assessment to one and two years after starting the treatment, T1 and T2), was analyzed analogously using mixed-effects linear regression models, this time allowing us to model intra- and inter-individual differences in clinical change over time (random intercept/ random slope models). To next examine cardiac autonomic measures obtained pre-treatment as predictors of clinical outcome over time, we included vmHRV and HR measures as predictors in the mixed-effects linear regression models of clinical change over time (random intercept/ random slope models). Models were adjusted for a time lag between the measurement of cardiac autonomic data and clinical baseline assessments that occurred due to characteristics of the recruitment processes of the studies from which the present data was drawn. Finally, we examined ELM exposure as a potential moderator of the association between ANS measures and clinical outcomes. To perform sensitivity analyses of the mixed-effects modelling approach, and for graphical illustrative purposes, we also derived delta scores to quantify clinical change over time by subtracting clinical values obtained at the baseline assessments from those at follow-up 1, and those at follow-up 1 from those at follow-up 2, respectively, and calculated (non-parametric) Spearman rank correlations (Spearman's ρ) between cardiac autonomic (delta score) measures and clinical delta scores.

Each analytical step was conducted using complete-case analyses, and all statistical analyses were performed using Stata/SE (Version 16.0; StataCorp LP, College Station, TX, US) with alpha set to 0.05 (two-sided). Corresponding figures were prepared using R version 3.5.2 (R Core Team, 2018).

3. Results

3.1 Sample descriptive statistics

At baseline assessment (T0), the present sample comprised $N = 27$ female adolescents, with a mean age of 14.93 years ($SD = 1.24$; range: 13 – 17), a mean body height of 164.46 cm ($SD = 6.54$; range: 152 – 178), and a mean body weight of 57.33 kg ($SD = 8.49$; range: 39 – 82). A summary of clinical ICD-10 diagnoses and BPD diagnostic criteria met at T0 is provided in *Table 1* below. At the 1-year follow-up assessment (T1), the sample comprised $N = 18$ participants, with a mean age of 16.11 years ($SD = 1.08$; range: 14 – 18), a mean height of 164.56 cm ($SD = 6.34$; range: 153 – 178), and a mean weight of 56.72 kg ($SD = 7.23$; range: 41 – 75). The sample at the 2-year follow-up (T2) consisted of $N = 16$ participants, with a mean age of 16.67 years ($SD = 1.05$; range: 15 – 18), a mean height of 163.53 cm ($SD = 6.21$; range: 153 – 177), and a mean weight of 57.93 kg ($SD = 10.10$; range: 39 – 75). A tabular summary of sample descriptive and clinical information at each measurement time-point as well as covariates and cardiac autonomic parameters measured at baseline and during the MIST, respectively, is presented in *Table 2* below. Paired comparisons over time revealed significant differences between T0 and T1 for the variables age, severity of psychopathology (CGI-S), and global functioning (GAF scores). Between T1 and T2, the sample significantly differed in the variables age and number of participants receiving psychotropic medication. A correlation heat map and dendrogram of all variables obtained at baseline assessments (T0) can be seen in *Supplementary Figure 1* (a corresponding correlation matrix of zero-order and point-biserial Pearson correlations, respective *p*-values, and *N* observations, can be provided upon request).

3.2 Cardiac autonomic stress response

Mixed-effects linear regression models of cardiac autonomic stress response indexed by HR and vmHRV measures (illustrated in *Supplementary Figures 2A* and *2B*) revealed a statistically significant change in individual HR (overall model: $\chi^2_{15} = 173.57$, $p < .001$) across task conditions of the MIST. HR was significantly different between the resting-state and stress exposure ($z = 10.15$, $p < .001$) and between stress exposure and recovery ($z = -8.77$, $p < .001$), but not between resting-state and recovery ($z = 1.38$, $p = .167$). HR throughout the MIST was significantly influenced by drug consumption ($z = -2.58$, $p = .010$) and physical activity level ($z = -2.98$, $p < .003$), either measured over the previous three months. Furthermore, ELM exposure ($z = -3.89$, $p < .001$) and ELM severity ($z = 4.66$, $p < .001$) had a significant influence on overall HR throughout the stress task. Testing interactions, the influence of ELM exposure on HR was not moderated by task condition.

Opposite to HR, vmHRV did not vary as a function of stress exposure, neither with nor without inclusion of potential confounders (overall models: $\chi^2_{(2)} = 2.23$, $p < .328$; $\chi^2_{(15)} = 42.67$, $p < .001$). VmHRV throughout conditions of the MIST was significantly influenced by BMI ($z = -2.57$, $p = .010$), smoking ($z = 2.71$, $p = .007$), and physical activity level ($z = 3.07$, $p = .002$). Both ELM exposure ($z =$

2.68, $p = .007$) and severity ($z = -2.35$, $p = .019$) had a significant influence on vmHRV overall, while no significant interactions between ELM exposure and task condition on vmHRV were observed.

Table 1. BPD diagnostic criteria (DSM-IV) and clinical diagnoses (ICD-10) met at T0 ($N = 27$).

Borderline Personality Disorder - Diagnostic Criteria	**N**	**%**
BPD diagnostic criteria met	**13**	**48.15**
Fear of abandonment	8	29.63
Unstable relationships	11	40.74
Identity disturbances	7	25.93
Impulsivity	5	18.52
Self-harm/Suicidality	25	96.15
Affective instability	17	62.96
Inner emptiness	11	40.74
Inappropriate anger	11	40.74
Paranoia/Dissociation	9	33.33
Diagnosis (ICD-10)	**N**	**%**
Clinical primary diagnosis (ICD-10) other than BPD	**15**	**55.56**
F0 - Organic, including symptomatic, mental disorders	0	-
F1 - Mental and behavioral disorders due to psychoactive substance use	0	-
F2 - Schizophrenia, schizotypal and delusional disorders)	0	-
F3 - Mood [affective] disorders	7	25.93
F4 - Neurotic, stress-related and somatoform disorders	2	7.41
F5 - Behavioral syndromes associated with physiological disturbances and physical factors	1	3.70
F6 - Disorders of personality and behavior	2	7.41
F8 - Disorders of psychological development	0	-
F9 - Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	1	3.70
Z00.4 - General psychiatric examination, not elsewhere classified	2	7.41

Note. BPD = Borderline Personality Disorder.

Table 2. Summary of sample descriptive and clinical data at each measurement time-point, as well as cardiac autonomic parameters during the MIST.

Demographics / Clinical Measures	T0 (N = 27)		T1 (N = 18)		T2 (N = 16)		T0 vs. T1	T1 vs. T2
	M (SD) or N	Range or %	M (SD) or N	Range or %	M (SD) or N	Range or %	*p*-value	*p*-value
Days between measurements [a]	219.26 (221.65)	190 – 761	362.50 (45.24)	315 – 455	405.38 (125.19)	275 – 694		
Age	14.93 (1.24)	13 – 17	16.11 (1.08)	14 - 18	16.67 (1.05)	15 - 18	< 0.001***	0.259
BMI	21.16 (2.98)	16.03 – 30.12)	20.94 (2.38)	16.63 – 26.89	21.59 (3.03)	16.03 – 26.57	0.829	0.090
Diagnosed BPD	13	48.15	7	38.89	4	26.67	0.257	0.237
Number BPD	3.85 (2.35)	0 – 9	4.33 (2.11)	1 - 9	3.27 (2.74)	0 - 8	0.926	0.259
CGI	5.12 (0.82)	3 – 6	4.17 (1.34)	2 - 7	3.80 (1.26)	2 - 6	0.014*	0.090
GAF	45.63 (10.83)	25 – 75	55.94 (13.10)	31 - 81	57.60 (15.98)	31 - 80	0.019*	0.237
ELM	15	55.56						
ELM Severity	3.15 (3.12)	0 – 10						
Medication Use	4	14.81						
Hormonal Contraceptives	9	33.33						
Smoking	15	55.56						
Alcohol Consumption	2.15 (1.59)	1 – 7						
Drug Consumption	1.63 (1.15)	1 – 5						
Illness	11	40.74						
Physical Activity	3.22 (1.45)	1 – 5						
Menstrual Cycle	15	57.69						
Cardiac measures	Run 1		Run 2		Run 3		Run 1 vs. Run 2	Run 2 vs. Run 3
	M (SD)	Range	M (SD)	Range	M (SD)	Range	*p*-value	*p*-value
vmHRV	83.24 (57.57)	22.04 – 320.96	98.45 (72.63)	30.99 – 362.69	90.82 (62.74)	26.01 – 293.81	0.456	0.683
HR	72.10 (10.44)	54.46 – 93.62	84.70 (13.36)	63.17 – 110.41	73.30 (9.46)	56.09 – 93.42	< 0.001***	< 0.001***

Note. For paired comparisons of continuous demographic and clinical variables, paired t-tests (normal data) or Wilcoxon signed-rank test (non-normal data) were used, while for binary variables, McNemar's test was applied. Paired comparisons were calculated only for measures that were assessed at each measurement time-point, as opposed to measures assessed only at baseline. [a]Days passed between measurements either refers to number of days that passed between baseline assessments of both studies involved (T0), or to number of days that passed between clinical baseline and follow-up assessments (T1 and T2). Menstrual cycle: Day of the menstrual cycle (continuous); Smoking: Days of smoking per month during the past 3 months, 1 = never, 2 = 1 – 2 days, 3 = on 3 – 5 days, 4 = on 6 – 9 days, 5 = on 10 – 19 days, 6 = on 20 – 29 days, 7 = on 30 days. Alcohol: Days of alcohol consumption per month during the past 3 months, 1 = never, 2 = on 1 – 2 days, 3 = on 3 – 5 days, 4 = on 6 – 9 days, 5 = on 10 – 19 days, 6 = on 20 – 29 days, 7 = on 30 days. Drug consumption: Drug consumption during the past 3 months: 1 = never, 2 = on 1 – 2 days, 3 = on 3 – 9 days, 4 = on 10 – 19 days, 5 = on 20 or more days; Medication: Physical activity level: 1 = never, 2 = 1 – 3 times a month, 3 = once a week, 4 = 2 times a week, 5 = at least 3 times a week.

3.3 Clinical outcome over time

First, we examined mixed-effects linear regression models testing each clinical outcome measure at a time as a function of time. All resulting models were statistically significant. Aiming to reduce dimensionality and multiplicity of statistical tests performed and reported, provided that all three outcome measures showed significant improvement over time, we derived a clinical composite score by averaging inverted and normalized values of the three outcome measures (in the resulting composite score, lower values mean clinical improvement). Examining change in the resulting composite score over time revealed a significant overall model ($X^2_{15} = 96.83$, $p < .001$), and significant improvement between T0 and T1 ($z = -4.03$, $p < .001$), between T1 and T2 ($z = -3.01$, $p = .003$), and between T0 and T2 ($z = -3.18$, $p = .001$). Clinical improvement over time was significantly associated with age ($z = 2.04$, $p = 0.041$), ELM exposure (yes; $z = 4.12$, $p < 0.001$), medication (yes; $z = 3.80$, $p < 0.001$), oral contraceptives (yes; $z = -2.48$, $p = 0.013$), alcohol consumption ($z = 3.10$, $p = 0.002$), and recent illness ($z = -3.03$, $p = 0.002$). Linear patterns of change over time for individual clinical outcome measures as well as the composite score are illustrated in *Supplementary Figure 3*.

3.4 Cardiac autonomic predictors of long-term clinical outcome

We limit reporting of results in this section to considering the composite score derived from individual outcome measures as our main outcome of interest, and only report model statistics for models that revealed significant ANS predictors of interest. According model results considering each outcome measure independently can be seen in the Supplementary Model Results. Considering HR measures, resting HR was identified as a significant predictor of overall clinical outcome, after controlling for potential confounders ($\chi_{215} = 111.20$, $p < .001$, $z = -4.13$, $p < .001$), but no significant interaction with time was observed, suggesting that resting HR was not a significant predictor of clinical improvement over time. ELM exposure did not moderate the relationship between resting HR and overall clinical outcome, nor over time. HR reactivity did not significantly predict overall clinical outcome, and no significant interaction with time was observed. ELM exposure was not a significant moderator in this model. HR recovery was a significant predictor of overall clinical outcome after controlling for potential confounders ($\chi_{215} = 60.75$, $p < .001$, $z = 1.98$, $p = .048$), while no significant interactions with time or ELM exposure alone were observed. A significant HR recovery x time x ELM exposure interaction however suggested that in patients who reported no exposure to ELM, in contrast to ELM-exposed patients, higher pre-treatment HR recovery (more negative values) predicted significant clinical improvement, as evident by lower residual composite scores at T2 ($\chi_{217} = 64.66$, $p < .001$; $z = 2.11$, $p = .035$).

Considering vmHRV measures, after controlling for the potential confounders of age, BMI, menstrual cycle, cardio-active medication, oral contraceptives, smoking behavior, alcohol consumption and drug consumption, physical activity level, and illness during the three months preceding the

collection of cardiac data, resting-state vmHRV was a significant predictor of overall clinical outcome (χ_{215} = 100.24, p < .001, z = 3.25, p = .001). A significant interaction with time was observed (χ_{217} = 125.06, p < .001, z = -2.04, p = .042), such that higher vmHRV measured pre-treatment significantly predicted clinical improvement over time, evident at T2. ELM was not a significant moderator of resting-state vmHRV on clinical outcome. VmHRV reactivity was not found to be a significant predictor of overall clinical outcome, but ELM exposure significantly modulated the relationship between vmHRV reactivity and overall outcome (χ_{217} = 62.43, p < .001, z = 2.05, p = .041), such that in ELM exposed as compared to non-exposed patients, vmHRV reactivity was a significant predictor of overall composite scores. However, no significant (three-way) interaction with time was observed. Considering vmHRV recovery, after controlling for potential confounders, significant time effects were observed, such that higher (more negative) vmHRV recovery significantly predicted clinical improvement over time (χ_{217} = 98.53, p < .001, z = 2.15, p = .031), evident at T1. No significant interaction with ELM was observed.

3.5 Exploratory correlational analyses

We conducted correlational sensitivity analyses between cardiac autonomic predictors and delta scores of individual outcome measures between each measurement time point. Significant positive Spearman rank correlations between resting HR and T2 GAF delta scores were observed (T2 – T0: p = .67, p = .035), suggesting that higher pre-treatment resting HR was associated with stronger improvement in level of functioning between T0 and T2. HR recovery was significantly and negatively correlated with T1 GAF delta scores (T1 – T0: p = .71, p = 0.022), and was significantly and positively correlated with T2 CGI-S delta scores (T2 – T0: p = .68, p = .015), suggesting significant associations between greater (more negative) pre-treatment HR recovery values and improvement in global level of functioning between T0 and T1, and between greater HR recovery values and severity of psychopathology between T0 and T2. Both vmHRV reactivity and recovery were significantly linked with T1 CGI-S delta scores. For vmHRV reactivity, we found a significant negative correlation (T1 – T0: p = -.70, p = .012), while for vmHRV recovery, a significant positive correlation (T1 – T0: p = .61, p = .035) was observed, suggesting that greater pre-treatment vmHRV reactivity and recovery were both associated with significant reductions in symptom severity between T0 and T1. Furthermore, pre-treatment vmHRV reactivity was significantly and negatively associated with T1 delta scores of the composite measure (T1 – T0: p = -.68, p = .029), suggesting that vmHRV reactivity also predicted significant improvement in the composite of measures at T1. In *Figures 1* and *2* below, these significant associations between cardiac autonomic predictors and clinical delta scores are visualized.

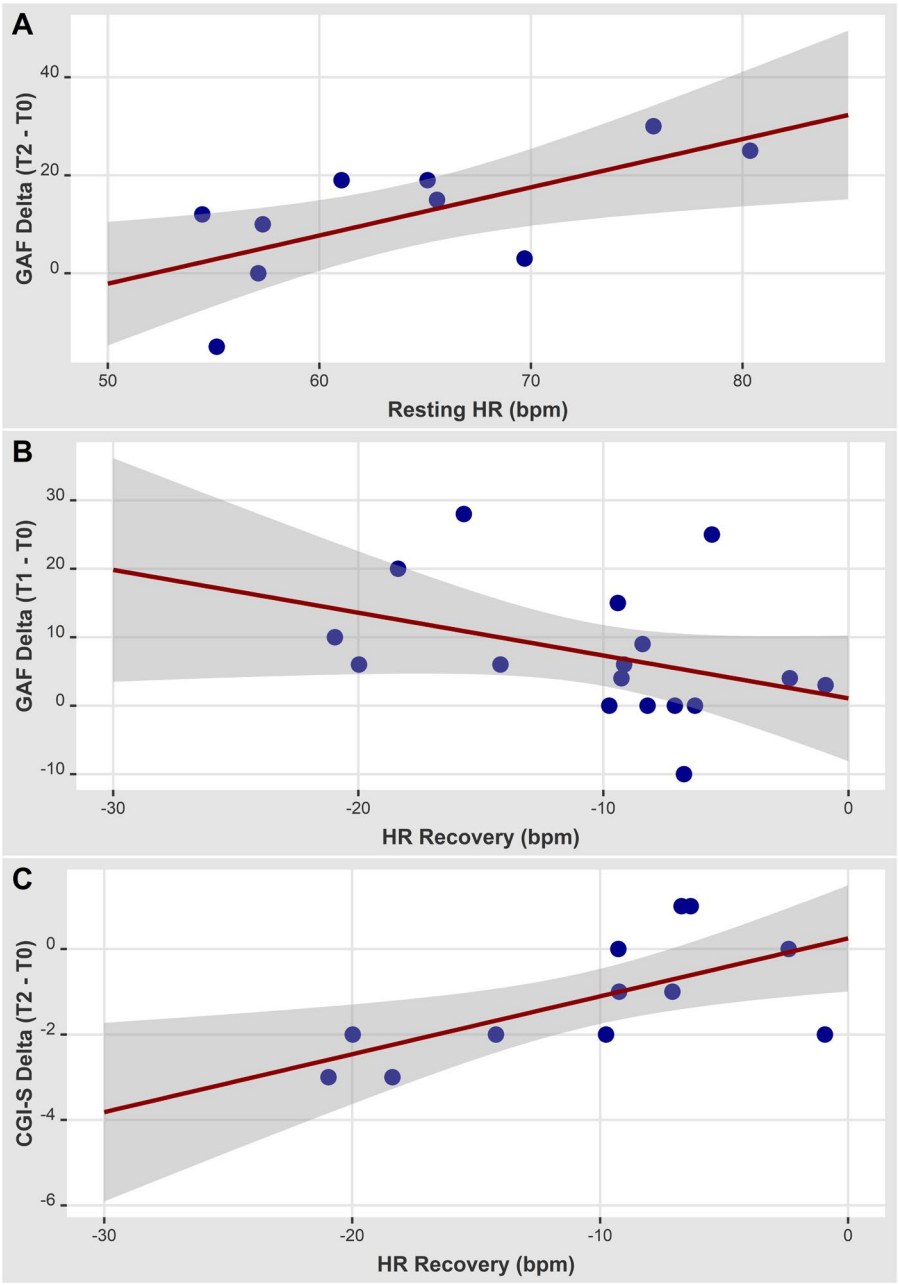

Figure 1. Scatter plots depicting significant bivariate Spearman rank correlations between cardiac autonomic predictors of heart rate (HR) measured at T0 and clinical delta scores; Resting HR: Resting-state HR. HR Recovery: Delta score between HR during stress exposure and resting postline; grey areas represent 95% confidence intervals.

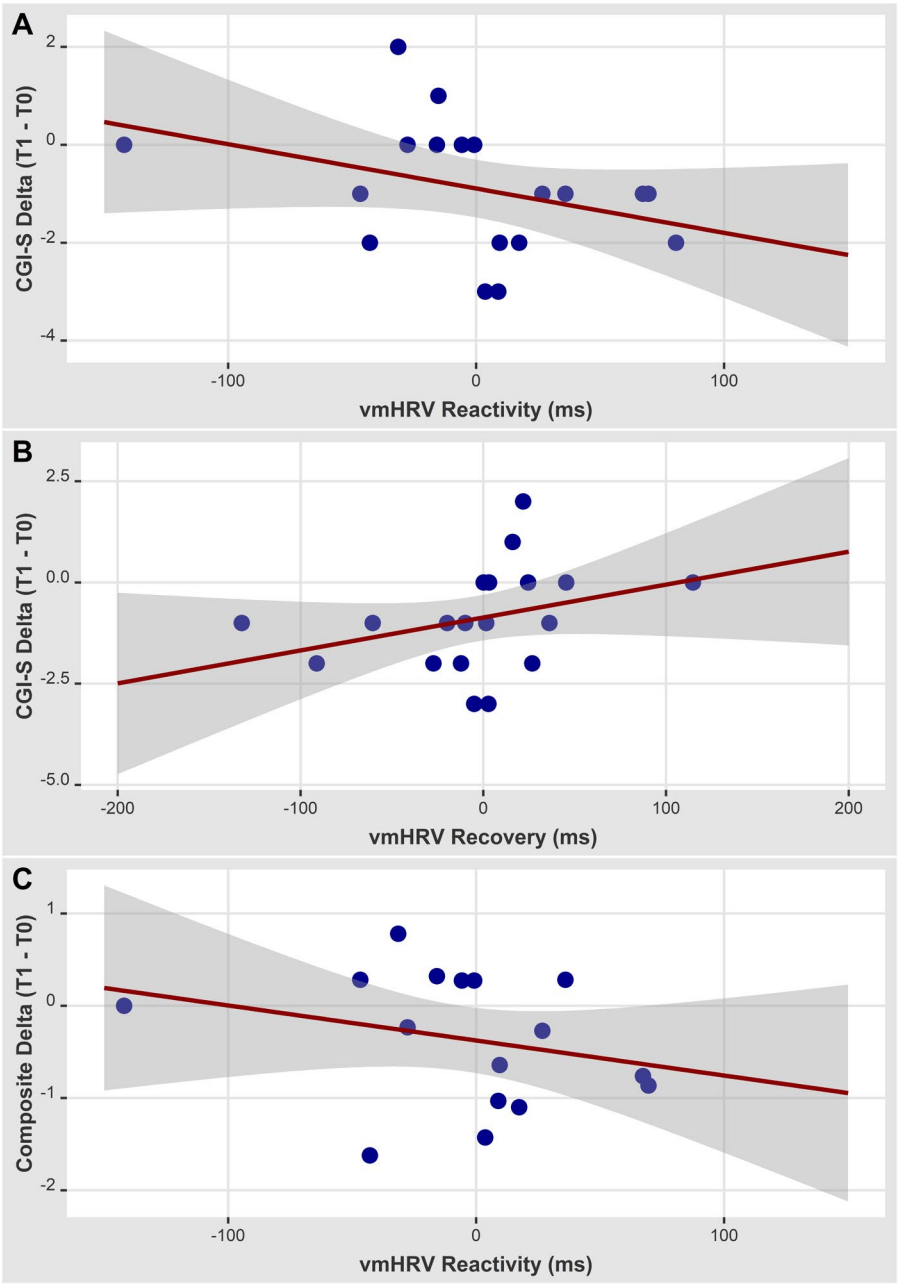

Figure 2. Scatter plots depicting significant bivariate correlations between cardiac autonomic predictors of vagally-mediated heart rate variability (vmHRV) measured at T0 and clinical delta scores; vmHRV Reactivity: Delta score between resting-state vmHRV and vmHRV during stress exposure; vmHRV Recovery: Delta score between vmHRV during stress exposure and resting postline; grey areas represent 95% confidence intervals.

4. Discussion

To our knowledge, this is the first study to investigate the potential use of ANS functioning indexed by not only resting-state, but also reactivity and recovery HR and vmHRV measures in response to psychosocial evaluative stress exposure for clinical outcome prediction in adolescent BPD. The present study is to be seen as an exploratory investigation with preliminary results, and as such, has several significant findings.

Firstly, our findings demonstrate that measures of ANS functioning are influenced by various factors, and most consistently by level of physical activity (which significantly influenced both HR and vmHRV measures throughout the MIST), but also by other health-related factors, including BMI, drug consumption, and smoking behavior. Next, and presenting as the main result of this study, after controlling for variables that supposedly influence ANS functioning (i.e., age, BMI, medication, oral contraceptive intake, smoking behavior, alcohol consumption, physical activity, drug consumption, menstrual cycle, and recent illness), we found both vmHRV resting-state and recovery measures to significantly predict clinical improvement over time. As a further finding, ELM exposure had a significant influence on both HR and vmHRV measured throughout the different conditions of the psychosocial stress task currently employed, while it did not moderate cardiac autonomic stress response per se. Yet, and of further note, a significant three-way-interaction was observed between ELM exposure, HR recovery, and clinical outcome over time.

The present results of significant health-related confounds of different measures of ANS functioning are in line with previous studies examining cardiac autonomic function (e.g., Barutcu et al., 2005; Eddie et al., 2018; Ghuran et al., 2001; Hansen et al., 2017; Rennie, 2003; Saboul et al., 2014) and further highlight the importance for research studies to take potentially influential factors into account when treating cardiac autonomic markers as variables of interest; according recommendations can be found elsewhere (e.g., Quintana et al., 2016; Quintana & Heathers, 2014; Task Force of the European Society of Cardiology, 1996). Of note, it has previously been suggested that a lack of physical activity, as observed in a study examining cardiac autonomic function in BPD, might fully explain higher HR levels at baseline and during stress exposure in BPD patients compared to healthy controls (Eddie et al., 2018), highlighting physical activity as a particularly influential factor to be considered.

The current main results are in line with findings from previous psychotherapy and pharmacological treatment studies conducted in adult psychopathology (Angelovski et al., 2016; Bär et al., 2004; Blanck et al., 2019; Kircanski et al., 2019; Soder et al., 2019) and from a previous study on resting-state markers of ANS activity as outcome predictors in adolescent BPD (Weise et al., 2020), in that higher pre-treatment resting-state vmHRV significantly predicted better clinical improvement over time. Also in line with a previous study in adolescent BPD, pre-treatment resting HR was not a significant predictor of clinical outcome over time (but see model results reported for individual

outcome measures, as reported in the Supplementary Model Results). Concerning our initial evaluation of the predictive value of ANS reactivity and recovery measures, the present results are mixed. Results from mixed-effects linear regression models suggest vmHRV recovery (but not reactivity) to be a potential predictor of clinical improvement over time during the earlier course of treatment, as significant effects were evident at 12 but not at 24 months post-baseline assessments (in correlational sensitivity analyses, however, both vmHRV reactivity and recovery measures were associated with a reduction in symptom severity measured using the CGI-S, again at T1, but not at T2). These results should be interpreted with caution, however, also owing to the currently observed lack of a significant vmHRV stress response to the MIST. Furthermore, in prediction models of individual outcome measures (Supplementary Model Results), vmHRV measures (resting-state and recovery) were significantly associated solely with change in BPD symptomatology over time, but not with change scores in the severity of psychopathology or global level of functioning. Vice versa, apart from resting HR, HR measures in these analyses were more consistently associated with severity of psychopathology and global level of functioning change scores (two potentially highly correlated constructs), rather than with change in BPD symptomatology. Based on meta-analytic results, reduced resting-state vmHRV might present "an important trait characteristic underlying BPD" (Koenig et al., 2016b), and the presently observed patterns might be interpreted in accordance with this assumption. Given that resting-state vmHRV correlates negatively with resting HR (Koenig, 2020); also see *Supplementary Figure 1*), the finding that resting HR was a significant predictor of change in BPD symptomatology over time, might also align with this assumption. HR reactivity and recovery, in turn, might present more global indices of psychopathology. Clearly, future studies are needed to rigorously investigate the temporal dynamics and associations considering different measures of ANS functioning and clinical outcome over time.

Interestingly, considering potential moderating influences of ELM exposure on the predictive relationship between ANS measures and clinical outcome (while controlling for potential confounders), higher pre-treatment HR recovery was associated with significant clinical improvement over time visible at T2 in BPD patients who reported no ELM exposure, contrasting ELM-exposed patients. Given the relatively small sample size remaining at T2 (8 patients with versus 8 patients without reported ELM exposure), one needs to be cautious when interpreting these results. However, such potential deviations in the relationship between post-stress recovery and clinical outcome in ELM-exposed patients could have important clinical implications, and should be addressed in future larger-scale studies. Furthermore, subjectively rated ELM exposure as well as the severity of ELM significantly influenced both overall HR and vmHRV measures throughout the different conditions of the MIST, however, we did not find ELM exposure to moderate either HR or vmHRV responses. Generally, the current literature on the influence of ELM exposure on ANS responsivity is limited and mixed, and further investigation is clearly needed (Young-Southward et al., 2020). However, the lack of an interaction between ELM exposure and MIST task condition in predicting vmHRV is likely explained by the fact that, as compared to HR, we did not find a significant stress response considering vmHRV in the first place. This deviates

from results of previous studies reporting significant vmHRV responses to the MIST (Brugnera 2017a,b). Of note, respective studies were conducted in adults, while our study sample was composed of adolescents. Adolescence is a developmental period during which assumingly significant changes in physiological stress reactivity as marked by hormonal and shifts in hypothalamic-pituitary-adrenal (HPA) axis reactivity might occur (Romeo, 2013), which could have contributed to the present deviation of vagal function responsivity. As an important limitation of the present study, while existing studies highlight the importance of age-related differences in vmHRV between different developmental stages (Koenig, 2020), presently we did not take pubertal development into account, and future studies should consider and examine the stage of puberty as a potentially influential factor on ANS functioning.

The present study has several further limitations that should be addressed. Firstly, the study is characterized by a small sample size and three measurement time-points only, and replication while recruiting a larger sample as well as conducting more frequent measurements will allow to derive more definite and fine-grained conclusions, and may allow for implications with regards to clinical decision making processes and treatment planning. Furthermore, the present sample consisted of female participants, and thus, we could not control for potential sex differences in ANS function and in association with treatment outcome. While sex differences in autonomic function in adolescents and adults have been shown in previous studies and meta-analyses (Abhishekh et al., 2013; Koenig et al., 2017c; Thayer & Koenig, 2019), the present study can be generalized to female populations only (or at most). Also, the presently used stress paradigm did not elicit a significant stress response considering vmHRV measures, and other paradigms such as the widely employed Trier Social Stress Test (TSST; Kirschbaum et al., 1993) might be more suitable to induce a significant ANS response to psychosocial stress exposure. Furthermore, a control group, e.g. characterized by one or various different psychiatric conditions, should be included in future studies of adolescent BPD, to further characterize the predictive effects of ANS measures for clinical improvement concerning different dimensions of psychopathology. Finally, inherent of the study design underlying the clinical data currently gathered, a naturalistic follow-up approach was applied, and consequently, patients did not receive identical standardized treatments – potentially increasing external at the expense of internal validity of our results. Future studies conducted in the form of randomized-controlled trials (RCTs), including detailed documentation of deployed interventions, will allow to more specifically investigate potential interactions between pre-treatment cardiac autonomic function and different treatment components.

It has been pointed out that adolescence may present a particularly sensitive period for the development of the prefrontal cortex (PFC) and associated development of social-cognitive functions (Blakemore, 2012; Casey et al., 2008; Vögele et al., 2010), and insufficient PFC maturation during this critical time could be linked with impairments in various domains of functioning. Expanding on the prominent Neurovisceral Integration Model (NIM; for an elaboration, please see (Thayer & Lane, 2000; Thayer & Lane, 2009), it has been suggested that adolescents who, in the transitional period to early

adulthood, show sufficient "vagal support" through the ANS indexed by high vmHRV, are potentially more likely to exhibit continued PFC maturation, and to subsequently maintain affective resilience. Adolescents with insufficient ANS vagal support ("vagal insufficiency") indexed by low vmHRV, in turn, might be at risk to develop severe psychopathology (for detailed elaboration, see (Koenig, 2020). Based on the growing number of studies supporting resting-state vmHRV as valuable predictor of treatment outcome in both adult and adolescent samples, clinical outcome might be enhanced by actively targeting and increasing vagal activity before or during psychotherapeutic and/or pharmacological treatment, while means to increase cardiac vagal activity might include different kinds of interventions, such as meditation, exercise training, biofeedback, or transcutaneous auricular vagus nerve stimulation (Weise et al., 2020; Wendt et al., 2018). For treatment planning including such future applications, in turn, actionable markers of cardiac autonomic function that predict discrete intervention options might be useful for appropriate timing and treatment selection. Increases in vmHRV might lead to enhanced PFC maturation, which in turn could increase affective resilience (Koenig, 2020; Van Eden & Buijs, 2000), lowering physiological stress reactivity and overall arousal, and might especially benefit psychiatric conditions characterized by maladaptive emotional reactivity patterns, such as BPD.

5. Conclusion

To summarize, the present study adds to a relatively limited literature examining markers of cardiac autonomic function as outcome predictors in adolescent BPD, as well as factors that potentially moderate these relationships (Lesnewich et al., 2019; Weise et al., 2020). We were interested mainly in vmHRV measures in relation to treatment outcome in BPD because firstly, vmHRV is associated with both physical and mental health outcomes, and furthermore, vmHRV reflects adaptability, emotion regulation, and behavioral flexibility, features highly likely to be compromised in BPD patients (Alderman & Olson, 2014; Beauchaine & Thayer, 2015; Ehrenthal et al., 2010; Hamilton & Alloy, 2016; Joormann & Gotlib, 2010; Kemp & Quintana, 2013; Sgoifo et al., 2015; Stange et al., 2017; Thayer et al., 2012; Thayer & Lane, 2009; Tsuji et al., 1996; Udo et al., 2013). The present findings are encouraging overall because they support the potential value of cardiac autonomic biomarkers for predicting which patient could be more likely to benefit from psychiatric treatment, and strengthen our understanding of the conditions by which a particular biomarker, such as resting-state vmHRV, reveals an advantage for a particular treatment in a particular patient group. The present study is by no means meant to drive clinical application, but will hopefully encourage researchers planning and conducting future large-scale psychotherapy and pharmacological studies to implement markers of cardiac autonomic function, which present a highly attractive prediction tool also in economic terms, as objective measures in the monitoring of patient progress and assessment of treatment outcome.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

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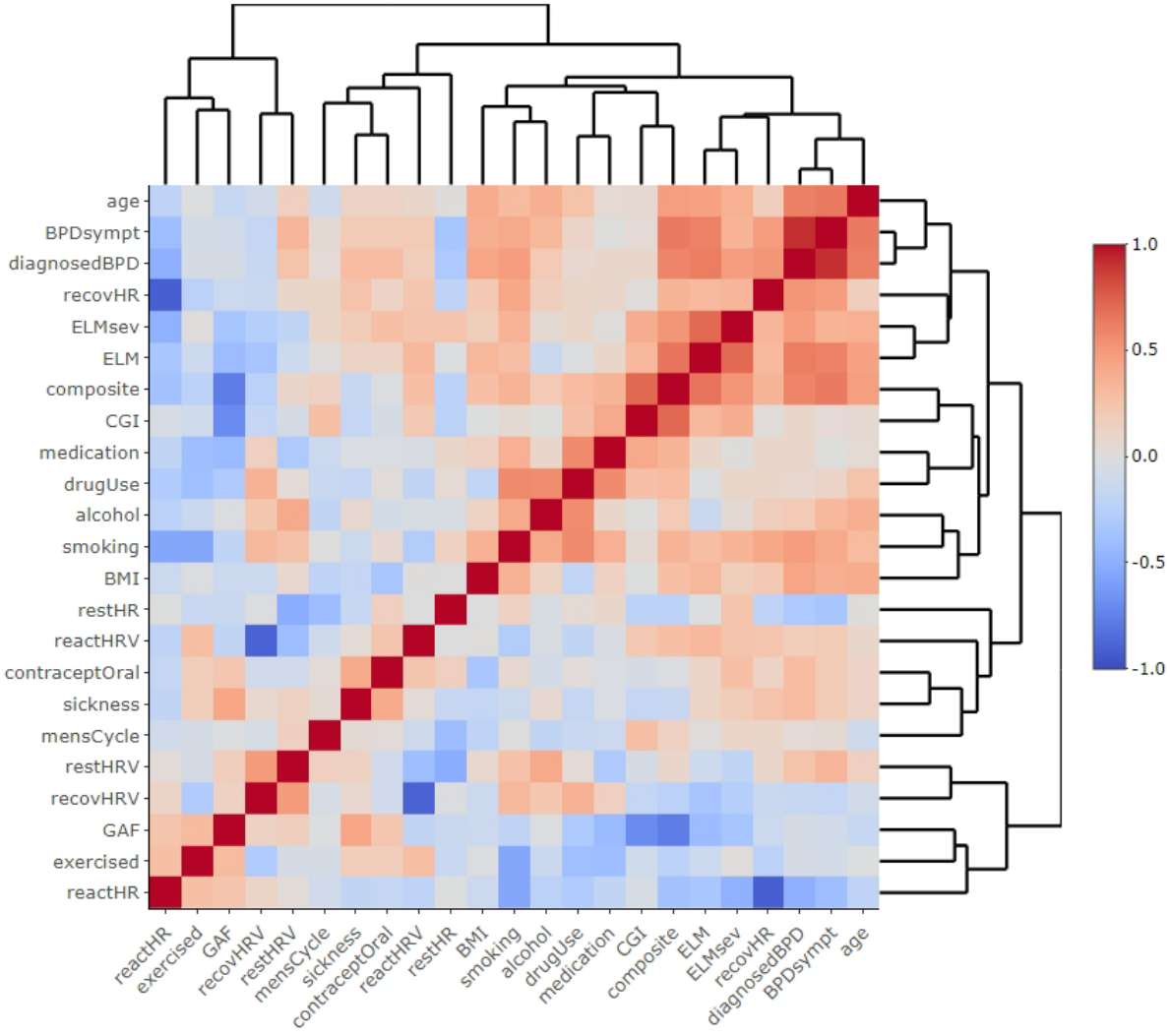
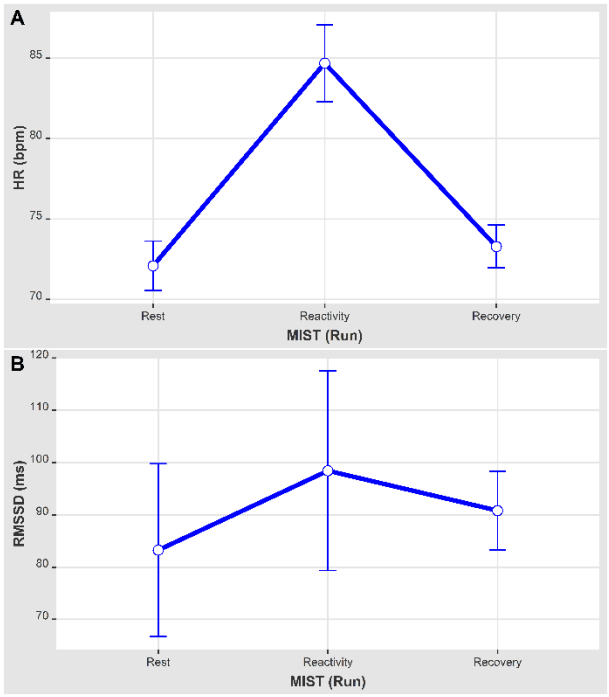
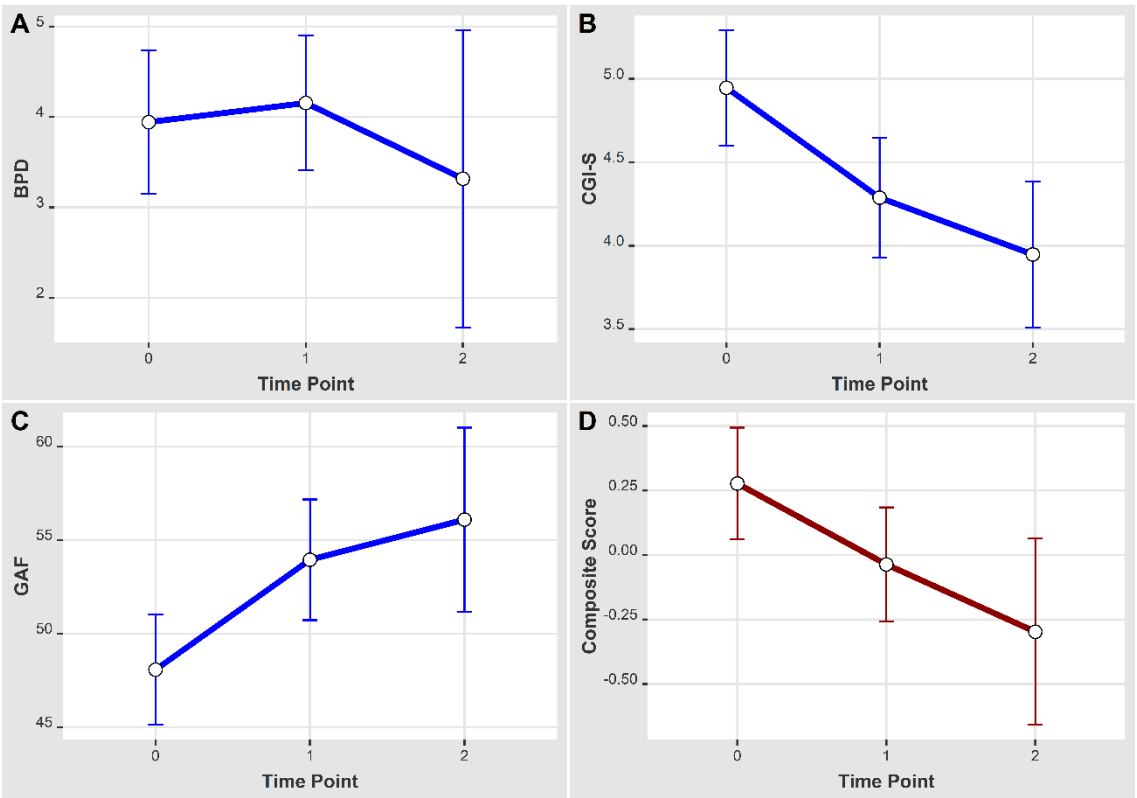
Supplementary data



Supplementary Figure 1. Correlation heatmap of all variables measured at baseline (T0) and corresponding dendrogram showing clustering patterns underlying the data. BPDsympt = number of BPD criteria fulfilled, ELM = early life maltreatment, restHR = resting heart rate, recovHR = heart rate recovery, reactHRV = hrv reactivity, exercised = physical activity level, drugUse = drug consumption, contraceptOral = takes oral contraceptives (yes, no), diagnosedBPD = received BPD diagnosis, ELMsev = early life maltreatment severity score, reactHR heart rate reactivity, restHRV = resting-state vmHRV, recovHRV = vmHRV recovery, composite = composite score of clinical measures, mensCycle = menstrual cycle.



Supplementary Figure 2. Cardiac autonomic stress response as measured during each condition of the social-evaluative stress paradigm (MIST). A: Mean HR (beats per minute) and corresponding error-bars per condition of the stress task. B: Mean vmHRV (RMSSD, ms) and corresponding error bars per condition of the stress task.



Supplementary Figure 3. Mean values and corresponding error bars over time for the three clinical outcome measures presently analyzed, as well as their composite score (average of normalized values). BPD: Number of symptoms for Borderline Personality Disorder fulfilled at the time-point of measurement; CGI-S: Clinical Global Impression Scale severity index; GAF: Global Assessment of Functioning.

Supplementary Model Results

Supplementary Table 1. Mixed-effects linear regression model results with pre-treatment vmHRV measures as predictors of BPD symptomatology at T1 and T2, controlling for potential confounders.

Random intercept-only models (BPD)				T1		T2	
vmHRV	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting-state	61.28	18	<0.001***	-0.36	0.719	-3.15	0.002**
Reactivity	56.58	18	<0.001***	-2.43	0.015*	-1.80	0.071
Recovery	59.70	18	<0.001***	3.01	0.003**	2.31	0.021*

Note. vmHRV = vagally-mediated heart rate variability.

Random intercept random slope models (BPD)				T1		T2	
vmHRV	χ2	DF	p	z	p	z	p
Resting-state	51.61	18	<0.001***	-0.36	0.721	-2.26	0.024*
Reactivity	55.20	18	<0.001***	-2.09	0.036*	-1.19	0.233
Recovery	43.27	18	<0.001***	2.30	0.021*	1.44	0.149

Note. vmHRV = vagally-mediated heart rate variability.

Supplementary Table 2. Mixed-effects linear regression model results with pre-treatment HR measures as predictors of BPD symptomatology at T1 and T2, controlling for potential confounders.

Random intercept-only models (BPD)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	64.44	18	<0.001***	-0.07	0.940	3.64	<0.001***
Reactivity	51.70	18	<0.001***	0.32	0.749	-1.17	0.242
Recovery	52.98	18	<0.001***	-0.26	0.796	-0.97	0.333

Note. HR = heart rate.

Random intercept random slope models (BPD)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	58.78	18	<0.001***	0.46	0.646	2.13	0.033*
Reactivity	42.14	18	0.001**	0.26	0.793	-0.70	0.487
Recovery	45.68	18	<0.001***	-0.18	0.853	-0.31	0.760

Note. HR = heart rate.

Supplementary Table 3. Mixed-effects linear regression model results with pre-treatment vmHRV measures as predictors of severity of psychopathology at T1 and T2, controlling for potential confounders.

Random intercept-only models (CGI-S)				T1		T2	
vmHRV	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting-state	130.09	18	<0.001***	1.34	0.180	-0.28	0.783
Reactivity	90.19	18	<0.001***	-0.78	0.433	-0.24	0.813
Recovery	99.42	18	<0.001***	1.61	0.108	0.13	0.898

Note. vmHRV = vagally-mediated heart rate variability.

Random intercept random slope models (CGI-S)				*T1*		*T2*	
vmHRV	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting-state	117.96	18	<0.001***	1.42	0.155	-0.31	0.756
Reactivity	83.93	18	<0.001***	-0.87	0.384	-0.13	0.898
Recovery	94.75	18	<0.001***	1.80	0.072	0.02	0.987

Note. vmHRV = vagally-mediated heart rate variability.

Supplementary Table 4. Mixed-effects linear regression model results with pre-treatment HR measures as predictors of severity of psychopathology at T1 and T2, controlling for potential confounders.

Random intercept-only models (CGI-S)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	112.84	18	<0.001***	-1.01	0.315	-0.18	0.858
Reactivity	121.42	18	<0.001***	-2.70	0.007**	-2.77	0.006**
Recovery	135.99	18	<0.001***	3.15	0.002**	3.26	0.001**

Note. HR = heart rate.

Random intercept random slope models (CGI-S)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	128.33	18	<0.001***	-1-13	0.219	-0.28	0.783
Reactivity	145.43	18	<0.001***	-3.16	0.002**	-2.60	0.009**
Recovery	168.83	18	<0.001***	3.76	<0.001***	3.35	0.001**

Note. HR = heart rate.

Supplementary Table 5. Mixed-effects linear regression model results with pre-treatment vmHRV measures as predictors of global level of functioning at T1 and T2, controlling for potential confounders.

Random intercept-only models (GAF)				T1		T2	
vmHRV	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting-state	147.05	18	<0.001***	-0.89	0.374	0.03	0.979
Reactivity	116.31	18	<0.001***	-0.13	0.893	0.53	0.597
Recovery	110.73	18	<0.001***	-0.18	0.861	-0.25	0.803

Note. vmHRV = vagally-mediated heart rate variability.

Random intercept random slope models (GAF)				*T1*		*T2*	
vmHRV	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting-state	135.90	18	<0.001***	-0.87	0.386	-0.01	0.995
Reactivity	103.45	18	<0.001***	-0.14	0.891	0.52	0.600
Recovery	98.39	18	<0.001***	-0.10	0.924	-0.17	0.862

Note. vmHRV = vagally-mediated heart rate variability.

Supplementary Table 6. Mixed-effects linear regression model results with pre-treatment HR measures as predictors of global level of functioning at T1 and T2, controlling for potential confounders.

Random intercept-only models (GAF)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	130.40	18	<0.001***	2.15	0.032*	1.35	0.178
Reactivity	143.19	18	<0.001***	1.25	0.210	1.03	0.303
Recovery	118.51	18	<0.001***	-1.74	0.083	-0.77	0.440

Note. HR = heart rate.

Random intercept random slope models (GAF)				T1		T2	
HR	χ^2	*DF*	*p*	*z*	*p*	*z*	*p*
Resting	133.78	18	<0.001***	2.17	0.030*	1.37	0.170
Reactivity	233.39	18	<0.001***	2.80	0.005**	1.91	0.056
Recovery	133.78	18	<0.001***	-1.88	0.060	-0.94	0.350

Note. HR = heart rate.

MIST Protocol

The present task protocol encompassed an initial 5 min training session conducted outside the imaging unit, followed by a 10 min testing session, including three conditions (experimental, control, and rest condition). In the *training session* outside the imaging unit, the participant's ability to perform mental arithmetic was assessed, recording the average time needed to solve problems at various levels of difficulty, and neither a time limit was enforced, nor a time progress bar or performance indicators were displayed. Inside the scanner, the recorded time during the training session was used to set the default time limit in the *experimental condition*. Therefore, to induce a high failure rate, the program was set to a time limit that is 10% less than the subject's average response time. Additionally, participants' average response time and the number of correct responses were continuously recorded, based on which task difficulty was continuously adjusted to enforce a range of 20% to 45% correct answers. To further increase stress, participants' performance was illustrated in comparison with a (fictitious) norm sample's performance, while participants' performance was always suggested to be inferior. Furthermore, automated feedback was provided ("correct", "incorrect", or "time-out"). Also, scripted negative verbal feedback was delivered by the experimenter repeatedly in-between runs, and the need to improve performance was emphasized via headphones. The experimenter therefore asked participants to repeat the task and to increase their performance, remarking that due to under average performance of the respective participant, the data would be useless otherwise. In the *control condition*, mental arithmetic tasks were presented at the same frequency and difficulty level as in the experimental condition, but without enforcing time restriction and without displaying any performance measures. To match task frequency between experimental and control condition, the time between tasks was varied as a function of the time limit imposed during the experimental condition, resulting in an identical total number of tasks per condition. Feedback ("correct" or "incorrect") was also provided, but with the absence of a time limit, average performance was raised to about 90%. Scripted feedback between runs was provided by the experimenter also in the control condition, and the subject was told to try and perform the task as quickly and accurately as possible. However, it was also stated that individual performance was not being evaluated because this was a control condition. In the *rest condition*, recording a baseline state, the interface of the computer program remained active but no tasks were shown. Participants were asked not to move the mouse until the next mental arithmetic task appeared. Participants were debriefed after the stress paradigm had been completed.

2.3 Manuscript

Circadian Variation of Cardiac Autonomic Activity in Adolescent Non-Suicidal Self-Injury

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Research on Child and Adolescent Psychopathology

Abstract

Decreased heart rate variability (HRV) is associated with maladaptive stress regulation. Non-suicidal self-injury (NSSI) in adolescents is associated with difficulties in stress regulation. Existing research in adolescent psychopathology mainly focused on short-term recordings of HRV under resting conditions. Evidence in adult psychiatric patients suggests alterations of circadian variation patterns (CVP) of autonomic nervous system (ANS) activity. In the present study, we examined for the first time, whether CVP of cardiac autonomic activity, indexed by heart rate (HR) and vagally-mediated HRV (vmHRV) derived from 48 hours of ambulatory ECG recording, are altered in female adolescent NSSI disorder, compared to healthy, age- and sex-matched controls (HC; $N = 30$ per study group). We furthermore examined potential associations between altered CVP and NSSI frequency, as well as a range of dimensional clinical predictors, including early life maltreatment (ELM), borderline personality disorder (BPD), difficulties in emotion regulation, depressive symptoms, and sleep duration. Several confounders, including physical activity, were controlled for. Adolescents with NSSI are characterized by altered CVP of ANS activity, indexed by a greater HR amplitude, MESOR and acrophase, as well as a lower amplitude, MESOR and acrophase of vmHRV – although the later findings were not robust when adjusting for important confounds. Further, CVP of ANS activity in adolescent NSSI is characterized by a general shift in rhythmicity of about one hour, indexed by a later acrophase in HR and vmHRV. ELM severity significantly predicted CVP of HR and vmHRV in unadjusted but not fully-adjusted models. BPD symptomatology was a significant predictor of CVP of HR but not vmHRV. While chronobiological interventions in stress- and emotion regulation disorders might be translationally relevant avenues of future research, the present results also highlight the need for more rigorous control of critical confounders in studies focusing on the interrelation of clinical variables with ANS activity and disruptions of the circadian system.

Keywords: *Stress Regulation*; *Emotion Regulation*; *Non-Suicidal Self-Injury*; *Adolescents*; *Heart Rate*; *Heart Rate Variability*; *Circadian Variation*

1. Introduction

Non-suicidal self-injury (NSSI) encompasses deliberate and voluntary physical self-injurious behavior that is not life-threatening, conducted without any conscious suicidal intent (Laye-Gindhu & Schonert-Reichl, 2005). Of note, NSSI disorder, characterized by the engagement in NSSI, severe enough to cause minor or moderate damage at 5 or more days during the previous 12 months, has been included as a condition for further study in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013). NSSI predicts the onset of later mental illness (Mars et al., 2014), and a higher prevalence of NSSI is associated with merely any mental disorder (Nock et al., 2006) – borderline personality disorder (BPD) and depressive disorders represent the most prominent comorbid conditions. Among adolescent populations, the prevalence of NSSI disorder (according to DSM-5 diagnostic criteria) is estimated at 5% among non-clinical samples, and may lie between 50 to 80% among in-patients (Plener et al., 2016; Zetterqvist, 2015). Among adolescent populations engaging in NSSI, between 74% and 78% meet full criteria for NSSI disorder (Glenn & Klonsky, 2013; Washburn et al., 2015). NSSI is generally assumed to be most frequent in adolescent females (Barrocas et al., 2012); but also see (Klonsky & Muehlenkamp, 2007).

Considering the etiology of the behavior, within a model of developmental psychopathology (Yates, 2004), exposure to different forms of adverse environmental factors during critical developmental periods are discussed as potential mediators of the engagement in NSSI. Exposure to early life stress, and in particular exposure to very severe forms such as early life maltreatment (ELM; i.e., physical, emotional, and sexual abuse, and physical and emotional neglect), has been suggested as one contributing factor that has strongly and consistently been associated with both NSSI (Fliege et al., 2009; Gratz et al., 2002; Kaess et al., 2013; Liu et al., 2018; Maniglio, 2011) and BPD (Kaess et al., 2013; Laye-Gindhu & Schonert-Reichl, 2005; Maniglio, 2011). ELM exposure might create vulnerabilities in an individual's ability to adaptively cope with stress, e.g., through a failure to achieve critical developmental competencies, including socio-emotional regulatory skills. In an effort to cope with normal and abnormal stressors experienced during childhood and adolescence, deficient socio-emotional regulation and heightened stress vulnerability may result in maladaptive compensatory behaviors, including NSSI (Yates, 2004). Notably, ELM exposure has been linked with the emergence of other psychiatric conditions characterized by stress vulnerability and emotion dysregulation, in particular, depression (Hill, 2003; Klumparendt et al., 2019). In fact, emotion dysregulation may present a significant mediator of the relationship between ELM exposure and NSSI (Muehlenkamp et al., 2010), indicating deficient stress regulation.

Individuals at risk for NSSI often report chronic emptiness, alienation, and isolation in combination with intense, overwhelming negative emotions (Gratz, 2003). Acute negative affect, including fear and anxiety, sadness, worthlessness, and/or strong inner tension, is reported to often

precede the engagement in NSSI, which is followed by a subsequent reduction in negative affectivity (e.g., Briere & Gil, 1998; Klonsky, 2009; Kumar et al., 2004; Laye-Gindhu & Schonert-Reichl, 2005). Alongside studies using retrospective self-reports or those conducted under laboratory conditions, studies that used ecological momentary assessments (EMA) provide further support for an emotion-regulatory function of NSSI (Armey et al., 2011; Nock et al., 2009). NSSI may not only temporarily reduce negative emotions, but also promote positive affect, and temporarily increased positive affectivity following NSSI has been shown to predict greater lifetime frequency of the behavior (Armey et al., 2011; Jenkins & Schmitz, 2012; Kemperman et al., 1997). As highlighted above, there is a notable overlap between NSSI and the diagnosis of BPD: while self-injury is one of the BPD symptom criteria most frequently met among adolescents (Chanen et al., 2008), both NSSI and BPD show marked associations with emotion dysregulation (Fliege et al., 2009; Fossati et al., 1999; Gratz et al., 2002; Kaess et al., 2013; Liu et al., 2018; Maniglio, 2011; Porter et al., 2020; Winsper et al., 2016). Empirical evidence for treatment options in NSSI, as well as BPD, has been strongest for interventions with a specific focus on improving the capacity to regulate one's emotions, such as dialectic behavior therapy and emotion regulation group therapy (Gratz & Gunderson, 2006; Gratz & Tull, 2011; Linehan, 1993). Research focusing on NSSI disorder however indicates that NSSI might be uniquely associated with emotion dysregulation over and above the diagnosis of BPD (Glenn & Klonsky, 2013), suggesting that the role of emotion dysregulation in NSSI might not simply be accounted for by BPD characteristics (Andover & Morris, 2014).

There is an increase in scientific endeavors thriving to understand and integrate psychological and neurobiological aspects of NSSI. However, and despite the growing amount of neurobiological studies focusing on the behavior, there is still only little understanding of the exact psychological and neurobiological mechanisms that promote NSSI and its maintenance (Groschwitz & Plener, 2012). Advances in the understanding of the (stress) regulatory functions of NSSI and underlying neurobiology might essentially guide the innovation of new intervention and prevention strategies to target this behavior (Westlund Schreiner et al., 2015), expanding the rather small array of treatments of NSSI that are currently available (Calati & Courtet, 2016; Liu et al., 2018; Ougrin et al., 2015).

Difficulties in stress and emotion regulation may constitute a central underlying dysfunctional component that is shared among clinical and non-clinical populations engaging in NSSI (Aldao et al., 2010), observed both at the psychological (Berking & Wupperman, 2012) and neurobiological levels - the latter including alterations of the functional flexibility of the autonomic nervous system (ANS; Thayer & Lane, 2000; Thayer & Lane, 2009). The Central Autonomic Network (CAN) essentially involves brain regions associated with inhibitory processes, stress, and emotion regulation, i.e., the right ventrolateral prefrontal cortex (PFC) and medial PFC (Cechetto, 1987; Hagemann et al., 2003). According to the *Neurovisceral Integration Model* (NIM; Thayer & Lane, 2000; Thayer & Lane, 2009), the primary output of the CAN is directly linked to heart rate variability (HRV), a biomarker derived

from heart rate recordings and interpreted as an index of cardiac autonomic activity (Shaffer & Ginsberg, 2017); for an in-depth elaboration of the NIM, please see (Thayer & Lane, 2000; Thayer & Lane, 2009). As such, HRV has served as an objective and transdiagnostic marker of emotion (dys-) regulation and psychopathology (Balzarotti et al., 2017; Thayer & Lane, 2000; Thayer & Lane, 2009) in numerous psychological and neurobiological research studies. Meta-analyses imply reduced resting-state short-term HRV in both adult (Kemp et al., 2010) and adolescent depressive disorder (Koenig et al., 2016a), as well as adult (Koenig et al., 2016b) and adolescent BPD (Koenig et al., 2017b; Weise et al., 2020). Studies on autonomic vagal (parasympathetic) activity in NSSI have shown reduced resting-state HRV and increased HRV reactivity in response to negative mood induction in para-suicidal adolescents (Crowell et al., 2005), while in adolescents engaging in NSSI, resting-state short-term HRV was found to be inversely related with the severity of BPD symptomatology, providing evidence for generally altered autonomic vagal activity in adolescents engaging in NSSI (Koenig et al., 2017a). Interestingly, in two recent studies, pre-treatment HRV, both at resting-state and during recovery from a psychosocial stress task, were identified as predictors of treatment outcome in adolescents characterized by subthreshold or full-blown BPD (Sigrist et al., 2021; Weise et al., 2020), thereby replicating findings from previous psychotherapy studies (Angelovski et al., 2016; Bär et al., 2004; Blanck et al., 2019; Kircanski et al., 2019; Soder et al., 2019), and suggesting HRV as a potentially useful biomarker in the treatment of adolescent emotional and deficient stress regulation.

In addition to the investigation of tonic (resting-state) and phasic (reactivity and recovery) levels of HRV in the context of psychological processes and psychiatric symptoms, interest in the *circadian* (Latin for "about a day") variation of cardiac autonomic activity recently arose (Jarczok et al., 2019). In line with other physiological mechanisms (e.g., control of core body temperature, urine volume, or cerebral blood flow), cardiac autonomic activity is following a pattern of diurnal variation with a frequency of an approximate solar day (24-h), and peak levels during nighttime (Huikuri et al., 1994; Jarczok, Aguilar-Raab, et al., 2018; Li et al., 2011). Circadian variation of cardiac autonomic activity indexed by HR and HRV has been observed in children already from 1 year of age but not in neonates (Massin et al., 2000; Weinert et al., 1994), and continues throughout adolescence (Schubert et al., 1995) and adulthood (Furlan et al., 1990; Huikuri et al., 1994; Lombardi et al., 1992; Malpas & Purdie, 1990; Nakagawa et al., 1998), while it might diminish in older age (Thayer et al., 2010). Previous research focusing on circadian variation patterns (CVP) of cardiac autonomic activity substantiated sex-specific patterns of variation in association with depressive symptoms (Chambers & Allen, 2002; Garcia et al., 2017; Thayer et al., 1998; Verkuil et al., 2015a), as well as potential alterations in CVP in association with depressive disorders and difficulties in emotion regulation in the context of adult BPD (Wainsztein et al., 2020). In general, research in this field is only just evolving, and thus far exclusively focused on adult populations or nun-human primates (Jarczok et al., 2018). Vast evidence however suggests that disruptions in the circadian system in association with psychiatric

symptoms and disorders might emerge already in childhood or adolescence (Grierson et al., 2016; Harvey et al., 2006; Logan et al., 2018; Molina-Carballo et al., 2013; Naismith et al., 2012), while it has been highlighted that future research should examine disturbances within different components of the circadian system in association with NSSI (Westlund Schreiner et al., 2015). Importantly, while research examining the functions of NSSI largely focused on socio-emotional regulation, NSSI, as we would argue, may generally function as a strategy of stress regulation (Kaess et al., 2012; Kleindienst et al., 2008; Sachsse et al., 2002; Yates, 2004). Crucially, stress and emotions have many concomitant physiological characteristics that are indistinct, also including autonomic regulatory processes. Numerous studies provide evidence that cardiac autonomic markers (i.e., resting-state HRV measures) are associated with both emotion and stress regulation (Appelhans & Luecken, 2006; Thayer et al., 2012; Thayer & Lane, 2009), and that greater resting-state HRV and greater activity in brain regions related to emotion regulation (i.e., regions of the PFC) are associated with both implicit and explicit regulation of emotion and the regulation of stress (Angius et al., 2019; De Witte et al., 2020; Era et al., 2021; Pulopulos, 2020; Wiliams et al., 2019a; Williams et al., 2015). Studies further investigating the neurobiology of NSSI from a neurovisceral perspective, considering CVP patterns of cardiac autonomic activity, could provide important transferrable insights to the neurobiology of stress regulation. To date, no study assessed potential alterations in CVP patterns of cardiac autonomic activity in adolescent NSSI, or in association with any other psychiatric disorder or symptoms in adolescent populations.

In the present study, we therefore aimed to address this gap by examining CVP of cardiac autonomic activity in adolescent NSSI disorder. We were interested in potential disruptions of CVP of cardiac autonomic activity in the presence of NSSI disorder, and in association with NSSI frequency and the severity of BPD symptomatology, severity of experiences of ELM, depressive symptoms, difficulties in emotion regulation, and sleep duration. We assessed circadian variation of cardiac autonomic activity in a sample of female adolescents fulfilling DSM-5 criteria of NSSI disorder in comparison to healthy, age-matched control females. Based on preliminary findings of reduced 24-h HRV in association with greater difficulties in emotion regulation in adult BPD (Wainsztein et al., 2020), and of blunted HRV increase at nighttime in association with both acute and chronic stress exposure (Jarczok et al., 2013; Karhula et al., 2014; Thayer et al., 2010), we hypothesized that: In female adolescent NSSI disorder, we would find altered CVP of cardiac autonomic activity characterized by reduced rhythm-adjusted mean level, Amplitude, and Acrophase of vmHRV, and elevations in respective parameters of CVP of HR, compared to healthy, age-matched control females (H1), and in association with the (self-rated) frequency of engagement in NSSI during the past 12 months (H2a), as well as with higher severity of BPD symptomatology (H2b). Furthermore, we examined whether severity of ELM exposure (H2c), depressive symptomatology (H2d), difficulties in emotion regulation (H2e), and sleep duration (H2f) would be significantly linked with alterations in CVP of cardiac autonomic activity in the present sample of female adolescents with and without NSSI disorder, based

on findings from previous studies in adults and female macaques (Jarczok et al., 2018; Jarczok et al., 2018; Wainsztein et al., 2020).

Of note, and based on the current literature, it might be self-evident that when examining HRV measures as outcome of interest, and in association with, e.g., clinical variables, accounting for other influential factors known to affect (measures of) ANS activity would be of high importance (see e.g., Quintana et al., 2016; Quintana & Heathers, 2014; Task Force of the European Society of Cardiology, 1996 for respective guidelines). Yet, and as has been pointed out previously (e.g., Verkuil et al., 2016), in many studies focusing on HRV, and especially in studies of ambulatory ECG measurements, potentially influential factors remain critically unaddressed. In particular, most existing ambulatory HRV studies refrained from considering physical activity as a potential confounder (Verkuil et al., 2016), despite of evidently strong influences of physical activity levels on HRV. Furthermore, in clinical studies examining associations of psychological variables with ANS functioning, aspects regarding the quality of cardiac data recordings are widely neglected. In the present study, we therefore aimed to explicitly address the robustness of clinical predictors of interest against these critical factors.

2. Methods

2.1 Participants

The present study was conducted at the Department of Child and Adolescent Psychiatry, Heidelberg University, Germany, and also included EMAs (published elsewhere; Koenig et al., 2020). The present sample comprised $N = 60$ female adolescents aged 12 – 17 years, half of which fulfilled the criteria for NSSI disorder (NSSI group; $N = 30$), while the other half were healthy controls (HC; $N = 30$). Inclusion criteria for the NSSI study group were five or more incidences of self-harm during the past year, and one incidence or more in the past month (NSSI disorder criteria; American Psychiatric Association, 2013). Participants in the control group had no lifetime history of self-harm or suicidal behavior, were free from any psychiatric disorder, and did not receive any psychiatric or psychotherapeutic treatment during the previous 2 years. Participants in the NSSI group were recruited from the outpatient clinic for risk-taking and self-harming behavior (AtR!Sk; *Ambulanz für Risikoverhaltensweisen und Selbstschädigung*; Kaess et al., 2017b). Healthy controls were recruited from the general community by Email advertisements distributed via Department and University mailing lists. Before study inclusion, all participants underwent extensive clinical interviews to assert eligibility. Individuals with neurological or endocrinological disorders, acute psychotic symptoms, acute suicidality, or lack of understanding of the German language were excluded from the study. All study procedures were approved by the ethics committee of the Medical Faculty at Heidelberg University (Approval Number: S-448/2014) and complied with the Helsinki Declaration of 1975, as

revised in 2013. All participants and their legal guardians signed written informed consent prior to participation in the study.

2.2 Measures

2.2.1 Clinical measures

All participants underwent structured clinical interviews using the following instruments. The German version of the *Mini-International Neuropsychiatric Interview for Children and Adolescents* (M.I.N.I.-KID 6.0; Sheehan et al., 2010), a short and structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders in children and adolescents, was used to screen for potentially comorbidity in psychiatric diagnoses. The M.I.N.I.-KID has been demonstrated to generate reliable and valid psychiatric diagnoses (Sheehan et al., 2010). The German version of the *Self-Injurious Thoughts and Behavior Interview* (SITBI-G; Fischer et al., 2014) a clinician-administered interview that assesses suicidal thoughts, suicidal behaviors, and NSSI, was used to assess NSSI. In prior work, the SITBI has shown strong inter-rater reliability (average k = .99, r = 1.0) and test–retest reliability over a 6-month period (average k = .70, *ICC* = .44; (Nock et al., 2007). ELM exposure was measured using the *German version of the Childhood Experience of Care and Abuse Questionnaire* (CECA.Q; Kaess et al., 2011). The CECA.Q assesses four dimensions of ELM including parental care (neglect and antipathy), parental physical abuse, and sexual abuse (by any adult) before age 17, and has been confirmed a reliable and valid measure to screen for experiences of severe adversity in childhood, in clinical (Smith et al., 2002) as well as community samples (Bifulco et al., 2005). For the present analyses, a binary score was created indicating presence versus absence of any of the ELM subtypes assessed, and a severity score was calculated as the average of individual severity ratings for each of the ELM subtypes. To assess BPD pathology, we used the German version of the *Structured Clinical Interview for DSM-IV-Axis II* (SKID-II; Fydrich et al., 1997), which has been developed to assess DSM-IV-TR Personality Disorders and shown to reliably assess personality disorders in adolescents (Salbach-Andrae et al., 2008). For the purpose of the present study, the SKID-II module designed to assess BPD traits was conducted. To assess the current severity of depressive symptoms, the German Version of the *Children's Depression Inventory* (CDI; Kovacs, 1992; Kovacs & Staff, 2012) was used ("*Depressionsinventar für Kinder und Jugendliche*", *DIKJ*; Stiensmeier-Pelster et al., 2000). The DIKJ is a 26-item self-rating instrument which has been demonstrated to have high internal consistency (α = .82 – .88), and has widely been used to assess depressive symptomatology in children and adolescents from 8 to 17 years of age (Frühe et al., 2012). The German version of the *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2003) was used to measure emotional dysregulation. The DERS is a self-report measure designed to assess six dimensions of emotion dysregulation. Subscale scores reflecting each of these factors are available, while the DERS is often reported as a total score. The DERS is used in nearly all studies of trait-level emotion dysregulation in self-harm, but has been used to assess emotion

dysregulation in other psychological disorders as well (Fox et al., 2007, 2008; Harrison et al., 2010; Whiteside et al., 2007). The DERS has high internal consistency, good test–retest reliability, and adequate construct and predictive validity (Gratz & Roemer, 2003)

2.2.2 Cardiac autonomic data

We report recording and analyses of cardiac autonomic data in accordance with the 'Guidelines for Reporting Articles on Psychiatry and Heart rate variability' (GRAPH; Quintana et al., 2016). Heart rate was continuously recorded as beat-to-beat intervals at 1024 Hz for 48 hours using an ECG Move III chest belt (movisens, Karlsruhe, Germany). The ECG Move III is a state-of-the-art sensor to record ECG at a high-frequency sampling rate through an ambulatory sensor attached to an elastic chest belt, and allows to simultaneously record 3D acceleration and temperature. Participants were instructed to wear the HR recorder for two consecutive days over a weekend, starting Saturday morning, 10 AM until Monday morning, 10 AM, resulting in 48-h of total recording time. Raw ECG recordings were manually, visually inspected and pre-processed using the Kubios Premium 3.0 Software (Kubios, Finland; Tarvainen, 2014) allowing for R-Peak detection and correction of raw ECG data. Peak detection was manually corrected and artifacts were removed. Smoothing priors were selected as detrending method (λ 500) for IBI data. Kubios output was saved in the txt format for later automated readout of corrected inter-beat-intervals (IBIs) and analysis of HRV in R (Martínez et al., 2017). IBIs corresponding to a mean HR < 30 or > 200 bpm were discarded. After pre-processing, each 24-h recording period was further segmented into 5-minute intervals, resulting in a total of 288 segments per measurement day. Segments with less than 30 seconds of consecutive IBI data were discarded for analyses. For each of the resulting 5-min segments, the following cardiac autonomic parameters were calculated: Mean HR in beats per minute (bpm), and the time-domain measure root mean square of successive inter beat intervals (RMSSD) in milliseconds (ms) obtained by calculating each successive time difference between heartbeats in milliseconds after which each of the values was squared and the result averaged before the square root of the total was obtained. RMSSD presents a stable and valid measure of autonomic vagal (parasympathetic) activity, and is less affected by respiration and artifacts from body movement than other HRV measures (e.g., Hill et al., 2009; Penttilä et al., 2001). The total of 5-min segments available per participant from 48-h recordings were collapsed, resulting in a total of (maximally) 288 segments (24-h) per participant. Based on these segments, we identified and quantified circadian rhythmicity of HR and vmHRV. In accordance with available guidelines and previous studies, for the calculation of circadian rhythmicity of cardiac autonomic activity, the cosinor method was applied (Cornelissen, 2014; Refinetti et al., 2007). Three individual-level cosine function parameters were estimated for each outcome (HR and vmHRV) by linear models with ordinary least square estimations to quantify the circadian variation pattern: i) MESOR (Midline Estimating Statistic Of Rhythm) defined as the rhythm adjusted 24h mean fitted to the data, ii) Amplitude, defined as the distance between MESOR and the maximum of the cosine curve (i.e. half the extent of rhythmic change

in a cycle), and iii) Acrophase, defined as the phase shift of amplitude from a given reference time point when the highest oscillation is reached (i.e. time lag) (Fernández et al., 2009). The period was assumed to be 24-h. We calculated individual-level cosinor per participant for further statistical analysis, as well as population-mean cosinor per study group and day of measurement merely to examine cosinor model fit. For cosinor analyses, we used the R-package '*cosinor2*' (Mutak, 2018) presenting an extension of the R-package '*cosinor*' (Sachs, 2014).

2.2.3 Covariates

We assessed and calculated potential covariates, including age, body mass index (BMI; height/ weight²), physical activity, and quality of ambulatory ECG recordings. To obtain a measure of physical activity, raw acceleration data (measured in g) available from ECG Move III sensor recordings was averaged over 60-s periods, and individual step count (total number of steps per day) was calculated using the Movisens Data-Analyzer software (Version 1.13.5; movisens GmbH, Karlsruhe, Germany). Of note, from raw acceleration data and using the same software, we also derived sleep, wake, and non-wear time per participant and measurement day. The total number of 5-min segments, calculated as the sum of 5-min segments available per participant over 48-h of cardiac recording, was used as a proxy of cardiac data quality.

2.3 Statistical Procedure

First, data were explored visually (i.e. boxplots, histograms), and univariate normality of continuous data was examined using skewness and kurtosis tests for normality. Descriptive statistics of demographic, physical, and clinical data were calculated, and differences between the two study groups (NSSI group and HC) were examined using independent group *t*-test (or a non-parametric equivalent) for continuous, and $\chi 2$ test (or Fisher's exact test in the case of expected frequencies of 5 or less) for categorical data. Next, to test the hypothesis of (1) group differences in CVP of cardiac autonomic activity between the NSSI group and HC, differential rhythmicity analysis was performed, including an analysis of significant differences in amplitude and analysis of acrophase shift, followed by univariate multiple linear regression models, controlling for potential confounders (age, BMI, physical activity, and data quality), thus considering each of the three cosinor parameters of HR and vmHRV separately. Next, bivariate correlations of MESOR, Amplitude, and Acrophase of HR and vmHRV with each dimensional clinical predictor of interest (hypotheses 2a – 2f, i.e., ELM exposure severity, NSSI frequency, BPD symptomatology, sleep duration, depressive symptomatology, and emotional dysregulation) were explored using the non-parametric Spearman's rank correlation coefficient (Spearman's ρ). Finally, we calculated multivariate single and multiple linear regression models (unadjusted and fully-adjusted models), which allowed us to examine the impact of each clinical predictor of interest (hypotheses 1 – 2f) on CVP of HR and vmHRV while considering MESOR, Amplitude, and Acrophase simultaneously. Accordingly, two multivariate linear regression models

were calculated for each predictor and outcome (i.e., HR and vmHRV) combination: Unadjusted (multivariate single linear regression) models which considering solely the effect of a clinical predictor on CVP, and a fully-adjusted (multivariate multiple linear regression) model, where we additionally controlled for critical confounds (i.e., age, BMI, physical activity, and quality of cardiac data) while considering the effect of each clinical predictor on CVP of HR and vmHRV.

Data pre-processing as well as descriptive and statistical analyses were performed using Stata/SE (Version 16.0; StataCorp LP, College Station, TX, US), with alpha set to 0.05 (two-sided). Figures were prepared using R version 4.0.2 (R Core Team, 2020), and CosinorPy (Moškon, 2020).

3. Results

3.1 Descriptive statistics

Descriptive statistics of demographic, physical, and clinical data, separated by study group, are presented in *Table 1* below. Mean age (SD) of the total sample (N = 60) was 14.93 (1.31; range 12 – 17). No significant differences between study groups regarding age, height, weight, BMI, number of steps per day, and time spent asleep, were observed. A statistically significant difference in non-wear time was observed between study groups, with the NSSI group exhibiting a slightly longer non-wear time on average compared to HC (see *Table 1* below). Regarding clinical characteristics, the NSSI group scored significantly higher on the DIKJ, indicating more severe depressive symptoms, compared to HC. Within the NSSI group, NSSI frequency during the past 12 months varied between 5 and 365 days (M = 92.17, SD = 100.62) and twelve participants (40%) fulfilled diagnostic criteria for BPD (5 or more BPD symptom criteria fulfilled), while eight participants met criteria for a subthreshold diagnosis (fulfilling 3 - 4 BPD symptom criteria), and ten participants were below subthreshold. No participant within the HC group fulfilled more than 1 BPD symptom criterion. As expected, the NSSI group experienced significantly more severe ELM exposure, and scored significantly higher on all subscales of the DERS, indicating greater difficulties in emotion regulation compared to HC. Considering cardiac autonomic data, a total of 27’879 (80.67%) 5-min segments were available for further analysis. Of note, EGC-data was missing for one participant in the NSSI group. In *Figure 1* below, cardiac autonomic data of mean HR (bpm) and vmHRV (ms) over 24-h are shown (collapsed data), including smoothed conditional means to aid visual detection of potentially underlying patterns. Descriptive information on population-mean cosinor parameters (used for group comparison), separated by study group, as well as respective cosinor model fit statistics, are shown in *Table 2* below. In *Supplementary Table 1*, descriptive summary statistics of single cosinor model parameters per study group (based on collapsed data) used for testing of hypotheses 2a – 2f are presented. Rhythm detection tests (testing of cosinor model fit) yielded significant results regarding all cosinor models, suggesting they fit the present data well on a group level.

Table 1. Descriptive Statistics of demographic, physical, and clinical data, separated by study group.

	NSSI (*N* = 30)		Controls (*N* = 30)		NSSI vs. Controls			
	M (SD)	Min - Max	M (SD)	Min - Max	*t* (DF)	*z*	χ^2 (DF)	*p*-value
age [years]	15.10 (1.06)	13 – 17	14.77 (1.52)	12 – 17	.983 (58)	-		.330
height [cm]	165.37 (5.70)	156 – 175	165.07 (6.03)	150 – 176	.198 (58)	-		.844
weight [kg]	60.83 (15.42)	38 – 110	54.60 (6.28)	44 – 69	-	1.490		.138
BMI [m/ kg^2]	22.12 (4.94)	14.69 – 38.51	20.02 (1.86)	17.18 – 25.39		1.745		.081
Step count [No. steps]	11887 (7135.69)	359 – 36’609	10’226.62 (4’694.02)	4’671 – 25’390		.956		.346
Sleep time [hours]	7.31 (3.25)	0 – 16.78	7.64 (1.73)	4.62 – 11.92		.237		.815
Segments [*N* available]	428.31 (154.14)	69 – 576	510 (98.41)	193 – 574		-2.78		**.005**
Non-wear time [min]	5.14 (2.03)	0 – 8	2.76 (1.53)	0 – 5		4.90		**<.001**

	NSSI (N = 23)			Controls (N = 30)			NSSI vs. Controls		
	N (%)	M (SD)	Min - Max	*N* (%)	M (SD)	Min - Max	*z*		*p*-value
CECA.Q[1]									
Total									
any ELM subtype	17 (73.91)			1 (3.33)					
ELM severity		11.24 (4.03)	5.43 – 17.57		5.98 (1.26)	4.57 – 8.86	4.67		**<.001**
Subtypes									
maternal antipathy	8 (34.78)	19.61 (7.76)	8 – 32	0 (0)	10.5 (2.90)	8 – 19	4.38		**<.001**
maternal neglect	7 (30.43)	16.91 (7.37)	8 – 34	0 (0)	10.03 (2.37)	8 – 17	3.99		**<.001**

maternal physical abuse	2 (8.70)	.17 (0.65)	0 – 3	0 (0)	0 (0)	-	1.67	.348
paternal antipathy	8 (34.78)	20.57 (9.81)	8 – 38	0 (0)	10.37	8 – 19	4.10	**<.001**
paternal neglect	9 (39.13)	19.78 (9.39)	8 – 40	0 (0)	10.90 (2.72)	8 – 19	4.07	**<.001**
paternal physical abuse	1 (4.35)	.04 (0.21)	0 – 1	1 (3.33)	.07 (0.37)	0 – 2	.20	.846
sexual abuse	8 (34.78)	1.61 (2.41)	0 – 7	0 (0)	0 (0)	-	3.54	**<.001**

	NSSI ($N = 30$)		Controls ($N = 30$)		NSSI vs. Controls	
	M (SD)	Min - Max	M (SD)	Min - Max	z	p-value
DERS						
total score	111.76 (23.36)	59 – 149	54.30 (10.72)	36 – 82	6.427	**<.001**
non-acceptance	17.37 (5.81)	6 – 27	9.63 (3.52)	6 – 18	4.869	**<.001**
goals	17.50 (4.64)	8 – 24	9.33 (3.97)	5 – 20	5.387	**<.001**
impulse	17.13 (6.67)	6 – 29	8.37 (2.98)	6 – 17	5.158	**<.001**
awareness	20.9 (5.23)	9 – 29	11.03 (3.55)	7 – 21	5.629	**<.001**
strategies	27.37 (6.83)	14 – 39	11.07 (3.71)	8 – 23	6.373	**<.001**
clarity	17.20 (5.01)	7 – 25	7.60 (2.25)	5 - 12	6.039	**< .001**

	NSSI (N = 30)			Controls (N = 30)	
	M (SD)	Min - Max	N (%)	M (SD)	Min - Max
NSSI Frequency					

Past 6 months [days]		47.37 (43.37)	0 – 120		-	-		
Past 12 months [days]		92.17 (100.62)	5 – 365		-	-		

	NSSI ($N = 30$)			Controls ($N = 30$)			NSSI vs. Controls	
	N (%)	M (SD)	Min - Max	N (%)	M (SD)	Min - Max	χ^2 (DF)	p-value
BPD							30.00 (2)	**<0.001**
full diagnosis	12 (40.00)	6 (0.73)	5 – 8	0	-	-		
sub-threshold	8 (26.67)	3.63 (0.52)	3 – 4	0	-	-		
below sub-threshold	10 (33.33)	1.5 (0.53)	1 – 2	30 (100.00)	.07 (0.25)	0 - 1		

	NSSI ($N = 30$)			Controls ($N = 30$)			NSSI vs. Controls	
		M (SD)	Min - Max	N (%)	M (SD)	Min - Max	t (DF)	p-value
DIKJ								
total score		25.52 (10.65)	3 – 44	30	5.27 (3.04)	0 – 13	9.95 (53)	**<0.001**

	NSSI ($N = 30$)	Controls ($N = 30$)
	N (%)	N (%)
M.I.N.I.-KID		
ICD-10: F0	2 (8.00)	-
ICD-10: F1	1 (4.00)	-
ICD- 10: F2	-	-

ICD-10: F3	11 (44.00)	-
ICD-10: F4	3 (12.00)	-
ICD-10: F5	-	-
ICD-10: F6	7 (28.00)	-
ICD-10: F8	-	-
ICD-10: F9	1 (4.00)	-

Note. [1] $N = 7$ missings in the NSSI group.

3.2 Analyses results

3.2.1 Differences in CVP of HR and vmHRV between study groups

Graphical consideration of cardiac autonomic data (*Figure 1*) implicated potential group effects regarding both 24-h HR and vmHRV. In *Table 2* below, results of differential rhythmicity and analysis of acrophase shifts are shown. These cosinor-specific group comparisons revealed statistically significant differences between study groups in MESOR (illustrated in *Figure 2* below), as well as significant Acrophase shifts (visualized in *Supplementary Figure 1*), of both HR and vmHRV. Of note, since Acrophases of HR and vmHRV were significantly different between study groups, potential differences in Amplitude could not be examined reliably using differential rhythmicity analysis. Group comparisons concerning Amplitudes were therefore performed using unpaired group *t*-tests (also reported in *Table 2* below), which yielded statistically significant differences in Amplitudes of HR and vmHRV between study groups (*Figure 2*). Overall, the NSSI group showed a significantly higher rhythm-adjusted mean HR and lower HR Amplitude, as well as significantly lower rhythm adjusted mean vmHRV and higher respective Amplitude, compared to the HC group. Furthermore, Acrophases of HR and vmHRV in the NSSI group compared to HC were shifted significantly with the clock, meaning that peak levels in both HR and vmHRV were reached at a later time point in the NSSI group. Considering HR, Acrophase was reached approximately 0.96 h (57 min 28 sec) later in the NSSI compared to the HC group, while concerning RMSSD, Acrophase was shifted for 1.10 h (1 h 5 min 57 sec) with clock time in NSSI compared to HC (*Supplementary Figure 1*).

Next, we examined whether controlling for potentially confounding factors (i.e., age, BMI, physical activity, and cardiac data quality indexed by available 5-min segments) using univariate multiple linear regression models altered the effect of study group as a statistically significant predictor of CVP of HR and vmHRV. In adjusted (univariate multiple linear) regression models, study group was still a statistically significant predictor of the cosinor parameter MESOR of 24-h HR, B = -.32, t_{57} = 2.28, p = .027, while BMI, B = -.42, t_{57} = -.27, p = .008, and the quality of cardiac data, B = -.33, t_{57} = -2.60, p = .012, also significantly influenced MESOR of HR in the respective model. Study group was no longer a statistically significant predictor of MESOR of vmHRV, or Amplitude or Acrophase of vmHRV or HR, in adjusted univariate multiple linear regression models.

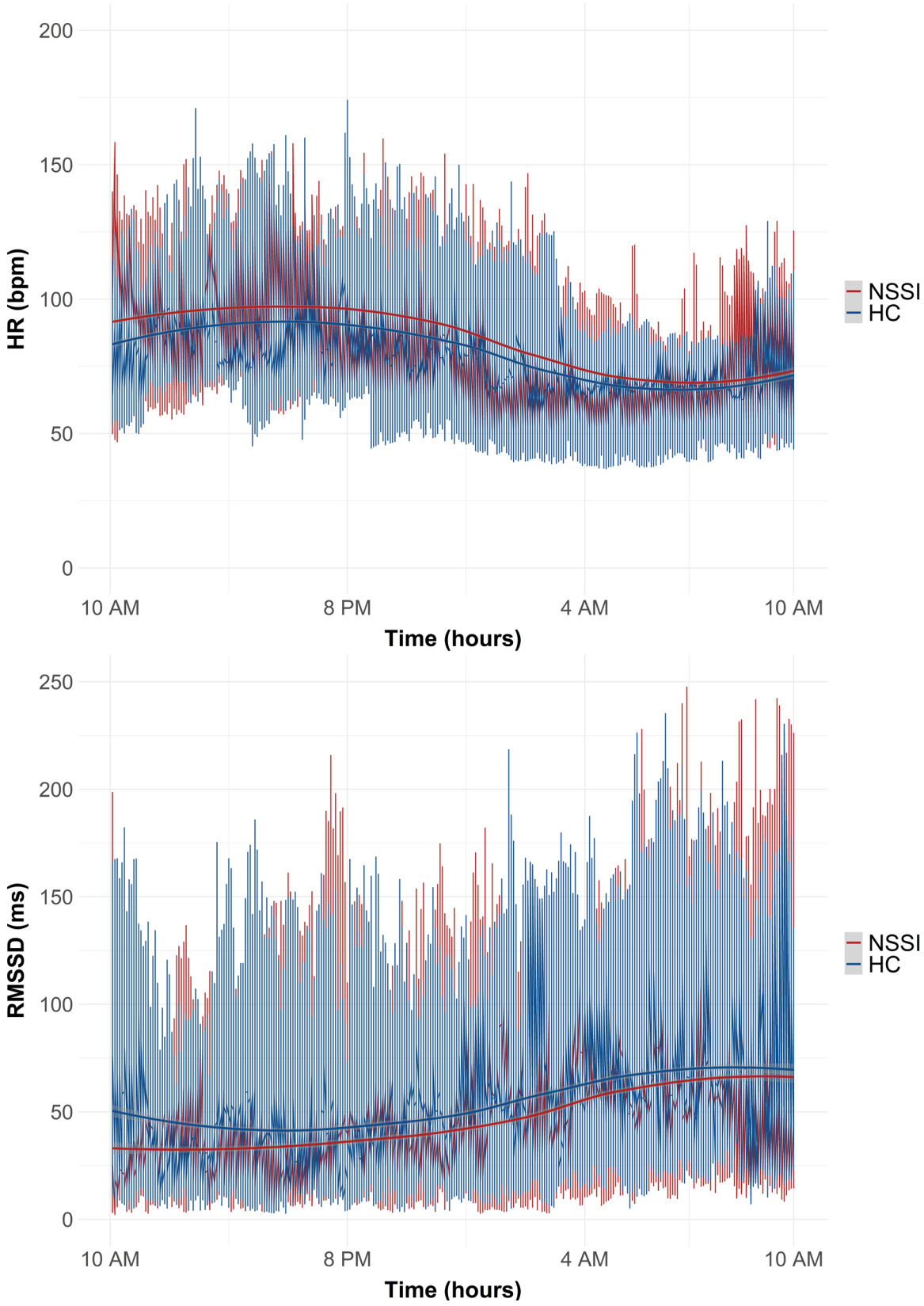

Figure 1. Visualization of 48-h cardiac autonomic data recordings split into 5-min segments of mean HR and HRV (collapsed to one circadian cycle), separated by study group.

Table 2. Descriptive information on population-mean cosinor parameters (separated by study group), respective model fit to the underlying data, and group comparisons.

							Cosinor Model Fit					
	NSSI			HC			NSSI		HC		NSSI vs. Controls		
	N	Pop. Mean	95% [CI]	*N*	Pop. Mean	Conf. Int.	F (DF^1, DF^2)	*p*-value	F (DF^1, DF^2)	*p*-value	*F*(FD1, DF2)	*t*(DF)	*p*-value
HR													
MESOR	29	85.98	81.74 – 90.22	30	79.44	76.14 – 82.74					6.27 (1, 57)		**.015**
Amplitude	29	12.42	9.26 – 15.56	30	12.30	10.43 – 14.17	39.87 (2, 27)	**<.001**	89.85 (2, 28)	**<.001**		-2.19 (57)	**.032**
Acrophase	29	-1.81	-2.04 –- 1.63	30	-1.56	-1.71 – -1.40					11.08 (1, 57)		**.002**
HRV													
MESOR	29	44.82	37.38 – 52.26	30	55.79	48.41 – 63.18					4.59 (1, 57)		**.036**
Amplitude	29	13.90	7.68 – 20.11	30	14.45	10.30 – 18.60	24.99 (2, 28)	**<.001**	10.35 (2, 27)	**<.001**		1.86 (57)	**.034**
Acrophase	29	-5.02	-5.33 – -4.75	30	-4.73	-4.90 – -4.57					5.69(1, 57)		**.021**

Note. HR = Heart Rate; HRV = Heart rate variability (RMSSD, ms); MESOR = Midline estimating statistic of rhythm.

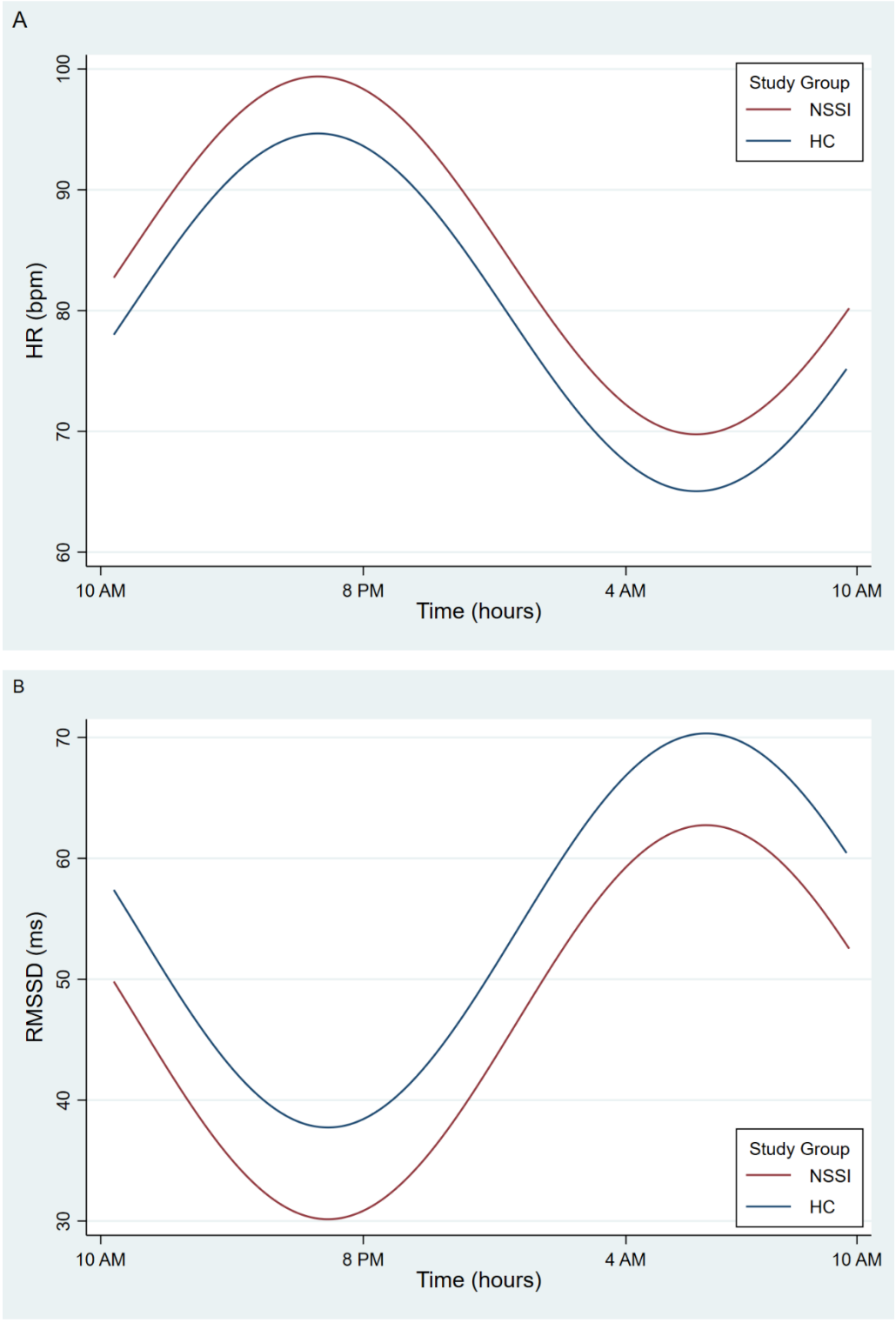

Figure 2. Illustration of the effect of study group on CVP of HR (A) and vmHRV (B). Differential rhythmicity analysis yielded statistically significant differences in MESOR, Amplitude, and Acrophase of both HR and vmHRV between study groups. Robustness of NSSI disorder as a clinical predictor of CVP against critical confounds was observed for HR, but not vmHRV.

3.2.2 Correlational analyses

Next, we were interested in examining a range of dimensional clinical variables as predictors of CVP of HR and vmHRV, either considering the NSSI group in isolation (i.e., NSSI frequency, and BPD symptoms) or the total sample (i.e., severity of ELM exposure, depressive symptoms, emotional dysregulation, and sleep hours). In preliminary correlational analyses using Spearman's ρ, we examined bivariate correlations between each of these clinical predictors of interest and the cosinor parameters MESOR, Amplitude, and Acrophase of HR and vmHRV. In *Supplementary Figure 2*, a heat map of the corresponding correlation coefficients, including bivariate correlations with potentially confounding factors (i.e., age, BMI, physical activity, and quality of cardiac data), is shown. A significant negative correlation was observed between sleep hours and MESOR of HR (Spearman ρ = -.33, p = .010), and MESOR of HR and step count (Spearman ρ = .30, p = .024). Amplitude of HR was significantly linked with quality of cardiac data (Spearman ρ = .36, p = .005). Regarding vmHRV, a significant association between Amplitude of vmHRV and step count was identified (Spearman ρ = .28, p = .032). No further predictor of interest was observed to be significantly linked with CVP in bivariate correlational analyses.

3.2.3 Multivariate linear regression results

In a final analytic step, examining the influence of each clinical predictor of interest on the cosinor parameters MESOR, Amplitude, and Acrophase of HR and vmHRV, as well as their robustness against potentially confounding factors (i.e., age, BMI, physical activity, and quality of cardiac data), we calculated both unadjusted (simple) and fully-adjusted (multiple) multivariate linear regression model. These models allowed us to consider the cosinor parameters MESOR, Amplitude, and Acrophase as outcome simultaneously in a single regression model, while we also considered their interdependencies.

3.2.3.1 Unadjusted multivariate linear regression models

In *Table 3*, full model results from multivariate simple linear regression models are shown. In line with the results from simple group comparisons (*Section 3.2.1* above and *Figure 2*), the variable study group was identified as a significant predictor of both MESOR and Amplitude of 24-h HR, and predicted significant differences in MESOR of 24-h vmHRV. Furthermore, the severity of ELM exposure was identified as a significant predictor of Amplitude of both 24-h HR and vmHRV (visualized in *Figure 3*). None of the remaining clinical predictors was significantly linked with CVP of HR and vmHRV in unadjusted multivariate regression models.

Table 3. Full results from multivariate single linear regression analyses (unadjusted models). The cosinor parameters MESOR, Amplitude, and Acrophase of HR and vmHRV, respectively, were considered as multivariate outcome.

		HR								**RMSSD**					
		N	*B*	95% [CI]	Std.	*z*	*p*			*N*	*B*	95% [CI]	Std.	*z*	*p*
MESOR	**Study Group**	**59**	**.62**	**.14 – 1.10**	**.25**	**2.55**	**.011**	MESOR	Study Group	**59**	**-.54**	**-1.03 - -.05**	**.25**	**-2.18**	**.028**
	NSSI Frequency	29	-.05	-.43 - .33	.20	-.25	.802		NSSI Frequency	29	-.08	-.43 - .26	.18	-.46	.643
	BPD Symptoms	29	-.06	-.51 - .40	.23	-.24	.811		BPD Symptoms	29	.08	-.33 - .49	.21	.37	.710
	ELM Severity	59	.15	-.09 - .39	.12	1.25	.212		ELM Severity	59	.25	.01 - .50	.14	-1.11	.268
	DIKJ	59	.14	-.09 - .37	.12	1.20	.230		DIKJ	59	-.14	-.41 - .12	-13	-1.06	.291
	DERS	59	.19	-.06 - .44	.13	1.49	.136		DERS	59	-.15	-.40 - .10	.13	-1.20	.230
	Sleep hours	59	-.23	-.48 - .02	.13	-1.79	.073		Sleep hours	59	-.08	-.34 - .17	.13	-.64	.521
Amplitude	**Study Group**	**59**	**-.55**	**-1.04 - .07**	**.25**	**-2.23**	**.026**	Amplitude	Study Group	59	.47	-.02 - .97	.25	.34	.736
	NSSI Frequency	29	.14	-.23 - .50	.19	.73	.467		NSSI Frequency	29	-.10	-.53 - .32	.22	-.47	.637
	BPD Symptoms	29	.22	-.21 - .66	.22	1.02	.307		BPD Symptoms	29	-.38	-.86 - .11	.25	-1.52	.129
	ELM Severity	**59**	**-.26**	**-.49 - -.04**	**.12**	**-2.29**	**.022**		ELM Severity	**59**	**.25**	**.01 - .50**	**.12**	**1.98**	**.048**
	DIKJ	59	-.14	-.39 - .11	.13	-1.08	.282		DIKJ	59	.21	-.05 - .47	.13	1.58	.114
	DERS	59	-.12	-.37 - .13	.13	-.92	.358		DERS	59	.10	-.15 - .36	.13	.81	.419
	Sleep hours	59	.13	-.13 - .38	.13	.96	.339		Sleep hours	59	-.14	-.40 - .12	.13	-1.08	.282

	Study Group	59	-.03	-.54 - .47	.26	-.13	.900		Study Group	59	.09	-.42 - .59	.26	.34	.736
	NSSI Frequency	29	.14	-.31 - .58	.23	.60	.548		NSSI Frequency	29	-.03	-.46 - .39	.22	-.14	.889
	BPD Symptoms	29	-.46	-.96 - .04	.26	-1.79	.073		BPD Symptoms	29	.13	-.37 - .63	.26	.51	.613
Acrophase	ELM Severity	59	.11	-.13 - .35	.12	.88	.377	Acrophase	ELM Severity	59	.03	-.23 - .30	.14	.28	.783
	DIKJ	59	.09	-.14 - .31	.12	.74	.460		DIKJ	59	-.04	-.30 - .22	.13	-.31	.756
	DERS	59	.01	-.25 - .26	.13	.03	.978		DERS	59	.01	-.24 - .27	.13	.10	.919
	Sleep hours	59	-.04	-.30 - .21	.13	-.34	.734		Sleep hours	59	.10	-.16 - .36	.13	.76	.447

Note. Standardized beta coefficients are reported. HR = Heart rate (bpm); vmHRV = vagally-mediated Heart rate variability (RMSSD, ms). MESOR = Midline estimating statistic of rhythm.

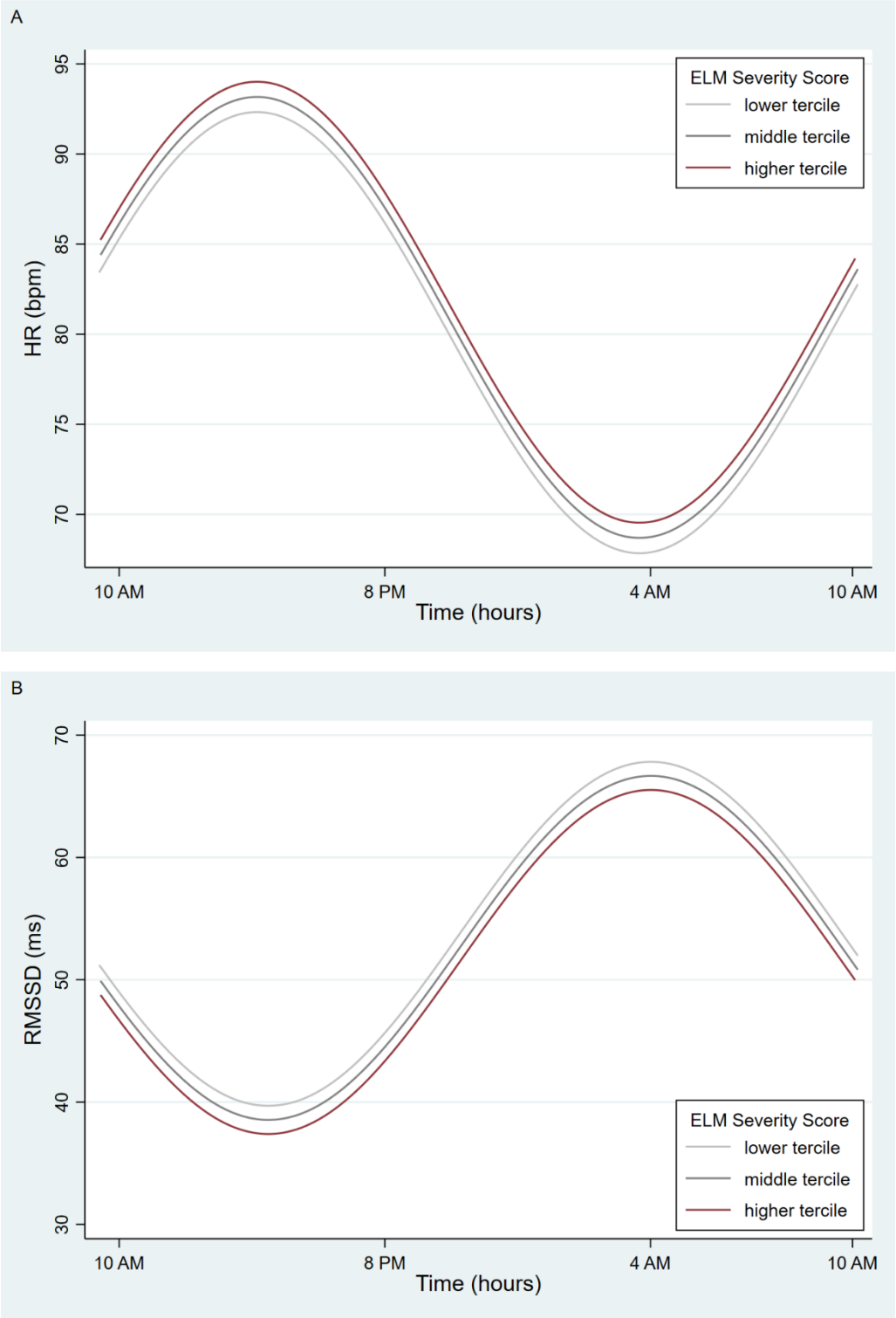

Figure 3. Illustration of the effect of ELM exposure severity on Amplitude of HR (A) and vmHRV (B). Multivariate simple linear regression models yielded a statistically significant influence of the severity of ELM exposure on Amplitude of both HR and vmHRV (which, after controlling for critical confounders, was no longer observed).

3.2.3.2 Fully-adjusted multivariate linear regression models

Results for significant predictors from multivariate multiple linear regression models are presented in *Supplementary Table 2*. After including the covariates age, BMI, step count, and cardiac data quality in the multivariate simple linear regression models, in line with univariate multiple regression results (*Section 3.2.1* above), the variable study group was still a significant predictor of MESOR of HR, while in the respective model, data quality significantly influenced all three cosinor parameters MESOR, Amplitude and Acrophase, BMI significantly influenced MESOR, and age the Amplitude, of 24-h HR. Group differences in MESOR of vmHRV or Amplitude of HR were no longer statistically significant, also in line with univariate multiple linear regression results. In fully-adjusted models, the variable BPD symptomatology (NSSI subgroup) additionally predicted Amplitude of 24-h HR (*Figure 4* below), while in the respective model, data quality again significantly influenced all three cosinor parameters MESOR, Amplitude and Acrophase, BMI significantly influenced MESOR, and age the Amplitude, of 24-h HR. None of the remaining clinical predictors was significantly linked with CVP of HR or vmHRV in these models.

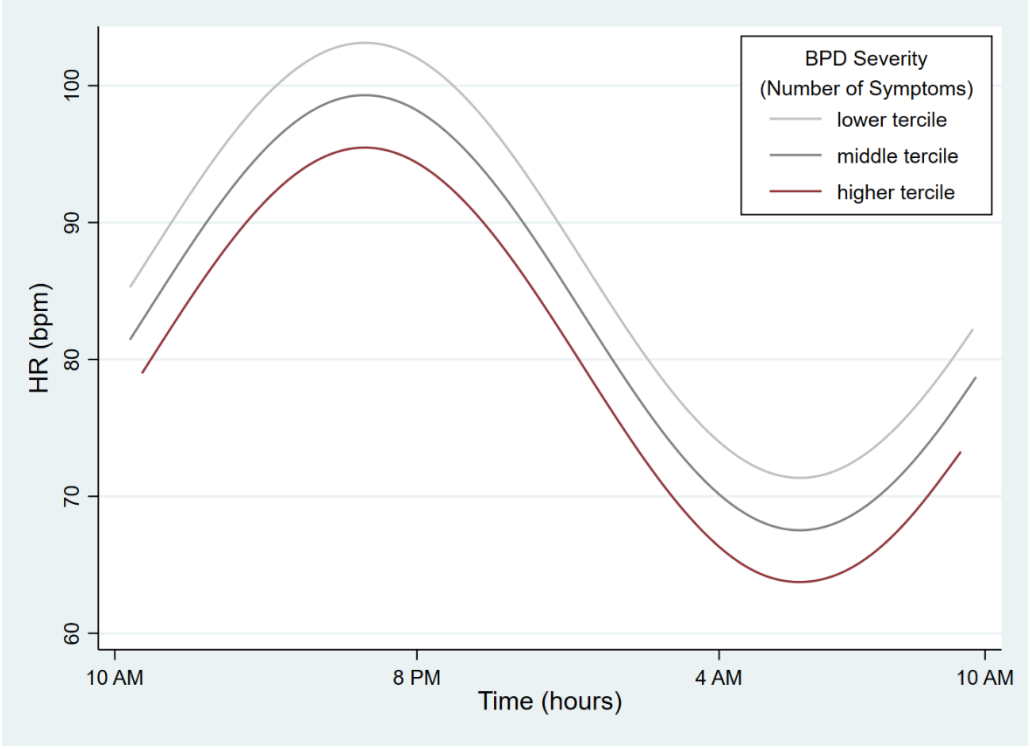

Figure 4. Illustration of the effect of BPD symptomatology on Amplitude of HR. Multivariate multiple linear regression (but not unadjusted) models yielded a statistically significant influence of the severity of BPD symptomatology on CVP of 24-h HR (Amplitude).

4. Discussion

While the investigation of the link between psychiatric symptoms and disorders and CVP of cardiac autonomic activity is an emerging field of interest, to the best of our knowledge, the present study is the first to investigate CVP of cardiac autonomic activity in association with psychopathology in adolescence. Our main findings provide insights concerning potential disruptions in the maturation of autonomic regulation associated with impairments in stress- end emotion-regulatory domains in adolescents. Furthermore, these findings have critical implications for the future conduct of chronobiological research in the field of child and adolescent psychiatry. Finally, the presented results highlight critical methodological aspects in the collection and analysis of long-term cardiac autonomic data in psychiatric samples, which will need to be addressed thoroughly through refinements of cardiac data collection and respective protocols for analysis.

As a main finding of the present study, by conducting differential analyses of CVP using cosinor-based rhythmicity analysis, we found significant differences in CVP of cardiac autonomic activity between female adolescents meeting diagnostic criteria for NSSI disorder and well-matched healthy controls. Within the present recoding period of 48 hours, the NSSI group showed significantly altered rhythm-adjusted mean levels of both 24-h HR and 24-h vmHRV compared to HC. Furthermore, significant alterations in Amplitudes, as well as a significant shift in Acrophases of both 24-h HR and vmHRV were observed in NSSI compared to HC. Amplitude of 24-h HR was significantly lower in NSSI, while Amplitude of 24-h vmHRV was significantly higher in the NSSI group compared to HC. Regarding both cardiac autonomic parameters, an Acrophase shift of approximately 1-h was observed, such that the NSSI group reached peak levels in both 24-h HR and vmHRV about 1 hour later. In chronobiological research, significant changes in Amplitude and Acrophase (*phase shift*) of circadian rhythm, commonly referred to as circadian rhythm disruption (Kirlioglu & Balcioglu, 2020), have been associated with increased risk for physical and psychiatric disorders (Baron & Reid, 2014). Relatedly, circadian disruption in the form of misalignment between the circadian system and daily sleep-wake behaviors were shown to adversely affect mood levels and cortical activity underlying mood regulation (Chellappa, 2020). Brain imaging studies suggest adolescence to present a sensitive period for brain maturation and particularly maturation of prefrontal regions, where dramatic changes on both structural and functional levels can be observed (Casey et al., 2008; Giedd et al., 1999; Koenig, 2020; Paus et al., 2008; Spear, 2000). Such changes might be linked with lower impulse control inhibition, poorer decision making in emotional context, greater risk-taking behavior, and heightened patterns of emotional instability in adolescence (Bailen et al., 2019; Casey et al., 2008). Evidence also suggests that adolescence is characterized by normative changes in the circadian rhythm of numerous physiological processes, affecting sleep-wake patterns and preference for chronotype (i.e., the underlying diurnal preference for evening vs. morning that shapes sleep timing and other behaviors) (Benard et al., 2015; Rumble et al., 2018). Physiologically-mediated shifts toward evening preferences,

in combination with earlier school start times in adolescence, and social factors such as athletic and other after-school activities, may contribute to irregular sleep schedules and a general mismatch between behaviors and circadian rhythms (Cespedes Feliciano et al., 2019). While sleep deprivation in adolescents has been associated with deficits in emotion regulation (e.g., Baum et al., 2015), there is substantial evidence that sleep problems such as disrupted sleep, poor sleep quality and shorter sleep duration increases risk of engagement in NSSI - and that such associations are particularly high among adolescents (Khazaie et al., 2020). Interestingly, the results of previous studies examining NSSI attendances in the accident and emergency department (Horrocks et al., 2003), as well as help-seeking female adolescents engaging in NSSI using high-frequency EMA (Koenig et al., 2020), suggest that NSSI is most frequently conducted in the evening hours - further highlighting a potential link with shifts towards evening preferences. Generally, prevalence rates of NSSI peak around mid-adolescence, while repetitive NSSI in adolescence is a strong risk factor for mental health problems in young adulthood (Daukantaitė et al., 2020). The present findings of both significantly altered Amplitude and significant phase shifts of cardiac autonomic activity in NSSI compared to HC align with previous studies in the field of chronobiology, and further corroborate circadian disruption as well as significant phase shifts in circadian rhythm as potential risk factors in adolescence. Currently, there is a substantial lack of studies that address disrupted circadian patterns in NSSI (Westlund Schreiner et al., 2015). Further insights into the neurobiology of circadian rhythms in adolescence and potential disruptions among vulnerable subgroups will therefore be important for the development of neurobiologically-based interventions that have the potential to restore affect regulatory processes and reduce the risk for more severe psychopathological outcomes in the long run.

The finding of a significantly lower MESOR (rhythm adjusted mean levels) of 24-h vmHRV and significantly higher MESOR of 24-h HR in NSSI compared to HC (and the relatively strong negative correlation between MESOR and Acrophase of vmHRV; r = -.70, p = <.001; *Supplementary Figure 2*), suggests chronically-low levels of autonomic vagal (parasympathetic) activity in NSSI relative to HC. As a basic presupposition of the presently underlying psychophysiological framework, the NIM (Thayer & Lane, 2000, 2009), shared neural circuits involved in the regulation of ANS activity and emotion form a functional overlap between autonomic arousal and emotion regulation. Essentially, in a recent principal outline and further elaboration of the NIM, the *dynamic model of neurovisceral integration in development* (Koenig, 2020), it has been suggested that the functional interaction of the ANS and CNS is shaped early in the course of life, and that adolescence might represent the most sensitive period in development of this circuitry (Koenig, 2020). In normative development, vagal influence over cardiac autonomic activity is assumed to increase, indexed by normative decreases in HR and increases in vmHRV, respectively. ANS maturation, in turn, is assumed to be critical for patterns of PFC maturation and associated regulatory capacities over sub-cortical regions to emerge, affecting stress and emotion regulation (Koenig, 2020). Chronically-low vmHRV and high HR,

respectively, as observed over 24-h in the present group of female adolescents with NSSI disorder compared to HC, might reflect a relative absence of normative ANS maturation. ANS dys-maturation, in turn, might further reflect disruption in developmental patterns of PFC maturation (i.e., *cortical thinning*) (Koenig, 2020) linked with heightened sensitivity to stressors, maladaptive coping, and increased risk for psychopathology in the present sample.

We examined the influence of a range of dimensional clinical predictors on CVP of cardiac autonomic activity in the present sub-sample of female adolescents with NSSI disorder (i.e., NSSI frequency and BPD symptomatology), and the total sample of NSSI and HC (i.e., ELM exposure, depressive symptoms, emotional dysregulation, and sleep duration), using multivariate simple linear regression models. Of the respective clinical predictors examined, only ELM exposure showed significant associations with CVP of 24-h HR and vmHRV, such that higher severity of ELM exposure was linked with significant alterations in the Amplitudes of both HR and vmHRV. In participants reporting higher severity of exposure to the ELM subtypes as presently assessed (i.e., emotional neglect and/ or abuse by primary caregivers, parental physical abuse, sexual abuse by any adult before age 17) a significantly lower oscillation in 24-h HR and respective higher oscillation in 24-h vmHRV were observed, in accordance with the effects of the presence of NSSI disorder. Among potential antecedent factors of a disruption of ANS-CNS co-maturation in development (Koenig, 2020), analogously to potential disruption in other stress-regulatory systems such as the HPA-axis (Bunea et al., 2017; Schär et al., *under review*), exposure to severe stressors early in live has been discussed. The present results of a potential influence of ELM exposure on CVP of 24-h HR and vmHRV in adolescents may support the notion that such early and adverse environmental influences might critically affect the development of neurobiological endophenotypes (Teicher & Samson, 2013), in particular during sensitive periods of development, critically affecting ANS maturation (Koenig, 2020). A previous study investigating the effects of ELM exposure on volumes of key stress- and emotion-associated brain structures (i.e. the amygdala, hippocampus, and anterior cingulate cortex) as pre-defined regions of interest, identified both amygdala and hippocampal volume to be affected by ELM severity during a period covering pre-adolescence and early adolescence, while according effects were driven by the severity of the ELM subtype of neglect (Herzog et al., 2020). Various physiological and neural systems associated with stress and emotion regulation (i.e., limbic brain regions, or the HPA axis – and essentially also the ANS) are under circadian regulation, and circadian disruption of these systems might be a critical patho-mechanism involved in the etiology of disordered stress and emotion regulation, increasing the risk for psychopathology (Kirlioglu & Balcioglu, 2020; Walker et al., 2020). Clearly, how early severe stress exposure might affect CVP of cardiac autonomic activity and other stress-regulatory systems should be addressed in future large-scale studies, recruiting samples characterized by varying degrees of severity of ELM exposure and psychopathology, and by differing developmental periods and age groups.

The influence of potential confounders is a critical yet often neglected aspect in research examining cardiac autonomic activity as predictor or outcome of interest. A potentially confounding factor that is relevant in the context of the present study is the influence of physical activity on markers of cardiac autonomic activity. Firstly, it had been reported previously that physical activity has hardly ever been controlled for in studies of ambulatory ECG recordings (Verkuil et al., 2016). Furthermore, considering the synchronization of an individual's endogenous rhythm of physiological regulation processes (including ANS activity) to the external world, besides the presence of environmental input-light, third factor variables are likely to influence this synchronization process, including physical activity (Kirlioglu & Balcioglu, 2020). As a further critical confounder, while the number of studies examining potential associations between cardiac autonomic measures and clinical variables has increased exponentially over the last decade, relevant aspects in ECG methodology, such as the quality of cardiac data recordings, have merely been considered. Crucially, in the present sample of female adolescents, we observed significant differences in the duration of non-wear time of the cardiac data collection device and resulting differences in the amount of cardiac data available for further analysis, such that for the NSSI disorder sub-group, the amount of available cardiac data was significantly reduced compared to HC (*Table 1*). We therefore aimed to examine the robustness of clinical predictors of CVP of cardiac autonomic activity against these critical confounders, by performing both unadjusted and fully-adjusted analyses (included age, BMI, physical activity, and cardiac data quality as covariates), to further highlight the importance to consider these factors during data collection and analysis.

First, examining the robustness of significant group differences between NSSI and HC in CVP of cardiac autonomic activity identified in rhythmicity analyses revealed that only rhythm adjusted mean-levels of 24-h HR, but not any of the other outcome parameters of interest, was still significantly altered in NSSI compared to HC after inclusion of age, BMI, physical activity, and data quality in the respective univariate linear regression models. Of note, besides study group, both the variables BMI and data quality significantly influenced MESOR of 24-h HR in the respective model. Furthermore, data quality, besides MESOR, also significantly predicted Amplitude and Acrophase of 24-h HR, as well as Acrophase of 24-h vmHRV, and thus presented a rather consistent confounder. In subsequently conducted multivariate simple linear regression models, considering fully-adjusted models, again, study group significantly predicted MESOR of 24-h HR, but not any other CVP parameter of HR or vmHRV. Furthermore, ELM exposure was no longer a significant predictor of CVP of HR or vmHRV in adjusted multivariate models, while BPD symptomatology significantly predicted the Amplitude of 24-h HR. These findings underline the importance for future neurobiological studies to rigorously assess and control for potential covariates of autonomic and clinical variables of interest, while special attention should be paid to issues of quality of cardiac autonomic data. Especially in the examination of adolescent psychiatric samples, additional measures to increase wear-time of ambulatory devices and

to ensure high quality of cardiac data recordings should be introduced, as such factors may critically influence study results.

Importantly, while previous studies in adults and non-human primates substantiated potential alterations in CVP of cardiac autonomic activity in association with depressive symptoms and disorders, as well as with difficulties in emotion regulation in the context of BPD (Jarczok et al., 2018; Jarczok et al., 2018; Verkuil et al., 2015; Wainsztein et al., 2020), in the present study of female adolescents with and without NSSI disorder, we did not find significantly altered CVP of HR or vmHRV in association with depressive symptoms or emotion dysregulation. Of note, previous studies examining the association of CVP of cardiac autonomic activity with depressive symptoms (Jarczok et al., 2018; Verkuil et al., 2015) did not recruit psychiatric samples but included relatively healthy adults. Furthermore, the only study examining CVP of cardiac autonomic activity in clinical populations of psychiatric patients again recruited adults, and furthermore, a fairly different analytical approach was taken: While we and others (Jarczok et al., 2018) used cosinor to derive parameters of circadian rhythmicity (as suggested in recent recommendations (Jarczok et al., 2019), in the aforementioned study (Wainsztein et al., 2020), in the circadian analysis, ECG recordings were segmented in 30-min epochs and averaged according to the sleep or wake periods, allowing to examine associations of clinical variables with mean-level during these two periods, as well as with mean-level differences between sleep and wake periods, while no inferences regarding the range of oscillation or potential phase shift can be made. Thus, the results of previous studies not readily be comparable to the findings of the study at hand, recruiting a high-risk sample of female adolescents with and without NSSI disorder and conducting designated rhythmicity analyses.

The presented results must be considered within the context of the limitations inherent to the study at hand. One important limitation is that the present data were measured only cross-sectionally, making it impossible to draw inferences about the directionality of findings. Furthermore, several remarks should be made about the recruited sample: Firstly, our sample consisted of female adolescents with and without NSSI disorder, therefore, results and implications drawn from our study cannot be generalized to adolescents characterized by other psychiatric conditions, or to male adolescents. While it has been suggested that females more frequently engage in NSSI compared to males (Barrocas et al., 2012), other studies have substantiated that this might not necessarily be the case (Klonsky & Muehlenkamp, 2007). Future studies should be conducted that reflect more recent advents in the study of NSSI including both male and female populations, and consider further sub-groups characterized by developmental psychopathology. Furthermore, besides the presently included covariates, there might be a range of further variables that could equally influence cardiac autonomic function, including puberty status, menstrual cycle, psychotropic medication, and alcohol, nicotine, or caffeine consumption (Lesnewich et al., 2019; Licht et al., 2010; Quintana et al., 2016; Schmalenberger et al., 2019; Schmalenberger et al., 2019; Vloet et al., 2019). Of note, one previous study assessed potential

covariates such as consumed units of tobacco, coffee, and alcohol on an hourly basis (Verkuil et al., 2015), which from a methodological perspective potentially presents a highly valuable approach. Future studies should more rigorously measure and control for potential confounders, to further substantiate the validity and credibility of results (for current guidelines, see e.g., (Camm et al., 1996; Quintana et al., 2016; Quintana & Heathers, 2014). Previous research substantiated significant associations between sleep problems and lower daytime HRV in both children (Michels et al., 2013) and adults (Jackowska et al., 2012) (whereby in the latter, HRV during nighttime was not significantly affected by sleep problems), as well as a significant association of irregular sleep patterns with increased HR and decreased HRV in healthy adolescents (Rodríguez-Colón et al., 2015). Also, a previous longitudinal study found poor sleep (self-reports "to never or seldom sleep well") to be associated prospectively with incident NSSI among adolescent females, but not males (Lundh et al., 2013). Alterations in sleep-derived heart rate patterns in MDD were furthermore associated with sleep disturbances (Kwon et al., 2019; Pawlowski et al., 2017; Saad et al., 2019, 2020). In previous studies, the melatonergic system, with effects on sleep pattern, as well as the HPA axis has been described as commonly disrupted neurobiological mechanisms related to the circadian rhythm in psychiatric disorders (Kirlioglu & Balcioglu, 2020). While NSSI disorder might be associated with sleep disruptions (Westlund Schreiner et al., 2015), in the present study, we did not find statistically significant differences in sleep duration derived from acceleration data between study groups, nor was the duration of sleep a significant predictor of CVP of cardiac autonomic activity in multivariate analyses (of note, however, in correlational analyses we found sleep duration to be significantly linked with rhythm-adjusted mean levels of 24-h HR). Future studies concerned with autonomic measures and their circadian variation in adolescent NSSI should measure sleep, both objectively and subjectively, to simultaneously explore and also control for associations between sleep and patterns of variation of physiological regulatory systems. Future studies might investigate how CVP, along with potential sleep disruption, independently and together, may affect the development of NSSI, and whether interventions that target these systems might be clinically beneficial. In the literature pertaining to cosinor analysis, it has been pointed out that, particularly when sampling is performed on more than one single individual, it is important that they are synchronized (Cornelissen, 2014). Such synchronizers represent environmental periodicities that determine the temporal placement of biological rhythms, however, synchronization of biological rhythms might not be achievable under a naturalistic study setting, which again highlights the importance of rigorous assessment and statistical control of influential factors. As a further limitation of the present study, while we aimed to control for physical activity as a confounder in our statistical analyses, we used step count, assessed during the same 48-h time period where cardiac data were collected, as a measure of physical activity. In line with previous studies of ambulatory ECG measurements (e.g., (Janz et al., 1992), in bivariate correlational analyses we found a significant positive association between step count and rhythm-adjusted mean levels of 24-h HR. Furthermore, a small negative (but non-significant) association of step count with MESOR of vmHRV was observed.

In contrast, general physical activity levels (physical fitness), might be assumed to show opposite relationships with HR and vmHRV levels, such that higher general physical activity may predict lower mean HR and higher mean vmHRV levels (e.g., Gutin et al., 2005; Oliveira et al., 2017). Future studies of ambulatory ECG measurements examining or controlling for the influence of physical activity levels on HR and vmHRV measures should therefore consider both general and immediate levels of physical activity in the collection and analysis of cardiac autonomic data.

5. Conclusion

The present findings of circadian rhythm disruption in cardiac autonomic activity in NSSI disorder highlight the importance of neurobiological research concerned with the physiology and pathology of circadian rhythmicity in the etiology of psychiatric illness, and with potential disruption of the circadian system in clinical high-risk populations. The present study revealed a significant difference in CVP of cardiac autonomic activity in female adolescents with NSSI disorder compared to healthy controls, characterized by significantly increased and decreased rhythm adjusted mean levels of 24-h HR and vmHRV, significant alterations in respective Amplitudes, and significant phase shifts. Furthermore, significant associations of ELM exposure severity and BPD symptomatology with specific components of CVP of cardiac autonomic activity were identified. Determining whether different components of the circadian system might interact in their association with psychopathological conditions including NSSI, and whether chronobiological interventions might prevent or ameliorate engagement in NSSI, might present important translationally relevant avenues of future research. Furthermore, the role of antecedent factors, such as early severe stress exposure, on CVP of stress-regulatory systems warrants further investigation. Finally, future studies should introduce measures to ensure high quality of cardiac autonomic data recordings especially in adolescent psychiatric populations, and should more rigorously control for further potentially confounding factors. In sum, the present results further underline that in the investigation of psychiatric disorders and the development of appropriate treatment strategies, special attention should also be paid towards the physiology and pathology of physiological systems and processes subjected to circadian rhythms.

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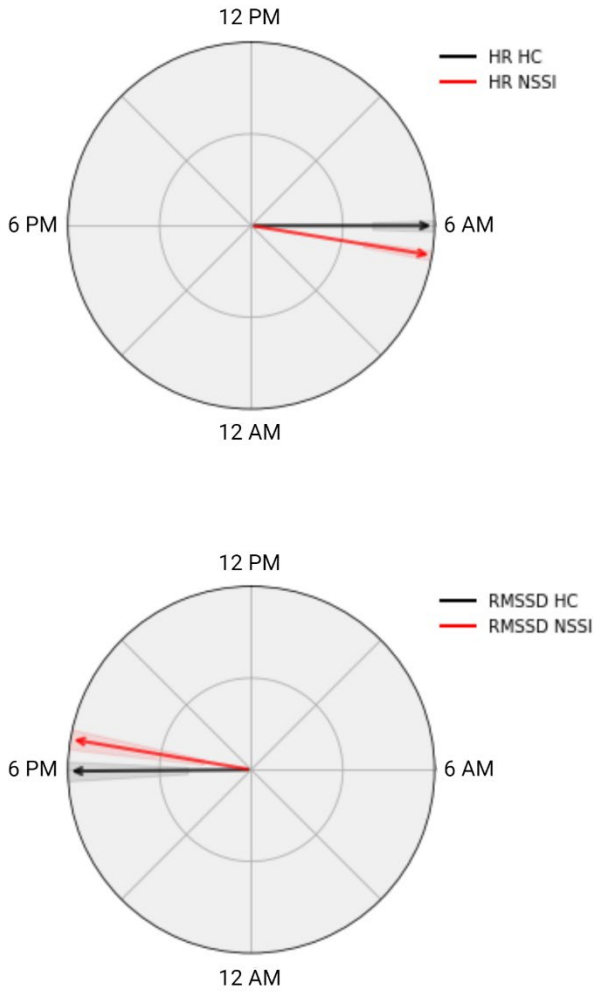
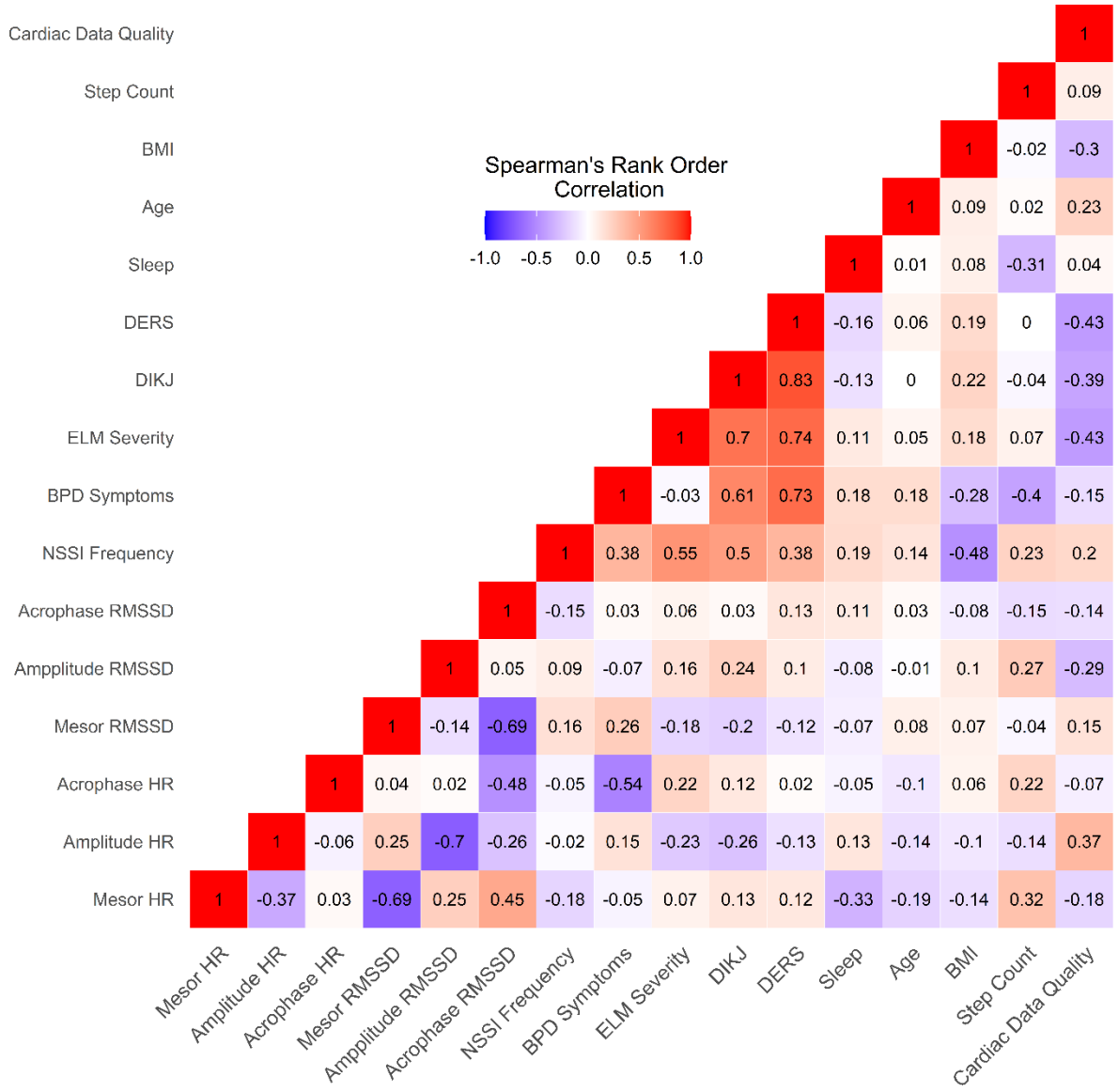
Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data



Supplementary Figure 1. Visualization of Acrophase shifts in HR (top) and vmHRV (bottom) between study groups (differential rhythmicity analysis). Acrophase was shifted significantly with clock time in the NSSI compared to the HC group.



Supplementary Figure 2. Heat map of Spearman's Rank Order Correlation Coefficients (Spearman's ρ) between cosinor parameters of HR and vmHRV, clinical predictors, and potential confounders.

Supplementary Table 1. Summary statistics of single (individual-level) cosinor parameters of HR and vmHRV by study group.

	NSSI (*N* = 30)			Controls (*N* = 30)		
HR	*N*	M (SD)	Min – Max	*N*	M (SD)	Min - Max
MESOR	29	85.98 (11.14)	68.97 – 119.66	30	79.44 (8.83)	54.24 – 96.10
Amplitude	29	-2.91 (5.74)	-15.11 – 7.47	30	.17 (5.05)	-10.55 – 8.18
Acrophase	29	12.07 (8.85)	-15.57 – 23.57	30	12.30 (5.02)	4.68 – 26.06

	NSSI (*N* = 30)			Controls (*N* = 30)		
vmHRV	*N*	M (SD)	Min – Max	*N*	M (SD)	Min - Max
MESOR	29	44.82 (19.55)	12.16 – 97.17	30	55.79 (19.77)	32.46 – 97.15
Amplitude	29	4.20 (9.78)	-9.30 – 34.61	30	.28 (6.02)	-9.94 – 15.19
Acrophase	29	-13.25 (16.27)	-47.37 – 22.13	30	-14.45 (11.13)	-36.73 – 4.58

Note. HR = Heart rate (bpm); vmHRV = vagally-mediated Heart rate variability (RMSSD, ms). MESOR = Midline estimating statistic of rhythm.

Supplementary Table 2. Fully-adjusted multivariate multiple linear regression model results for significant clinical predictors of CVP of ANS activity. The cosinor parameters MESOR and Amplitude of HR were significantly influenced by the variables study group and BPD symptomatology, respectively.

							HR							
		N	*B*	95%[CI]	Std.	*z*	*p*		*N*	*B*	95%[CI]	Std.	z	*p*
MESOR		59							29					
	Study Group		**.57**	**.11 – 1.04**	**.24**	**2.41**	**.016**		BPD	-.12	-.51 – .26	.20	-.63	.529
	No. Segments		**-.33**	**-.57 – -.10**	**.12**	**-2.75**	**.006**		**No. Segments**	**-.47**	**-.77 – -.17**	**.15**	**-3.03**	**.002**
	Step count		.16	-.06 - .39	.11	1.45	.147	MESOR	Step Count	.11	-.17 – .39	.14	.75	.451
	Age		-.13	-.35 - .09	.11	-1.20	.232		Age	-.36	-.75 – .03	.20	-1.82	.069
	BMI		**-.42**	**-.71 - -.14**	**.15**	**-2.90**	**.004**		**BMI**	**-.45**	**-.79 – -.11**	**.17**	**-2.58**	**.010**
Amplitude	Study Group		-.32	-.85 – .21	.27	-1.21	.233		**BPD**	**.43**	**.06 – .81**	**.19**	**2.26**	**.024**
	No. Segments		**.32**	**.07 - .58**	**.13**	**2.52**	**.012**		**No. Segments**	**.51**	**.22 – .81**	**.15**	**3.43**	**.001**
	Step count		-.13	-.37 – .01	.12	-1.12	.264	Amplitude	Step count	-.05	-.32 – .22	.14	-.35	.726
	Age		**-.26**	**-.49 – -.03**	**.12**	**-2.21**	**.027**		**Age**	**-.42**	**-.80 – -.05**	**.19**	**-2.20**	**.028**
	BMI		.07	-.23 – .37	.15	.45	.652		BMI	.13	-.20 – .46	.17	.77	.440
Acrophase	Study Group		.15	-.39 – -69	.27	.55	.587		BPD	-.19	-.63 – .25	.22	-.84	.401
	No. Segments		**.45**	**.19 – .71**	**.13**	**3.45**	**.001**		**No. Segments**	**.63**	**.29 – .98**	**.18**	**3.61**	**<.001**
	Step count		.18	-.05 – .42	.12	1.51	.130	Acrophase	Step count	.12	-.20 – .44	.16	.75	.453
	Age		-.24	-.37 – .10	.12	-1.16	.247		Age	-.20	-.64 – .25	.23	-.87	.386
	BMI		.24	-.07 – .54	.16	1.51	1.31		BMI	.32	-.07 – .70	.20	1.60	.110

Note. No. segments = Number of 5-min segments of cardiac data available per participant. Standardized beta-coefficients are reported. MESOR = Midline estimating statistic of rhythm.

3. Discussion

3.1 Implications

To recapitulate, the *dynamic model of neurovisceral development* assumes that ANS maturation, characterized by a (non-linear) increase in vagal activity starting in early childhood, and continuing throughout adolescence, is tightly linked with ER capacities. A lack of the organism to promote sufficient ANS maturation during sensitive neurodevelopmental periods is assumed to be linked with insufficient maturation of prefrontal brain regions further involved in ER, resulting in emotion dysregulation, increased vulnerability, and an associated risk for the development of psychopathology. In the respective model, exposure to severe forms of ELS are discussed as one potential antecedent factor contributing to abnormal brain and ANS maturation. This notion is supported by related strands of neurodevelopmental research, including the three-hit concept of vulnerability and resilience (Daskalakis et al., 2013) aiming to provide an explanatory model for the neurodevelopmental consequences of exposure to severe ELS. Both the *dynamic model of neurovisceral development* and the three-hit concept of vulnerability and resilience assume that potential consequences - as a result of early adversity exposure - can range from heightened vulnerability and disease risk on the one end, to resilience based on protective factors on the other end of a continuum.

3.1.1 Meta-Analysis

As part of the present thesis, the relationship between ELM exposure as one potential precursor of impaired socio-emotional development and ANS dys-maturation, with vagal activity indexed by resting-state HRV, has been addressed in a comprehensive meta-analytic study. The aggregation of primary studies available at the time, and identified during the systematic search process, did not reveal a general association of ELM exposure with vagal activity in principal. Yet, in meta-regression, several factors were identified to significantly moderate the respective relationship, of which the factors of age and the presence of psychopathology might be particularly relevant. These meta-analytic main findings of no association between ELM exposure and vagal activity in general, but in interaction with the moderators *age* and *presence of psychopathology* can be interpreted in line with certain assumptions put forth in the *dynamic model of neurovisceral integration in development*.

The present meta-analysis provides an aggregation of studies assumed to present a representative sample of available studies on the relationship between ELM exposure and vagal activity. Given that the resulting consequences of the influence of ELM exposure on a range of developmental mechanisms, including ANS maturation, is assumed to vary on a continuum ranging from heightened vulnerability (decreased vagal activity) to resilience (increased vagal activity), such aggregation may plausibly result in an overall non-significant effect. While in some individuals (and population

samples), ELM exposure resulted in ANS dys-maturation linked with relatively low vagal activity (decreased resting-state HRV), in others, the presence of protective factors from the influences of ELM might have affected ANS maturation to proceed normatively, resulting in a normative increase of vagal activity in development (normal to relatively high resting-state HRV). The finding of a significant association between ELM exposure and vagal activity in samples characterized by ELM exposure and psychopathology, as compared to ELM-exposed samples without psychopathology, may support this notion. Those individuals with sufficient ANS maturation indexed by high vagal activity and thus relatively high resting-state HRV, even though exposed to ELM, might be those more resilient in terms of psychopathological outcomes, while those individuals exhibiting insufficient ANS maturation in association with ELM exposure, indexed by relatively decreased HRV, might be those who continued to develop some form of psychopathology. The finding of age as a significant moderator, such that the assumed relationship between ELM exposure and relatively decreased vagal activity was more likely observed in study samples of higher mean age, might also be explained within the present framework. The periods of childhood and adolescence in particular are assumed to be marked by a high degree of inter-individual variability even in normative physiological development (Koenig, 2020), such that ANS dys-maturation might become visible only at older age. Strong inter-individual differences in the development and respective pace of physiological regulatory systems may be observed, effected by diverse influences. As a result, during the developmental periods of childhood and adolescence, relative alterations in resting-state markers of ANS activity in association with ELM exposure might be obscured by large inter-individual variance. The assumed associations may become evident only after full maturation of the ANS, at which state inter-individual differences might be inherently smaller and potential differences or alterations more obvious on a group level. Of note, given the merely correlational nature of the present findings on which these assumptions are based, further research enabling causal inferences is clearly needed. Ideally, such research would comprise large-scale studies that aim to assess longitudinally the interrelations between antecedent genetic and environmental factors, ANS maturation during sensitive developmental periods, and resulting inter- and intra-individual differences in vulnerability and resilience over the later life course.

3.1.2 Prediction of Treatment Outcome

In a preliminary experimental psychotherapy study, an adolescent sample characterized by less and more severe manifestations of BPD symptomatology recruited at a specialized outpatient clinic for adolescent risk-taking and self-harm behavior was investigated. At pre-treatment (non-standardized out- and/ or inpatient treatment), ANS functioning was measured during standardized psychosocial stress exposure, and examined as potential predictor of treatment outcome over two years. VmHRV assessed during a (pre-stress) resting-condition, as well as vmHRV recovery values after, but not reactivity values in response to, standardized psychosocial stress exposure significantly predicted

clinical improvement over time, while improvement was defined as reductions in a summary score composed of three individual outcome measures (a methodological issue, that will be addressed in Section 3.2). The finding of resting-state vmHRV as significant predictor of treatment outcome over time replicated the results of previous studies in adult samples as well as a study in adolescent BPD. This finding might align well with the here proposed framework: Relatively higher values of resting-state vmHRV indicate higher vagal activity, further assumed to reflect better ANS and maturation of prefrontal regions, associated with higher physiological and psychological adaptability and flexibility to change (Thayer & Lane, 2000; 2009; Koenig, 2020). This might imply that vagal activity could present some sort of indicator of the momentary capability or capacity of the organism (individual) to enter a process of change as conveyed in psychotherapeutic treatment, mediating the amelioration of psychopathological symptoms. Findings that vagal activity over time (and over psychotherapeutic treatment) might be associated with the course of clinical symptomatology and general functioning in adolescent BPD and NSSI (Koenig et al., 2018; Weise et al., 2020) might support this notion. Interestingly, higher psychological flexibility has recently been identified as a predictor of higher responsivity to psychotherapeutic treatment (Åkerblom et al., 2021; Brandon et al., 2021). VmHRV as an index of vagal activity might be used as a marker of the "readiness" to immediately profit from psychotherapeutic treatment. In case of relatively low vmHRV, interventions to specifically target psychological flexibility (vmHRV), including e.g., specific components of Acceptance and Commitment Therapy (ACT), biofeedback, transcutaneous vagus nerve stimulation (tVNS), or pharmacological treatment administered before the initiation of the psychotherapeutic process, might then be used to benefit patients' treatment responsivity. The potential clinical benefits of monitoring and targeting cardiac vagal activity before initiating psychotherapeutic treatment might therefore provide valuable avenues of future research.

The present finding that vmHRV recovery might present a significant predictor of treatment outcome in adolescent BPD is a novel finding. Higher values in measures of vagal recovery (re-increases to resting-state levels) after psychosocial stress exposure could similarly present a measure of more adaptive forms of ANS flexibility. This might similarly be associated with better responsivity to psychotherapeutic treatment, and better clinical recovery. Arguably, in order to observe higher values of cardiac vagal recovery, cardiac vagal reactivity must also be high. Yet, values of cardiac vagal reactivity were not identified to significantly predict treatment outcome over the course of two years in the present thesis. Potentially noteworthy, ANS reactivity might not clearly be interpreted as either adaptive or maladaptive forms of ANS flexibility in the context of psychosocial stress exposure. In other lines of psychophysiological research, higher values in measures of cardiac vagal reactivity to psychological stress exposure have been interpreted as potentially detrimental to health. Longstanding evidence suggests that individuals who exhibit large-magnitude cardiovascular reactions to psychological stress are at elevated risk for clinical and preclinical cardiovascular disease (CVD)

outcomes (Balanos et al., 2010; Carroll et al., 2009; Obrist, 1981; Sherwood et al., 1986; Turner & Carroll, 1985). In physiological research, cardiovascular responses during acute psychological stress exposure, that is, stress that might not actually require physical exertion, has been considered as "metabolically inappropriate", suggesting that the cardiovascular system is working in excess of metabolic demand (Turner & Carroll, 1985). In these lines of research, repeated and cumulative metabolically-disproportionate, stressor-evoked, cardiovascular reactions are assumed to contribute to, or exacerbate, pathophysiological mechanisms, which in vulnerable individuals might be conductive of CVD risk and outcomes (Ginty et al., 2017). Stressor-evoked cardiovascular reactions are assumed to result from both intermediate changes in sympathetic and parasympathetic as well as HPA axis activity (outflow) to the heart and vasculature, influencing cardiovascular parameters (such as, e.g., cardiac output, or peripheral vessel resistance) to redirect blood flow according to momentary or anticipated behavioral needs (Ginty et al., 2017). Autonomic dysregulation is however thought to underlie a substantial part of risk for CVD and increased mortality (Nemeroff & Goldschmidt-Clermont, 2012; Thayer et al., 2010). Psychiatric disorders characterized by emotional dysregulation, such as depressive disorders, have been associated quite consistently with CVD, and are assumed to increase CVD risk (Kemp & Quintana, 2013; Pan et al., 2011; Schmitz et al., 1999). In the context of the dynamic model of neurovisceral integration in development, developmental disruption of ANS-CNS co-regulation might be assumed to result in both disordered emotion regulation, and increased CVD risk. Future research might focus on the potential role of developmental disruption of ANS-CNS co-regulation as a shared patho-mechanism causally involved in the etiology of both disordered ER and CVD.

3.1.3 Circadian Variation of Cardiac Autonomic Activity

The discovery of the central molecular mechanism of circadian rhythm presents a remarkable scientific milestone in the field of chronobiology, which has essentially resulted from research dating back to the early 1970s, conducted in fruit flies (Konopka & Benzer, 1971). In 2017, the researchers Jeffrey C. Hall, Michael Young, and Michael Rosbash received the Nobel Prize in Physiology and Medicine for their explanatory findings of molecular mechanisms of circadian rhythm control (Huang, 2018) and their genetic model revealing the generator of an autonomous internal oscillator is still used to understand circadian cycles. Based on the aforementioned groundwork, a large number of studies revealed that a broad range of cell types in the brain and peripheral organs contain biologic clocks, raising important questions regarding the specific functions of circadian rhythm and their respective contribution to illnesses (Kirlioglu & Balcioglu, 2020).

Of particular relevance for this thesis, chronobiological research has revealed that circadian rhythms in peripheral organ systems, and their associations with other physiological and metabolic mechanisms as well as with the master circadian pacemaker, the suprachiasmatic nucleus (SCN), are essential in terms

of both physical and mental health (Kirlioglu & Balcioglu, 2020). Affective disorders have quite consistently been associated with disruptions in circadian clock-controlled systems including the sleep-wake cycle and cortisol secretion, while vice versa, disruption of circadian rhythms oftentimes precipitate or exacerbate symptoms of affective disorders, especially in susceptible individuals (Bedrosian & Nelson, 2017; W. H. Walker et al., 2020b). Evidence therefore suggests a bidirectional relationship between the circadian system and psychiatric disorders. Notably, various physiological and neural systems associated with affective regulation (e.g., limbic brain regions, or the hypothalamic-pituitary-adrenal axis – and essentially also the ANS) are under circadian regulation (Harbour et al., 2011; Li et al., 2013; Oster et al., 2006; Schade et al., 1995; Sleipness et al., 2007; Walker et al., 2020). Existing research on the association between disruptions of the circadian system and psychiatric disorders has previously focused on the melatonergic system and its effect on sleep pattern, on the HPA axis, and on gene polymorphisms in circadian rhythm genes (Benedetti et al., 2003; Lee et al., 2010; Takao et al., 2007).

Potential associations between CVP of ANS activity and physical and mental health disparities have only very recently come into focus. Research in adults and animal models so far aligns with research focusing on circadian disruption of other physiological regulatory systems, in that quite consistent associations between affective symptoms and disorders and altered CVP of ANS activity have been identified. The aspect of circadian rhythmicity underlying cardiac autonomic activity, and potential alterations of the circadian rhythm of ANS activity in association with affective disorders and disordered ER, might have relevant implications for the psychophysiological framework underlying this thesis, where aspects of CVP of ANS activity have so far not been incorporated. As mentioned previously, as a basic presupposition of the NIM (Thayer & Lane, 2000, 2009), shared neural circuits involved in the regulation of ANS activity and emotion form a functional overlap between autonomic arousal and emotion regulation. Furthermore, “the afferent vagal loop provides a neuroanatomical pathway through which the ANS is directly linked to the serotonergic and noradrenergic systems involved in emotion”, and “efferent vagal fibers innervate almost all organs of the body, supplying motor fibers to enable parasympathetic control of organ function” (Koenig, 2020). Accordingly, the “efferent vagal loop” is assumed to provide a neuroanatomical pathway that enables the brain to adjust organ function in accordance with environmental and intra-individual demands, by integrating affective processes. The SCN, which functions as an internal “master clock”, synchronizes the individual’s endogenous rhythm to the external world. Furthermore, the serotonergic system plays an important role in the regulation of circadian rhythm (Zhang et al., 2016). Importantly, while the interactions between the brain and the body are modulated by the SCN as critically involved in the organism’s adjustment to the environment through internal signals, these signals are partly mediated by the ANS (Kirlioglu & Balcioglu, 2020). Monosynaptic outputs of the SCN are conferred mainly to pre-autonomic neurons of the paraventricular nucleus (PVN) in the hypothalamus. Projections of the SCN to preganglionic

parasympathetic regions of the brainstem and to sympathetic preganglionic motor neurons of the spinal cord enable the rhythmic control of hormone release and metabolism of all visceral structures through parasympathetic and sympathetic outputs (Kirlioglu & Balcioglu, 2020). In the dynamic model of neurovisceral integration in development it is assumed that the functional interaction of the ANS and CNS is shaped early in the course of life, and that adolescence might represent the most sensitive period in development of this circuitry (Koenig, 2020). Circadian variation of cardiac autonomic activity, in turn, can be observed in children already from 1 year of age (Massin et al., 2000; Weinert et al., 1994), and continues throughout adolescence (Schubert et al., 1995) and adulthood (Furlan et al., 1990; Huikuri et al., 1994; Lombardi et al., 1992; Malpas & Purdie, 1990; Nakagawa et al., 1998). In the present thesis, potential alterations in CVP of cardiac autonomic activity in adolescents in association with disordered ER has been observed, providing the first study on CVP of ANS activity in developmental psychopathology. In the respective study, conducting designated rhythmicity analyses based on cosinor methodology, we identified significant differences between a vulnerable group of female adolescents fulfilling DSM-V criteria for NSSI disorder and healthy controls. In the NSSI group, the cosinor parameters MESOR, Amplitude and Acrophase of both 24-h HR and vmHRV showed significant alterations compared to HC. Based on the assumption that normative increases in vagal activity early in the course of human development are important in shaping emotional development (Koenig, 2020), these findings may corroborate environmental influences during developmental periods to interfere with ANS maturation, further linked with deficient socio-emotional development as manifest in NSSI disorder - characterized also by altered CVP of ANS activity. The present thesis might provide some preliminary evidence in this regard, as our analyses showed that, at least in unadjusted models, the severity of ELM exposure might significantly influence CVP pf both HR and vmHRV in NSSI disorder. However, whether circadian disruption of ANS activity may result from environmental influences also effecting ANS dys-maturation (such as, e.g., severe adversity early in life), and precede disordered ER and stress regulation, remains to be addressed in future studies.

Similar to physiologically disproportionate reactions to psychosocial stress exposure, disruption of circadian rhythm might have several detrimental health consequences, including cardiovascular disease, diabetes, or immune deficiencies (Brainard et al., 2015). In terms of future perspectives, it might be fruitful to investigate deficient top-down control and potential links with emotional dysregulation, impaired stress regulation, and cardiovascular disease risk in association with circadian disruption in adolescents. Mutually involved pathogenic processes might be identified which, in young age and particularly during adolescence, will more likely be reversible (sensitive developmental period perspective). Different approaches are already available to study sensitive developmental periods in humans (Gabard-Durnam & McLaughlin, 2020), which, in combination with relevant psychophysiological measures, will provide important insights regarding optimal treatment provision. By focusing on sensitive periods, we might identify time-spans where specific interventions targeting

circadian rhythms are highly effective, tackling both mental and physiological health.

3.2 Methodological Considerations and Limitations

Considering the studies constituting the present thesis, several aspects await to be addressed on a methodological level, which might be critical not only for a qualified interpretation of the respective results, but also for the conduct of future studies. This section aims to address methodological considerations and concerns regarded as relevant, and to elucidate how these aspects might be addressed in the future.

By closer examination of the results of the meta-analytic study that forms part of this thesis, it becomes apparent that there is a substantial lack of uniformity between included primary studies, as indicated by a large amount of between-study-heterogeneity. While different approaches might have been useful to reduce this heterogeneity, the according observation might as well lead to the question of whether the conduct of the present meta-analysis was appropriate in the first place. Concerning the former, more stringent inclusion criteria in the search and screening phase of the meta-analytic study (regarding, e.g., the conceptual definition of the variables of interest and respective measures deployed, as well as regarding the characteristics of the included study populations) might have led to a higher uniformity and better comparability between studies. Yet, this certainly would have led to a smaller number of included studies, as well as lower generalizability of the meta-analytic results. Concerning the appropriateness of the present study, while the conduct of meta-analysis has gained increasing popularity in many different research fields, the pros and cons of meta-analysis in general, and particularly in the case of clinical observational studies, is certainly a matter of ongoing debates (Lee, 2019; Walker et al., 2008). Crucially, the conduct of the present meta-analysis revealed a substantial lack of power in many of the included primary studies. Of course, it is exactly the conduct of meta-analysis that presents a statistical tool to address problems of this kind: Meta-analysis, by combining primary studies, while considering the size of studies included, increases overall sample size, and consequently, the power to study the effects of interest (Lee, 2019; Walker et al., 2008). Meta-analysis is assumed to provide a more precise estimate of the effect. A well-designed meta-analysis performed appropriately is considered a powerful research tool, in fact providing evidence with the highest level of accuracy (Lee, 2019). Also, the conduct of meta-analysis is assumed to minimize bias by employing a methodological approach where decisions are transparent, statistical analyses result in an objective measure of the integrated quantitative evidence, and results of primary studies are converted into a common metric, making different measures comparable against each other (Bailar, 1997; Lee, 2019) - yielding conclusions that are finally more significant. Despite these considerable advantages, meta-analysis may also produce misleading results, especially if the primary studies included exhibit considerable heterogeneity – as observed in the present meta-analysis. Based on these methodological

limitations, the most appropriate (preliminary) conclusion to be drawn might be that the present meta-analysis critically elucidates many of the problems and complexities inherent to this field, which, in order to effect meaningful advances, will need to address these issues rigorously. Focus should thereby also lie on potential causes of, and on how to overcome, the heterogeneity of existing studies.

An apparent methodological issue critically limiting the credibility and interpretability of study results, including the second study that forms part of the present thesis, is that of sample size. It has been known for a number of decades that many studies in the psychological sciences in particular contain too few observations to properly investigate the effects under examination, as considerably revealed in Cohen's (1962) classic study on statistical power. As a conventional rule, it has been suggested that a well-designed experiment should have an 80% a priori chance of finding an effect of interest (provided that the respective effect is present at the population level), presenting a compromise between certainty about the true effect and the relative costs that arise when further increasing the statistical power (Brysbaert & Stevens, 2018). Cohen (1962) showed that many published studies had a power considerably below the 80% conventionally aspired, and in fact, in most studies, power ranged between 30-40%. There is little evidence that this situation has changed much over the years (Brysbaert & Stevens, 2018; Dumas-Mallet et al., 2017; Smaldino & McElreath, 2016; Vankov et al., 2014), and strong evidence that studies in the field of neuroscience are equally affected (Button et al., 2013). As mentioned above, the presently conducted meta-analysis also revealed substantial lack of power in many of the included studies, and similarly to the results presented by Cohen (1962), a considerable amount of group-comparison studies were shown to exhibit a statistical power even below 40%. Crucially, while power of study findings largely depends on sample size, a study with low statistical power not only has a reduced chance of detecting a true effect, but also is the likelihood that a statistically significant result reflects a true effect drastically reduced. While the consequences of underpowered studies are becoming increasingly apparent (Brysbaert & Stevens, 2018; Loken & Gelman, 2017), it has been pointed out that only in a system where underpowered studies are not being rewarded, an actual decrease of the problem might be realistic (Smaldino and McElreath, 2016). It has been discussed previously (e.g., Kessler, 2018) that studies of larger sample size will be needed in order to critically advance the field of treatment outcome prediction. Some orientation on sample sizes required to achieve various levels of statistical power considering available clinical case-control studies in the field, as well as analytic means to calculate the distribution of effect sizes and required sample sizes using a subset of available studies considered relevant for the planning of a particular study, has been previously provided (Quintana, 2017). In this regard, however, it needs to be considered that if a condition of interest is relatively rare (such as, e.g., a psychiatric disorder), reasonably achievable sample sizes might be much smaller - while the respective study might still provide valuable scientific insights.

A further methodological issue regarding the second study in this thesis concerns the clinical measure used to map treatment outcome over time. Concretely, a summary score compounded of three individual clinical measures was calculated as a measure of treatment outcome. These measures included symptom severity as measured with the Clinical Global Impression scale (CGI; Guy, 1976), global level of functioning measured with the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) scale, and the severity of BPD symptomatology (number of symptoms) measured using the Structured Clinical Interview for DSM-IV-Axis II (SKID-II; Fydrich, 1997). When deriving such summary scores from individual measures as presently deployed (i.e., combining CGI, GAF, and BPD symptomatology scores), to validate that the combined measures can in fact be represented by one underlying (latent) factor, factor analysis (FA) should be routinely conducted (e.g., Bartholomew, 2015). In the case of the present thesis, we refrained from such multivariate techniques given the exploratory nature and sample size of this study (yet, it might also be possible to make use of resampling methods such as bootstrap or other simulation methods to support the conduct of FA in small samples). As CGI and GAF scores are usually highly correlated, it should furthermore be acknowledged that as a result, BPD symptom scores might have lost influential weight on the resulting summary score, affecting our according results. Due to these limitations, the study at hand should be considered not anything but an indicator that the conduct of future, large-scale studies examining cardiac autonomic markers as predictors of treatment outcome in adolescent BPD might be a valuable avenue of future research.

Further focusing from a methodological perspective on potential future directions in the research of treatment outcome prediction and the respective role of biological markers, two issues might stand out. First, there will be a need to transfer established findings from experimental studies to actual clinical application. Concerning the potential use of cardiac autonomic markers for treatment outcome prediction, clearly, additional and larger-scale studies with more rigorous methodological planning will be needed before clinical usage can be considered. However, once empirical evidence has substantiated predictors of interest to a large enough degree to be credible, clinical application studies will need to examine aspects of feasibility and clinical benefit. In terms of implementation, in many strands of research including neurophysiological and psychiatric research, machine learning algorithms gain increasing popularity, often applied with the objective to extract certain patterns from large and complex datasets of clinical and physiological data. Besides providing another scientific tool to investigate the predictive use of cardiac autonomic biomarkers in experimental psychotherapy research, such machine learning frameworks will potentially be useful in implementation phases, where they may serve the prediction of individual treatment outcomes in the form of application tools.

Comparing clinically vulnerable subgroups with age- and gender-matched healthy controls, statistically significant associations of parameters indexing components of cardiac autonomic activity with clinical variables might on the one hand reflect persistent alterations of ANS functioning linked

with patho-physiological and psychopathological mechanisms, as assumed in the present thesis. On the other hand – and partly suggested by the present results – such findings might be associated with, or obscured by, physiological and methodological artefacts. At first sight, the present study comparing female adolescents fulfilling the diagnostic criteria for NSSI disorder with HC revealed significant group differences in, as well as significant associations of certain clinical variables with, parameters of CVP of cardiac autonomic activity. However, most of these effects were strongly influenced by confounds: After the inclusion of the covariates of age, BMI, physical activity, and quality of cardiac data recordings in our statistical analyses, significant group differences in CVP of vagal activity and respective associations with clinical predictors were no longer observed. Among the included covariates, the influence of cardiac data quality was particularly apparent: Firstly, the clinical study group showed significant deviations in terms of compliance with the intended study protocol, observed as significantly longer non-wear time as compared to the HC group. Furthermore, individual differences in data-quality (i.e., the amount of cardiac data actually available per participant and suitable for hypothesis testing) significantly influenced the present study results, raising concerns regarding the validity of results obtained in previous studies of ambulatory ECG measurements. Besides highlighting current issues regarding the conduct of psychophysiological research studies that will need to be addressed, this finding elucidates obstacles that might also impede actual clinical application. One question that will need to be addressed will be: How can we achieve ambulatory recordings of cardiac autonomic data in clinical populations that are accurate and reliable?

Studying the functioning of the ANS (i.e., balance and interplay between sympathetic and parasympathetic activity) is complex, and it is has been pointed out previously that, to study the complexity of autonomic regulatory processes, it might not be enough to focus on one single marker at a time (Pozzato et al., 2019). Instead, a combination of several markers indicating differing states of ANS activity (Prinsloo et al., 2014; Walker et al., 2017), or combining autonomic with markers from other stress-response systems, such as the HPA axis, might increase predictive ability concerning outcomes of interest. Regarding the former, a preliminary attempt was made in the present thesis (study two), where autonomic resting-state, reactivity, and recovery measures were assessed in a comprehensive manner. The combination of markers from different physiological systems within a machine-learning framework might present a promising research avenue, as demonstrated in a previous study focusing on various autonomic and endocrine markers in the context of early life adversity (Aimie-Salleh et al., 2019). Indeed, also the dynamic model of neurovisceral integration in development is calling to "disentangle findings on aberrant and normative development rooted in the complex interplay of various physiological systems and their interaction under development" (Koenig, 2020; pp. 2).

3.3 Preliminary Conclusion

Prevalence rates of psychiatric disorders in childhood and adolescence have been increasing rather steadily, highlighting the relevance of research aiming to address the developmental trajectories that lead towards psychopathological outcomes. From a developmental psychophysiology perspective, the profound understanding of developmental aspects of mental illness physiology is a key element in the pursuit to prevent or reverse patho-physiological mechanisms involved in the development of psychiatric disorders, and to lead young individuals onto trajectories of health and adaptation. On grounds of the *dynamic model of neurovisceral integration in development*, the body of results derived from the present thesis provides further evidence that early developmental disruption may affect autonomic development on various functional levels, further associated with disrupted socio-emotional development, resulting in deficient ER, heightened vulnerability to stress, and disease risk. The results of the studies comprising the thesis at hand illustrate the potential of research conducted from a developmental psychophysiology perspective to advance our current understanding of adverse trajectories and on how to potentially reverse them, contributing to the development of successful strategies for early detection and intervention. However, the studies also emphasize critical methodological issues currently limiting existing evidence in the field, and hampering major advances in translational efforts of clinical application - and to address them will present important future research objectives.

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Statement of Authorship

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I hereby certify that this doctoral thesis has been composed by myself, and describes my own work, unless otherwise acknowledged in the text. All references and verbatim extracts have been quoted, and all sources of information have been specifically acknowledged. The work has not been accepted in any previous application for a degree. I am aware that in the case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me based on the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 36, of 5 September 1996, and Art. 69, of 7 June 2011.

Place, date:

Bern, 01 March 2021

Signature

References

Abhishekh, H., Nisarga, P., Kisan, R., Meghana, A., Chandran, S., Trichur, R., & et al. (2013). Influence of age and gender on autonomic regulation of heart. *J Clin Monit Comput*, *27*(3), 259–264.

Agorastos, A., Pervanidou, P., Chrousos, G. P., & Baker, D. G. (2019). Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects beyond Stress System Dysregulation. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00118

Ahmed, S. P., Bittencourt-Hewitt, A., & Sebastian, C. L. (2015). Neurocognitive bases of emotion regulation development in adolescence. *Developmental Cognitive Neuroscience*, *15*, 11–25. https://doi.org/10.1016/j.dcn.2015.07.006

Aimie-Salleh, N., Malarvili, M. B., & Whittaker, A. C. (2019). Fusion of heart rate variability and salivary cortisol for stress response identification based on adverse childhood experience. *Medical & Biological Engineering & Computing*, *57*(6), 1229–1245. https://doi.org/10.1007/s11517-019-01958-3

Åkerblom, S., Perrin, S., Rivano Fischer, M., & McCracken, L. M. (2021). Predictors and mediators of outcome in cognitive behavioral therapy for chronic pain: The contributions of psychological flexibility. *Journal of Behavioral Medicine*, *44*(1), 111–122. https://doi.org/10.1007/s10865-020-00168-9

Albott, C. S., Forbes, M. K., & Anker, J. J. (2018). Association of Childhood Adversity with Differential Susceptibility of Transdiagnostic Psychopathology to Environmental Stress in Adulthood. *JAMA Network Open*, *1*(7), e185354. https://doi.org/10.1001/jamanetworkopen.2018.5354

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004

Alderman, B. L., & Olson, R. L. (2014). The relation of aerobic fitness to cognitive control and heart rate variability: A neurovisceral integration study. *Biological Psychology*, *99*, 26–33. https://doi.org/10.1016/j.biopsycho.2014.02.007

Alvares, G. A., Quintana, D. S., Hickie, I. B., & Guastella, A. J. (2016). Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. *Journal of Psychiatry & Neuroscience*, *41*(2), 89–104. https://doi.org/10.1503/jpn.140217

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

Anacker, C., O'Donnell, K. J., & Meaney, M. J. (2014). Early life adversity and the epigenetic programming of hypothalamic-pituitary- adrenal function. *Translational Research*, *16*(3), 13.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, Ch., Perry, B. D., Dube, Sh. R., & Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience*, *256*(3), 174–186. https://doi.org/10.1007/s00406-005-0624-4

Andover, M. S., & Morris, B. W. (2014). Expanding and Clarifying the Role of Emotion Regulation in Nonsuicidal Self-Injury. *The Canadian Journal of Psychiatry*, *59*(11), 569–575. https://doi.org/10.1177/070674371405901102

Angelovski, A., Sattel, H., Henningsen, P., & Sack, M. (2016). Heart rate variability predicts therapy outcome in pain-predominant multisomatoform disorder. *Journal of Psychosomatic Research*, *83*, 16–21. https://doi.org/10.1016/j.jpsychores.2016.02.003

Angius, L., Santarnecchi, E., Pascual-Leone, A., & Marcora, S. M. (2019). Transcranial Direct Current Stimulation over the Left Dorsolateral Prefrontal Cortex Improves Inhibitory Control and Endurance Performance in Healthy Individuals. *Neuroscience*, *419*, 34–45. https://doi.org/10.1016/j.neuroscience.2019.08.052

Appelhans, B. M., & Luecken, L. J. (2006). Heart Rate Variability as an Index of Regulated Emotional Responding. *Review of General Psychology*, *10*(3), 229–240. https://doi.org/10.1037/1089-2680.10.3.229

Ardizzi, M., Umiltà, M. A., Evangelista, V., Di Liscia, A., Ravera, R., & Gallese, V. (2016). Less Empathic and More Reactive: The Different Impact of Childhood Maltreatment on Facial Mimicry and Vagal Regulation. *PLOS ONE*, *11*(9), e0163853. https://doi.org/10.1371/journal.pone.0163853

Armey, M. F., Crowther, J. H., & Miller, I. W. (2011). Changes in Ecological Momentary Assessment Reported Affect Associated With Episodes of Nonsuicidal Self-Injury. *Behavior Therapy*, *42*(4), 579–588. https://doi.org/10.1016/j.beth.2011.01.002

Bailar, J. C. (1997). The Promise and Problems of Meta-Analysis. *N Engl J Med*, *337*, 559–561. https://doi.org/10.1056/NEJM199708213370810

Bailen, N. H., Green, L. M., & Thompson, R. J. (2019). Understanding Emotion in Adolescents: A Review of Emotional Frequency, Intensity, Instability, and Clarity. *Emotion Review*, *11*(1), 63–73. https://doi.org/10.1177/1754073918768878

Balanos, G. M., Phillips, A. C., Frenneaux, M. P., McIntyre, D., Lykidis, C., Griffin, H. S., & Carroll, D. (2010). Metabolically exaggerated cardiac reactions to acute psychological stress: The effects of resting blood pressure status and possible underlying mechanisms. *Biological Psychology*, *85*(1), 104–111. https://doi.org/10.1016/j.biopsycho.2010.06.001

Baldwin, J. R., Reuben, A., Newbury, J. B., & Danese, A. (2019). Agreement Between Prospective and Retrospective Measures of Childhood Maltreatment: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *76*(6), 584. https://doi.org/10.1001/jamapsychiatry.2019.0097

Balzarotti, S., Biassoni, F., Colombo, B., & Ciceri, M. R. (2017). Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. *Biological Psychology*, *130*, 54–66. https://doi.org/10.1016/j.biopsycho.2017.10.008

Balzarotti, S., Biassoni, F., Villani, D., Prunas, A., & Velotti, P. (2016). Individual Differences in Cognitive Emotion Regulation: Implications for Subjective and Psychological Well-Being. *Journal of Happiness Studies*, *17*(1), 125–143. https://doi.org/10.1007/s10902-014-9587-3

Banihashemi, L., Sheu, L. K., Midei, A. J., & Gianaros, P. J. (2015). Childhood physical abuse predicts stressor-evoked activity within central visceral control regions. *Social Cognitive and Affective Neuroscience*, *10*(4), 474–485. https://doi.org/10.1093/scan/nsu073

Bär, K.-J., Greiner, W., Jochum, T., Friedrich, M., Wagner, G., & Sauer, H. (2004). The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. *Journal of Affective Disorders*, *82*(2), 245–252. https://doi.org/10.1016/j.jad.2003.12.016

Barnes, A. J., Anthony, B. J., Karatekin, C., Lingras, K. A., Mercado, R., & Thompson, L. A. (2019). Identifying adverse childhood experiences in pediatrics to prevent chronic health conditions. *Pediatric Research*. https://doi.org/10.1038/s41390-019-0613-3

Barnett, D., Manly, J. T., & Cicchetti, D. (1993). Defining Child Maltreatment: The Interface between Policy and Research. In *Child Abuse, Child Development, and Social Policy* (D. Cicchetti, S. L. Toth). Ablex.

Baron, K. G., & Reid, K. (2014). Circadian misalignment and health. *International Review of Psychiatry*, *26*(2), 139–154. https://doi.org/10.3109/09540261.2014.911149

Barrocas, A. L., Hankin, B. L., Young, J. F., & Abela, J. R. Z. (2012). Rates of Nonsuicidal Self-Injury in Youth: Age, Sex, and Behavioral Methods in a Community Sample. *Pediatrics*, *130*(1), 39–45. https://doi.org/10.1542/peds.2011-2094

Bartholomew, D. J. (2015). *Factor Analysis and Latent Structure Analysis: Overview*. https://doi.org/10.1016/B978-0-08-097086-8.42043-X

Barutcu, I., Esen, A. M., Kaya, D., Turkmen, M., Karakaya, O., Melek, M., Esen, O. B., & Basaran, Y. (2005). Cigarette Smoking and Heart Rate Variability: Dynamic Influence of Parasympathetic and Sympathetic Maneuvers. *Annals of Noninvasive Electrocardiology*, *10*(3), 324–329. https://doi.org/10.1111/j.1542-474X.2005.00636.x

Baum, K. T., Desai, A., Field, J., Miller, L. E., Rausch, J., & Beebe, D. W. (2015). *Sleep restriction worsens mood and emotion regulation in adolescents*. 21.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6

and tumour necrosis factor-α. *Molecular Psychiatry*, *21*(5), 642–649. https://doi.org/10.1038/mp.2015.67

Beauchaine, T. P. (2015a). Respiratory sinus arrhythmia: A transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current Opinion in Psychology*, *3*, 43–47. https://doi.org/10.1016/j.copsyc.2015.01.017

Beauchaine, T. P. (2015b). Future Directions in Emotion Dysregulation and Youth Psychopathology. *Journal of Clinical Child & Adolescent Psychology*, *44*(5), 875–896. https://doi.org/10.1080/15374416.2015.1038827

Beauchaine, T. P., & Gatzke-Kopp, L. M. (2012). Instantiating the multiple levels of analysis perspective in a program of study on externalizing behavior. *Development and Psychopathology*, *24*(3), 1003–1018. https://doi.org/10.1017/S0954579412000508

Beauchaine, T. P., Gatzke-Kopp, L., & Mead, H. K. (2007). Polyvagal Theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology*, *74*(2), 174–184. https://doi.org/10.1016/j.biopsycho.2005.08.008

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology*, *98*(2), 338–350. https://doi.org/10.1016/j.ijpsycho.2015.08.004

Beckham, J. C., Kirby, C., Hertzberg, A., Crawford, L., Davidson, R. T., & Fairbank, J. A. (1997). Prevalence and correlates of heavy smoking in Vietnam veterans with chronic posttraumatic stress disorder. *Addictive Behaviors*, *22*(5), 637–647.

Bedrosian, T. A., & Nelson, R. J. (2017). Timing of light exposure affects mood and brain circuits. *Translational Psychiatry*, *7*(1), e1017–e1017. https://doi.org/10.1038/tp.2016.262

Beissner, F., Meissner, K., Bar, K.-J., & Napadow, V. (2013). The Autonomic Brain: An Activation Likelihood Estimation Meta-Analysis for Central Processing of Autonomic Function. *Journal of Neuroscience*, *33*(25), 10503–10511. https://doi.org/10.1523/JNEUROSCI.1103-13.2013

Beitchman, J., Beitchman, J. H., Adlaf, E. M., Douglas, L., Atkinson, L., Young, A., Johnson, C. J., Escobar, M., & Wilson, B. (2001). Comorbidity of Psychiatric and Substance Use Disorders

in Late Adolescence: A Cluster Analytic Approach. *The American Journal of Drug and Alcohol Abuse*, *27*(3), 421–440. https://doi.org/10.1081/ADA-100104510

Bellis, M. D. D., Baum, A. S., Birmaher, B., Keshavan, M. S., Eccard, C. H., Boring, A. M., Jenkins, F. J., & Ryan, N. D. (1999). Developmental Traumatology Part I: Biological Stress Systems. *Biol Psychiatry*, 12.

Benard, V., Geoffroy, P. A., & Bellivier, F. (2015). Saisons, rythmes circadiens, sommeil et vulnérabilité aux conduites suicidaires. *L'Encéphale*, *41*(4), S29–S37. https://doi.org/10.1016/S0013-7006(15)30004-X

Benarroch, E. E. (1993). The Central Autonomic Network: Functional Organization, Dysfunction, and Perspective. *Mayo Clinic Proceedings*, *68*(10), 988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1

Benarroch, E. E. (1997). The central autonomic network. In *Clinical Autonomic Disorders: Vol. 2nd Edition* (Low, P.A., pp. 17–23). Lippincott-Raven.

Benedetti, F., Serretti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E., & Smeraldi, E. (2003). Influence ofCLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *American Journal of Medical Genetics*, *123*(1), 23–26. https://doi.org/10.1002/ajmg.b.20038

Berking, M., & Wupperman, P. (2012). Emotion regulation and mental health: Recent findings, current challenges, and future directions. *Current Opinion in Psychiatry*, *25*(2), 128–134. https://doi.org/10.1097/YCO.0b013e3283503669

Bernstein, D. P., Cohen, P., Velez, C. N., Schwab-Stone, M., Siever, L. J., & Shinsato, L. (1993). Prevalence and stability of the DSM-III-R personality disorders in a community-based survey of adolescents. *Am. J. Psychiatry*, *150*, 1237–1243.

Bernstein, D. P., & Fink, L. (1988). *Childhood trauma questionnaire: A retrospective self-report: Manual.* Harcourt Brace & Company.

Berntson, G. G., Bigger, J. T., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., Nagaraja, H. N., Porges, S. W., Saul, J. P., Stone, P. H., & Van der Molen, M. W. (1997). Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology*, *34*(6), 623–648.

Bifulco, A., Bernazzani, O., Moran, P. M., & Jacobs, C. (2005). The childhood experience of care and abuse questionnaire (CECA.Q): Validation in a community series. *British Journal of Clinical Psychology*, *44*(4), 563–581. https://doi.org/10.1348/014466505X35344

Bifulco, A., Brown, G., Lillie, A., & Jarvis, J. (1997). Memories of childhood neglect and abuse: Corroboration in a series of sisters. *Journal of Child Psychology and Psychiatry*, *38*, 365–374.

Bifulco, A., Brown, G. W., & Harris, T. O. (1994). Childhood experience of care and abuse (CECA): A retrospective interview measure. *Journal of Child Psychology and Psychiatry*, *35*, 1419–1435.

Blakemore, S.-J. (2012). Development of the social brain in adolescence. *J R Soc Med*, *105*, 111–116. https://doi.org/10.1258/jrsm.2011.110221

Blanck, P, Stoffel, M., Bents, H., Ditzen, B., & Mander, J. (2019). Heart Rate Variability in Individual Psychotherapy: Associations With Alliance and Outcome. *J Nerv Ment Dis*, *207*(6), 451–458. https://doi.org/10.1097/NMD.0000000000000994

Blanck, P., Stoffel, M., Bents, H., Ditzen, B., & Mander, J. (2019). Heart Rate Variability in Individual Psychotherapy: Associations With Alliance and Outcome. *The Journal of Nervous and Mental Disease*, *207*(6), 451–458. https://doi.org/10.1097/NMD.0000000000000994

Boccadoro, S., Siugzdaite, R., Hudson, A. R., Maeyens, L., Van Hamme, C., & Mueller, S. C. (2019). Women with early maltreatment experience show increased resting-state functional connectivity in the theory of mind (ToM) network. *European Journal of Psychotraumatology*, *10*(1), 1647044. https://doi.org/10.1080/20008198.2019.1647044

Booth, A., Clarke, M., Dooley, G., Ghersi, D., Moher, D., Petticrew, M., & Stewart, L. (2012). The nuts and bolts of PROSPERO: An international prospective register of systematic reviews. *Systematic Reviews*, *1*(1). https://doi.org/10.1186/2046-4053-1-2

Borenstein, M. (Ed.). (2009). *Introduction to meta-analysis*. John Wiley & Sons.

Brainard, J., Gobel, M., Scott, B., Koeppen, M., & Eckle, T. (2015). Health Implications of Disrupted Circadian Rhythms and the Potential for Daylight as Therapy. *Anesthesiology*, *122*(5), 1170–1175. https://doi.org/10.1097/ALN.0000000000000596

Brandon, S., Pallotti, C., & Jog, M. (2021). Exploratory Study of Common Changes in Client Behaviors Following Routine Psychotherapy: Does Psychological Flexibility Typically Change and Predict Outcomes? *Journal of Contemporary Psychotherapy*, *51*(1), 49–56. https://doi.org/10.1007/s10879-020-09468-2

Bremner, D. J., Southwick, S. M., Johnson, D. R., Yehuda, R., & Charney, D. S. (1993). Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. 150.2 (1993): 235. *The American Journal of Psychiatry*, *150*(2), 253–239.

Briere, J., & Gil, E. (1998). Self-mutilation in clinical and general population samples: Prevalence, correlates, and functions. *American Journal of Orthopsychiatry*, *68*(4), 609–620. https://doi.org/10.1037/h0080369

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. *Journal of Psychosomatic Research*, *60*(2), 113–124. https://doi.org/10.1016/j.jpsychores.2005.06.074

Brugnera, A., Zarbo, C., Adorni, R., Compare, A., & Sakatani, K. (2017a). Cortical and Autonomic Stress Responses in Adults with High Versus Low Levels of Trait Anxiety: A Pilot Study. In H. J. Halpern, J. C. LaManna, D. K. Harrison, & B. Epel (Eds.), *Oxygen Transport to Tissue XXXIX* (Vol. 977, pp. 127–132). Springer International Publishing. https://doi.org/10.1007/978-3-319-55231-6_17

Brugnera, A., Zarbo, C., Adorni, R., Gatti, A., Compare, A., & Sakatani, K. (2017b). Age-Related Changes in Physiological Reactivity to a Stress Task: A Near-Infrared Spectroscopy Study. In H. J. Halpern, J. C. LaManna, D. K. Harrison, & B. Epel (Eds.), *Oxygen Transport to Tissue XXXIX* (Vol. 977, pp. 155–161). Springer International Publishing. https://doi.org/10.1007/978-3-319-55231-6_21

Brysbaert, M., & Stevens, M. (2018). Power Analysis and Effect Size in Mixed Effects Models: A Tutorial. *Journal of Cognition*, *1*(1), 9. https://doi.org/10.5334/joc.10

Buisman, R. S. M., Bakermans-Kranenburg, M. J., Pittner, K., Compier-de Block, L. H. C. G., van den Berg, L. J. M., van IJzendoorn, M. H., Tollenaar, M. S., Elzinga, B. M., Lindenberg, J., & Alink, L. R. A. (2019). Parents' experiences of childhood abuse and neglect are differentially

associated with behavioral and autonomic responses to their offspring. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21822

Bunea, I. M., Szentágotai-Tătar, A., & Miu, A. C. (2017). Early-life adversity and cortisol response to social stress: A meta-analysis. *Translational Psychiatry*, *7*(12), 1274. https://doi.org/10.1038/s41398-017-0032-3

Burgermeister, D. (2007). Childhood Adversity: A Review of Measurement Instruments. *Journal of Nursing Measurement*, *15*(3), 163–176. https://doi.org/10.1891/106137407783095766

Burt, K. B., & Obradović, J. (2013). The construct of psychophysiological reactivity: Statistical and psychometric issues. *Developmental Review*, *33*(1), 29–57. https://doi.org/10.1016/j.dr.2012.10.002

Bush, N. R., Lane, R. D., & McLaughlin, K. A. (2016). Mechanisms Underlying the Association between Early-Life Adversity and Physical Health: Charting a Course for the Future. *Psychosomatic Medicine*, *78*(9), 1114–1119. https://doi.org/10.1097/PSY.0000000000000421

Busner, J., & Targum, S. D. (2007). The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. *Psychiatry*, 29–37.

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365–376. https://doi.org/10.1038/nrn3475

Calati, R., & Courtet, P. (2016). Is psychotherapy effective for reducing suicide attempt and non-suicidal self-injury rates? Meta-analysis and meta-regression of literature data. *Journal of Psychiatric Research*, *79*, 8–20. https://doi.org/10.1016/j.jpsychires.2016.04.003

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., Coumel, P., Fallen, E. L., Kennedy, H. L., Kleiger, R. E., & Lombardi, F. (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*, *93*, 1043–1065.

Capitanio, J. P., Mendoza, S. P., Mason, W. A., & Maninger, N. (2005). Rearing environment and hypothalamic-pituitary-adrenal regulation in young rhesus monkeys (Macaca mulatta). *Developmental Psychobiology*, *46*(4), 318–330. https://doi.org/10.1002/dev.20067

Card, J., Rinaman, L., Lynn, R., Lee, B., Meade, R., Miselis, R., & Enquist, L. (1993). Pseudorabies virus infection of the rat central nervous system: Ultrastructural characterization of viral replication, transport, and pathogenesis. *The Journal of Neuroscience*, *13*(6), 2515–2539. https://doi.org/10.1523/J NEUROSCI.13-06-02515.1993

Cărnuță, M., Crișan, L. G., Vulturar, R., Opre, A., & Miu, A. C. (2015). Emotional non-acceptance links early life stress and blunted cortisol reactivity to social threat. *Psychoneuroendocrinology*, *51*, 176–187. https://doi.org/10.1016/j.psyneuen.2014.09.026

Carroll, D., Phillips, A. C., & Balanos, G. M. (2009). Metabolically exaggerated cardiac reactions to acute psychological stress revisited. *Psychophysiology*, *46*(2), 270–275. https://doi.org/10.1111/j.1469-8986.2008.00762.x

Carroll, D., Phillips, A. C., & Lovallo, W. R. (2011). The behavioural and health corollaries of blunted physiological reactions to acute psychological stress: Revising the reactivity hypothesis. *Motivation Perspectives of Cardiovascular Response.*, 243–263.

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, *28*(1), 62–77. https://doi.org/10.1016/j.dr.2007.08.003

Cechetto, D. F. (1987). Central representation of visceral function. *Federation Proceedings*, *46*(1), 17–23.

Cespedes Feliciano, E. M., Rifas-Shiman, S. L., Quante, M., Redline, S., Oken, E., & Taveras, E. M. (2019). Chronotype, Social Jet Lag, and Cardiometabolic Risk Factors in Early Adolescence. *JAMA Pediatrics*, *173*(11), 1049. https://doi.org/10.1001/jamapediatrics.2019.3089

Chalmers, J. A., Quintana, D. S., Abbott, M. J.-A., & Kemp, A. H. (2014). Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. *Frontiers in Psychiatry*, *5*. https://doi.org/10.3389/fpsyt.2014.00080

Chambers, A. S., & Allen, J. J. B. (2002). Vagal tone as an indicator of treatment response in major depression. *Psychophysiology*, *39*(6), 861–864. https://doi.org/10.1111/1469-8986.3960861

Chanen, A., Jovev, M., McCutcheon, L., Jackson, H., & McGorry, P. (2008). Borderline Personality Disorder in Young People and the Prospects for Prevention and Early Intervention. *Current Psychiatry Reviews*, *4*(1), 48–57. https://doi.org/10.2174/157340008783743820

Chanen, A. M., Jackson, H. J., McGorry, P. D., Allot, K. A., Clarkson, V., & Yuen, H. P. (2004). Two-Year Stability of Personality Disorder in Older Adolescent Outpatients. *Journal of Personality Disorders*, *18*(6), 526–541. https://doi.org/10.1521/pedi.18.6.526.54798

Chang, J. P.-C., Mondelli, V., Satyanarayanan, S. K., Chiang, Y.-J., Chen, H.-T., Su, K.-P., & Pariante, C. M. (2020). Cortisol, inflammatory biomarkers and neurotrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan. *Brain, Behavior, and Immunity*, *88*, 105–113. https://doi.org/10.1016/j.bbi.2020.05.017

Chellappa, S. L. (2020). Circadian misalignment: A biological basis for mood vulnerability in shift work. *European Journal of Neuroscience*, *52*(8), 3846–3850. https://doi.org/10.1111/ejn.14871

Chen, S.-R., Chiu, H.-W., Lee, Y.-J., Sheen, T.-C., & Jeng, C. (2012). Impact of Pubertal Development and Physical Activity on Heart Rate Variability in Overweight and Obese Children in Taiwan. *The Journal of School Nursing*, *28*(4), 284–290. https://doi.org/10.1177/1059840511435248

Chugani, H. T., Behen, M. E., Muzik, O., Juhász, C., Nagy, F., & Chugani, D. C. (2001). Local Brain Functional Activity Following Early Deprivation: A Study of Postinstitutionalized Romanian Orphans. *NeuroImage*, *14*(6), 1290–1301. https://doi.org/10.1006/nimg.2001.0917

Churchwell, J. C., Morris, A. M., Heurtelou, N. M., & Kesner, R. P. (2009). Interactions between the prefrontal cortex and amygdala during delay discounting and reversal. *Behavioral Neuroscience*, *123*(6), 1185–1196. https://doi.org/10.1037/a0017734

Cicchetti, D., & Toth, S. L. (1998). The Development of Depression in Children and Adolescents. *American Psychologist*, 21.

Clamor, A., Lincoln, T. M., Thayer, J. F., & Koenig, J. (2016). Resting vagal activity in schizophrenia: Meta-analysis of heart rate variability as a potential endophenotype. *British Journal of Psychiatry*, *208*(1), 9–16. https://doi.org/10.1192/bjp.bp.114.160762

Coêlho, B. M., Santana, G. L., Viana, M. C., Andrade, L. H., & Wang, Y.-P. (2018). Gender-related dimensions of childhood adversities in the general population. *Revista Brasileira de Psiquiatria*, *40*(4), 394–402. https://doi.org/10.1590/1516-4446-2017-2366

Cohen, J. (1962). The statistical power of abnormal-social psychological research: A review. *Journal of Abnormal and Social Psychology*, *65*(3), 145–153. https://doi.org/10.1037/h0045186

Cohen, J. (1988). Set Correlation and Contingency Tables. *Applied Psychological Measurement*, *12*(4), 425–434. https://doi.org/10.1177/014662168801200410

Colich, N. L., Rosen, M. L., Williams, E. S., & McLaughlin, K. A. (2019). Biological Aging in Childhood and Adolescence Following Experiences of Threat and Deprivation: A Systematic Review and Meta-Analysis. *BioRxiv*. https://doi.org/10.1101/642405

Cooper, H., & Hedges, L. V. (1993). *The handbook of research synthesis*. Russell Sage Foundation.

Corey, D. M., Dunlap, W. P., & Burke, M. (1998). Averaging Correlations: Expected Values and Bias in Combined Pearson rs and Fisher's z Transformations. *The Journal of General Psychology*, *125*(3), 245–261.

Cornelissen, G. (2014). Cosinor-based rhythmometry. *Theoretical Biology and Medical Modelling*, *11*(1), 16. https://doi.org/10.1186/1742-4682-11-16

Crowell, S. E., Beauchaine, T. P., McCauley, E., Smith, C. J., Stevens, A. L., & Sylvers, P. (2005). Psychological, autonomic, and serotonergic correlates of parasuicide among adolescent girls. *Development and Psychopathology*, *17*(04). https://doi.org/10.1017/S0954579405050522

Cuthbert, B. N. (2015). Research Domain Criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97. https://doi.org/10.31887/DCNS.2015.17.1/bcuthbert

Dahmen, B., Puetz, V. B., Scharke, W., von Polier, G. G., Herpertz-Dahlmann, B., & Konrad, K. (2018). Effects of Early-Life Adversity on Hippocampal Structures and Associated HPA Axis Functions. *Developmental Neuroscience*, *40*(1), 13–22. https://doi.org/10.1159/000484238

Dale, L. P., Shaikh, S. K., Fasciano, L. C., Watorek, V. D., Heilman, K. J., & Porges, S. W. (2018). College females with maltreatment histories have atypical autonomic regulation and poor psychological wellbeing. *Psychological Trauma: Theory, Research, Practice, and Policy*, *10*(4), 427–434. https://doi.org/10.1037/tra0000342

Danese, A., & Baldwin, J. R. (2017). Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annual Review of Psychology*, *68*(1), 517–544. https://doi.org/10.1146/annurev-psych-010416-044208

Dangardt, F., Volkmann, R., Chen, Y., Osika, W., Mårild, S., & Friberg, P. (2010). Reduced cardiac vagal activity in obese children and adolescents: Cardiac vagal activity in obese. *Clinical Physiology and Functional Imaging*, no-no. https://doi.org/10.1111/j.1475-097X.2010.00985.x

Daskalakis, N. P., Bagot, R. C., Parker, K. J., Vinkers, C. H., & de Kloet, E. R. (2013). The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology*, *38*(9), 1858–1873. https://doi.org/10.1016/j.psyneuen.2013.06.008

Daukantaitė, D., Lundh, L.-G., Wångby-Lundh, M., Claréus, B., Bjärehed, J., Zhou, Y., & Liljedahl, S. I. (2020). What happens to young adults who have engaged in self-injurious behavior as adolescents? A 10-year follow-up. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-020-01533-4

De Witte, S., Baeken, C., Pulopulos, M. M., Josephy, H., Schiettecatte, J., Anckaert, E., De Raedt, R., & Vanderhasselt, M.-A. (2020). The effect of neurostimulation applied to the left dorsolateral prefrontal cortex on post-stress adaptation as a function of depressive brooding. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *96*, 109687. https://doi.org/10.1016/j.pnpbp.2019.109687

Dedovic, K., Duchesne, A., Andrews, J., Engert, V., & Pruessner, J. C. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *NeuroImage*, *47*(3), 864–871. https://doi.org/10.1016/j.neuroimage.2009.05.074

Dedovic, K., Renwick, R., Mahani, N. K., Engert, V., Lupien, S. J., & Pruessner, J. C. (2005). The Montreal Imaging Stress Task: Using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci*, *30*(5), 319–325.

Dennis, P. A., Watkins, L. L., Calhoun, P. S., Oddone, A., Sherwood, A., Dennis, M. F., Rissling, M. B., & Beckham, J. C. (2014). Posttraumatic Stress, Heart Rate Variability, and the Mediating Role of Behavioral Health Risks: *Psychosomatic Medicine*, *76*(8), 629–637. https://doi.org/10.1097/PSY.0000000000000110

Dennison, M. J., Rosen, M. L., Sambrook, K. A., Jenness, J. L., Sheridan, M. A., & McLaughlin, K. A. (2019). Differential Associations of Distinct Forms of Childhood Adversity with Neurobehavioral Measures of Reward Processing: A Developmental Pathway to Depression. *Child Development*, *90*(1), e96–e113. https://doi.org/10.1111/cdev.13011

Dileo, J. F., Brewer, W., Northam, E., Yucel, M., & Anderson, V. (2017). Investigating the neurodevelopmental mediators of aggression in children with a history of child maltreatment:An exploratory field study. *Child Neuropsychology*, *23*(6), 655–677. https://doi.org/10.1080/09297049.2016.1186159

Dumas-Mallet, E., Button, K. S., Boraud, T., Gonon, F., & Munafò, M. R. (2017). Low statistical power in biomedical science: A review of three human research domains. *Royal Society Open Science*, *4*(2), 160254. https://doi.org/10.1098/rsos.160254

Duprey, E. B., Oshri, A., & Liu, S. (2019). Childhood Maltreatment, Self-esteem, and Suicidal Ideation in a Low-SES Emerging Adult Sample: The Moderating Role of Heart Rate Variability. *Archives of Suicide Research*, *23*(2), 333–352. https://doi.org/10.1080/13811118.2018.1430640

Eddie, D., Bates, M. E., Vaschillo, E. G., Lehrer, P. M., Retkwa, M., & Miuccio, M. (2018). Rest, Reactivity, and Recovery: A Psychophysiological Assessment of Borderline Personality Disorder. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00505

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Ehrenthal, J. C., Herrmann-Lingen, C., Fey, M., & Schauenburg, H. (2010). Altered cardiovascular adaptability in depressed patients without heart disease. *The World Journal of Biological Psychiatry*, *11*(3), 586–593. https://doi.org/10.3109/15622970903397714

Ellis, R. J., Zhu, B., Koenig, J., Thayer, J. F., & Wang, Y. (2015). A careful look at ECG sampling frequency and R-peak interpolation on short-term measures of heart rate variability. *Physiological Measurement*, *36*(9), 1827–1852. https://doi.org/10.1088/0967-3334/36/9/1827

El-Sheikh, M., Hinnant, J. B., & Erath, S. (2011). Developmental trajectories of delinquency symptoms in childhood: The role of marital conflict and autonomic nervous system activity. *Journal of Abnormal Psychology*, *120*(1), 16–32. https://doi.org/10.1037/a0020626

Eluvathingal, T. J. (2006). Abnormal Brain Connectivity in Children After Early Severe Socioemotional Deprivation: A Diffusion Tensor Imaging Study. *PEDIATRICS*, *117*(6), 2093–2100. https://doi.org/10.1542/peds.2005-1727

English, T., John, O. P., & Gross, J. J. (2013). Emotion regulation in close relationships. In *The Oxford handbook of close relationships* (J. A. Simpson&L. Campbell, pp. 500–513). Oxford University Press.

Era, V., Carnevali, L., Thayer, J. F., Candidi, M., & Ottaviani, C. (2021). Dissociating cognitive, behavioral and physiological stress-related responses through dorsolateral prefrontal cortex inhibition. *Psychoneuroendocrinology*, *124*, 105070. https://doi.org/10.1016/j.psyneuen.2020.105070

Evans, G. W., Dongping, L., & Sepanski Whipple, S. (2013). Cumulative risk and child development. *Psychological Bulletin*, *139*(6), 1342.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults. *American Journal of Preventive Medicine*, *14*(4), 245–258. https://doi.org/10.1016/S0749-3797(98)00017-8

Fergusson, D. M., Horwood, L. J., & Woodward, L. J. (2000). The stability of child abuse reports: A longitudinal study of the reporting behaviour of young adults. *Psychological Medicine*, *30*(3), 529–544. https://doi.org/10.1017/S0033291799002111

Fernández, J. R., Hermida, R. C., & Mojón, A. (2009). Chronobiological analysis techniques. Application to blood pressure. *Philosophical Transactions of the Royal Society A:*

Mathematical, Physical and Engineering Sciences, *367*(1887), 431–445. https://doi.org/10.1098/rsta.2008.0231

Fischer, G., Ameis, N., Parzer, P., Plener, P. L., Groschwitz, R., Vonderlin, E., Kölch, M., Brunner, R., & Kaess, M. (2014). The German version of the self-injurious thoughts and behaviors interview (SITBI-G): A tool to assess non-suicidal self-injury and suicidal behavior disorder. *BMC Psychiatry*, *14*(1), 265. https://doi.org/10.1186/s12888-014-0265-0

Fliege, H., Lee, J.-R., Grimm, A., & Klapp, B. F. (2009). Risk factors and correlates of deliberate self-harm behavior: A systematic review. *Journal of Psychosomatic Research*, *66*(6), 477–493. https://doi.org/10.1016/j.jpsychores.2008.10.013

Fossati, A., Madeddu, F., & Maffei, C. (1999). Borderline Personality Disorder and Childhood Sexual Abuse: A Meta-Analytic Study. *Journal of Personality Disorders*, *13*(3), 268–280. https://doi.org/10.1521/pedi.1999.13.3.268

Fox, H. C., Axelrod, S. R., Paliwal, P., Sleeper, J., & Sinha, R. (2007). Difficulties in emotion regulation and impulse control during cocaine abstinence. *Drug and Alcohol Dependence*, *89*(2–3), 298–301. https://doi.org/10.1016/j.drugalcdep.2006.12.026

Fox, H. C., Hong, K. A., & Sinha, R. (2008). Difficulties in emotion regulation and impulse control in recently abstinent alcoholics compared with social drinkers. *Addictive Behaviors*, *33*(2), 388–394. https://doi.org/10.1016/j.addbeh.2007.10.002

Friedman, B. H. (2007). An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. *Biological Psychology*, *74*(2), 185–199. https://doi.org/10.1016/j.biopsycho.2005.08.009

Friedman, B. H., & Thayer, J. F. (1998). Autonomic balance revisited: Panic anxiety and heart rate variability. *Journal of Psychosomatic Research*, *44*(1), 133–151. https://doi.org/10.1016/S0022-3999(97)00202-X

Frühe, B., Allgaier, A.-K., Pietsch, K., & Schulte-Körne, G. (2012). Depressions-Screening bei pädiatrischen Patienten: Ein Vergleich der konkurrenten Validität des Depressions- inventars für Kinder und Jugendliche, des Depressionstests für Kinder und des Children's Depression

Screeners. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, *40*(3), 161–169. https://doi.org/10.1024/1422-4917/a000166

Fukasaki, C., Kawakubo, K., & Yamamoto, Y. (2000). Assessment of the primary effect of aging on heart rate variability in humans. *Clinical Autonomic Research*, *10*, 123–130.

Furlan, R., Guzzetti, S., & Crivellaro, W. (1990). Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation*, *81*, 537–547.

Fydrich, T., Renneberg, B., Schmitz, B., & Wittchen, H. U. (1997). *Strukturiertes Klinisches Interview für DSM-IV Achse II: Persönlichkeitsstörungen (SKID-II)* (Hogrefe).

Gabard-Durnam, L., & McLaughlin, K. A. (2020). Sensitive periods in human development: Charting a course for the future. *Current Opinion in Behavioral Sciences*, *36*, 120–128. https://doi.org/10.1016/j.cobeha.2020.09.003

Gaebler, M., Daniels, J. K., Lamke, J.-P., Fydrich, T., & Walter, H. (2013). Heart rate variability and its neural correlates during emotional face processing in social anxiety disorder. *Biological Psychology*, *94*(2), 319–330. https://doi.org/10.1016/j.biopsycho.2013.06.009

Garcia, R. G., Lin, R. L., Lee, J., Kim, J., Barbieri, R., Sclocco, R., Wasan, A. D., Edwards, R. R., Rosen, B. R., Hadjikhani, N., & Napadow, V. (2017). Modulation of brainstem activity and connectivity by respiratory-gated auricular vagal afferent nerve stimulation in migraine patients: *PAIN*, *158*(8), 1461–1472. https://doi.org/10.1097/j.pain.0000000000000930

Ghuran, A., van Der Wieken, L. R., & Nolan, J. (2001). Cardiovascular complications of recreational drugs: Are an important cause of morbidity and mortality. *BMJ*, 464–466.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–863. https://doi.org/10.1038/13158

Gil, E., Orini, M., Bailón, R., Vergara, J. M., Mainardi, L., & Laguna, P. (2010). Photoplethysmography pulse rate variability as a surrogate measurement of heart rate

variability during non-stationary conditions. *Physiological Measurement*, *31*(9), 1271–1290. https://doi.org/10.1088/0967-3334/31/9/015

Gilbert, L. K., Breiding, M. J., Merrick, M. T., Thompson, W. W., Ford, D. C., Dhingra, S. S., & Parks, S. E. (2015). Childhood Adversity and Adult Chronic Disease. *American Journal of Preventive Medicine*, *48*(3), 345–349. https://doi.org/10.1016/j.amepre.2014.09.006

Gilbert, R., Widom, C. S., Browne, K., Fergusson, D., Webb, E., & Janson, S. (2009). Burden and consequences of child maltreatment in high-income countries. *The Lancet*, *373*(9657), 68–81. https://doi.org/10.1016/S0140-6736(08)61706-7

Ginty, A. T., Kraynak, T. E., Fisher, J. P., & Gianaros, P. J. (2017). Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. *Autonomic Neuroscience*, *207*, 2–9. https://doi.org/10.1016/j.autneu.2017.03.003

Giuliano, R. J., Roos, L. E., Farrar, J. D., & Skowron, E. A. (2018). Cumulative risk exposure moderates the association between parasympathetic reactivity and inhibitory control in preschool-age children. *Developmental Psychobiology*, *60*(3), 324–332. https://doi.org/10.1002/dev.21608

Glaser, D. (2000). *Child Abuse and Neglect and the Brain—A Review*. 20.

Glenn, C. R., & Klonsky, E. D. (2013). Nonsuicidal Self-Injury Disorder: An Empirical Investigation in Adolescent Psychiatric Patients. *Journal of Clinical Child & Adolescent Psychology*, *42*(4), 496–507. https://doi.org/10.1080/15374416.2013.794699

Goedhart, A. D., van der Sluis, S., Houtveen, J. H., Willemsen, G., & de Geus, E. J. C. (2007). Comparison of time and frequency domain measures of RSA in ambulatory recordings. *Psychophysiology*, *44*(2), 203–215. https://doi.org/10.1111/j.1469-8986.2006.00490.x

Goodman, L. A., Corcoran, C., Turner, K., Yuan, N., & Green, B. L. (1998). Assessing traumatic event exposure: General issues and preliminary findings for the Stressful Life Events Screening Questionnaire. *Journal of Traumatic Stress*, *11*(3), 521–542. https://doi.org/10.1023/A:1024456713321

Gordis, E. B., Feres, N., Olezeski, C. L., Rabkin, A. N., & Trickett, P. K. (2010). Skin Conductance Reactivity and Respiratory Sinus Arrhythmia Among Maltreated and Comparison Youth:

Relations with Aggressive Behavior. *Journal of Pediatric Psychology*, *35*(5), 547–558. https://doi.org/10.1093/jpepsy/jsp113

Gore, F. M., Bloem, P. J., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., Sawyer, S. M., & Mathers, C. D. (2011). Global burden of disease in young people aged 10–24 years: A systematic analysis. *The Lancet*, *377*(9783), 2093–2102. https://doi.org/10.1016/S0140-6736(11)60512-6

Gorka, A. X., Hanson, J. L., Radtke, S. R., & Hariri, A. R. (2014). Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. *Biology of Mood & Anxiety Disorders*, *4*(1), 12. https://doi.org/10.1186/2045-5380-4-12

Goulter, N., Kimonis, E. R., Denson, T. F., & Begg, D. P. (2019). Female primary and secondary psychopathic variants show distinct endocrine and psychophysiological profiles. *Psychoneuroendocrinology*, *104*, 7–17. https://doi.org/10.1016/j.psyneuen.2019.02.011

Gratz, K. L. (2003). Risk Factors for and Functions of Deliberate Self-Harm: An Empirical and Conceptual Review. *Clinical Psychology: Science and Practice*, *10*(2), 192–205. https://doi.org/10.1093/clipsy.bpg022

Gratz, K. L., Conrad, S. D., & Roemer, L. (2002). Risk factors for deliberate self-harm among college students. *American Journal of Orthopsychiatry*, *72*(1), 128–140.

Gratz, K. L., & Gunderson, J. G. (2006). Preliminary Data on an Acceptance-Based Emotion Regulation Group Intervention for Deliberate Self-Harm Among Women With Borderline Personality Disorder. *Behavior Therapy*, *37*(1), 25–35. https://doi.org/10.1016/j.beth.2005.03.002

Gratz, K. L., & Roemer, L. (2003). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment*, 14.

Gratz, K. L., & Tull, M. T. (2011). Extending research on the utility of an adjunctive emotion regulation group therapy for deliberate self-harm among women with borderline personality

pathology. *Personality Disorders: Theory, Research, and Treatment*, *2*(4), 316–326. https://doi.org/10.1037/a0022144

Grenyer, B. F., Ng, F. Y., Townsend, M. L., & Rao, S. (2017). Personality disorder: A mental health priority area. *Australian & New Zealand Journal of Psychiatry*, *51*(9), 872–875. https://doi.org/10.1177/0004867417717798

Grierson, A. B., Hickie, I. B., Naismith, S. L., Hermens, D. F., Scott, E. M., & Scott, J. (2016). Circadian rhythmicity in emerging mood disorders: State or trait marker? *International Journal of Bipolar Disorders*, *4*(1), 3. https://doi.org/10.1186/s40345-015-0043-z

Groschwitz, R. C., & Plener, P. L. (2012). The Neurobiology of Non-suicidal Self-injury (NSSI): A review. *Suicidology Online*, *3*, 24–32.

Gross, J. J. (2001). Emotion Regulation in Adulthood: Timing Is Everything. *Current Directions in Psychological Science*, *10*(6), 214–219. https://doi.org/10.1111/1467-8721.00152

Gross, J. J. (2007). *Handbook of emotion regulation* (J.J. Gross). Guildford Press.

Gross, J. J., & Feldman Barrett, L. (2011). Emotion Generation and Emotion Regulation: One or Two Depends on Your Point of View. *Emotion Review*, *3*(1), 8–16. https://doi.org/10.1177/1754073910380974

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, *85*(2), 348–362. https://doi.org/10.1037/0022-3514.85.2.348

Gross, J. J., & Thompson, R. A. (2007). Emotion Regulation: Conceptual Foundations. In *Handbook of emotion regulation* (J.J. Gross, pp. 3–24). Guildford Press.

Grossman, P., Wilhelm, F. H., & Spoerle, M. (2004). Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. *American Journal of Physiology-Heart and Circulatory Physiology*, *287*(2), H728–H734. https://doi.org/10.1152/ajpheart.00825.2003

Grossman, P., & Taylor, E. W. (2007). Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology*, *74*(2), 263–285. https://doi.org/10.1016/j.biopsycho.2005.11.014

Gunnar, M. R., DePasquale, C. E., Reid, B. M., & Donzella, B. (2019). Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. *Proceedings of the National Academy of Sciences*, *116*(48), 23984–23988. https://doi.org/10.1073/pnas.1909699116

Gutin, B., Yin, Z., Humphries, M. C., & Barbeau, P. (n.d.). *Relations of moderate and vigorous physical activity to fitness and fatness in adolescents1–3*. 5.

Haga, S. M., Kraft, P., & Corby, E.-K. (2009). Emotion Regulation: Antecedents and Well-Being Outcomes of Cognitive Reappraisal and Expressive Suppression in Cross-Cultural Samples. *Journal of Happiness Studies*, *10*(3), 271–291. https://doi.org/10.1007/s10902-007-9080-3

Hagan, M. J., Bush, N., Mendes, W. B., Arenander, J., Epel, E., & Puterman, E. (2017). Associations between childhood adversity and daily suppression and avoidance in response to stress in adulthood: Can neurobiological sensitivity help explain this relationship? *Anxiety, Stress, & Coping*, *30*(2), 163–175. https://doi.org/10.1080/10615806.2016.1259473

Hagemann, D., Waldstein, S. R., & Thayer, J. F. (2003). Central and autonomic nervous system integration in emotion. *Brain and Cognition*, *52*(1), 79–87. https://doi.org/10.1016/S0278-2626(03)00011-3

Hamilton, J. L., & Alloy, L. B. (2016). Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research. *Clinical Psychology Review*, *50*, 67–79. https://doi.org/10.1016/j.cpr.2016.09.003

Hammen, C., Henry, R., & Daley, S. E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology*, *68*(5), 782–787. https://doi.org/10.1037//0022-006X.68.5.782

Hansen, C. S., Vistisen, D., Jørgensen, M. E., Witte, D. R., Brunner, E. J., Tabák, A. G., Kivimäki, M., Roden, M., Malik, M., & Herder, C. (2017). Adiponectin, biomarkers of inflammation and changes in cardiac autonomic function: Whitehall II study. *Cardiovascular Diabetology*, *16*(1). https://doi.org/10.1186/s12933-017-0634-3

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., Shirtcliff, E. A., Pollak, S. D., & Davidson, R. J. (2015). Behavioral Problems after Early Life

Stress: Contributions of the Hippocampus and Amygdala. *Biological Psychiatry*, *77*(4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020

Harbour, V. L., Robinson, B., & Amir, S. (2011). Variations in Daily Expression of the Circadian Clock Protein, PER2, in the Rat Limbic Forebrain during Stable Entrainment to a Long Light Cycle. *Journal of Molecular Neuroscience*, *45*(2), 154–161. https://doi.org/10.1007/s12031-010-9469-z

Harrison, A., Sullivan, S., Tchanturia, K., & Treasure, J. (2010). Emotional functioning in eating disorders: Attentional bias, emotion recognition and emotion regulation. *Psychological Medicine*, *40*(11), 1887–1897. https://doi.org/10.1017/S0033291710000036

Hartmann, R., Schmidt, F. M., Sander, C., & Hegerl, U. (2019). Heart Rate Variability as Indicator of Clinical State in Depression. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00735

Harvey, A. G., Mullin, B. C., & Hinshaw, S. P. (2006). Sleep and circadian rhythms in children and adolescents with bipolar disorder. *Development and Psychopathology*, *18*(04). https://doi.org/10.1017/S095457940606055X

Heathers, J. A. J., & Goodwin, M. s. (2017). Dead Science in Live Psychology: A Case Study from Heart Rate Variability (HRV). *PsyArXiv*.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Academic press.

Heim, C. M., Entringer, S., & Buss, C. (2019). Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. *Psychoneuroendocrinology*, *105*, 123–137. https://doi.org/10.1016/j.psyneuen.2018.12.011

Herbert, B. M., Pollatos, O., Flor, H., Enck, P., & Schandry, R. (2010). Cardiac awareness and autonomic cardiac reactivity during emotional picture viewing and mental stress. *Psychophysiology*, *47*(2), 342–354. https://doi.org/10.1111/j.1469-8986.2009.00931.x

Herman, J. P., Cullinan, W. E., Ziegler, D. R., & Tasker, J. G. (2002). Role of the paraventricular nucleus microenvironment in stress integration: PVN microenvironment and stress

integrations. *European Journal of Neuroscience*, *16*(3), 381–385. https://doi.org/10.1046/j.1460-9568.2002.02133.x

Herzog, J. I., Thome, J., Demirakca, T., Koppe, G., Ende, G., Lis, S., Rausch, S., Priebe, K., Müller-Engelmann, M., Steil, R., Bohus, M., & Schmahl, C. (2020). Influence of Severity of Type and Timing of Retrospectively Reported Childhood Maltreatment on Female Amygdala and Hippocampal Volume. *Scientific Reports*, *10*(1), 1903. https://doi.org/10.1038/s41598-020-57490-0

Herzog, S., D'Andrea, W., DePierro, J., & Khedari, V. (2018). When stress becomes the new normal: Alterations in attention and autonomic reactivity in repeated traumatization. *Journal of Trauma & Dissociation*, *19*(3), 362–381. https://doi.org/10.1080/15299732.2018.1441356

Higgins, J. P. T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions.* www.handbook.cochrane.org

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558. https://doi.org/10.1002/sim.1186

Hill, J. (2003). Childhood trauma and depression. *Current Opinion in Psychiatry*, *16*(1), 3–6.

Hill, L. K., Hu, D. D., Koenig, J., Sollers, J. J., Kapuku, G., Wang, X., Snieder, H., & Thayer, J. F. (2015). Ethnic Differences in Resting Heart Rate Variability: A Systematic Review and Meta-Analysis. *Psychosomatic Medicine*, *77*(1), 16–25. https://doi.org/10.1097/PSY.0000000000000133

Hill, L. K., Siebenbrock, A., Sollers III, J. J., & Thayer, J. F. (2009). Are All Measures Created Equal? Heart Rate Variability and Respiration. *Biomedical Sciences Instrumentation*, *45*, 71–76.

Hill, L., Siebenbrock, A., Sollers, J. J., & Thayer, J. F. (2009). Are All Measures Created Equal? Heart Rate Variability and Respiration. *Biomed Sci Instrum*, *45*, 71–76.

Hilt, L. M., Hanson, J. L., & Pollak, S. D. (2011). Emotion Dysregulation. In *Encyclopedia of adolescence* (B. B. Brown&M. J. Prinstein (Eds.), Vol. 3, pp. 160–169). Elsevier.

Hood, L. (2004). Systems Biology and New Technologies Enable Predictive and Preventative Medicine. *Science*, *306*(5696), 640–643. https://doi.org/10.1126/science.1104635

Horrocks, J., Price, S., House, A., & Owens, D. (2003). Self-injury attendances in the accident and emergency department. *BRITISH JOURNAL OF PSYCHIATRY*, *183*, 34–39.

Hostinar, C. E., Nusslock, R., & Miller, G. E. (2018). Future Directions in the Study of Early-Life Stress and Physical and Emotional Health: Implications of the Neuroimmune Network Hypothesis. *Journal of Clinical Child & Adolescent Psychology*, *47*(1), 142–156. https://doi.org/10.1080/15374416.2016.1266647

Huang, M., Shah, A., Su, S., Goldberg, J., Lampert, R. J., Levantsevych, O. M., Shallenberger, L., Pimple, P., Bremner, J. D., & Vaccarino, V. (2018). Association of Depressive Symptoms and Heart Rate Variability in Vietnam War–Era Twins: A Longitudinal Twin Difference Study. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2018.0747

Huang, R.-C. (2018). The discoveries of molecular mechanisms for the circadian rhythm: The 2017 Nobel Prize in Physiology or Medicine. *Biomed J*, *41*, 5–8.

Huikuri, H. V., Niemelä, M. J., Ojala, S., Rantala, A., Ikäheimo, M. J., & Airaksinen, K. E. (1994). Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. *Circulation*, *90*(1), 121–126. https://doi.org/10.1161/01.CIR.90.1.121

Hulme, P. A. (2007). Psychometric evaluation and comparison of three retrospective, multi-item measures of childhood sexual abuse. *Child Abuse & Neglect*, *31*(8), 853–869. https://doi.org/10.1016/j.chiabu.2007.03.016

Jackowska, M., Dockray, S., Endrighi, R., Hendrickx, H., & Steptoe, A. (2012). Sleep problems and heart rate variability over the working day: Sleep problems and heart rate variability. *Journal of Sleep Research*, *21*(4), 434–440. https://doi.org/10.1111/j.1365-2869.2012.00996.x

Jaffee, S. R., & Maikovich-Fong, A. K. (2011). Effects of chronic maltreatment and maltreatment timing on children's behavior and cognitive abilities: Effects of chronic maltreatment. *Journal of Child Psychology and Psychiatry*, *52*(2), 184–194. https://doi.org/10.1111/j.1469-7610.2010.02304.x

Jandackova, V. K., Britton, A., Malik, M., & Steptoe, A. (2016). Heart rate variability and depressive symptoms: A cross-lagged analysis over a 10-year period in the Whitehall II study. *Psychological Medicine*, *46*(10), 2121–2131. https://doi.org/10.1017/S003329171600060X

Janz, K., Golden, J., Hnsen, R., & Mahoney, L. (1992). Heart Rate Monitoring of Physical Activity in Children and Adolescents: The Muscatine Study. *Pediatrics*, *89*(2), 256–261.

Jarczok, M. N., Aguilar-Raab, C., Koenig, J., Kaess, M., Borniger, J. C., Nelson, R. J., Hall, M., Ditzen, B., Thayer, J. F., & Fischer, J. E. (2018). The Heart´s rhythm 'n' blues: Sex differences in circadian variation patterns of vagal activity vary by depressive symptoms in predominantly healthy employees. *Chronobiology International*, *35*(7), 896–909. https://doi.org/10.1080/07420528.2018.1439499

Jarczok, M. N., Koenig, J., Shively, C. A., & Thayer, J. F. (2018). Behavioral depression is associated with increased vagally mediated heart rate variability in adult female cynomolgus monkeys (Macaca fascicularis). *International Journal of Psychophysiology*, *131*, 139–143. https://doi.org/10.1016/j.ijpsycho.2017.11.004

Jarczok, M. N., Li, J., Mauss, D., Fischer, J. E., & Thayer, J. F. (2013). Heart Rate Variability is Associated with Glycemic Status after Controlling for Components of the Metabolic Syndrome. *International Journal of Cardiology*, *167*(3), 855–861. https://doi.org/10.1016/j.ijcard.2012.02.002

Jenkins, A. L., & Schmitz, M. F. (2012). The Roles of Affect Dysregulation and Positive Affect in Non-Suicidal Self-Injury. *Archives of Suicide Research*, *16*(3), 212–225. https://doi.org/10.1080/13811118.2012.695270

Jenness, J. L., Miller, A. B., Rosen, M. L., & McLaughlin, K. A. (2019). Extinction Learning as a Potential Mechanism Linking High Vagal Tone with Lower PTSD Symptoms among Abused Youth. *Journal of Abnormal Child Psychology*, *47*(4), 659–670. https://doi.org/10.1007/s10802-018-0464-0

Jeong, H., Dimick, M. K., Sultan, A., Duong, A., Park, S. S., El Soufi El Sabbagh, D., Goldstein, B. I., & Andreazza, A. C. (2020). Peripheral biomarkers of mitochondrial dysfunction in

adolescents with bipolar disorder. *Journal of Psychiatric Research*, *123*, 187–193. https://doi.org/10.1016/j.jpsychires.2020.02.009

Jin, M. J., Kim, J. S., Kim, S., Hyun, M. H., & Lee, S.-H. (2018). An Integrated Model of Emotional Problems, Beta Power of Electroencephalography, and Low Frequency of Heart Rate Variability after Childhood Trauma in a Non-Clinical Sample: A Path Analysis Study. *Frontiers in Psychiatry*, *8*. https://doi.org/10.3389/fpsyt.2017.00314

Johnson, J. G., Cohen, P., Kasen, S., Skodol, A. E., Hamagami, F., & Brook, J. S. (2000). Age-related change in personality disorder trait levels between early adolescence and adulthood: A community-based longitudinal investigation: Change in personality disorder trait levels. *Acta Psychiatrica Scandinavica*, *102*(4), 265–275. https://doi.org/10.1034/j.1600-0447.2000.102004265.x

Johnson, J. G., Cohen, P., Skodol, A. E., Oldham, J. M., Kasen, S., & Brook, J. S. (1999). Personality Disorders in Adolescence and Risk of Major Mental Disorders and Suicidality during Adulthood. *Archives of General Psychiatry*, *56*(9), 805. https://doi.org/10.1001/archpsyc.56.9.805

Joormann, J., & Gotlib, I. H. (2010). Emotion regulation in depression: Relation to cognitive inhibition. *Cognition & Emotion*, *24*(2), 281–298. https://doi.org/10.1080/02699930903407948

Kaess, M., Brunner, R., & Chanen, A. (2014). Borderline Personality Disorder in Adolescence. *Pediatrics*, *134*(4), 782–793. https://doi.org/10.1542/peds.2013-3677

Kaess, M., Fischer-Waldschmidt, G., Resch, F., & Koenig, J. (2017a). Health related quality of life and psychopathological distress in risk taking and self-harming adolescents with full-syndrome, subthreshold and without borderline personality disorder: Rethinking the clinical cut-off? *Borderline Personality Disorder and Emotion Dysregulation*, *4*(1). https://doi.org/10.1186/s40479-017-0058-4

Kaess, M., Ghinea, D., Fischer-Waldschmidt, G., & Resch, F. (2017b). Die Ambulanz für Risikoverhalten und Selbstschädigung (AtR!Sk) – ein Pionierkonzept der ambulanten Früherkennung und Frühintervention von Borderline-Persönlichkeitsstörungen [The

outpatient clinic for risk-taking and self-harming behavior (AtR!Sk)—A pioneer concept of ambulant early detection and intervention fot borderline personality disorder]. *Praxis Der Kinderpsychologie Und Kinderpsychiatrie*, *66*(6), 404–422. https://doi.org/10.13109/prkk.2017.66.6.404

Kaess, M., Hille, M., Parzer, P., Maser-Gluth, C., Resch, F., & Romuald, B. (2012). Alterations in the neuroendocrinological stress response to acute psychosocial stress in adolescents engaging in nonsuicidal self-injury. *Psychoneuroendocrinology*, *37*, 157–161.

Kaess, M., Parzer, P., Mattern, M., Plener, P. L., Bifulco, A., Resch, F., & Brunner, R. (2013). Adverse childhood experiences and their impact on frequency, severity, and the individual function of nonsuicidal self-injury in youth. *Psychiatry Research*, *206*(2–3), 265–272. https://doi.org/10.1016/j.psychres.2012.10.012

Kaess, M., Parzer, P., Mattern, M., Resch, F., Bifulco, A., & Brunner, R. (2011). Childhood Experiences of Care and Abuse (CECA): Validierung der deutschen Version von Fragebogen und korrespondierendem Interview sowie Ergebnisse einer Untersuchung von Zusammenhängen belastender Kindheitserlebnisse mit suizidalen Verhaltensweisen. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, *39*(4), 243–252. https://doi.org/10.1024/1422-4917/a000115

Kalmakis, K. A., & Chandler, G. E. (2015). Health consequences of adverse childhood experiences: A systematic review: *Journal of the American Association of Nurse Practitioners*, *27*(8), 457–465. https://doi.org/10.1002/2327-6924.12215

Karhula, K., Henelius, A., Härmä, M., Sallinen, M., Lindholm, H., Kivimäki, M., Vahtera, J., & Puttonen, S. (2014). Job strain and vagal recovery during sleep in shift working health care professionals. *Chronobiology International*, *31*(10), 1179–1189. https://doi.org/10.3109/07420528.2014.957294

Kasen, S., Cohen, P., Skodol, A. E., Johnson, J. G., & Brook, J. S. (1999). Influence of Child and Adolescent Psychiatric Disorders on Young Adult Personality Disorder. *American Journal of Psychiatry*, *156*(10), 1529–1535. https://doi.org/10.1176/ajp.156.10.1529

Katz, L. F. (2007). Domestic violence and vagal reactivity to peer provocation. *Biological Psychology*, *74*(2), 154–164. https://doi.org/10.1016/j.biopsycho.2005.10.010

Kemp, A. H., Koenig, J., & Thayer, J. F. (2017). From psychological moments to mortality: A multidisciplinary synthesis on heart rate variability spanning the continuum of time. *Neuroscience & Biobehavioral Reviews*, *83*, 547–567. https://doi.org/10.1016/j.neubiorev.2017.09.006

Kemp, A. H., & Quintana, D. S. (2013). The relationship between mental and physical health: Insights from the study of heart rate variability. *International Journal of Psychophysiology*, *89*(3), 288–296. https://doi.org/10.1016/j.ijpsycho.2013.06.018

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of Depression and Antidepressant Treatment on Heart Rate Variability: A Review and Meta-Analysis. *Biological Psychiatry*, *67*(11), 1067–1074. https://doi.org/10.1016/j.biopsych.2009.12.012

Kemperman, I., Russ, M. J., Crawford Clark, W., Kakuma, T., Zanine, E., & Harrison, K. (1997). Pain assessment in self-injurious patients with borderline personality disorder using signal detection theory. *Psychiatry Research*, *70*(3), 175–183. https://doi.org/10.1016/S0165-1781(97)00034-6

Kessler, R. C. (2018). The potential of predictive analytics to provide clinical decision support in depression treatment planning. *Current Opinion in Psychiatry*, *31*(1), 32–39. https://doi.org/10.1097/YCO.0000000000000377

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: A review of recent literature: *Current Opinion in Psychiatry*, *20*(4), 359–364. https://doi.org/10.1097/YCO.0b013e32816ebc8c

Khazaie, H., Zakiei, A., McCall, W. V., Noori, K., Rostampour, M., Sadeghi Bahmani, D., & Brand, S. (2020). Relationship between Sleep Problems and Self-Injury: A Systematic Review. *Behavioral Sleep Medicine*, 1–16. https://doi.org/10.1080/15402002.2020.1822360

Kirby, A. C., Hertzberg, B. P., Collie, C. F., Yeatts, B., Dennis, M. F., McDonald, S. D., Calhoun, P. S., & Beckham, J. C. (2008). Smoking in help-seeking veterans with PTSD returning from

Afghanistan and Iraq. *Addictive Behaviors*, *33*(11), 1448–1453. https://doi.org/10.1016/j.addbeh.2008.05.007

Kircanski, K., Williams, L. M., & Gotlib, I. H. (2019). Heart rate variability as a biomarker of anxious depression response to antidepressant medication. *Depression and Anxiety*, *36*(1), 63–71. https://doi.org/10.1002/da.22843

Kirlioglu, S. S., & Balcioglu, Y. H. (2020). Chronobiology Revisited in Psychiatric Disorders: From a Translational Perspective. *Psychiatry Investigation*, *17*(8), 725–743. https://doi.org/10.30773/pi.2020.0129

Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*, *28*(1–2), 76–81. https://doi.org/10.1159/000119004

Kleindienst, N., Bohus, M., Ludäscher, P., Limberger, M. F., Kuenkele, K., Ebner-Priemer, U. W., Chapman, A. L., Reicherzer, M., Stieglitz, R.-D., & Schmahl, C. (2008). Motives for Nonsuicidal Self-Injury Among Women With Borderline Personality Disorder: *The Journal of Nervous and Mental Disease*, *196*(3), 230–236. https://doi.org/10.1097/NMD.0b013e3181663026

Klonsky, E. D. (2009). The functions of self-injury in young adults who cut themselves: Clarifying the evidence for affect-regulation. *Psychiatry Research*, *166*(2–3), 260–268. https://doi.org/10.1016/j.psychres.2008.02.008

Klonsky, E. D., & Muehlenkamp, J. J. (2007). Self-injury: A research review for the practitioner. *Journal of Clinical Psychology*, *63*(11), 1045–1056. https://doi.org/10.1002/jclp.20412

Klumparendt, A., Nelson, J., Barenbrügge, J., & Ehring, T. (2019). Associations between childhood maltreatment and adult depression: A mediation analysis. *BMC Psychiatry*, *19*(1), 36. https://doi.org/10.1186/s12888-019-2016-8

Klumpers, F., Kroes, M. C. W., Baas, J. M. P., & Fernández, G. (2017). How Human Amygdala and Bed Nucleus of the Stria Terminalis May Drive Distinct Defensive Responses. *The Journal of Neuroscience*, *37*(40), 9645–9656. https://doi.org/10.1523/JNEUROSCI.3830-16.2017

Koenig, J. (2020). Neurovisceral regulatory circuits of affective resilience in youth: Principal outline of a dynamic model of neurovisceral integration in development. *Psychophysiology*, *57*(5). https://doi.org/10.1111/psyp.13568

Koenig, J., Kemp, A. H., Beauchaine, T. P., Thayer, J. F., & Kaess, M. (2016a). Depression and resting state heart rate variability in children and adolescents—A systematic review and meta-analysis. *Clinical Psychology Review*, *46*, 136–150. https://doi.org/10.1016/j.cpr.2016.04.013

Koenig, J., Kemp, A. H., Feeling, N. R., Thayer, J. F., & Kaess, M. (2016b). Resting state vagal tone in borderline personality disorder: A meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, 18–26. https://doi.org/10.1016/j.pnpbp.2015.07.002

Koenig, J., Klier, J., Parzer, P., Santangelo, P., Resch, F., Ebner-Priemer, U., & Kaess, M. (2020). High-frequency ecological momentary assessment of emotional and interpersonal states preceding and following self-injury in female adolescents. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-020-01626-0

Koenig, J., Rinnewitz, L., Warth, M., Hillecke, T.K., Brunner, R., Resch, F., Kaess, M. (2017a). Psychobiological response to pain in female adolescents with nonsuicidal self-injury. *J Psychiatry Neurosci*, *42*(*3*), 189-199. https://doi.org/10.1503/jpn.160074

Koenig, J., Rinnewitz, L., Parzer, P., Resch, F., Thayer, J. F., & Kaess, M. (2017b). Resting cardiac function in adolescent non-suicidal self-injury: The impact of borderline personality disorder symptoms and psychosocial functioning. *Psychiatry Research*, *248*, 117–120. https://doi.org/10.1016/j.psychres.2016.12.024

Koenig, J., Rash, J. A., Campbell, T. S., Thayer, J. F., Kaess, M. (2017c). A Meta-Analysis on Sex Differences in Resting-State Vagal Activity in Children and Adolescents. *Front. Physiol., 8*(*582*). https://doi.org/10.3389/fphys.2017.00582

Koenig, J., Weise, S., Rinnewitz, L., Parzer, P., Resch, F., & Kaess, M. (2018). Longitudinal covariance of resting-state cardiac function and borderline personality disorder symptoms in adolescent non-suicidal self-injury. *The World Journal of Biological Psychiatry*, *19*(2), 152–157. https://doi.org/10.1080/15622975.2017.1342046

Koffel, E., Khawaja, I. S., & Germain, A. (2016). Sleep Disturbances in Posttraumatic Stress Disorder: Updated Review and Implications for Treatment. *Psychiatric Annals*, *46*(3), 173–176. https://doi.org/10.3928/00485713-20160125-01

Kok, B. E., Coffey, K. A., Cohn, M. A., Catalino, L. I., Vacharkulksemsuk, T., Algoe, S. B., Brantley, M., & Fredrickson, B. L. (2013). How Positive Emotions Build Physical Health: Perceived Positive Social Connections Account for the Upward Spiral Between Positive Emotions and Vagal Tone. *Psychological Science*, *24*(7), 1123–1132. https://doi.org/10.1177/0956797612470827

Konopka, R., & Benzer, S. (1971). Clock mutants of Drosophila melanogaster. *Proc Natl Acad Sci U S A.*, *68*, 2112–2116.

Koole, S. L. (2009). The psychology of emotion regulation: An integrative review. *Cognition & Emotion*, *23*(1), 4–41. https://doi.org/10.1080/02699930802619031

Kossmeier, M., Tran, U. S., & Voracek, M. (2019a). *metaviz: Forest Plots, Funnel Plots, and Visual Funnel Plot Inference for Meta-Analysis*. R package version 0.3.0. https://CRAN.R-project.org/package=metaviz

Kossmeier, M., Tran, U. S., & Voracek, M. (2019b). *Power-enhanced funnel plots for meta-analysis: The sunset funnel plot*. https://hdl.handle.net/20.500.12034/2098

Kovacs, M. (1992). *Children's Depression Inventory: Manual.* Multi-Health Systems.

Kovacs, M., & Staff, M. (2012). *Children's Depression Inventory 2 (CDI2)*. Multi-Health Systems.

Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics: NIMH Research Domain Criteria initiative. *Psychophysiology*, *53*(3), 286–297. https://doi.org/10.1111/psyp.12518

Kraynak, T. E., Marsland, A. L., Hanson, J. L., & Gianaros, P. J. (2019). Retrospectively reported childhood physical abuse, systemic inflammation, and resting corticolimbic connectivity in midlife adults. *Brain, Behavior, and Immunity*. https://doi.org/10.1016/j.bbi.2019.08.186

Kreibig, S. D. (2010). Autonomic nervous system activity in emotion: A review. *Biological Psychology*, *84*(3), 394–421. https://doi.org/10.1016/j.biopsycho.2010.03.010

Krugers, H. J., Arp, J. M., Xiong, H., Kanatsou, S., Lesuis, S. L., Korosi, A., Joels, M., & Lucassen, P. J. (2017). Early life adversity: Lasting consequences for emotional learning. *Neurobiology of Stress*, *6*, 14–21. https://doi.org/10.1016/j.ynstr.2016.11.005

Kuhlman, K. R., Horn, S. R., Chiang, J. J., & Bower, J. E. (2019). Early life adversity exposure and circulating markers of inflammation in children and adolescents: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*. https://doi.org/10.1016/j.bbi.2019.04.028

Kumar, G., Pepe, D., & Steer, R. A. (2004). Adolescent Psychiatric Inpatients??? Self-Reported Reasons for Cutting Themselves: *The Journal of Nervous and Mental Disease*, *192*(12), 830–836. https://doi.org/10.1097/01.nmd.0000146737.18053.d2

Kundakovic, M., & Champagne, F. A. (2015). Early-Life Experience, Epigenetics, and the Developing Brain. *Neuropsychopharmacology*, *40*(1), 141–153. https://doi.org/10.1038/npp.2014.140

Kuss, O., Schumann, B., Kluttig, A., Greiser, K. H., & Haerting, J. (2008). Time domain parameters can be estimated with less statistical error than frequency domain parameters in the analysis of heart rate variability. *Journal of Electrocardiology*, *41*(4), 287–291. https://doi.org/10.1016/j.jelectrocard.2008.02.014

Kwon, H. B., Yoon, H., Choi, S. H., Choi, J.-W., Lee, Y. J., & Park, K. S. (2019). Heart rate variability changes in major depressive disorder during sleep: Fractal index correlates with BDI score during REM sleep. *Psychiatry Research*, *271*, 291–298. https://doi.org/10.1016/j.psychres.2018.11.021

Lawson, G. M., Camins, J. S., Wisse, L., Wu, J., Duda, J. T., Cook, P. A., Gee, J. C., & Farah, M. J. (2017). Childhood socioeconomic status and childhood maltreatment: Distinct associations with brain structure. *PLOS ONE*, *12*(4), e0175690. https://doi.org/10.1371/journal.pone.0175690

Laye-Gindhu, A., & Schonert-Reichl, K. A. (2005). Nonsuicidal Self-Harm Among Community Adolescents: Understanding the “Whats” and “Whys” of Self-Harm. *Journal of Youth and Adolescence*, *34*(5), 447–457. https://doi.org/10.1007/s10964-005-7262-z

Lee, K. Y., Song, J. Y., Kim, S. H., Kim, S. C., Joo, E.-J., Ahn, Y. M., & Kim, Y. S. (2010). Association between CLOCK 3111T/C and preferred circadian phase in Korean patients with bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(7), 1196–1201. https://doi.org/10.1016/j.pnpbp.2010.06.010

Lee, Y. H. (2019). Strengths and Limitations of Meta-Analysis. *The Korean Journal of Medicine*, *94*(5), 391–395. https://doi.org/10.3904/kjm.2019.94.5.391

Leeb, R. T., Paulozzi, L. J., Melanson, C., Simon, T. R., & Arias, I. (2008). *Child maltreatment surveillance. Uniform defi nitions for public health and recommended data elements.* Centers for Disease Control and Prevention.

Leichsenring, F., Leibing, E., Kruse, J., New, A. S., & Leweke, F. (2011). Borderline personality disorder. *The Lancet*, *377*(9759), 74–84. https://doi.org/10.1016/S0140-6736(10)61422-5

Lesnewich, L. M., Conway, F. N., Buckman, J. F., Brush, C. J., Ehmann, P. J., Eddie, D., Olson, R. L., Alderman, B. L., & Bates, M. E. (2019a). Associations of depression severity with heart rate and heart rate variability in young adults across normative and clinical populations. *International Journal of Psychophysiology*, *142*, 57–65. https://doi.org/10.1016/j.ijpsycho.2019.06.005

Lewis, M. D., & Douglas, L. (1988). A Dynamic Systems Approach to Cognition—Emotion Interactions in Development. In *What Develops in Emotional Development? Emotions, Personality, and Psychotherapy.* (Mascolo M.F., Griffin S. (eds)). Springer. https://doi.org/10.1007/978-1-4899-1939-7_7

Lewis, M. D., Todd, R., & Xu, X. (2010). The development of emotion regulation: A neuropsychological perspective. In *The Handbook of Life-Span Development*.

Li, J. Z., Bunney, B. G., Meng, F., Hagenauer, M. H., Walsh, D. M., Vawter, M. P., Evans, S. J., Choudary, P. V., Cartagena, P., Barchas, J. D., Schatzberg, A. F., Jones, E. G., Myers, R. M., Watson, S. J., Akil, H., & Bunney, W. E. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proceedings of the National Academy of Sciences*, *110*(24), 9950–9955. https://doi.org/10.1073/pnas.1305814110

Li, X., Shaffer, M. L., Rodriguez-Colon, S., He, F., Wolbrette, D. L., Alagona, P., Wu, C., & Liao, D. (2011). The circadian pattern of cardiac autonomic modulation in a middle-aged population. *Clinical Autonomic Research*, *21*(3), 143–150. https://doi.org/10.1007/s10286-010-0112-4

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Medicine*, *6*(7), e1000100. https://doi.org/10.1371/journal.pmed.1000100

Licht, C. M. M., de Geus, E. J. C., van Dyck, R., & Penninx, B. W. J. H. (2010). Longitudinal Evidence for Unfavorable Effects of Antidepressants on Heart Rate Variability. *Biological Psychiatry*, *68*(9), 861–868. https://doi.org/10.1016/j.biopsych.2010.06.032

Liddell, B. J., Kemp, A. H., Steel, Z., Nickerson, A., Bryant, R. A., Tam, N., Tay, A. K., & Silove, D. (2016). Heart rate variability and the relationship between trauma exposure age, and psychopathology in a post-conflict setting. *BMC Psychiatry*, *16*(1). https://doi.org/10.1186/s12888-016-0850-5

Linehan, M. M. (1993). *Diagnosis and treatment of mental disorders. Cognitive-behavioral treatment of borderline personality disorder*. Guildford Press.

Liu, R. T., Scopelliti, K. M., Pittman, S. K., & Zamora, A. S. (2018). Childhood maltreatment and non-suicidal self-injury: A systematic review and meta-analysis. *The Lancet Psychiatry*, *5*(1), 51–64. https://doi.org/10.1016/S2215-0366(17)30469-8

Llabre, M. M., Spitzer, S. B., Saab, P. G., Ironson, G. H., & Schneiderman, N. (1991). The Reliability and Specificity of Delta Versus Residualized Change as Measures of Cardiovascular Reactivity to Behavioral Challenges. *Psychophysiology*, *28*(6), 701–711.

Logan, R. W., Hasler, B. P., Forbes, E. E., Franzen, P. L., Torregrossa, M. M., Huang, Y. H., Buysse, D. J., Clark, D. B., & McClung, C. A. (2018). Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents. *Biological Psychiatry*, *83*(12), 987–996. https://doi.org/10.1016/j.biopsych.2017.11.035

Loken, E., & Gelman, A. (2017). Measurement error and the replication crisis. *Science*, *355*(6325), 584–585. https://doi.org/10.1126/science.aal3618

Lombardi, F., Sandrone, G., & Mortara, A. (1992). Circadian variation of spectral indices of heart rate variability after myocardial infarction. *Am Heart J*, *123*, 1521–1529.

Lotufo, P. A., Valiengo, L., Benseñor, I. M., & Brunoni, A. R. (2012). A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs: HRV in Epilepsy. *Epilepsia*, *53*(2), 272–282. https://doi.org/10.1111/j.1528-1167.2011.03361.x

Lovallo, W. R., Farag, N. H., Sorocco, K. H., Cohoon, A. J., & Vincent, A. S. (2012). Lifetime Adversity Leads to Blunted Stress Axis Reactivity: Studies from the Oklahoma Family Health Patterns Project. *Biological Psychiatry*, *71*(4), 344–349. https://doi.org/10.1016/j.biopsych.2011.10.018

Lu, G., Yang, F., Taylor, J. A., & Stein, J. F. (2009). A comparison of photoplethysmography and ECG recording to analyse heart rate variability in healthy subjects. *Journal of Medical Engineering & Technology*, *33*(8), 634–641. https://doi.org/10.3109/03091900903150998

Lundh, L.-G., Bjärehed, J., & Wångby-Lundh, M. (2013). Poor Sleep as a Risk Factor for Nonsuicidal Self-Injury in Adolescent Girls. *Journal of Psychopathology and Behavioral Assessment*, *35*(1), 85–92. https://doi.org/10.1007/s10862-012-9307-4

Lunkenheimer, E., Busuito, A., Brown, K. M., & Skowron, E. A. (2018). Mother–Child Coregulation of Parasympathetic Processes Differs by Child Maltreatment Severity and Subtype. *Child Maltreatment*, *23*(3), 211–220. https://doi.org/10.1177/1077559517751672

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Lynch, M., Manly, J. T., & Cicchetti, D. (2015). A multilevel prediction of physiological response to challenge: Interactions among child maltreatment, neighborhood crime, endothelial nitric oxide synthase gene (*eNOS*), and GABA(A) receptor subunit alpha-6 gene (*GABRA6*). *Development and Psychopathology*, *27*(4pt2), 1471–1487. https://doi.org/10.1017/S0954579415000887

MacMillan, H. L., Jamieson, E., & Walsh, C. A. (2003). Reported contact with child protection services among those reporting child physical and sexual abuse: Results from a community survey. *Child Abuse & Neglect*, *27*(12), 1397–1408. https://doi.org/10.1016/j.chiabu.2003.06.003

Malpas, S., & Purdie, G. (1990). Circadian variation of heart rate variability. *Cardiovasc Res*, *24*, 210–213.

Manassis, K., & Hood, J. (1998). Individual and Familial Predictors of Impairment in Childhood Anxiety Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(4), 428–434. https://doi.org/10.1097/00004583-199804000-00021

Maniglio, R. (2011). The role of child sexual abuse in the etiology of suicide and non-suicidal self-injury: Child sexual abuse and self-injury. *Acta Psychiatrica Scandinavica*, *124*(1), 30–41. https://doi.org/10.1111/j.1600-0447.2010.01612.x

Maniglio, R. (2009). The impact of child sexual abuse on health: A systematic review of reviews. *Clinical Psychology Review*, *29*(7), 647–657. https://doi.org/10.1016/j.cpr.2009.08.003

Manly, J. T., Kim, J. E., Rogosch, F. A., & Cicchetti, D. (2001). *Dimensions of child maltreatment and children's adjustment: Contributions ofdevelopmental timing and subtype*. 24.

Marceau, E. M., Meuldijk, D., Townsend, M. L., Solowij, N., & Grenyer, B. F. S. (2018). Biomarker correlates of psychotherapy outcomes in borderline personality disorder: A systematic review. *Neuroscience & Biobehavioral Reviews*, *94*, 166–178. https://doi.org/10.1016/j.neubiorev.2018.09.001

Mars, B., Heron, J., Crane, C., Hawton, K., Lewis, G., Macleod, J., Tilling, K., & Gunnell, D. (2014). Clinical and social outcomes of adolescent self harm: Population based birth cohort study. *BMJ*, *349*(oct20 5), g5954–g5954. https://doi.org/10.1136/bmj.g5954

Martínez, C. A. G., Quintana, A. O., Vila, X. A., Touriño, M. J. L., Rodríguez-Liñares, L., Presedo, J. M. R., & Penín, A. J. M. (2017). *Heart Rate Variability Analysis with the R package RHRV*. Springer International Publishing. //www.springer.com/de/book/9783319653549

Massin, M. M., Maeyns, K., Withofs, N., Ravet, F., & Gérard, P. (2000). Circadian rhythm of heart rate and heart rate variability. *Arch Dis Child*, *83*, 179–182.

Mauss, I. B., & Robinson, M. D. (2009). Measures of emotion: A review. *Cognition & Emotion*, *23*(2), 209–237. https://doi.org/10.1080/02699930802204677

May-Chahal, C., & Cawson, P. (2005). Measuring child maltreatment in the United Kingdom: A study of the prevalence of child abuse and neglect. *Child Abuse & Neglect*, *29*(9), 969–984. https://doi.org/10.1016/j.chiabu.2004.05.009

McCrory, E. J., De Brito, S. A., Kelly, P. A., Bird, G., Sebastian, C. L., Mechelli, A., Samuel, S., & Viding, E. (2013). Amygdala activation in maltreated children during pre-attentive emotional processing. *British Journal of Psychiatry*, *202*(4), 269–276. https://doi.org/10.1192/bjp.bp.112.116624

McCrory, E. J., De Brito, S. A., Sebastian, C. L., Mechelli, A., Bird, G., Kelly, P. A., & Viding, E. (2011). Heightened neural reactivity to threat in child victims of family violence. *Current Biology*, *21*(23), R947–R948. https://doi.org/10.1016/j.cub.2011.10.015

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *The New England Journal of Medicine*, 9.

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and Allostasis-Induced Brain Plasticity. *Annual Review of Medicine*, *62*(1), 431–445. https://doi.org/10.1146/annurev-med-052209-100430

Mcfarlane, A. C. (1998). Epidemiological evidence about the relationship between PTSD and alcohol abuse: The nature of the association. *Addictive Behaviors*, *23*(6), 813–825.

McLaughlin, K. A. (2016). Future Directions in Childhood Adversity and Youth Psychopathology. *Journal of Clinical Child & Adolescent Psychology*, *45*(3), 361–382. https://doi.org/10.1080/15374416.2015.1110823

McLaughlin, K. A., Sheridan, M. A., Alves, S., & Mendes, W. B. (2014). Child Maltreatment and Autonomic Nervous System Reactivity: Identifying Dysregulated Stress Reactivity Patterns by Using the Biopsychosocial Model of Challenge and Threat. *Psychosomatic Medicine*, *76*(7), 538–546. https://doi.org/10.1097/PSY.0000000000000098

McLaughlin, K. A., Sheridan, M. A., Tibu, F., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2015). Causal effects of the early caregiving environment on development of stress response systems

in children. *Proceedings of the National Academy of Sciences*, *112*(18), 5637–5642. https://doi.org/10.1073/pnas.1423363112

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood Adversity and Neural Development: A Systematic Review. *Annual Review of Developmental Psychology*, *1*(1). https://doi.org/10.1146/annurev-devpsych-121318-084950

McMahon, F. J. (2014). Prediction of treatment outcomes in psychiatry—Where do we stand? *Dialogues in Clinical Neuroscience*, *16*(4), 455–464. https://doi.org/10.31887/DCNS.2014.16.4/fmcmahon

McMurran, M., Huband, N., & Overton, E. (2010). Non-completion of personality disorder treatments: A systematic review of correlates, consequences, and interventions. *Clinical Psychology Review*, *30*(3), 277–287. https://doi.org/10.1016/j.cpr.2009.12.002

Menke, A. (2018). Precision pharmacotherapy: Psychiatry's future direction in preventing, diagnosing, and treating mental disorders. *Pharmacogenomics and Personalized Medicine*, *11*, 211–222. https://doi.org/10.2147/PGPM.S146110

Merikangas, K. R., He, J., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., & Swendsen, J. (2010). Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(10), 980–989. https://doi.org/10.1016/j.jaac.2010.05.017

Merikangas, K. R., Nakamura, E. F., & Kessler, R. C. (2009). Epidemiology of mental disorders in children and adolescents. *Dialogues in Clinical Neuroscience*, *11*(1), 14.

Meyer, H. C., & Lee, F. S. (2019). Translating Developmental Neuroscience to Understand Risk for Psychiatric Disorders. *American Journal of Psychiatry*, *176*(3), 179–185. https://doi.org/10.1176/appi.ajp.2019.19010091

Meyer, P.-W., Müller, L. E., Zastrow, A., Schmidinger, I., Bohus, M., Herpertz, S. C., & Bertsch, K. (2016). Heart rate variability in patients with post-traumatic stress disorder or borderline personality disorder: Relationship to early life maltreatment. *Journal of Neural Transmission*, *123*(9), 1107–1118. https://doi.org/10.1007/s00702-016-1584-8

Michels, N., Clays, E., Buyzere, M. D., Vanaelst, B., Henauw, S. D., & Sioen, I. (2013). Children's Sleep and Autonomic Function: Low Sleep Quality Has an Impact on Heart Rate Variability. *Sleep*, *36*(12), 1939–1946. https://doi.org/10.5665/sleep.3234

Michonski, J. D., Sharp, C., Steinberg, L., & Zanarini, M. C. (2013). An item response theory analysis of the DSM-IV borderline personality disorder criteria in a population-based sample of 11- to 12-year-old children. *Personality Disorders: Theory, Research, and Treatment*, *4*(1), 15–22. https://doi.org/10.1037/a0027948

Milicević, G., Smolej Narancić, N., Steiner, R., & Rudan, P. (2003). Increase in Cardiac Contractility During Puberty. *Coll. Antropol.*, *27*(1), 335–341.

Miskovic, V., Schmidt, L. A., Georgiades, K., Boyle, M., & MacMillan, H. L. (2009). Stability of resting frontal electroencephalogram (EEG) asymmetry and cardiac vagal tone in adolescent females exposed to child maltreatment. *Developmental Psychobiology*, *51*(6), 474–487. https://doi.org/10.1002/dev.20387

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), 6.

Molina-Carballo, A., Naranjo-Gómez, A., Uberos, J., Justicia-Martínez, F., Ruiz-Ramos, M.-J., Cubero-Millán, I., Contreras-Chova, F., Augustin-Morales, M.-C., Khaldy-Belkadi, H., & Muñoz-Hoyos, A. (2013). Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. *Journal of Psychiatric Research*, *47*(3), 377–383. https://doi.org/10.1016/j.jpsychires.2012.09.020

Monninger, M., Kraaijenvanger, E. J., Pollok, T. M., Boecker-Schlier, R., Jennen-Steinmetz, C., Baumeister, S., Esser, G., Schmidt, M., Meyer-Lindenberg, A., Laucht, M., Brandeis, D., Banaschewski, T., & Holz, N. E. (2019). The Long-Term Impact of Early Life Stress on Orbitofrontal Cortical Thickness. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhz167

Moos, R. H., McCoy, L., & Moos, B. S. (2000). Global assessment of functioning (GAF) ratings: Determinants and role as predictors of one-year treatment outcomes. *Journal of Clinical Psychology*, *56*(4), 449–461. https://doi.org/10.1002/(SICI)1097-4679(200004)56:4<449::AID-JCLP1>3.0.CO;2-8

Moškon, M. (2020). CosinorPy: A python package for cosinor-based rhythmometry. *BMC Bioinformatics*, *21*(1), 485. https://doi.org/10.1186/s12859-020-03830-w

Muehlenkamp, J. J., Kerr, P. L., Bradley, A. R., & Adams Larsen, M. (2010). Abuse Subtypes and Nonsuicidal Self-Injury: Preliminary Evidence of Complex Emotion Regulation Patterns. *The Journal of Nervous and Mental Disease*, *198*(4), 258–263. https://doi.org/10.1097/NMD.0b013e3181d612ab

Mulkey, S. B., & du Plessis, A. J. (2019). Autonomic nervous system development and its impact on neuropsychiatric outcome. *Pediatric Research*, *85*(2), 120–126. https://doi.org/10.1038/s41390-018-0155-0

Murray-Close, D., & Rellini, A. H. (2012). Cardiovascular reactivity and proactive and reactive relational aggression among women with and without a history of sexual abuse. *Biological Psychology*, *89*(1), 54–62. https://doi.org/10.1016/j.biopsycho.2011.09.008

Mutak, A. (2018). *cosinor2: Extended Tools for Cosinor Analysis of Rhythms* (0.2.1). https://CRAN.R-project.org/package=cosinor2

N. Jarczok, M., Guendel, H., J. McGrath, J., & M. Balint, E. (2019). Circadian Rhythms of the Autonomic Nervous System: Scientific Implication and Practical Implementation. In P. Svorc (Ed.), *Chronobiology—The Science of Biological Time Structure*. IntechOpen. https://doi.org/10.5772/intechopen.86822

Nagai, N., & Moritani, T. (2004). Effect of physical activity on autonomic nervous system function in lean and obese children. *International Journal of Obesity*, *28*(1), 27–33. https://doi.org/10.1038/sj.ijo.0802470

Naismith, S. L., Hermens, D. F., Ip, T. K. C., Bolitho, S., Scott, E., Rogers, N. L., & Hickie, I. B. (2012). Circadian profiles in young people during the early stages of affective disorder. *Translational Psychiatry*, *2*(5), e123–e123. https://doi.org/10.1038/tp.2012.47

Nakagawa, M., Iwao, T., & Ishida, S. (1998). Circadian rhythm of the signal averaged electrocardiogram and its relation to heart rate variability in healthy subjects. *Heart*, *79*, 493–496.

Nederhof, E., & Schmidt, M. V. (2012). Mismatch or cumulative stress: Toward an integrated hypothesis of programming effects. *Physiology & Behavior*, *106*(5), 691–700. https://doi.org/10.1016/j.physbeh.2011.12.008

Nemeroff, C. B. (2016). Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect. *Neuron*, *89*(5), 892–909. https://doi.org/10.1016/j.neuron.2016.01.019

Nemeroff, C. B., & Goldschmidt-Clermont, P. J. (2012). Heartache and heartbreak—The link between depression and cardiovascular disease. *Nature Reviews Cardiology*, *9*(9), 526–539. https://doi.org/10.1038/nrcardio.2012.91

Ng, M. Y., & Weisz, J. R. (2016). Annual Research Review: Building a science of personalized intervention for youth mental health. *Journal of Child Psychology and Psychiatry*, *57*(3), 216–236. https://doi.org/10.1111/jcpp.12470

Nock, M. K., Joinerjr, T., Gordon, K., Lloydrichardson, E., & Prinstein, M. (2006). Non-suicidal self-injury among adolescents: Diagnostic correlates and relation to suicide attempts. *Psychiatry Research*, *144*(1), 65–72. https://doi.org/10.1016/j.psychres.2006.05.010

Nock, M. K., Holmberg, E. B., Photos, V. I., & Michel, B. D. (2007). Self-Injurious Thoughts and Behaviors Interview: Development, reliability, and validity in an adolescent sample. *Psychological Assessment*, *19*(3), 309–317. https://doi.org/10.1037/1040-3590.19.3.309

Nock, M. K., Prinstein, M. J., & Sterba, S. K. (2009). Revealing the form and function of self-injurious thoughts and behaviors: A real-time ecological assessment study among adolescents and young adults. *Journal of Abnormal Psychology*, *118*(4), 816–827. https://doi.org/10.1037/a0016948

Nolte, I. M., Munoz, M. L., Tragante, V., Amare, A. T., Jansen, R., Vaez, A., von der Heyde, B., Avery, C. L., Bis, J. C., Dierckx, B., van Dongen, J., Gogarten, S. M., Goyette, P., Hernesniemi, J., Huikari, V., Hwang, S.-J., Jaju, D., Kerr, K. F., Kluttig, A., … de Geus, E. J. C. (2017). Genetic loci associated with heart rate variability and their effects on cardiac disease risk. *Nature Communications*, *8*(1), 15805. https://doi.org/10.1038/ncomms15805

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic

Review and Meta-Analysis. *PLoS Medicine*, *9*(11), e1001349. https://doi.org/10.1371/journal.pmed.1001349

Nurius, P. S., Green, S., Logan-Greene, P., & Borja, S. (2015). Life course pathways of adverse childhood experiences toward adult psychological well-being: A stress process analysis. *Child Abuse & Neglect*, *45*, 143–153. https://doi.org/10.1016/j.chiabu.2015.03.008

Nusslock, R., & Miller, G. E. (2016). Early-Life Adversity and Physical and Emotional Health across the Lifespan: A Neuroimmune Network Hypothesis. *Biological Psychiatry*, *80*(1), 23–32. https://doi.org/10.1016/j.biopsych.2015.05.017

O'Brien, I. A., O'Hare, P., & Corrall, R. J. (1986). Heart rate variability in healthy subjects: Effect of age and the derivation of normal ranges for tests of autonomic function. *Heart*, *55*(4), 348–354. https://doi.org/10.1136/hrt.55.4.348

Obrist, P. A. (1981). *Cardiovascular Psychophysiology: A Perspective. Plenum Press, New York, NY.* Plenum Press.

Oh, D. L., Jerman, P., Purewal Boparai, S. K., Koita, K., Briner, S., Bucci, M., & Harris, N. B. (2018). Review of Tools for Measuring Exposure to Adversity in Children and Adolescents. *Journal of Pediatric Health Care*, *32*(6), 564–583. https://doi.org/10.1016/j.pedhc.2018.04.021

Oliveira, R. S., Barker, A. R., Wilkinson, K. M., Abbott, R. A., & Williams, C. A. (2017). Is cardiac autonomic function associated with cardiorespiratory fitness and physical activity in children and adolescents? A systematic review of cross-sectional studies. *International Journal of Cardiology*, *236*, 113–122. https://doi.org/10.1016/j.ijcard.2017.02.022

Oshri, A., Liu, S., Duprey, E. B., & MacKillop, J. (2018). Child Maltreatment, Delayed Reward Discounting, and Alcohol and Other Drug Use Problems: The Moderating Role of Heart Rate Variability. *Alcoholism: Clinical and Experimental Research*, *42*(10), 2033–2046. https://doi.org/10.1111/acer.13858

Oster, H., Damerow, S., Kiessling, S., Jakubcakova, V., Abraham, D., Tian, J., Hoffmann, M. W., & Eichele, G. (2006). The circadian rhythm of glucocorticoids is regulated by a gating

mechanism residing in the adrenal cortical clock. *Cell Metabolism*, *4*(2), 163–173. https://doi.org/10.1016/j.cmet.2006.07.002

Ougrin, D., Tranah, T., Stahl, D., Moran, P., & Asarnow, J. R. (2015). Therapeutic Interventions for Suicide Attempts and Self-Harm in Adolescents: Systematic Review and Meta-Analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(2), 97-107.e2. https://doi.org/10.1016/j.jaac.2014.10.009

Pagoto, S. L., Schneider, K. L., Bodenlos, J. S., Appelhans, B. M., Whited, M. C., Ma, Y., & Lemon, S. C. (2012). Association of Post-Traumatic Stress Disorder and Obesity in a Nationally Representative Sample. *Obesity*, *20*(1), 200–205. https://doi.org/10.1038/oby.2011.318

Pan, A., Qi, S., Okereke, O., Rexrode, K. M., & Hu, F. B. (2011). Depression and Risk of Stroke Morbidity and Mortality: A Meta-analysis and Systematic Review. *JAMA*, *306*(11), 9.

Pan, Y., Lin, X., Liu, J., Zhang, S., Zeng, X., Chen, F., & Wu, J. (2019). *Prevalence of Childhood Sexual Abuse Among Women Using the Childhood Trauma Questionnaire: A Worldwide Meta-Analysis*. Pan, Yuli and Lin, Xiujin and Liu, Jianbo and Zhang, Shengjie and Zeng, Xuan and Chen, Fenglan and Wu, Junduan, Prevalence of Childhood Sexual Abuse Among Women Using the Childhood Trauma Questionnaire: A Worldwide Meta-Analysis (04/17/2019 04:48:47). Available at SSRN: https://ssrn.com/abstract=3373847

Park, G., Vasey, M. W., Van Bavel, J. J., & Thayer, J. F. (2014). When tonic cardiac vagal tone predicts changes in phasic vagal tone: The role of fear and perceptual load: Tonic and phasic cardiac activity under load. *Psychophysiology*, *51*(5), 419–426. https://doi.org/10.1111/psyp.12186

Patriquin, M. A., Wilson, L. C., Kelleher, S. A., & Scarpa, A. (2012). Psychophysiological Reactivity to Abuse-Related Stimuli in Sexually Revictimized Women. *Journal of Aggression, Maltreatment & Trauma*, *21*(7), 758–775. https://doi.org/10.1080/10926771.2012.690835

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947–957. https://doi.org/10.1038/nrn2513

Pawlowski, M. A., Gazea, M., Wollweber, B., Dresler, M., Holsboer, F., Keck, M. E., Steiger, A., Adamczyk, M., & Mikoteit, T. (2017). Heart rate variability and cordance in rapid eye

movement sleep as biomarkers of depression and treatment response. *Journal of Psychiatric Research*, *92*, 64–73. https://doi.org/10.1016/j.jpsychires.2017.03.026

Pears, K. C., & Capaldi, D. M. (2001). Intergenerational transmission of abuse: A two-generational prospective study of an at-risk sample. *Child Abuse & Neglect*, *25*(11), 1439–1461. https://doi.org/10.1016/S0145-2134(01)00286-1

Penttila, J., Helminen, A., Jartti, T., Kuusela, T., Huikuri, H. V., Tulppo, M. P., Coffeng, R., & Scheinin, H. (2001). Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: Effects of various respiratory patterns. *Clinical Physiology*, *21*(3), 365–376. https://doi.org/10.1046/j.1365-2281.2001.00337.x

Peters, J. L., Sutton, A. J., Jones, D. R., Abrams, K. R., & Rushton, L. (2008). Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *Journal of Clinical Epidemiology*, *61*(10), 991–996. https://doi.org/10.1016/j.jclinepi.2007.11.010

Petkova, E., Tarpey, T., Huang, L., & Deng, L. (2013). Interpreting meta-regression: Application to recent controversies in antidepressants' efficacy. *Statistics in Medicine*, *32*(17), 2875–2892. https://doi.org/10.1002/sim.5766

Peverill, M., Sheridan, M. A., Busso, D. S., & McLaughlin, K. A. (2019). Atypical Prefrontal–Amygdala Circuitry Following Childhood Exposure to Abuse: Links With Adolescent Psychopathology. *Child Maltreatment*, 107755951985267. https://doi.org/10.1177/1077559519852676

Pirkola, S., Isometsä, E., Aro, H., Kestilä, L., Hämäläinen, J., Veijola, J., Kiviruusu, O., & Lönnqvist, J. (2005). Childhood adversities as risk factors for adult mental disorders: Results from the Health 2000 study. *Social Psychiatry and Psychiatric Epidemiology*, *40*(10), 769–777. https://doi.org/10.1007/s00127-005-0950-x

Plener, P. L., Allroggen, M., Kapusta, N. D., Brähler, E., Fegert, J. M., & Groschwitz, R. C. (2016). The prevalence of Nonsuicidal Self-Injury (NSSI) in a representative sample of the German population. *BMC Psychiatry*, *16*(1), 353. https://doi.org/10.1186/s12888-016-1060-x

Porter, C., Palmier-Claus, J., Branitsky, A., Mansell, W., Warwick, H., & Varese, F. (2020). Childhood adversity and borderline personality disorder: A meta-analysis. *Acta Psychiatrica Scandinavica*, *141*(1), 6–20. https://doi.org/10.1111/acps.13118

Pozzato, I., Craig, A., Gopinath, B., Tran, Y., Dinh, M., Gillett, M., & Cameron, I. (2019). Biomarkers of autonomic regulation for predicting psychological distress and functional recovery following road traffic injuries: Protocol for a prospective cohort study. *BMJ Open*, *9*(4), e024391. https://doi.org/10.1136/bmjopen-2018-024391

Prado, D., Silva, A., Trombetta, I., Ribeiro, M., Guazzelli, I., Matos, L., Santos, M., Nicolau, C., Negrão, C., & Villares, S. (2010). Exercise Training Associated with Diet Improves Heart Rate Recovery and Cardiac Autonomic Nervous System Activity in Obese Children. *International Journal of Sports Medicine*, *31*(12), 860–865. https://doi.org/10.1055/s-0030-1267158

Prinsloo, G. E., Rauch, H. G. L., & Derman, W. E. (2014). A Brief Review and Clinical Application of Heart Rate Variability Biofeedback in Sports, Exercise, and Rehabilitation Medicine. *The Physician and Sportsmedicine*, *42*(2), 88–99. https://doi.org/10.3810/psm.2014.05.2061

Provençal, N., & Binder, E. B. (2015). The effects of early life stress on the epigenome: From the womb to adulthood and even before. *Experimental Neurology*, *268*, 10–20. https://doi.org/10.1016/j.expneurol.2014.09.001

Pulopulos, M. M. (2020). The effect of HF-rTMS over the left DLPFC on stress regulation as measured by cortisol and heart rate variability. *Hormones and Behavior*, 9.

Quintana, D. S., Alvares, G. A., & Heathers, J. A. J. (2016). Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): Recommendations to advance research communication. *Translational Psychiatry*, *6*(5), e803–e803. https://doi.org/10.1038/tp.2016.73

Quintana, D. S. (2017). Statistical considerations for reporting and planning heart rate variability case-control studies: Reporting heart rate variability studies. *Psychophysiology*, *54*(3), 344–349. https://doi.org/10.1111/psyp.12798

Quintana, D. S., & Heathers, J. A. J. (2014). Considerations in the assessment of heart rate variability in biobehavioral research. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.00805

R Core Team. (2020). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Rao, G., Lopez-Jimenez, F., Boyd, J., D'Amico, F., Durant, N. H., Hlatky, M. A., Howard, G., Kirley, K., Masi, C., Powell-Wiley, T. M., Solomonides, A. E., West, C. P., & Wessel, J. (2017). Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies: A Scientific Statement From the American Heart Association. *Circulation*, *136*(10). https://doi.org/10.1161/CIR.0000000000000523

Raudenbush, S. (2009). Analyzing effect sizes: Random-effects models. In *The handbook of research synthesis and meta-analysis.* (2nd ed., pp. 295–315). Russell Sage Foundation.

Refinetti, R., Cornélissen, G., & Halberg, F. (2007). Procedures for numerical analysis of circadian rhythms. *Biological Rhythm Research*, *38*(4), 275–325. https://doi.org/10.1080/09291010600903692

Reijman, S., Alink, L. R. A., Block, L. H. C. G. C., Werner, C. D., Maras, A., Rijnberk, C., IJzendoorn, M. H. van, & Bakermans-Kranenburg, M. J. (2014). Autonomic Reactivity to Infant Crying in Maltreating Mothers. *Child Maltreatment*, *19*(2), 101–112. https://doi.org/10.1177/1077559514538115

Reijman, S., Bakermans-Kranenburg, M. J., Hiraoka, R., Crouch, J. L., Milner, J. S., Alink, L. R. A., & van IJzendoorn, M. H. (2016). Baseline Functioning and Stress Reactivity in Maltreating Parents and At-Risk Adults: Review and Meta-Analyses of Autonomic Nervous System Studies. *Child Maltreatment*, *21*(4), 327–342. https://doi.org/10.1177/1077559516659937

Rennie, K. L. (2003). Effects of Moderate and Vigorous Physical Activity on Heart Rate Variability in a British Study of Civil Servants. *American Journal of Epidemiology*, *158*(2), 135–143. https://doi.org/10.1093/aje/kwg120

Rey, J. M., Morris-Yates, A., Singh, M., Andrews, G., & Stewart, G. W. (1995). Continuities between psychiatric disorders in adolescents and personality disorders in adults. *Am. J. Psychiatry*, *52*, 895–900.

Rey, J. M., Singh, M., Morris-Yates, A., & Andrews, G. (1997). Referred Adolescents as Young Adults: The Relationship between Psychosocial Functioning and Personality Disorder. *Australian & New Zealand Journal of Psychiatry*, *31*(2), 219–226. https://doi.org/10.3109/00048679709073824

Riem, M. M. E., Alink, L. R. A., Out, D., Van Ijzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2015). Beating the brain about abuse: Empirical and meta-analytic studies of the association between maltreatment and hippocampal volume across childhood and adolescence. *Development and Psychopathology*, *27*(2), 507–520. https://doi.org/10.1017/S0954579415000127

Roberts, A. L., Gilman, S. E., Breslau, J., Breslau, N., & Koenen, K. C. (2011). Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychological Medicine*, *41*(1), 71–83. https://doi.org/10.1017/S0033291710000401

Rodríguez-Colón, S. M., Bixler, E. O., Li, X., Vgontzas, A. N., & Liao, D. (2011). Obesity is associated with impaired cardiac autonomic modulation in children. *International Journal of Pediatric Obesity*, *6*(2), 128–134. https://doi.org/10.3109/17477166.2010.490265

Rodríguez-Colón, S. M., He, F., Bixler, E. O., Fernandez-Mendoza, J., Vgontzas, A. N., Calhoun, S., Zheng, Z.-J., & Liao, D. (2015). Sleep variability and cardiac autonomic modulation in adolescents – Penn State Child Cohort (PSCC) study. *Sleep Medicine*, *16*(1), 67–72. https://doi.org/10.1016/j.sleep.2014.10.007

Romeo, R. D. (2013). The Teenage Brain: The Stress Response and the Adolescent Brain. *Current Directions in Psychological Science*, *22*(2), 140–145. https://doi.org/10.1177/0963721413475445

Roy, C. A., & Perry, J. C. (2004). Instruments for the Assessment of Childhood Trauma in Adults: *The Journal of Nervous and Mental Disease*, *192*(5), 343–351. https://doi.org/10.1097/01.nmd.0000126701.23121.fa

Rubio-Aparicio, M., Sánchez-Meca, J., López-López, J. A., Botella, J., & Marín-Martínez, F. (2017). Analysis of categorical moderators in mixed-effects meta-analysis: Consequences of using pooled versus separate estimates of the residual between-studies variances. *British Journal of Mathematical and Statistical Psychology*, *70*(3), 439–456. https://doi.org/10.1111/bmsp.12092

Rumble, M. E., Dickson, D., McCall, W. V., Krystal, A. D., Case, D., Rosenquist, P. B., & Benca, R. M. (2018). The relationship of person-specific eveningness chronotype, greater seasonality, and less rhythmicity to suicidal behavior: A literature review. *Journal of Affective Disorders*, *227*, 721–730. https://doi.org/10.1016/j.jad.2017.11.078

Saad, M., Ray, L. B., Bradley-Garcia, M., Palamarchuk, I. S., Gholamrezaei, A., Douglass, A., Lee, E. K., Soucy, L., & Robillard, R. (2020). Autonomic Modulation of Cardiac Activity Across Levels of Sleep Depth in Individuals With Depression and Sleep Complaints: *Psychosomatic Medicine*, *82*(2), 172–180. https://doi.org/10.1097/PSY.0000000000000766

Saad, M., Ray, L. B., Bujaki, B., Parvaresh, A., Palamarchuk, I., De Koninck, J., Douglass, A., Lee, E. K., Soucy, L. J., Fogel, S., Morin, C. M., Bastien, C., Merali, Z., & Robillard, R. (2019). Using heart rate profiles during sleep as a biomarker of depression. *BMC Psychiatry*, *19*(1). https://doi.org/10.1186/s12888-019-2152-1

Saboul, D., Pialoux, V., & Hautier, C. (2014). The breathing effect of the LF/HF ratio in the heart rate variability measurements of athletes. *European Journal of Sport Science*, *14*(sup1), S282–S288. https://doi.org/10.1080/17461391.2012.691116

Sachs, M. (2014). *cosinor: Tools for estimating and predicting the cosinor model* (1.1). https://CRAN.R-project.org/package=cosinor

Sachsse, U., Von der Heyde, S., & Huether, G. (2002). Stress regulation and self-mutilation. *Am. J. Psychiatry*.

Saini, S. M., Hoffmann, C. R., Pantelis, C., Everall, I. P., & Bousman, C. A. (2019). Systematic review and critical appraisal of child abuse measurement instruments. *Psychiatry Research*, *272*, 106–113. https://doi.org/10.1016/j.psychres.2018.12.068

Salbach-Andrae, H., Bürger, A., Klinkowski, N., Lenz, K., Pfeiffer, E., Fydrich, T., & Lehmkuhl, U. (2008). Diagnostik von Persönlichkeitsstörungen im Jugendalter nach SKID-II. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, *36*(2), 117–125. https://doi.org/10.1024/1422-4917.36.2.117

Satapathy, S., Choudhary, V., & Sagar, R. (2017). Tools to assess psychological trauma & its correlates in child sexual abuse: A review & current needs in Asia. *Asian Journal of Psychiatry*, *25*, 60–73. https://doi.org/10.1016/j.ajp.2016.10.012

Saul, J. (1990). Beat-To-Beat Variations of Heart Rate Reflect Modulation of Cardiac Autonomic Outflow. *Physiology*, *5*(1), 32–37. https://doi.org/10.1152/physiologyonline.1990.5.1.32

Schade, R., Vick, K., Ott, T., Sohr, R., Pfister, C., Bellach, J., Golor, G., & Lemmer, B. (1995). Circadian Rhythms of Dopamine and Cholecystokinin in Nucleus Accumbens and Striatum of Rats—Influence on Dopaminergic Stimulation. *Chronobiology International*, *12*(2), 87–99. https://doi.org/10.3109/07420529509064504

Schär, S., Mürner-Lavanchy, I., Schmidt, S. J., Koenig, J., & Kaess, M. (*under review*). Child maltreatment and hypothalamic-pituitary-adrenal axis functioning: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews.*

Scheeringa, M. S., Zeanah, C. H., Myers, L., & Putnam, F. (2004). Heart period and variability findings in preschool children with posttraumatic stress symptoms. *Biological Psychiatry*, *55*(7), 685–691. https://doi.org/10.1016/j.biopsych.2004.01.006

Schmalenberger, K. M., & Eisenlohr-Moul, T. (2019). *Studying the menstrual cycle as an independent variable: Practical recommendations and tools for getting started*. https://doi.org/10.31219/osf.io/94jua

Schmalenberger, K. M., Eisenlohr-Moul, T. A., Eckstein, M., Würth, L., Schneider, E., Thayer, J. F., Jarczok, M. N., & Ditzen, B. (2019). Cardiac vagal activity across the menstrual cycle. *Psychoneuroendocrinology*, *107*, 67. https://doi.org/10.1016/j.psyneuen.2019.07.194

Schmalenberger, K. M., Eisenlohr-Moul, T. A., Würth, L., Schneider, E., Thayer, J. F., Ditzen, B., & Jarczok, M. N. (2019). A Systematic Review and Meta-Analysis of Within-Person Changes in Cardiac Vagal Activity across the Menstrual Cycle: Implications for Female Health and Future Studies. *Journal of Clinical Medicine*, *8*(11), 1946. https://doi.org/10.3390/jcm8111946

Schmitz, N., Kruse, J., Heckrath, C., Alberti, L., & Tress, W. (1999). Diagnosing mental disorders in primary care: The General Health Questionnaire (GHQ) and the Symptom Check List (SCL-90-R) as screening instruments. *Social Psychiatry and Psychiatric Epidemiology*, *34*(7), 360–366. https://doi.org/10.1007/s001270050156

Schubert, E., Kannenberg, A., Unbehaun, A., Lewinsohn, D., & Patzak, D. (1995). Circadian rhythms in the spectrum of heart rate variability. *Wien Med Wochenschr*, *145*, 460–462.

Schwarzer, G. (2007). meta: An R package for meta-analysis. *R News*, *7*(3), 40–45.

Selvaraj, N., Jaryal, A., Santhosh, J., Deepak, K. K., & Anand, S. (2008). Assessment of heart rate variability derived from finger-tip photoplethysmography as compared to electrocardiography. *Journal of Medical Engineering & Technology*, *32*(6), 479–484. https://doi.org/10.1080/03091900701781317

Sgoifo, A., Carnevali, L., Pico Alfonso, M. de los A., & Amore, M. (2015). Autonomic dysfunction and heart rate variability in depression. *Stress*, *18*(3), 343–352. https://doi.org/10.3109/10253890.2015.1045868

Shadish, W. R., & Haddock, C. K. (1994). Combining estimates of effect size. In *The handbook of research synthesis* (pp. 261–281). US: Russell Sage Foundation.

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, *5*. https://doi.org/10.3389/fpubh.2017.00258

Shakiba, N., Ellis, B. J., Bush, N. R., & Boyce, W. T. (2019). Biological sensitivity to context: A test of the hypothesized U-shaped relation between early adversity and stress responsivity. *Development and Psychopathology*, 1–20. https://doi.org/10.1017/S0954579419000518

Sharp, C., Ha, C., Michonski, J., Venta, A., & Carbone, C. (2012). Borderline personality disorder in adolescents: Evidence in support of the Childhood Interview for DSM-IV Borderline

Personality Disorder in a sample of adolescent inpatients. *Comprehensive Psychiatry*, *53*(6), 765–774. https://doi.org/10.1016/j.comppsych.2011.12.003

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M., & Dunbar, G. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, *12*(5), 232–241. https://doi.org/10.1016/S0924-9338(97)83297-X

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., Milo, K. M., Stock, S. L., & Wilkinson, B. (2010a). Reliability and Validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *The Journal of Clinical Psychiatry*, *71*(03), 313–326. https://doi.org/10.4088/JCP.09m05305whi

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., Milo, K. M., Stock, S. L., & Wilkinson, B. (2010b). Reliability and Validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *The Journal of Clinical Psychiatry*, *71*(03), 313–326. https://doi.org/10.4088/JCP.09m05305whi

Shenk, C. E., Noll, J. G., Putnam, F. W., & Trickett, P. K. (2010). A prospective examination of the role of childhood sexual abuse and physiological asymmetry in the development of psychopathology. *Child Abuse & Neglect*, *34*(10), 752–761. https://doi.org/10.1016/j.chiabu.2010.02.010

Shenk, C. E., Putnam, F. W., & Noll, J. G. (2012). Experiential avoidance and the relationship between child maltreatment and PTSD symptoms: Preliminary evidence. *Child Abuse & Neglect*, *36*(2), 118–126. https://doi.org/10.1016/j.chiabu.2011.09.012

Shenk, C. E., Putnam, F. W., Rausch, J. R., Peugh, J. L., & Noll, J. G. (2014). A longitudinal study of several potential mediators of the relationship between child maltreatment and posttraumatic stress disorder symptoms. *Development and Psychopathology*, *26*(1), 81–91. https://doi.org/10.1017/S0954579413000916

Sheppes, G., Suri, G., & Gross, J. J. (2015). Emotion Regulation and Psychopathology. *Annual Review of Clinical Psychology*, *11*(1), 379–405. https://doi.org/10.1146/annurev-clinpsy-032814-112739

Sherwood, A., Allen, M. T., Obrist, P. A., & Langer, A. W. (1986). Evaluation of Beta-Adrenergic Influences on Cardiovascular and Metabolic Adjustments to Physical and Psychological Stress. *Psychophysiology*, *23*(1), 89–104.

Sigrist, C., & Koenig, J. (2019). *ELM & HRV: Meta-Analysis*. https://osf.io/urxkh/

Sigrist, C., Reichl, C., Schmidt, S. J., Brunner, R., Kaess, M., & Koenig, J. (2021). Cardiac Autonomic Functioning and Clinical Outcome in Adolescent Borderline Personality Disorder Over Two Years. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 111,* 110336.

Silver, C. N., & Dunlap, W. P. (1987). Averaging Correlation Coefficients: Should Fisher's z Transformation Be Used? *Journal of Applied Psychology*, *72*(1), 146–148.

Sleipness, E. P., Sorg, B. A., & Jansen, H. T. (2007). Diurnal differences in dopamine transporter and tyrosine hydroxylase levels in rat brain: Dependence on the suprachiasmatic nucleus. *Brain Research*, *1129*, 34–42. https://doi.org/10.1016/j.brainres.2006.10.063

Smaldino, P. E., & McElreath, R. (2016). The natural selection of bad science. *Royal Society Open Science*, *3*(9), 160384. https://doi.org/10.1098/rsos.160384

Smith, C., Thienemann, M., & Steiner, H. (1992). Defense style and adaptation in adolescents with depressions and eating disorders. *Acta Paedopsychiatrica: International Journal of Child & Adolescent Psychiatry*, *55*(3), 185–186.

Smith, N., Lam, D., Bifulco, A., & Checkley, S. (2002). Childhood Experience of Care and Abuse Questionnaire (CECA.Q). *Social Psychiatry and Psychiatric Epidemiology*, *37*(12), 572–579. https://doi.org/10.1007/s00127-002-0589-9

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience & Biobehavioral Reviews*, *75*, 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003

Soder, H. E., Wardle, M. C., Schmitz, J. M., Lane, S. D., Green, C., & Vujanovic, A. A. (2019). Baseline resting heart rate variability predicts post-traumatic stress disorder treatment outcomes in adults with co-occurring substance use disorders and post-traumatic stress. *Psychophysiology*, e13377. https://doi.org/10.1111/psyp.13377

Spataro, J., Mullen, P. E., Burgess, P. M., Wells, D. L., & Moss, S. A. (2004). Impact of child sexual abuse on mental health: Prospective study in males and females. *British Journal of Psychiatry*, *184*(5), 416–421. https://doi.org/10.1192/bjp.184.5.416

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, *24*(4), 417–463. https://doi.org/10.1016/S0149-7634(00)00014-2

Squeglia, L. M., Jacobus, J., Sorg, S. F., Jernigan, T. L., & Tapert, S. F. (2013). Early Adolescent Cortical Thinning Is Related to Better Neuropsychological Performance. *Journal of the International Neuropsychological Society*, *19*(9), 962–970. https://doi.org/10.1017/S1355617713000878

Sroufe, L. A. (1997). Psychopathology as an outcome of development. *Development and Psychopathology*, *9*(2), 251–268. https://doi.org/10.1017/S0954579497002046

Stange, J. P., Hamilton, J. L., Fresco, D. M., & Alloy, L. B. (2017). Perseverate or decenter? Differential effects of metacognition on the relationship between parasympathetic inflexibility and symptoms of depression in a multi-wave study. *Behaviour Research and Therapy*, *97*, 123–133. https://doi.org/10.1016/j.brat.2017.07.007

Steptoe, A. (1998). 8.02—Psychophysiological bases of disease. In *Comprehensive Clinical Psychology* (Alan S. Bellack, Michel Hersen, Vol. 8, pp. 39–78). Pergamon. https://doi.org/10.1016/B0080-4270(73)00086-9

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., Carpenter, J., Rucker, G., Harbord, R. M., Schmid, C. H., Tetzlaff, J., Deeks, J. J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D. G., Moher, D., & Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, *343*(jul22 1), d4002–d4002. https://doi.org/10.1136/bmj.d4002

Sterne, Jonathan A C, & Egger, M. (2001). Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of Clinical Epidemiology*, 10.

Sterne, Jonathan A.C., & Egger, M. (2006). Regression Methods to Detect Publication and Other Bias in Meta-Analysis. In H. R. Rothstein, A. J. Sutton, & M. Borenstein (Eds.), *Publication Bias*

in Meta-Analysis (pp. 99–110). John Wiley & Sons, Ltd. https://doi.org/10.1002/0470870168.ch6

Stiensmeier-Pelster, J., Schürmann, M., & Duda, K. (2000). *Depressions-Inventar für Kinder und Jugendliche (DIKJ). Handanweisung (2., überarb. U. Neunorm. Aufl.)*. Hogrefe.

Stone, L. B., Amole, M. C., Cyranowski, J. M., & Swartz, H. A. (2018). History of childhood emotional abuse predicts lower resting-state high-frequency heart rate variability in depressed women. *Psychiatry Research*, *269*, 681–687. https://doi.org/10.1016/j.psychres.2018.08.106

Strand, V. C., Sarmiento, T. L., & Pasquale, L. E. (2005). Assessment and Screening Tools for Trauma in Children and Adolescents: A Review. *Trauma, Violence, & Abuse*, *6*(1), 55–78. https://doi.org/10.1177/1524838004272559

Tajima, E. A., Herrenkohl, T. I., Huang, B., & Whitney, S. D. (2004). Measuring child maltreatment: A comparison of prospective parent reports and retrospective adolescent reports. *American Journal of Orthopsychiatry*, *74*(4), 424–435. https://doi.org/10.1037/0002-9432.74.4.424

Takao, T., Tachikawa, H., Kawanishi, Y., Mizukami, K., & Asada, T. (2007). CLOCK gene T3111C polymorphism is associated with Japanese schizophrenics: A preliminary study. *European Neuropsychopharmacology*, *17*(4), 273–276. https://doi.org/10.1016/j.euroneuro.2006.09.002

Tanaka, H., Borres, M., Thulesius, O., Tamai, H., Ericson, M. O., & Lindblad, L.-E. (2000). Blood pressure and cardiovascular autonomic function in healthy children and adolescents. *The Journal of Pediatrics*, *137*(1), 63–67.

Tanaka, Y., Ishitobi, Y., Inoue, A., Oshita, H., Okamoto, K., Kawashima, C., Nakanishi, M., Aizawa, S., Masuda, K., Maruyama, Y., Higuma, H., Kanehisa, M., Ninomiya, T., & Akiyoshi, J. (2016). Sex determines cortisol and alpha-amylase responses to acute physical and psychosocial stress in patients with avoidant personality disorder. *Brain and Behavior*, *6*(8), e00506. https://doi.org/10.1002/brb3.506

Tarvainen, M. P. (2014). Kubios HRV – Heart rate variability analysis software. *Computer Methods and Programs in Biomedicine*, *11*.

Task Force of the European Society of Cardiology. (1996). Heart rate variability, standards of measurement, physiological interpretation, and clinical use. *Circulation*, *93*(5), 1043–1065.

Teicher, M. H. (2006). Neurobiological Consequences of Early Stress and Childhood Maltreatment: Are Results from Human and Animal Studies Comparable? *Annals of the New York Academy of Sciences*, *1071*(1), 313–323. https://doi.org/10.1196/annals.1364.024

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews*, *27*(1–2), 33–44. https://doi.org/10.1016/S0149-7634(03)00007-1

Teicher, M. H., & Parigger, A. (2015). The 'Maltreatment and Abuse Chronology of Exposure' (MACE) Scale for the Retrospective Assessment of Abuse and Neglect During Development. *PLOS ONE*, *10*(2), e0117423. https://doi.org/10.1371/journal.pone.0117423

Teicher, M. H., & Samson, J. A. (2013). Childhood Maltreatment and Psychopathology: A Case for Ecophenotypic Variants as Clinically and Neurobiologically Distinct Subtypes. *American Journal of Psychiatry*, *170*(10), 1114–1133. https://doi.org/10.1176/appi.ajp.2013.12070957

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews Neuroscience*, *17*(10), 652–666. https://doi.org/10.1038/nrn.2016.111

Tell, D., Mathews, H. L., Burr, R. L., & Witek Janusek, L. (2018). During stress, heart rate variability moderates the impact of childhood adversity in women with breast cancer. *Stress*, *21*(2), 179–187. https://doi.org/10.1080/10253890.2018.1424132

Thabrew, H., de Sylva, S., & Romans, S. (2011). Evaluating Childhood Adversity. In G. A. Fava, N. Sonino, & T. N. Wise (Eds.), *Advances in Psychosomatic Medicine* (Vol. 32, pp. 35–57). KARGER. https://doi.org/10.1159/000330002

Thayer, J.F., & Friedman, B. H. (1997). The heart of anxiety: A dynamical systems approach. In *The (Non)Expression of Emotions in Health and Disease* (Vingerhoets, A. (Ed.)). Springer.

Thayer, J.F., & Siegle, G. J. (2002). Neurovisceral integration in cardiac and emotional regulation. *IEEE Engineering in Medicine and Biology Magazine*, *21*(4), 24–29. https://doi.org/10.1109/MEMB.2002.1032635

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., & Brosschot, J. F. (2005). Psychosomatics and psychopathology: Looking up and down from the brain. *Psychoneuroendocrinology*, *30*(10), 1050–1058. https://doi.org/10.1016/j.psyneuen.2005.04.014

Thayer, J. F., & Koenig, J. (2019). Resting Cerebral Blood Flow and Ethnic Differences in Heart Rate Variability: Links to Self-Reports of Affect and Affect Regulation. *NeuroImage*, *202*, 116154. https://doi.org/10.1016/j.neuroimage.2019.116154

Thayer, J. F, & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, *61*(3), 201–216. https://doi.org/10.1016/S0165-0327(00)00338-4

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

Thayer, J. F, Smith, M., Rossy, L. A., Sollers, J. J., & Friedman, B. H. (1998). Heart period variability and depressive symptoms: Gender differences. *Biological Psychiatry*, *44*(4), 304–306. https://doi.org/10.1016/S0006-3223(98)00008-0

Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, *141*(2), 122–131. https://doi.org/10.1016/j.ijcard.2009.09.543

Thome, J., Densmore, M., Frewen, P. A., McKinnon, M. C., Théberge, J., Nicholson, A. A., Koenig, J., Thayer, J. F., & Lanius, R. A. (2017). Desynchronization of autonomic response and central autonomic network connectivity in posttraumatic stress disorder: CAN Connectivity and HRV in PTSD. *Human Brain Mapping*, *38*(1), 27–40. https://doi.org/10.1002/hbm.23340

Tsuji, H., Larson, M. G., Venditti, F. J., Manders, E. S., Evans, J. C., Feldman, C. L., & Levy, D. (1996). Impact of Reduced Heart Rate Variability on Risk for Cardiac Events: The Framingham Heart Study. *Circulation*, *94*(11), 2850–2855. https://doi.org/10.1161/01.CIR.94.11.2850

Turner, R. J., & Carroll, D. (1985). Heart Rate and Oxygen Consumption during Mental Arithmetic, a Video Game, and Graded Exercise: Further Evidence of Metabolically-Exaggerated Cardiac Adjustments? *Psychophysiology*, *22*(3), 261–267.

Uddin, M., & Diwadkar, V. A. (2014). Inflammation and psychopathology: What we now know, and what we need to know. *Social Psychiatry and Psychiatric Epidemiology*, *49*(10), 1537–1539. https://doi.org/10.1007/s00127-014-0934-9

Udo, T., Mun, E.-Y., Buckman, J. F., Vaschillo, E. G., Vaschillo, B., & Bates, M. E. (2013). Potential Side Effects of Unhealthy Lifestyle Choices and Health Risks on Basal and Reactive Heart Rate Variability in College Drinkers. *Journal of Studies on Alcohol and Drugs*, *74*(5), 787–796. https://doi.org/10.15288/jsad.2013.74.787

Van der Kolk, B. A. (2015). *Te body keeps the score: Brain, mind, and body in the healing of trauma*. Penguin Books.

Van Eden, C. G., & Buijs, R. M. (2000). Functional neuroanatomy of the prefrontal cortex: Autonomic interactions. In *Progress in Brain Research* (Vol. 126, pp. 49–62). Elsevier. https://doi.org/10.1016/S0079-6123(00)26006-8

Vankov, I., Bowers, J., & Munafò, M. R. (2014). Article Commentary: On the Persistence of Low Power in Psychological Science. *Quarterly Journal of Experimental Psychology*, *67*(5), 1037–1040. https://doi.org/10.1080/17470218.2014.885986

Verkuil, B., Brosschot, J. F., Marques, A. H., Kampschroer, K., Sternberg, E. M., & Thayer, J. F. (2015). Gender differences in the impact of daily sadness on 24-h heart rate variability: Gender, sadness, and HRV. *Psychophysiology*, *52*(12), 1682–1688. https://doi.org/10.1111/psyp.12541

Verkuil, B., Brosschot, J. F., Tollenaar, M. S., Lane, R. D., & Thayer, J. F. (2016). Prolonged Non-metabolic Heart Rate Variability Reduction as a Physiological Marker of Psychological Stress in Daily Life. *Annals of Behavioral Medicine*, *50*(5), 704–714. https://doi.org/10.1007/s12160-016-9795-7

Viechtbauer, W. (2005). Bias and Efficiency of Meta-Analytic Variance Estimators in the Random-Effects Model. *Journal of Educational and Behavioral Statistics*, *30*(3), 261–293. https://doi.org/10.3102/10769986030003261

Viechtbauer, W. (2010). Conducting Meta-Analyses in *R* with the **metafor** Package. *Journal of Statistical Software*, *36*(3). https://doi.org/10.18637/jss.v036.i03

Vijayakumar, N., Whittle, S., Yücel, M., Dennison, M., Simmons, J., & Allen, N. B. (2014). Thinning of the lateral prefrontal cortex during adolescence predicts emotion regulation in females. *Social Cognitive and Affective Neuroscience*, *9*(11), 1845–1854. https://doi.org/10.1093/scan/nst183

Vloet, T. D., Jans, T., Frey, A., Häußler, M., Vloet, A., Geissler, J., Susewind, M., von Dobschütz, B., Frantz, S., & Romanos, M. (2019). Mean Heart Rate and Parameters of Heart Rate Variability in Depressive Children and the Effects of Antidepressant Medication: An Exploratory Study. *Zeitschrift Für Kinder- Und Jugendpsychiatrie Und Psychotherapie*, *47*(3), 253–260. https://doi.org/10.1024/1422-4917/a000672

Vögele, C., Sorg, S., Studtmann, M., & Weber, H. (2010). Cardiac autonomic regulation and anger coping in adolescents. *Biological Psychology*, *85*(3), 465–471. https://doi.org/10.1016/j.biopsycho.2010.09.010

Voss, A, Heitmann, A., Schroeder, R., Peters, A., & Perz, S. (2012). Short-term heart rate variability—Age dependence in healthy subjects. *Physiological Measurement*, *33*(8), 1289–1311. https://doi.org/10.1088/0967-3334/33/8/1289

Voss, A., Schroeder, R., Heitmann, A., Peters, A., & Perz, S. (2015). Short-Term Heart Rate Variability—Influence of Gender and Age in Healthy Subjects. *PLOS ONE*, *10*(3), e0118308. https://doi.org/10.1371/journal.pone.0118308

Wainsztein, A. E., Abulafia, C., Goldberg, X., Camacho-Téllez, V., Vulcano, M., Vigo, D. E., José M., M., Soriano-Mas, C., Nemeroff, C. B., Salvador M., G., & Castro, M. N. (2020). Diurnal variation of heart rate variability as a physiological index of mood and emotion regulation processes in Major Depression and Borderline Personality Disorder. *Personalized Medicine in Psychiatry*, *23–24*, 100065. https://doi.org/10.1016/j.pmip.2020.100065

Waldron, J. C., Wilson, L. C., Patriquin, M. A., & Scarpa, A. (2015). Sexual Victimization History, Depression, and Task Physiology as Predictors of Sexual Revictimization: Results From a 6-Month Prospective Pilot Study. *Journal of Interpersonal Violence*, *30*(4), 622–639. https://doi.org/10.1177/0886260514535258

Walker, E., Hernandez, A. V., & Kattan, M. W. (2008). Meta-analysis: Its strengths and limitations. *Cleveland Clinic Journal of Medicine*, *75*(6), 431–439. https://doi.org/10.3949/ccjm.75.6.431

Walker, F. R., Pfingst, K., Carnevali, L., Sgoifo, A., & Nalivaiko, E. (2017). In the search for integrative biomarker of resilience to psychological stress. *Neuroscience & Biobehavioral Reviews*, *74*, 310–320. https://doi.org/10.1016/j.neubiorev.2016.05.003

Walker, W. H., Walton, J. C., DeVries, A. C., & Nelson, R. J. (2020). Circadian rhythm disruption and mental health. *Translational Psychiatry*, *10*(1), 28. https://doi.org/10.1038/s41398-020-0694-0

Wang, X., Ding, X., Su, S., Li, Z., Riese, H., Thayer, J. F., Treiber, F., & Snieder, H. (2009). Genetic influences on heart rate variability at rest and during stress. *Psychophysiology*, *46*(3), 458–465. https://doi.org/10.1111/j.1469-8986.2009.00793.x

Wang, X., Thayer, J. F., Treiber, F., & Snieder, H. (2005). Ethnic Differences and Heritability of Heart Rate Variability in African- and European American Youth. *The American Journal of Cardiology*, *96*(8), 1166–1172. https://doi.org/10.1016/j.amjcard.2005.06.050

Washburn, J. J., Potthoff, L. M., Juzwin, K. R., & Styer, D. M. (2015). Assessing DSM–5 nonsuicidal self-injury disorder in a clinical sample. *Psychological Assessment*, *27*(1), 31–41. https://doi.org/10.1037/pas0000021

Weinert, D., Sitka, U., Minors, D. S., & Waterhouse, J. M. (1994). The development of circadian rhythmicity in neonates. *Early Human Development*, *36*(2), 117–126. https://doi.org/10.1016/0378-3782(94)90039-6

Weise, S., Parzer, P., Fürer, L., Zimmermann, R., Schmeck, K., Resch, F., Kaess, M., & Koenig, J. (2020). Autonomic Nervous System Activity and Dialectical Behavioral Therapy Outcome in Adolescent Borderline Personality Disorder. *The World Journal of Biological Psychiatry*, *in press*.

Wendt, J., Hamm, A. O., Pané-Farré, C. A., Thayer, J. F., Gerlach, A., Gloster, A. T., Lang, T., Helbig-Lang, S., Pauli, P., Fydrich, T., Ströhle, A., Kircher, T., Arolt, V., Deckert, J., Wittchen, H.-U., & Richter, J. (2018). Pretreatment Cardiac Vagal Tone Predicts Dropout from and Residual Symptoms after Exposure Therapy in Patients with Panic Disorder and Agoraphobia. *Psychotherapy and Psychosomatics*, *87*(3), 187–189. https://doi.org/10.1159/000487599

Westlund Schreiner, M., Klimes-Dougan, B., Begnel, E. D., & Cullen, K. R. (2015). Conceptualizing the neurobiology of non-suicidal self-injury from the perspective of the Research Domain Criteria Project. *Neuroscience & Biobehavioral Reviews*, *57*, 381–391. https://doi.org/10.1016/j.neubiorev.2015.09.011

Whiteside, U., Chen, E., Neighbors, C., Hunter, D., Lo, T., & Larimer, M. (2007). Difficulties regulating emotions: Do binge eaters have fewer strategies to modulate and tolerate negative affect? *Eating Behaviors*, *8*(2), 162–169. https://doi.org/10.1016/j.eatbeh.2006.04.001

Whittle, S., Simmons, J. G., Hendriksma, S., Vijayakumar, N., Byrne, M. L., Dennison, M., & Allen, N. B. (2017). Childhood maltreatment, psychopathology, and the development of hippocampal subregions during adolescence. *Brain and Behavior*, *7*(2), e00607. https://doi.org/10.1002/brb3.607

Wiliams, D. P., Tracy, L. M., Gerardo, G. M., Rahman, T., Spangler, D. P., Koenig, J., & Thayer, J. F. (2019a). Sex moderates the relationship between resting heart rate variability and self-reported difficulties in emotion regulation. *Emotion*, *19*(10), 992–1001.

Williams, D. P., Cash, C., Rankin, C., Bernardi, A., Koenig, J., & Thayer, J. F. (2015). Resting heart rate variability predicts self-reported difficulties in emotion regulation: A focus on different facets of emotion regulation. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.00261

Williams, D. P., Koenig, J., Carnevali, L., Sgoifo, A., Jarczok, M. N., Sternberg, E. M., & Thayer, J. F. (2019b). Heart rate variability and inflammation: A meta-analysis of human studies. *Brain, Behavior, and Immunity*, *80*, 219–226. https://doi.org/10.1016/j.bbi.2019.03.009

Winsper, C., Lereya, S. T., Marwaha, S., Thompson, A., Eyden, J., & Singh, S. P. (2016). The aetiological and psychopathological validity of borderline personality disorder in youth: A systematic review and meta-analysis. *Clinical Psychology Review*, *44*, 13–24. https://doi.org/10.1016/j.cpr.2015.12.001

Winzeler, K., Voellmin, A., Hug, E., Kirmse, U., Helmig, S., Princip, M., Cajochen, C., Bader, K., & Wilhelm, F. H. (2017). Adverse childhood experiences and autonomic regulation in response to acute stress: The role of the sympathetic and parasympathetic nervous systems. *Anxiety, Stress, & Coping*, *30*(2), 145–154. https://doi.org/10.1080/10615806.2016.1238076

World Health Organization. (2016, September 30). *Child maltreatment*. https://www.who.int/en/news-room/fact-sheets/detail/child-maltreatment

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. (2013). *JAMA*, *310*(20), 2191. https://doi.org/10.1001/jama.2013.281053

Wulsin, L., Herman, J., & Thayer, J. F. (2018). Stress, autonomic imbalance, and the prediction of metabolic risk: A model and a proposal for research. *Neuroscience & Biobehavioral Reviews*, *86*, 12–20. https://doi.org/10.1016/j.neubiorev.2017.12.010

Yachi, C., Hitomi, T., & Yamaguchi, H. (2018). Two Experiments on the Psychological and Physiological Effects of Touching-Effect of Touching on the HPA Axis-Related Parts of the Body on Both Healthy and Traumatized Experiment Participants. *Behavioral Sciences*, *8*(10), 95. https://doi.org/10.3390/bs8100095

Yates, T. M. (2004). The developmental psychopathology of self-injurious behavior: Compensatory regulation in posttraumatic adaptation. *Clinical Psychology Review*, *24*(1), 35–74. https://doi.org/10.1016/j.cpr.2003.10.001

Yehuda, R., Kahana, B., Schmeidler, J., Southwick, S. M., Wilson, S., & Giller, E. L. (1995). Impact of cumulative lifetime trauma and recent stress on current posttraumatic stress disorder symptoms in holocaust survivors. *The American Journal of Psychiatry*, *152*(12), 1815–1818. http://dx.doi.org/10.1176/ajp.152.12.1815

Yeragani, V. K., Sobolewski, E., Kay, J., Jampala, V. C., & Igel, G. (1997). Effect of age on long-term heart rate variability. *Cardiovascular Research*, *35*(1), 35–42. https://doi.org/10.1016/S0008-6363(97)00107-7

Young-Southward, G., Svelnys, C., Gajwani, R., Bosquet Enlow, M., & Minnis, H. (2020). Child Maltreatment, Autonomic Nervous System Responsivity, and Psychopathology: Current State of the Literature and Future Directions. *Child Maltreatment*, *25*(1), 3–19. https://doi.org/10.1177/1077559519848497

Zanarini, M., & Wedig, M. (2014). Childhood Adversity and the Development of Borderline Personality Disorder. In *Handbook of Borderline Personality Disorder in Children and Adolescents*. Springer New York.

Zetterqvist, M. (2015). The DSM-5 diagnosis of nonsuicidal self-injury disorder: A review of the empirical literature. *Child and Adolescent Psychiatry and Mental Health*, *9*(1), 31. https://doi.org/10.1186/s13034-015-0062-7

Zhang, J. (2007). Effect of Age and Sex on Heart Rate Variability in Healthy Subjects. *Journal of Manipulative and Physiological Therapeutics*, *30*(5), 374–379. https://doi.org/10.1016/j.jmpt.2007.04.001

Zhang, T., Huang, L., Zhang, L., Tan, M., Pu, M., Pickard, G. E., So, K.-F., & Ren, C. (2016). ON and OFF retinal ganglion cells differentially regulate serotonergic and GABAergic activity in the dorsal raphe nucleus. *Scientific Reports*, *6*(1), 26060. https://doi.org/10.1038/srep26060

Zimmerman, M. (2011). A Critique of the Proposed Prototype Rating System for Personality Disorders in DSM-5. *Journal of Personality Disorders*, *25*(2), 206–221. https://doi.org/10.1521/pedi.2011.25.2.206