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Neurovisceral regulatory circuits of affective resilience in youth

Principal outline of a dynamic model of neurovisceral integration in development

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Abstract

The *Neurovisceral Integration Model* (NIM) is one of the most influential psychophysiological models addressing the interplay between the autonomic (ANS) and central nervous system (CNS). In their groundbreaking conceptual work, integrating autonomic, attentional, and affective systems into a functional and structural network, Thayer & Lane laid the foundation for empirical research in the past two decades. The present paper provides a principal outline aiming to reflect and further elaborate on the model from a dynamic developmental perspective. The central question at hand is, how does *neurovisceral integration* develop (early in life)? By reviewing the existing evidence, it is illustrated that key components of the model, both, on a physiological and psychological level, undergo extensive change early in the course of life. This sensitive period of human development seems key for our understanding of the integrated action of the ANS and CNS in emotion across the lifespan. Early life events may interfere with the fine-tuned interplay of this shared neural circuitry resulting in long-term dysfunction and psychiatric illness. In the absence of longitudinal data covering the entire co-development of the ANS and CNS from early childhood to adolescence into early adulthood, it is suggested, that vagal activity and its normative increase in adolescence is a key premise for normative brain development on a structural and functional level, subsequent psychological functioning and adaptive regulation. Implications from this dynamic perspective and suggestions for future research in the field of developmental psychophysiology are discussed.

KEYWORDS

adolescence, brain development, emotion regulation, heart rate variability, neurovisceral integration, psychopathology

1 | INTRODUCTION

Someone asked Bernard Shaw what, in his opinion, is the most beautiful thing in this world. "Youth," he replied, "is the most beautiful thing in this world—and what a pity that it has to be wasted on children!"[1]

Adolescence is a critical period of human development. The growing individual is facing tremendous change, experiencing challenges on a biological, societal, inter- and intra-individual level. The transition from childhood to puberty, to adolescence and early adulthood represents a sensitive period. These transitions are characterized by a steady decrease in parental influence and a gradual shift towards an individuals' independency. Progressive maturation in youth during this period exerts widespread influences on mood and emotion, straining cognitive capacities. The formation of personal relationships, self-confidence, interests, and ethical values, shape personality development and have long-term consequences on mental and physical well-being. The growing adolescent is confronted with legal rules and social norms, requiring decision making in accordance with individual goals and perspectives. During this period, teenagers are most vulnerable to influences from their environment (i.e., peers, social media) and prone to develop mental illnesses, as social and environmental demands require the establishment of strategies to cope with heightened emotional distress.

1.1 | The global burden of youth psychopathology

Psychiatric disorders are developmental disorders. About 75% of individuals with mental illness experience their first symptoms before the age of 25 years (Meyer & Lee, 2019). Among adolescents, more than 50% experience episodes of mental ill-health. Accordingly, nationally representative surveys estimate the life-time prevalence for any mental health disorder in this age group at around 45% (Merikangas et al., 2010), with a world-wide pooled point prevalence of 13% (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). These numbers indicate that currently about 96 million adolescents worldwide are affected by mental health problems. Affective disorders (i.e., depression and anxiety) are most common among adolescents and frequently comorbid (Merikangas, Nakamura, & Kessler, 2009). In 2014, an estimated 2.8 million adolescents in the United States experienced at least one major depressive episode, representing 11.4% of the underage U.S. population (Hedden, 2015). Representative data from European countries illustrate similar rates among adolescents (7.1%–19.4%) with regional differences (Balazs et al., 2012). Psychiatric disorders present a major burden for the individual and our society, placing them distant first in the global burden of disease statistics (Vigo, Thornicroft, & Atun, 2016). Still, this is not reflected in our global efforts, aiming to increase the understanding of clinical entities, ultimately reducing their harm and societal costs. As illustrated, the majority of mental disorders have their onset during childhood or adolescence—highlighting the important role of child and adolescent psychiatry. Identifying those at risk for the development of psychopathology and providing early intervention are the two incremental tasks, we as a field are facing. Our endeavors, trying to identify biological markers of psychopathological development, resulted in many promising approaches and techniques that, yet, have not fundamentally changed our clinical practice. I am convinced, that psychophysiological research from a developmental perspective can enhance our understanding of the developmental trajectories associated with normative affective function and translates to meaningful clinical applications.

1.2 | Psychophysiology and the psychiatric sciences

In the past century, psychophysiological research in adults with psychiatric disorders informed major theories of psychopathology, emphasizing the importance of psychophysiological processes underlying different domains of psychosocial functioning (Galderisi & Mucci, 2002). Considering that the vast majority of mental disorders have their onset during adolescence, psychophysiological research in youth is key for our understanding of developmental trajectories and the identification of early precursors of pathology. In the past decades, a focus on adolescents enabled us to differentiate effects and phenomena associated with first-onset pathology from those associated with long-term illness and chronicity, thereby guiding our efforts in early prevention and intervention. However, the aforementioned changes related to pubertal development pose a considerable challenge to the psychophysiological research methodology. Intra- and inter-individual differences on variables of interest present with greater variance during adolescence, calling to disentangle findings on aberrant and normative development rooted in the complex interplay of various physiological systems and their interaction under development, and natural variance. This theoretical perspective will review existing research on adolescent neurodevelopment, focusing on ANS and CNS function in association with psychopathology. Emphasis is placed on adolescence, given its importance for the timing

[1] 1931 February 14, Rockford Register-Republic, Cook-Coos by Ted Cook (King Features Syndicate), Quote Page 8, Column 1, Rockford, Illinois. (GenealogyBank).

of first-onset psychopathology—in particular in affective domains.

The psychiatric sciences themselves, experience a shift in paradigms, in our effort to overcome the static barriers of clinical entities (diagnoses). In the past decades, findings from neuroimaging and genetic studies, illustrating commonalities between (previously thought) distinct clinical disorders, failed to align with our consensus-based descriptions of pathology, as established in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or *International Classification of Disease* (ICD) systems. In consequence, ideas to formulate a new framework for research on mental disorders were generated (Insel et al., 2010; Kozak & Cuthbert, 2016). It was evident, that psychopathology cannot be sufficiently described on a single domain of functioning or level of observation (i.e., that psychiatric disorders are solely related to mechanisms of brain function). Although neuroimaging studies provided important insights into altered brain structure and function associated with psychiatric disorders or phenomena linked to psychiatric symptoms, they fell short in providing meaningful implications and applications for everyday clinical practice, beyond issues regarding the validity and replicability (Eklund, Nichols, & Knutsson, 2016) or costs associated with the clinical use of the respective assessment modalities. A more holistic view, integrating different physiological systems and their interactions in maintaining physiological and psychological wellbeing, came alive. My work addresses the integral function of the autonomic (ANS) and central nervous system (CNS) in youth with psychopathology, with a focus on emotion and emotion regulation in affective disorders or personality disorders characterized by affective instability.

Key to my understanding of psychiatric disorders from a psychophysiological perspective was (and is) the *Neurovisceral Integration Model* (NIM, Thayer & Lane, 2000, 2009) in context of the *Research Domain Criteria* (RDoC, (Kozak & Cuthbert, 2016). Let's assume psychiatric disorders—affective disorders in particular - represent the pathological endpoint on a continuum describing an individuals' capacity to regulate stress and states of heightened emotional distress. As conceptualized within the NIM, the capacity to regulate stress and emotions is closely linked to physiological systems regulating autonomic arousal and organ function. On the one hand, the experience of distinct emotional states induces defined patterns of physiological arousal. On the other hand, increased physiological arousal limits ones' capacity to willfully regulate momentary affective states. Typically, increased autonomic arousal is associated with greater difficulties in actively regulating emotions. From a simplified perspective (also see Berntson, Norman, Hawkley, & Cacioppo, 2008), vagal parasympathetic activity is required to counteract states of increased sympathetic activity, and therefore also critically implicated in the regulation of emotional states, characterized by increased physiological arousal. The RDoC (Kozak & Cuthbert, 2016), aiming to provide a research framework of basic dimensions of functioning underlying the full range of human behavior from normal to abnormal, acknowledge this interplay and highlight the importance of the **Arousal/Regulatory Systems** and **Positive/Negative Valence Systems** as important domains underlying psychopathology. But how do these domains and their interaction play out in the long run?

2 | FURTHER ELABORATION ON THAYER AND LANE

The functional overlap between autonomic arousal and emotion regulation is based on shared neural circuits involved in the regulation of the ANS and emotion, as illustrated in the case of emotion dysregulation in depression in Figure 1. This interconnection has been proposed and conceptualized by the *NIM* (Thayer & Lane, 2000, 2009). A key player involved in the coregulation of affect and arousal, exerting CNS control over organ function, is the *vagus nerve*. In brief, the vast majority of vagal fibers (80%–90%) are afferent, signaling information from all organs of the body to the brain. These afferent projections terminate in the *nucleus tractus solitarius* (NTS), with subsequent projections to limbic and cortical structures involved in emotion regulation (Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). These structures include brainstem regions that contain serotonergic (*raphe nucleus*) and noradrenergic (*locus coeruleus*) perikarya projecting to the forebrain. This "afferent vagal loop" enables the brain to receive information about the body's autonomic state and potential environmental or intra-individual demands that require timely adjustment of organ function. Further, the afferent vagal loop provides a neuroanatomical pathway through which the ANS is directly linked to the serotonergic and noradrenergic systems involved in emotion. Efferent vagal fibers innervate almost all organs of the body supplying motor fibers to enable parasympathetic control of organ function, including the heart, lungs and digestive tract. This "efferent vagal loop" enables the brain to adjust organ function in accordance with environmental or intra-individual demands and provides a neuroanatomical pathway through which emotions affect organ function. Afferent and efferent vagal pathways provide an anatomical framework to understand how (a) emotional states can affect physiological function and how (b) physiological function affects emotional states and their willful regulation. To illustrate two examples with practical and clinical relevance,

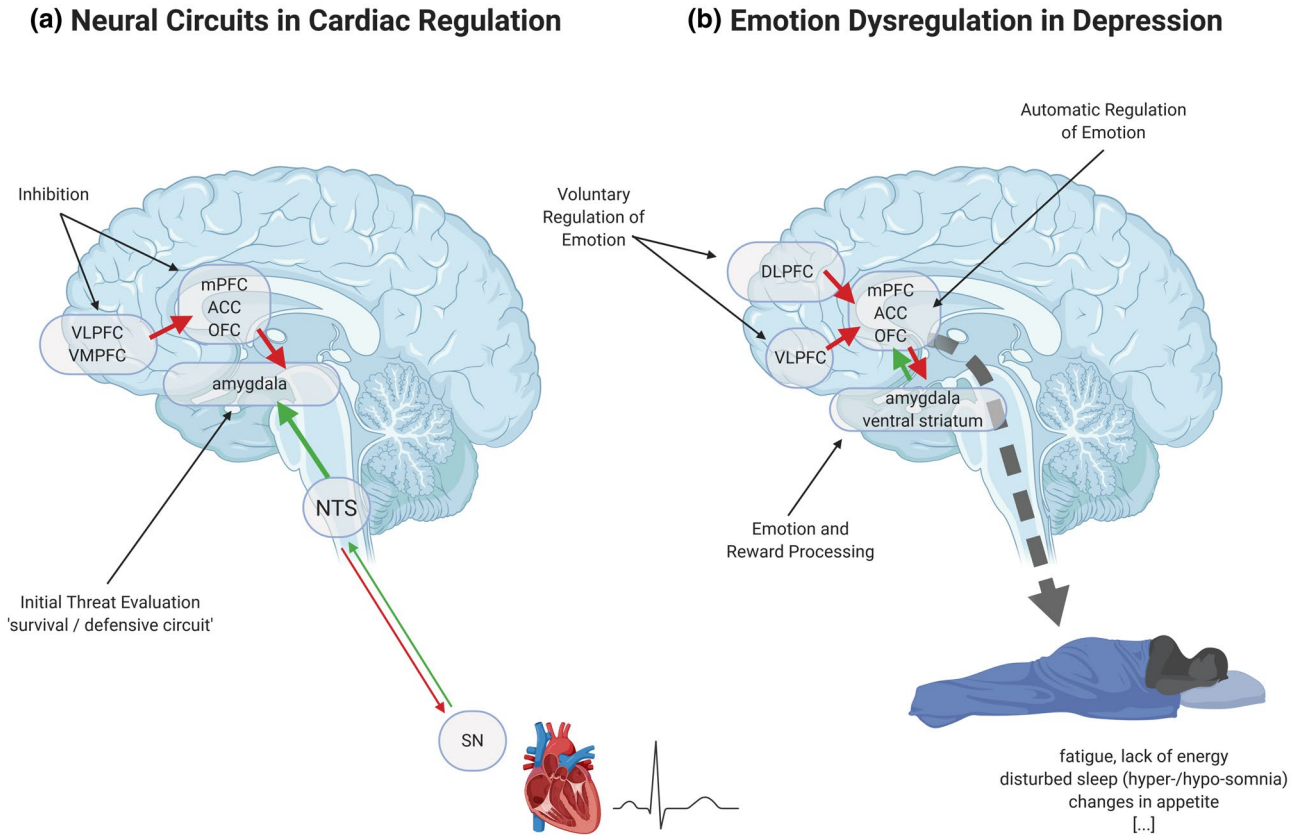

FIGURE 1 Shared Neural Circuits involved (a) Cardiac Regulation and (b) Emotion Dysregulation in Depression; Simplified illustration; Figure (b) adapted from (Kupfer, Frank, & Phillips, 2012); For further reading: (Compare, Zarbo, Shonin, Van Gordon, & Marconi, 2014)

vagal pathways are likely implicated in the loss of appetite in severe worry and depression (i.e., innervation of the gastrointestinal tract), and underlie increased physiological arousal (i.e., dyspnea, tachycardia) in panic and anxiety disorders. The developmental neurobiology of these pathways in children and adolescents with psychopathology, however, is not well understood.

A central thought of the NIM is that heart rate variability (HRV), a psychophysiological proxy of vagal activity, is capable to index activity in a "flexible network of neural structures that is dynamically organized in response to environmental challenges" (Thayer & Lane, 2009). It is suggested, that a common reciprocal inhibitory cortico-subcortical neural circuit, allows the prefrontal cortex (PFC) to exert an inhibitory influence on subcortical structures associated with defensive behavior (Thayer & Siegle, 2002). However, it remains unclear how these neural circuits develop and how the early environment may shape their functionality over the course of life. Extending on the NIM, I suggest that the functional interaction of the ANS and CNS is shaped early in the course of life and that adolescence, in particular, represents the most sensitive period of development of this circuitry, forming the foundation for adaptive neurovisceral regulation throughout the lifespan.

2.1 | Normative development of cardiac activity[2]

"The sympathetic impulses prod the heart at the earliest age almost as much as they do later in life. But the parasympathetic impulses have only a small restraining influence on heart rate before adulthood." Adolph concluding on a series of experiments in rats (Adolph, 1967).

To understand norm variants in the development of vagal activity in youth, it's critical to understand its normative development. Generally speaking, HRV decreases with increasing age in adults (O'Brien, O'Hare, & Corrall, 1986; Zhang, 2007). Surprisingly, there are relatively few longitudinal studies on normative HRV development in children and adolescents. We know from cross-sectional studies, that adolescents typically show greater vagally-mediate HRV compared to adults (Antelmi et al., 2004). Studies in younger children

[2]Most of my research focusses on cardiac vagal activity, utilizing physiological measures of resting state cardiac activity as proxies of vagal activity. Therefore, resting state heart rate (HR) and its variability (HRV) are central in the following. Alongside measures of resting state HR and HRV, a line of research focusses on altered ANS reactivity in developmental psychopathology that is not extensively covered in this review.

have shown steep increases between 4 months and 4 years of age (Bar-Haim, Marshall, & Fox, 2000). Across the pubertal age span, it has been shown, that HRV increases until age 18 and only thereafter declines (Silvetti, Drago, & Ragonese, 2001). Although we lack sufficient evidence from longitudinal studies on HRV development early in life, evidence on the development of HR in early childhood has previously been summarized in a systematic review of observational studies, providing some important insights into ANS function in young age. Findings suggest that after a peak at 1 month of age, mean HR continuously decreases until the age of 18, with particular steep decreases until 2 years of age (Fleming et al., 2011). The pattern of normative HR development is illustrated in Figure 2. In the absence of data, but knowing that HR and vagally-mediated HRV are typically negatively correlated (given that HR is a product of both sympathetic and parasympathetic activity), and based on the cross-sectional studies reviewed above we can assume that vagal activity steadily increases during adolescence. Note, early work by Larson and Porges illustrated similar patterns, suggesting increasing vagal control over heart function in early development in rats (Larson & Porges, 1982).

Importantly, studying the normative development of cardiac function in youth illustrates that measures of HR and HRV are not directly comparable in adults and children and adolescents. From a methodological perspective—and without going too much into detail—others have previously suggested that adjustments to the frequency windows used for HRV analysis must be made accordingly for children and adolescents of younger age (Shader et al., 2018). Illustrating that research in children and adolescents bears considerable challenges to our research methodology. Importantly, there are considerable sex differences in these trajectories. Whereas in adults we were able to show that women have greater HRV and HR (Koenig & Thayer, 2016), HRV is decreased and HR increased in girls compared to boys (Koenig, Rash, Campbell, Thayer, & Kaess, 2017). Importantly, there is evidence that these sex-related differences in ANS function emerge during adolescence (de Zambotti et al., 2017). Figure 3a provides an overview of the assumed developmental trajectories of HR and HRV across the lifespan. To briefly summarize, studying the normative development of HR and HRV illustrates that vagal influence over cardiac activity increases in normative development early in the course of life.

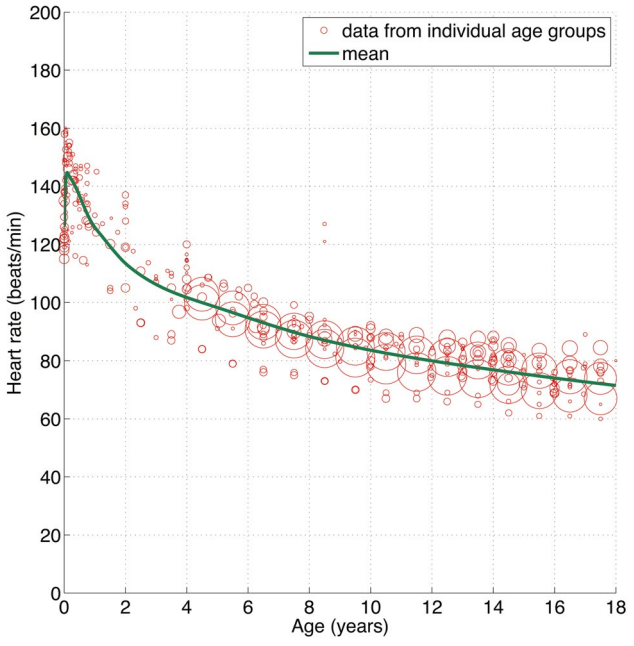

FIGURE 2 Normative Changes in Mean Heart Rate in Healthy Children and Adolescents Across Development; re-use with kind permission by Dr. Susannah Fleming. Originally published in (Fleming et al., 2011)

2.2 | Emotion regulation in youth and risk for psychopathology

Whereas infants rely on the interaction with their caregivers to regulate emotions, adolescents progressively internalize these abilities to independently regulate emotions (for detailed reviews: e.g. Bariola, Gullone, & Hughes, 2011; Diamond & Aspinwall, 2003; Zeman, Cassano, Perry-Parrish, & Stegall, 2006). Learning how to regulate one's own emotions is an essential component of adolescent development. The steadily increasing capacity to self-regulate emotions has been nicely summarized by Thompson:" […] whereas the newborn infant may cry uncontrollably when distressed, the toddler is capable of seeking assistance, the preschooler can reflect upon and talk about her feelings, the school-age child can re-direct attention and use other deliberate strategies to reduce distress (and can control its expression to others), and the adolescent has sufficient self-understanding to evoke more personal, idiosyncratic self-regulatory strategies." (Thompson, 1991, p. 270). The quote highlights that emotion regulation is related to a variety of intra- and inter-individual psychological processes, which are not reviewed here in detail. *But are these processes related?* Whereas the link between HRV and emotion regulation has been well established in adults (Appelhans & Luecken, 2006; Williams et al., 2015), what do we know about their relationship early in the course of life?

Focusing on the association between cardiac activity and emotion, early pioneering work by Fox and colleagues has shown that infants (5 months of age) with greater HRV were more reactive toward stimuli of negative and positive valence. Similarly, infants (14 months of age) with greater HRV were more sociable and approachful (Fox, 1989). Following this line of research, Stifter et al. were able to show, that children who maintained low cardiac vagal activity from 5 to 18 months of age, were rated as more fearful (Stifter & Jain, 1996). Overall supporting the idea, that infants with

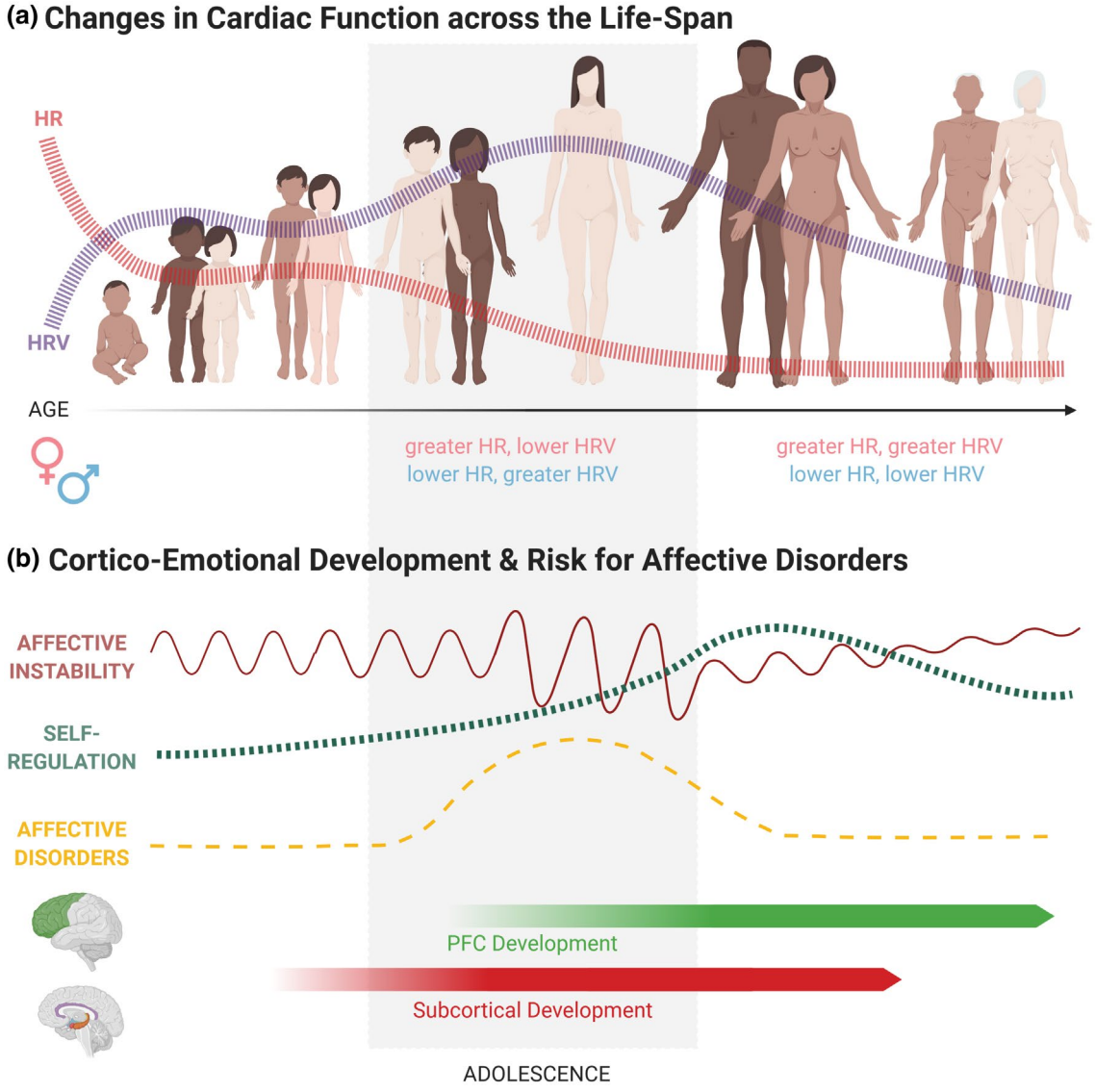

FIGURE 3 Changes in Cardiac and Psychological Function Across the Lifespan; (a): assumed trajectories of heart rate (HR) and heart rate variability (HRV) in aging including the notion of a change in sex differences: note: one has to assume that these trajectories differ by ethnicity (Eyre, Fisher, Smith, Wagenmakers, & Matyka, 2013; Hill et al., 2015), not further detailed here. (b): assumed trajectories in psychological function with a focus on emotion, incidence time of affective disorders and (simplified) underlying neural mechanisms

lower HRV are behaviorally inhibited (Kagan, Reznick, & Snidman, 1987). A study in 3–6-year-old children showed that great HRV is associated with better attention regulation in response to angry emotion and higher levels of prosocial behavior (Clark, Skowron, Giuliano, & Fisher, 2016). It seems evident, that early in the course of human development, normative increases in vagal activity are important in shaping our emotional development.

Of the few studies, studying the longitudinal association between HRV and emotion regulation in older youth, Vasilev et al. were able to show, that increasing HRV across early development (age of enrollment around 10 years) was associated with fewer difficulties in emotion regulation three years later (Vasilev, Crowell, Beauchaine, Mead, & Gatzke-Kopp, 2009). Interestingly, a recent meta-analysis showed that stronger associations between HRV and self-regulation in adult samples compared to youth samples, suggesting that such association is only fully established in early adulthood (Holzman & Bridgett, 2017). As reviewed above, vagal activity (indexed by HRV) seems to be related to explorative/defensive behavior very early in human development and normative increases early in adolescence are associated with better emotion regulation. As suggested by the NIM and detailed earlier, both, the control of cardiac function and emotion regulation have a shared neural basis. Reviewing research on brain maturation in early development will help to ingrate these lines of research, providing a holistic view, linking ANS and CNS development in emotion regulation.

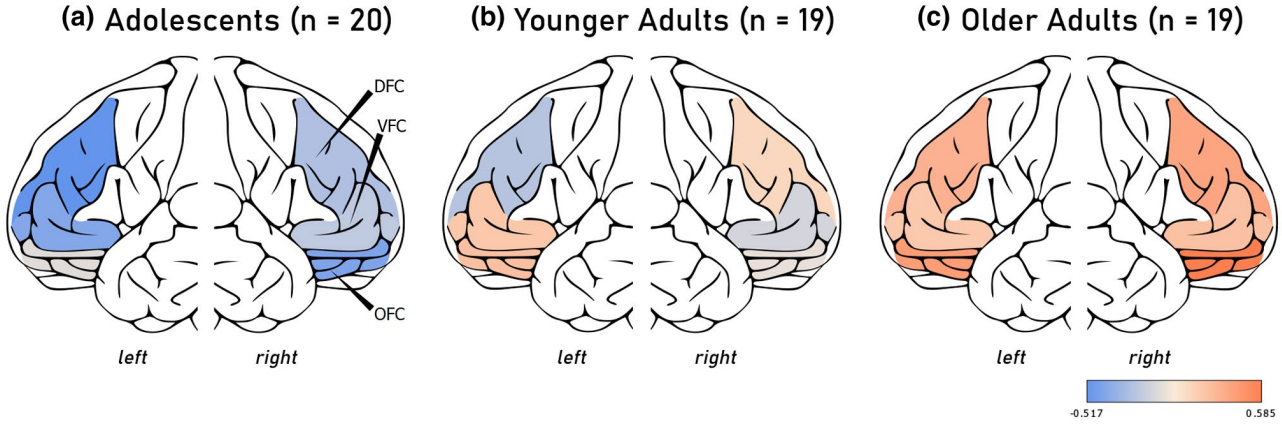

FIGURE 4 Changes in the Association between Heart Rate Variability and Cortical Thickness by Regions of Interest in the Prefrontal Cortex; illustrated is a gradual shift in the association from adolescence (negative) to adulthood (positive); illustrations done using cerebroViz in R (Bahl, Koomar, & Michaelson, 2017); Note data on cortical thickness based on Desikan-Killiany atlas; translation of regions as followed: dorsolateral prefrontal cortex (DFC): rostral middle frontal gyrus; orbital frontal cortex (OFC): lateral orbitofrontal cortex; ventrolateral prefrontal cortex (VFC): pars orbitalis; color bar: indicates the strength and direction of correlation (Pearson correlation coefficient); (a): data from (Koenig, Parzer, et al., 2018); (b and c) data from (Yoo et al., 2018)

2.3 | Early brain development

The NIM places emphasize on brain regions critically involved in regulating heart function (Ruiz Vargas, Sörös, Shoemaker, & Hachinski, 2016; Thayer et al., 2012). Key to the central idea of the NIM are prefrontal vagal pathways inhibiting activity of subcortical regions, in particular the amygdala. As illustrated in Figure 1, these subcortical and prefrontal brain regions are also critically implicated in emotion regulation (for a review and summary see Beauchaine & Cicchetti, 2019). The following will focus on these regions of interest (ROI). For a detailed review of HRV and brain morphology see Carnevali, Koenig, Sgoifo, & Ottaviani, 2018).

It is important to note that prefrontal and subcortical brain regions undergo extensive changes in early development. In fact, adolescence is the period where most dramatic changes in brain structure and function are seen. Focusing on cortical thickness, cortical thinning is observed—after an initial increase in cortical thickness up to 2 years of age—across the lifespan and most pronounced from 4 to 14 years of age, reflecting a decrease of about 1% in cortical thickness per decade (Fjell et al., 2015; Tamnes et al., 2017). The negative association between age and cortical thickness is particularly seen for frontal areas—to no surprise, normative cortical thinning has been linked to better neuropsychological performance (Squeglia, Jacobus, Sorg, Jernigan, & Tapert, 2013). Substantial thinning seems to occur between ages 12 and 14 and most interestingly, males show more accelerated thinning than females (Squeglia et al., 2013). Linking cortical thinning and emotion regulation, Vijayakumar were able to show, that greater cortical thinning of the left dorsolateral prefrontal cortex (dlPFC) and the left ventrolateral prefrontal cortex (vlPFC) during adolescence was significantly associated with greater use of more adaptive emotion regulation strategies in females but not in males (Vijayakumar et al., 2014). We were able to show that associations between brain morphology and HRV change as a function of age in healthy subjects. Drawing on two independent samples of adults (Yoo et al., 2018), we found positive correlations between resting state vagally-mediated HRV and cortical thickness of PFC regions. Aiming to replicate the findings in adolescents, we found an inverse pattern, such that in adolescents we found these ROI negatively associated with resting state vagally-mediated HRV (Koenig, Parzer, et al., 2018). Findings from these two studies are illustrated in Figure 4, illustrating only selected prefrontal ROI.

In the absence of longitudinal studies, we have previously speculated that greater vagal activity may have beneficial effects on the natural course of cortical thinning during adolescence (Koenig, Parzer, et al., 2018). While other explanations are possible (i.e., brain maturation driving vagal activity; third independent factor), this idea will be detailed in the following.

3 | A DYNAMICAL MODEL OF NEUROVISCERAL INTEGRATION

It is suggested, that connections between the PFC and subcortical regions (i.e., limbic structures) are finetuned during adolescence and that these processes underlie characteristic instabilities of affect and behavior in adolescents. Functional magnetic resonance imaging (fMRI) studies support these notions, illustrating that children of younger age recruit larger and more diffuse regions of the PFC and that these patterns become more refined with increasing age. In accordance with the model of adolescent brain maturation

by Casey et al., the "immature ventral [PFC] may not provide sufficient topdown control of robustly activated […] affect processing regions [i.e., the amygdala]," leading to poorer decision making in emotional context and greater risk-taking behavior (Casey, Jones, & Hare, 2008). The model has been confirmed by longitudinal fMRI studies across adolescence and a multitude of studies have linked affective development during adolescence to these specific trajectories in brain development (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015). I propose that ANS development, in particular the normative increase in vagal activity in the transition from adolescence to emerging adulthood, is critical for this pattern of PFC maturation, and associated psychological processes—in particular emotion regulation—thereby promoting affective resilience. I suggest that although youth typically represent increased risk-taking behavior and emotional instability, due to a normative delay in PFC maturation, only those with insufficient 'vagal support' continue to develop severe psychopathology (termed 'vagal insufficiency'). Adolescents with sufficient 'vagal support' in the transition to early adulthood will exhibit continued PFC maturation and subsequent affective resilience (i.e., termination of risk-taking behavior, mental well-being). This principle idea is illustrated in Figure 5.

The concept assumes causality, such that vagal activity influences CNS development. Research on CNS development in children with extreme cardiovascular conditions may help to better understand how ANS function may influence brain development. In a study including full-term infants with hypoplastic left heart syndrome or transposition of the great arteries, it has been shown that these children show delayed structural brain maturation (Licht et al., 2009). In a review of CNS outcomes in children with complex congenital heart disease, Wernovsky et al. address different mechanisms underlying CNS abnormalities in these patients. Alongside shared genetic mechanisms (that might also account for norm variants in CNS-ANS co-development in association with HRV (Bourdon et al., 2018; Golosheykin, Grant, Novak, Heath, & Anokhin, 2017; Nolte et al., 2017); hypoxemia, hypotension, hypo- or hyperglycemia, hyperventilation, and hyperthermia are discussed to result in long term CNS abnormalities (Wernovsky, Shillingford, & Gaynor, 2005). A similar mechanism may explain the association between vagal activity and brain development on a continuum in health and disease.

Following this thought, a potent physiological mechanism, potentially mediating the association between HRV and brain development is blood pressure. Hypertension is associated with reduced HRV and it has been shown that lower HRV predicts a greater risk of incident hypertension over 9 years (Schroeder et al., 2003). On a very interesting side note, arterial pressure is inversely related to HRV in rodent homologs of adolescence but not pre-adolescence (Tanaka et al., 2000). A study in rats with stress-induced arterial hypertension showed that hypertension was associated with an attenuation of the excitatory and energetic activity in the PFC (Seryapina, Shevelev, Moshkin, Markel, & Akulov, 2017).

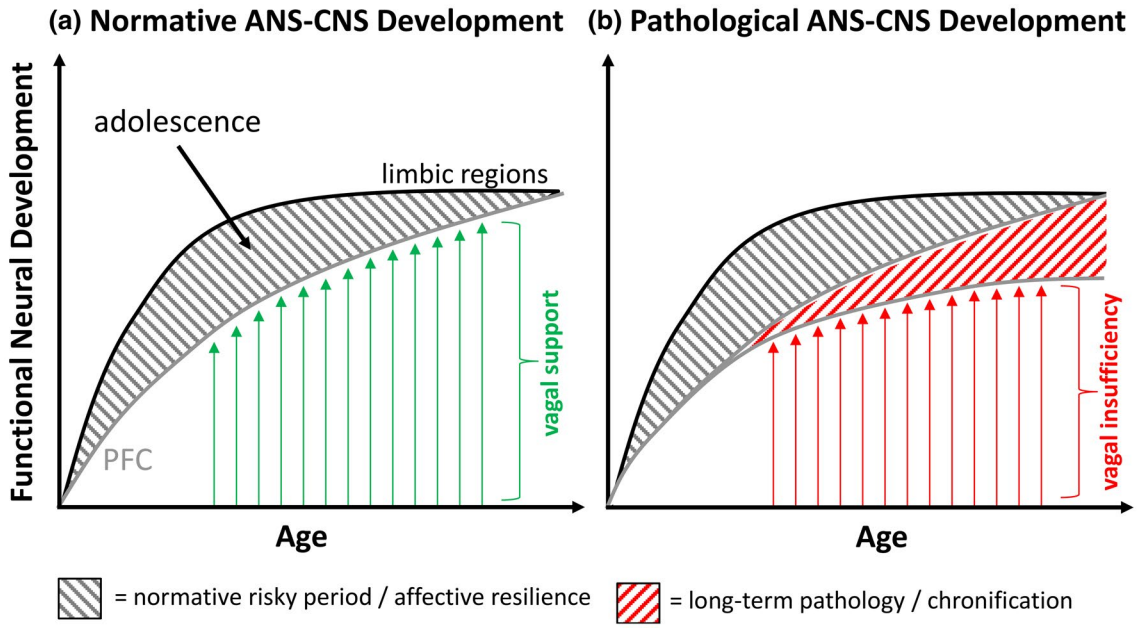

FIGURE 5 A Developmental Model of Central and Autonomic Nervous System Co-Regulation during Adolescence; illustration of prefrontal cortex and limbic maturation adapted from Casey et al., 2008; adolescence (shaded region) is considered a normative period of increased emotional instability and reactivity based on the asynchronous maturation of prefrontal and limbic brain areas. Factors explaining inter-individual variance in these trajectories, predicting long-term psychopathology and clinical outcome are not well understood. The model suggests that vagal activity may be one factor contributing to differences in the maturation of prefrontal brain areas, necessary for the top-down inhibitory control of limbic regions

In these hypertensive rats, an increase in energetic activity and prevalence of excitatory (glutamate and glutamine) over inhibitory neurotransmitters was noticed (gamma-aminobutyric acid (GABA) and glycine). Administration of GABA in rats results in greater HRV (Neckel et al., 2012). The association between vagal activity, GABA (in particular frontal lobe GABA maturation during adolescence (Silveri et al., 2013)) and psychopathology in development certainly deserves further exploration in the context of neurovisceral integration (Thayer & Friedman, 2002).

In human studies, longitudinal associations between blood pressure and brain morphology have been described, such that mean blood pressure has been linked to greater regional brain volume in men a lower regional brain volume in females (Cherbuin et al., 2015). A longitudinal study found greater increases in systolic blood pressure between 36 and 43 years of age were associated with smaller hippocampal volumes at 69–71 years of age (Lane et al., 2019). Interestingly, in children and adolescents, it has been shown that vagal activity and reactivity at 2 years of age, prospectively predicts blood pressure profiles at age 16 (Gangel et al., 2017). Considering cortical thickness (as focused on in the preceding paragraphs), it has been shown in adults, that hypertensive individuals show increased rates of cortical thinning (Gonzalez, Pacheco, Beason-Held, & Resnick, 2015). These findings are in line with our findings on the positive association of HRV and cortical thickness in adults (Yoo et al., 2018). However, respective longitudinal studies on cortical thickness and blood pressure in adolescents are warranted. Primary hypertension in children has been linked to reduced cognitive function later in life (Cha, Patel, Hains, & Mahan, 2012; Lande & Kupferman, 2019), at least implicating PFC alterations as a consequence of ANS dysfunction early in development.

3.1 | Vagal activity and youth psychopathology

Studying youth with affective disorders (on one extreme end of the continuum) may provide important insights into the aforementioned processes of development. One of the pioneers and of the first to systematically investigate HRV in association with psychopathology in youth was *Theodore Beauchaine*. Dr. Beauchaine was inspired by Steve Porges' 1994 Presidential Address to our society (published the year later in *Psychophysiology* (Porges, 1995)) and works in a 1994 *Monograph of the Society for Research in Child Development* (Porges, Doussard-Roosevelt, & Maiti, 1994). As rightfully noted by Dr. Porges, "[by then] most research on autonomic correlates of emotion [had] focused on sympathetic activation" (Porges et al., 1994, page 167). In the years to come, the prevailing paradigm would shift, and nowadays it's widely received, that parasympathetic vagal activity I critically implicated in emotion and emotion regulation.

Importantly, Beauchaine was of the first to (a) describe sex differences in the association between ANS function and psychopathology (i.e. conduct problems and aggression) (Beauchaine, Hong, & Marsh, 2008); (b) use multimodal psychophysiological measures of ANS function for differential diagnostics (i.e., discriminating conduct disorder from attention-deficit hyperactivity disorder) (Beauchaine, Katkin, Strassberg, & Snarr, 2001); and (c) using measures of ANS function as predictors of treatment outcome in youth with psychopathology (Beauchaine, Gartner, & Hagen, 2000). His work formulated the basis of his biosocial developmental model of conduct problems, emphasizing aberrant ANS function underlying deficiencies in approach motivation, reward insensitivity and emotion regulation (Beauchaine, Gatzke-Kopp, & Mead, 2007).

Regarding internalizing problems (affective disorders), there is nowadays good evidence that adolescents with MDD show reduced resting-state vagally mediated HRV (Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). Effect sizes reported across case-control studies included in meta-analyses (Hedges' $g = -0.59$; 95% CI [−1.05; −0.13]) even exceed those reported for adult samples (e.g. high-frequency HRV: Hedges' $g = -0.21$; 95% CI [−0.40; −0.24) (Kemp et al., 2010). These findings illustrate that reduced HRV in depression is not a consequence of long-term illness and/or medication intake as suggested by some. Importantly, results from two recent longitudinal studies (one being a well-controlled twin study) suggest that decreases in HRV precede the development of depressive symptoms (Huang et al., 2018; Jandackova, Britton, Malik, & Steptoe, 2016)—at least in men. One study even suggests, that autonomic hyperarousal, as indexed by lower HRV and higher HR at rest, maybe specifically associated with internalizing problems, whereas autonomic hypoarousal, indexed by higher HRV and lower HR at rest, maybe specifically associated with externalizing problems in children and adolescents (Dietrich et al., 2007). The latter findings are in line with a large-scale register-based study in more than 1 million Swedish men, illustrating that greater HR during late adolescence is associated with increased risk for the development of anxiety disorders (among others) later in life (Latvala et al., 2016). Recently, a study in children (enrolment at age 9), was able to show that reduced HRV predicted greater increased externalizing and internalizing behaviors one year later, again, only in boys (Zhang, Fagan, & Gao, 2017). Taken together, echoing an earlier statement by Huang et al.: "[ANS dysfunction] indexed [by] reduced HRV is more likely to be a risk factor for depression, rather than a consequence." (Huang et al., 2018). Several mechanisms, underlying this longitudinal association are discussed.

An overlap in brain areas involved in controlling ANS function and emotion regulation (as discussed above) may explain the association between reduced HRV and depression onset (see Figure 1). Considering existing longitudinal research, as reviewed above, ANS activity seems to be quite sensitive in its utility as an early biomarker (i.e. changes in HRV are observed before first symptoms occur). Linking evidence on the association between HRV and inflammation (Williams et al., 2019) as well as inflammation and depression (Miller & Raison, 2016), it has further been suggested, that inflammatory processes are a common cause for observed changes in ANS function and depression onset. However, we have shown that decreased HRV predicts increased inflammation (e.g. C-reactive protein) (Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014) not vice versa. Thus, it is unlikely that increased inflammation is underlying subsequent changes in HRV. Finally, it has been suggested that there might be a shared genetic predisposition (Vaccarino et al., 2008). The genetic contribution to MDD in general is considered 'moderate' with an estimate of heritability of liability around 40% (Fernandez-Pujals et al., 2015; Sullivan, Neale, & Kendler, 2000). Importantly, the discussion of mechanisms underlying the link between depression and HRV is based on arguments drawn on evidence collected in adult samples. Although these mechanisms may account for late-onset depression in adults, they are insufficient to explain the association between HRV and depression in adolescents. Studies in adolescents, for example, have shown, that inflammation can be considered an outcome of adolescent depression, rather than an initial contributing cause (Byrne, O'Brien-Simpson, Mitchell, & Allen, 2015). And while genes are clearly implicated in the risk for adolescent depression (Xia & Yao, 2015), environmental processes are considered most important (Rice, 2010). Existing theories neglect that ANS activity itself undergoes normative changes across development as reviewed above and that these changes might be critical for a cascade of processes, finally resulting in psychopathology onset. Importantly, I suggest that altered vagal activity initiates this cascade—or at least, presents the first observable endpoint to index norm-variants of development. Following this thought, vagal activity might present a sufficient condition for normative brain development or in the case of psychopathology: decreased vagal activity may result in pathological brain development leading to psychopathology.

For example, changes in cortical thickness in relation to depression have been shown to be observable only in adults, not adolescents (Schmaal et al., 2017). Studying potential differences in the association between brain structure and vagal activity in adolescents with MDD and controls, we found that cortical thickness of the right insula explained differences in HRV as a function of depression severity (Koenig et al., 2018). Importantly, healthy controls and adolescents with MDD did not differ in the right insula cortical thickness. In line with our earlier findings in healthy adolescents, we found that at low levels of depression severity, lower cortical thickness of the right insula was associated with greater vagally-mediated HRV. However, at levels of increased depression severity this pattern changed, such that greater cortical thickness was associated with greater vagally-mediated HRV. Adolescents with MDD show an 'adult-like' pattern in the association between cortical thickens and vagally-mediated HRV. Beyond subcortical ROI, an interesting pattern emerged when addressing the association between cortical thickness in PFC areas and HRV in depressed and non-depressed adolescents, as illustrated in Figure 6. Whereas healthy controls showed a negative association between PFC thickness and HRV (partially replicating our earlier findings (Koenig, Parzer, et al., 2018, see Figure 4 for comparison)),

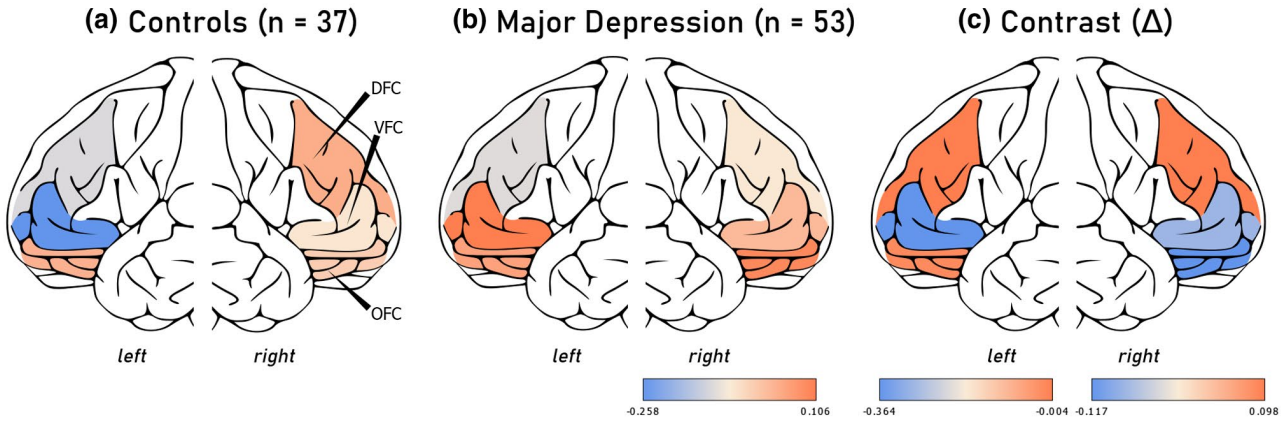

FIGURE 6 Differences in the Association between Heart Rate Variability and Cortical Thickness of Regions of Interest in the Prefrontal Cortex in Depressed and Non-Depressed Adolescents; illustrations done using cerebroViz in R (Bahl et al., 2017); Note data on cortical thickness based on Desikan-Killiany atlas; translation of regions as followed: dorsolateral prefrontal cortex (DFC): rostral middle frontal gyrus; orbital frontal cortex (OFC): lateral orbitofrontal cortex; ventrolateral prefrontal cortex (VFC): pars orbitalis; color bar: indicates the strength and direction of correlation (Pearson correlation coefficient); data taken from (Koenig et al., 2018)

adolescents with MDD show a positive correlation between vagal activity and PFC cortical thickness.

Here's the good news: these phenomena are reversible! In line with research in adults (Chambers & Allen, 2002; Jang, Hwang, Padhye, & Meininger, 2017), we have previously shown, that HRV re-increases following antidepressant treatment with selective serotonin reuptake inhibitors in adolescents with depression (Koenig et al., 2018). Clinical improvement (decrease in depression severity) was associated with increased HRV and decreased HR. Increased HRV was associated with the increased cortical thickness of left lateral orbitofrontal cortex and superior frontal cortex. This said, altered ANS activity indexed by lower HRV and greater HR in adolescents with depression seems reversible. Further, the finding that an increase in cortical thickness of prefrontal ROI was associated with the treatment-related increase in HRV, illustrates that the association between HRV and brain morphology is complex. Whereas greater vagal activity may be beneficial for normative cortical thinning in healthy adolescents, and such association is not seen (or inverse) in adolescents with affective disorders, different mechanisms may underlie treatment-related changes. However, these data are preliminary and require further replication.

3.2 | Beyond brain structure

Beyond the reviewed association between HRV and brain structure, vagal activity is associated with brain function (Ruiz Vargas et al., 2016; Thayer et al., 2012). Here, emphasis was placed on cortical thickness (one of many measures to study brain morphology) to reduce the complexity and extend of the literature reviewed. However, some recent findings on brain function need to be mentioned in support of the principal idea. Studying participants from 6 to 23 years of age using fMRI, Silvers et al. were able to show that better emotion regulation with increasing age is supported by changes in activation and connectivity among prefrontal–amygdala circuits, critically involving the ventromedial PFC (vmPFC) and vlPFC (Silvers et al., 2017). In particular, recruitment of the vlPFC mediated the relationship between increasing age and diminished amygdala responses. Most interestingly, we were previously able to show, that subjects with greater HRV are better able to recruit PFC regions for the modulation of amygdala activity during active emotion regulation (Steinfurth et al., 2018).

Previous studies have illustrated, that greater HRV is associated with stronger connectivity between the amygdala and the mPFC during rest across younger and older adults (Sakaki et al., 2016). Further, greater HRV was associated with stronger vlPFC-amygdala functional connectivity and this association was stronger in younger than older adults (Sakaki et al., 2016). Studies in adolescents with MDD show reduced resting-state functional connectivity between the amygdala and the dlPFC as well as the vmPFC (Connolly et al., 2017). Decreased connectivity of the PFC and amygdala is characteristic of psychiatric disorders in adults associated with difficulties in emotion regulation (Ramasubbu et al., 2014) such as depression (Gilboa et al., 2004; Kong et al., 2013). Treatment studies in adults suggest that PFC hypo-activity is reversible by efficient psychotherapeutic or pharmaceutical treatment in depressive patients (Fales et al., 2009). Studies in adolescents support these notions, indicating that dysregulation of PFC-limbic circuitry contributes to poor emotion regulation in adolescent depression (Kerestes, Davey, Stephanou, Whittle, & Harrison, 2013; Perlman et al., 2012).

In support of the assumed causality, suggesting that ANS development drives CNS maturation, are also animal studies illustrating that chronic stress in adolescent rats leads to significant remodeling of neurons in the PFC and amygdala associated with depressive-like behavior (Eiland, Ramroop, Hill, Manley, & McEwen, 2012). In the years to come, translational animal models on ANS-CNS co-development might also provide further insights into important processes underlying neurodevelopment, such as the myelination of prefrontal axons (McDougall et al., 2018), and how these are influenced by altered vagal activity. Linking myelination studies in healthy human infants (Deoni et al., 2011) with changes in ANS activity across development might further inform our limited understanding of these co-occurring processes. Interestingly, further research in rats has been shown that vagus nerve stimulation (VNS) alters functional connectivity among different brain networks and changes the brain's functional organization in particular within the limbic system (Cao, Lu, Powley, & Liu, 2017). Recently, it has been shown in a sample of depressed adults, that transcutaneous VNS (tVNS) increased functional connectivity between the right amygdala and left dlPFC and that this increase was associated with the decrease in depression severity (Liu et al., 2016, also see Cimpianu et al., 2017). In line with recent ideas by Mather and Thayer how HRV affects emotion regulation brain network (Mather & Thayer, 2018), it is possible that the increase in vagal activity during adolescence promotes functional connectivity in brain regions involved in emotion regulation, e.g. by stimulating oscillatory activity.

3.3 | Antecedents of aberrant neurovisceral development

Findings on decreased vagally-mediated HRV in adolescents with psychopathology need to be discussed in the light of normative changes. Thus, it is plausible, that decreased HRV in adolescents with e.g. depression (Koenig et al., 2016) is not a decrease per se, but represents the absence of a normative

increase. In the following, I will review potential antecedences of such developmental trajectory, focusing on early life stress. For a detailed review of ANS dysmaturation and different factors to influence these trajectories see (Mulkey & du Plessis, 2019).

One potential factor that may cause early alterations in ANS functioning, thereby initiating the cascade outlined above, is early life stress. More recent work illustrates that HRV is a reliable indicator of stress in young children (5–10 years of age), such that greater peer problems, anger, anxiety, and sadness are associated with lower HRV (Michels et al., 2013). Similar to work on the hypothalamus-pituitary-adrenal axis (Roberts & Lopez-Duran, 2019), it is suggested that early developmental influences and the caregiving environment (e.g. Calkins, Graziano, Berdan, Keane, & Degnan, 2008) may result in altered ANS functioning during adolescence (absence of normative increase in vagal activity) leading to heightened sensitivity to stressors and increased risk for psychopathology. For example, in adolescents, HRV has been shown to mediate the association between psychosocial stress and internalizing symptoms, such that in adolescents (13–17 years) with low HRV, stress and internalizing symptoms were positively correlated, but not in those with high HRV (McLaughlin, Rith-Najarian, Dirks, & Sheridan, 2015). Again, this was particularly the case for male subjects. Several mechanisms of how early (pre-pubertal) stress may lead to altered ANS function during adolescence can be considered, that will not be reviewed here in detail (e.g., wear and tear, hyperactivity to hypoactivity).

Following this thought it may be suggested, that alterations to the mPFC-amygdala network, frequently seen (Peverill, Sheridan, Busso, & McLaughlin, 2019) in children who experienced severe forms of early life stress (i.e., maltreatment and abuse) and other consequences of early adversity on brain morphology and function (Teicher & Samson, 2016) are mediated by an impaired vagal increase in adolescence. Childhood abuse has previously been linked to reduced cortical thickness in the vmPFC (among other regions) (Gold et al., 2016). Incorporating these findings, it is suggested that vagal activity promotes *optimal* cortical thinning during adolescence and that impaired vagal function may result in both accelerated and delayed cortical thinning. Therefore, focusing on pre-pubertal life events, the association between vagal activity and brain development may present itself different to the evidence reviewed for adolescents. Similar results have been found regarding the association between brain morphology and psychopathology. For example, it has been shown that in children of younger age (<9 years) anxiety and depression are negatively associated with vmPFC cortical thickness, whereas in adolescents and young adults (15–22 years) the association is positive (Ducharme et al., 2014). It has been shown that among maltreated youths, better recruitment of PFC areas when downregulating amygdala activity during emotion regulation is linked to a lower risk for the development of depressive symptoms (Rodman, Jenness, Weissman, Pine, & McLaughlin, 2019). In line with our findings that greater vagal activity is associated with better PFC recruitment during explicit emotion regulation (Steinfurth et al., 2018), vagal activity seems to present both: a marker of increased risk when decreased and a marker of better resilience when increased.

4 | SOME CONCLUSIONS

In an attempt to further elaborate on Thayer & Lane's NIM, potential developmental trajectories underlying dynamic CNS-ANS co-regulation have been presented. In sum, it has been suggested that (a) neurovisceral integration is shaped during sensitive periods of human development; (b) the normative increase in vagal activity during adolescence is critical for normative brain development - in particular facilitating the maturation of prefrontal brain regions involved in regulating emotions; (c) early life stress and adversity may interfere with these processes, whereby increased autonomic arousal impedes PFC maturation, subsequently leading to an incapacity to adequately regulate emotions resulting in an increased risk to develop affective disorders. It was further illustrated, that (d) these trajectories show sex differences, potentially linking pre- and post-pubertal differences in physiology to an increased risk for affective disorders in girls. Important findings from neighboring fields were not reviewed in detail (i.e., accelerated aging following trauma, changes in sex hormones during puberty), but should be integrated when further refining these principal ideas.

Importantly, while the outlined model might account for the associations between ANS activity and cortical development in youth with affective disorders, other pathways need to be considered in externalizing disorders and other forms of psychopathology. For example, the eating disorders seem to be associated with increased vagal activity (Peschel et al., 2016a, 2016b). Disorders such as attention deficit hyperactivity disorder have been associated with reduced cortical thickness in the PFC (Almeida Montes et al., 2013) without evident reductions in resting HRV (Koenig, Rash, Kemp, et al., 2017). Considering this, vagal activity likely mediates *optimal* cortical thinning (bidirectional) and the associations discussed in the above are of greater complexity considering the full range of youth psychopathology. To say it with the words from Carlos King: “If we look further, however, we find the exceptions to multiply, and we find mixed states to be the rule rather than the exception. We only propose that, in a given complex state of

emotion, the elements of fear and depression may be indicated by the relative amount of vagus influence manifest." (Kling, 1933[3]). Solving some of these inconsistencies and complexities is the task ahead. Turning our attention to the RDoC, trying to identify psychiatric phenomena with vagal involvement and taking a dynamic perspective in identifying sensitive periods of ANS-CNS co-development, may help to advance the field.

Importantly, here I focused on early development, but development has no defined endpoint! It will be worthwhile to examine late-life trajectories in the sense of the theoretical framework outlined here. For example, age-related differences in the association between brain morphology and HRV (Yoo et al., 2018) as well as HRV and functional brain connectivity (Kumral et al., 2019) have been shown. It will be worthwhile to examine how early ANS-CNS development relates to late-life phenomena.

Studies are needed addressing ANS-CNS co-development in large-scale longitudinal cohorts of children and adolescents to provide the empirical basis for some of the claims outlined in the above. In an attempt to provide a *Principal Outline of a Dynamic Model of Neurovisceral Development*, only some of the existing literature in the field was reviewed, connecting different lines of investigation. It will be up to the coming years and team effort to connect some of the remaining loose ends in understanding existing inconsistencies in our field. Beyond the heart, research should address the consequences of decreased vagal activity including the systematic investigation of different organs. Preliminary research in animals has shown, that subdiaphragmatic vagotomy abolishes the antidepressive effects of pharmacological treatment with selective serotonin reuptake inhibitors (Neufeld et al., 2019). It is research like this that questions our current understanding and conceptualization of psychiatric disorders. To conclude, here I presented the principal idea of a dynamic model of neurovisceral integration, acknowledging the influence of age and sensitive periods of development.

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