Vagal Signatures of Adolescent Depression

Autonomic and Immune Regulation within the Neurovisceral Integration Model and the Concept of the Anti-Inflammatory Reflex

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Abstract

Depressive disorders are one of the leading causes of disability worldwide and are characterized by a sharp increase in prevalence during adolescence. In adults, depressive psychopathology is associated with impairments in self-regulation and adaptability. Various indices of vagally mediated heart rate variability (vmHRV) as well as alterations in inflammatory responses provide evidence of such dysregulation. However, in adolescent depression, these indices remain understudied and insufficiently addressed.

Theoretically grounded in the *Neurovisceral Integration Model* and expanded by the concept of the cholinergic *Anti-Inflammatory Reflex*, this thesis addresses the overarching question of how and to what extent vagal activity and its immunological integration contribute to self-regulation as reflected in depressive psychopathology in adolescence. Three empirical studies pursued specific objectives: (1) Is resting-state vmHRV associated with depressive symptoms in adolescence as an index of self-regulatory capacity? (2) To what extent is the adaptability of vagal regulation (reactivity and recovery) related to depressive symptomatology in adolescents? (3) Does the interaction of vmHRV and markers of inflammation explain depressive symptoms in adolescents?

By integrating these perspectives, the thesis contributes to a multidimensional understanding of vmHRV as an indicator of self-regulation and highlights its relevance for depressive symptoms and associated psychophysiological profiles. Meta-analytic and empirical findings indicate adolescents with clinically significant depression exhibit reduced resting vmHRV, with gender- and development-related patterns such as delayed vagal reactivity and recovery, particularly in males. Additionally, depressive symptom severity is linked to vmHRV and inflammatory markers and moderates the association between vmHRV and one immunological parameter, leukocytes, highlighting the complex interplay between autonomic regulation, inflammation, and depression in adolescents.

The present dissertation comprises the following studies:

Study 1:

Baumeister-Lingens, L., Rothe, R., Wolff, L., Gerlach, A. L., Koenig, J., & Sigrist, C. (2023). Vagally-mediated heart rate variability and depression in children and adolescents - A meta-analytic update. *Journal of Affective Disorders, 339,* 237-255. https://doi.org/10.1016/j.jad.2023.07.027

Study 2:

Baumeister-Lingens, L., Markser, A., Gerlach, A. L., Kaess, M., Brunner, R., & Koenig, J. (2026). The Cardiac Orthostatic Stress Response as a Function of Internalizing Psychopathology and Sex in Typically Developing Youth—An Observational Study. *Developmental Psychobiology*, *68*(2). https://doi.org/10.1002/dev.70135

Study 3:

Nguyen, T. P., Baumeister-Lingens, L., Markser, A., Rösch, A. S., Kaess, M., & Koenig, J. (2025). The cholinergic anti-inflammatory reflex as a function of depression severity in adolescent non-suicidal self-injury. *The World Journal of Biological Psychiatry*, 1-10. https://doi.org/10.1080/15622975.2025.2521023

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Conceptual Framework

The Neurovisceral Integration Model and the Role of Vagal Function

In order to model the divers self-regulatory demands of a constantly changing environment on an organism, Thayer and Lane established the Neurovisceral Integration Model (NIM; Thayer & Lane, 2000, 2009), which integrates autonomic, attentional and affective systems into a functional and structural network, aimed at understanding mechanisms of emotion regulation and dysregulation. Within the central nervous system (CNS), the central autonomic network (CAN) represents an important element which is responsible for the flexible adaptation of an organism to its changing environment (Benarroch, 1993, 1997; Thayer & Lane, 2000). It comprises cortical and subcortical structures, such as the anterior cingulate cortex, the insular and ventromedial prefrontal cortex, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaquaductal grey matter, the parabrachial nucleus, the nucleus tractus solitaire, the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla and the medullary tegmental field (Thayer & Lane, 2000). The CAN integrates visceromotor, neuroendocrine and behavioural responses into an internal regulatory system that supports an organism's adaptability (Benarroch, 1993) and self-regulation (Thayer & Lane, 2000). It modulates preganglionic sympathetic and parasympathetic neurons, which form complementary parts of the autonomic nervous system (ANS), innervating peripheral organs such as the heart through the stellate ganglia and the vagus nerve (Thayer & Lane, 2000; Wulsin et al., 2018). Vagal activity exerts tonic inhibitory control over the heart, exemplifying the bidirectional nature of CNS–ANS interplay: While the ANS modulates autonomic output, peripheral organs, such as the heart, provide sensory feedback to the CNS via afferent pathways, thereby influencing central regulation in return (Saul, 1990; Thayer & Lane, 2000). Within this reciprocal inhibitory circuit, the prefrontal cortex (PFC) plays a central role in

exerting top-down control over subcortical and autonomic structures (Beauchaine, 2015). In the NIM, emotion is conceptualized as an integral component of self-regulatory processes. It is defined as an organismic response to environmental events, that coordinated multiple subsystems for adaptive action. Emotion therefore serves as an integrative feedback signal, reflecting the organism's moment-to-moment adjustments to environmental demands. By shaping behavioural responses, emotions help to activate the most appropriate action tendencies while simultaneously inhibiting less suitable responses from an existing behavioural repertoire (Thayer & Lane, 2000).

The functioning of the described bidirectional feedback system can be examined by assessing heart rate variability (HRV). It reflects the interplay of sympathetic and parasympathetic activity at the sinoatrial node of the heart: The naturally occurring beat-to-beat variability of heart rate (HR) over time. It is widely recognized as a non-invasive index of cardiac autonomic control (Berntson et al., 1997). Quantitative measures of HRV can be divided into time domain, frequency domain and non-linear measures (Shaffer & Ginsberg, 2017). Among these, the high-frequency power component (HF) and the root mean square of successive differences (RMSSD) represent reliable measures of parasympathetic vagal activity (Appelhans & Luecken, 2006; Thayer et al., 2010; Thayer & Lane, 2000), further referred to as vagally-mediated HRV (vmHRV). Within this framework, vmHRV serves as a peripheral marker of the functional integrity of the CAN (Beauchaine & Thayer, 2015) and of the organism's self-regulatory capacities (Thayer & Lane, 2000).

Higher resting-state vmHRV indicates greater adaptability and regulatory efficiency (Thayer & Lane, 2000), whereas reduced vmHRV at rest, in turn, indicate vagal withdrawal associated with prefrontal hypoactivity, amygdala hyperactivity, a predisposition to threat perception and negative biasing (Kemp et al., 2017). Under acute stress or threat, PFC activity typically declines, leading to vagal withdrawal and sympatho-excitation. This shift facilitates

an acute physiological response, but, when chronically dysregulated, may contribute to maladaptive stress responses and affective dysregulation (Beauchaine, 2015). It should be noted that although the sympathetic and parasympathetic nervous systems have been identified as key components in the autonomic regulation of the heart, this process is highly complex. The NIM provides a simplified explanatory framework for understanding this regulation (Nolte et al., 2017; Smith et al., 2017). While it offers considerable explanatory potential, it inevitably involves simplifications and generalizations. The mechanistic interpretation of vmHRV is theory driven and primarily based on empirical associations. HRV does not represent a direct measure of *vagal tone* or sinoatrial node activity but reflects a composite signal influenced by several factors including respiratory patterns, baroreflex sensitivity, and sympathetic co-activation (Laborde et al., 2017; Quintana et al., 2016). Therefore, interpretations of vmHRV should remain context-sensitive.

Much of the current conceptualization centres around tonic vmHRV, a measurement of resting-state vmHRV at one time point. It is essential to distinguish this resting state vmHRV from the phasic vmHRV (Porges, 2007; Thayer et al., 2012). Phasic vmHRV shows how the system responds to environmental events and has been conceptualized in several ways, including stimulus-response changes, delta vmHRV, and vagal withdrawal, all of which index changes in vmHRV across two time points. This concept encompasses changes between baseline and event, referred to as reactivity, and change between task and post-event, also referred to as recovery. Thayer et al. (2012) point out that both cardiac vagal control at rest as well as reactivity can be seen as indicators of the integrity of the resources on which self-regulation is based. A high level of vagal withdrawal, indexed by decreased vmHRV, may be considered adaptive, when the person is faced with a physical stressor (Porges, 2007). Recovery is generally seen as a process of restoring a previous or improved condition (Laborde et al., 2018). It plays a crucial role in the organism's adaptability to face an event

and then return to a state of rest (Stanley et al., 2013). Previous studies have shown that individuals may show high resting-state vmHRV yet exhibit blunted reactivity or delayed recovery in response to physical challenges, such as postural changes, indicating potential dysregulation under physical load despite an adaptive resting profile (Jiang et al., 2015; Mestanikova et al., 2019). Summing up, the described dynamic responses in vmHRV offer complementary insights into the flexibility and robustness of the neurovisceral system (Laborde et al., 2018) and offer a multidimensional perspective on autonomic functioning.

Integrating Immune Function: The Cholinergic Anti-Inflammatory Reflex as an Extension of the NIM

From a neurovisceral perspective, it has been emphasized that, in order to develop a comprehensive model, the wide range of complex pathways leading to a specific disorder must be taken into account (Brosschot et al., 2006). The NIM describes how the PFC exerts top-down control over autonomic and subcortical structures, shaping stress responses, executive function, and emotional self-regulation (Thayer & Lane, 2000). The parasympathetic branch of the CAN, particularly activity of the vagus nerve, has already been highlighted as key factor in this regulatory process. It further plays a crucial role in controlling inflammatory processes (Tracey, 2002). In this regard, the NIM can undergo physiological expansion: through vagal regulation of immune responses, the scope of neural-autonomic coordination is expanded to include neuroimmune feedback, linking the brain, autonomic function, and systemic inflammation. In this context, the term “anti-inflammatory reflex” (AIR) is introduced (Tracey, 2002). The AIR is based on an autonomic feedback loop in which the vagus nerve detects and modulates inflammatory responses. When pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are released into circulation, afferent vagal fibers transmit these

signals to the nucleus tractus solitarius in the brainstem. In response, efferent vagal pathways activate the splenic nerve, which releases acetylcholine (ACh) and thereby inhibits macrophage activity, reducing the production of these pro-inflammatory cytokines (Pavlov & Tracey, 2005; Tracey, 2002). The release of anti-inflammatory mediators such as interleukin-10 remains unaffected, however (Rüegg, 2007). A key molecular component of this process is the nicotinic α7 acetylcholine receptor, which functions as a switch to suppress excessive inflammation without impairing necessary immune responses (Borovikova et al., 2000). This autonomic-immune interaction is embedded within the broader CAN, which, to reiterate, integrates autonomic, cognitive, and emotional processes (Benarroch, 1993). Given that the PFC exerts inhibitory control over subcortical and autonomic structures, its influence on vagal activity extends beyond heart rate regulation to include immune system modulation. As a result, reduced PFC activity, such as that observed during chronic stress, can lead to vagal withdrawal and a loss of inhibitory control over inflammatory pathways, increasing systemic inflammation (Thayer & Lane, 2009).

A dysfunction of this system has profound implications for mental health. Research has consistently shown that individuals with internalizing symptoms such as depression and anxiety exhibit elevated levels of IL-6, TNF-α, and CRP, suggesting a strong inflammatory component in the pathophysiology of these conditions (Felger & Lotrich, 2013; Haapakoski et al., 2015). HRV as indicator of vagal activity, has been found to correlate inversely with inflammatory markers. Reduced vmHRV has been associated with higher circulating levels of IL-6 and CRP, supporting the link between vagal dysregulation, inflammation, and mood disorders (Kemp et al., 2010; Williams et al., 2019). These findings suggest that diminished vagal activity may contribute to both heightened inflammatory responses and emotion dysregulation. Together, the AIR and NIM highlight a unified pathway through which reduced

prefrontal control and vagal withdrawal can manifest both emotionally and physiologically in psychopathology, contributing to a more holistic perspective on self-regulation.

Self-Regulation in Adolescence: Neurovisceral and Immunological Integration of Depression

The adolescent development is characterized by various transitions in the phase between childhood and adulthood. These transitions include hormonal changes and sexual maturation on the one hand, and neurodevelopmental changes on the other, processes that contribute to typical behavioural changes (Spear, 2000). During adolescence, the brain undergoes processes of neural reorganization. This includes synaptic pruning in some brain regions (Selemon, 2013), the formation of new connections in others (Cunningham et al., 2002), and, in yet others, the repurposing of receptors (Tseng & O'Donnell, 2007). This primarily affects areas of the brain involved in emotion and learning processes, including the PFC, hippocampus, amygdala, and nucleus accumbens (Brenhouse & Schwarz, 2016). The PFC in particular is responsible for higher-order cognitive functions, emotion regulation, and impulse control (Casey et al., 2008). While subcortical regions, such as the amygdala, mature earlier and are highly responsive to emotional stimuli, the PFC undergoes a more gradual development (Galván, 2010). This asynchronous maturation between the PFC and subcortical regions can lead to temporary imbalances in regulatory control, resulting in heightened emotional reactivity and reduced regulatory efficiency. Such imbalances can increase adolescents' susceptibility to stress and emotional dysregulation, which may contribute to increased vulnerability to the development of mental illnesses (Casey et al., 2008; Koenig, 2020). The NIM posits that the ability to self-regulate is based on an efficient integration of the PFC, subcortical structures and the ANS. The model thus provides a theoretical framework that contributes to understanding the increased susceptibility to emotional

dysregulation and mental illness during critical phases of development (Thayer & Lane, 2000; Thayer & Lane, 2009).

In addition to these neurovisceral dynamics, adolescence represents a developmental period in which inflammatory processes are also becoming increasingly relevant to an understanding of depression. In adults, inflammatory activity is considered a causal risk factor for depressive symptoms (Miller & Raison, 2016). In contrast, studies in adolescents suggest that inflammation more often follows depressive episodes than precedes them (Byrne et al., 2015). Moreover, initial evidence suggests that pubertal status modulates the association between depression and inflammation (Keller et al., 2010). These results suggest a developmentally driven shift in the temporal dynamics of the relationship between depression and inflammation, emphasizing the need to consider age-specific mechanisms.

Altogether, the presented considerations suggest that adolescence is not only a period of ongoing maturation of neurovisceral integration, but also a period of heightened immunological plasticity, both of which may contribute to increased vulnerability to depressive psychopathology. Ultimately, the NIM, in conjunction with developmental findings from the literature, helps to clarify why adolescence is a particularly vulnerable period for depression: the protracted maturation of prefrontal control over autonomic circuits, combined with hormonally sensitive immune processes, creates developmental conditions under which maladaptive self-regulation patterns can emerge.

Present Thesis

Overview and Research Question

The present thesis is located at the interface of psychophysiological and clinical research and focuses on adolescence as a critical period for the development of depressive disorders. Its empirical basis consists of three manuscripts conducted in distinct adolescent

populations (clinically depressed, typically developing with subclinical internalizing symptoms, and female adolescents with non-suicidal self-injury (NSSI)). Based on the *Neurovisceral Integration Model* and extended by the concept of the A*nti-Inflammatory Reflex*, this thesis investigates how different states of vmHRV (resting state, reactivity, recovery) and inflammatory markers interact to shape the phenotype of adolescent depression. Methodologically, the work combines meta-analytic, experimental and inflammatory biomarker-based approaches to provide a multidimensional description on psychopathological dysregulation. This integrative approach aims to refine existing models of self-regulation and to gain new insights into the underlying physiological mechanisms of adolescent depression.

Against this background, the dissertation addresses the overarching research question: How are vagal activity and its immunological integration related to self-regulation and manifestations of depressive psychopathology during adolescence?

To answer this question, the presented manuscripts examine three complementary sub-questions:

Vagal activity at rest (1): Is resting-state vmHRV associated with depressive symptoms in adolescence as an index of self-regulatory capacity?

Dynamic vagal regulation (2): To what extent are phasic aspects of vmHRV, namely reactivity and recovery under orthostatic challenge, related to depressive symptoms in adolescence?

Vagal-immune interactions (3): How does the coupling of vmHRV and inflammatory markers show in adolescents in relation to depressive symptoms?

The empirical basis of the dissertation thus consists of three studies, each presented in manuscript form, which together enhance our understanding of autonomic and immunologic regulation in adolescent depression.

Contributions of Authorship

Author contributions were documented using the CRediT (Contributor Roles Taxonomy) framework (Brand et al., 2015).

	Manuscript 1	**Manuscript 2**	**Manuscript 3**
Conceptualization	-	-	-
Data Curation	✓	✓	-
Formal analysis	✓	✓	✓(partial)
Visualization	✓	✓	✓ (partial)
Writing – original draft	✓	✓	-
Writing – review & editing	✓	✓	✓

Manuscript #1

Vagally-Mediated Heart Rate Variability and Depression in Children and Adolescents - A Meta-Analytic Update

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Manuscript #2

The Cardiac Orthostatic Stress Response as a Function of Internalizing Psychopathology and Sex in Typically Developing Youth - An Observational Study

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Manuscript #3

The Cholinergic Anti-Inflammatory Reflex as a Function of Depression Severity in Adolescent Non-Suicidal Self-Injury

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Discussion

Theoretical and Empirical Integration of Vagal Regulation, Immune Regulation, and Depression in Adolescence

This thesis aims to determine the extent to which the function of the ANS, particularly vagal activity, as measured by vmHRV and its immunological integration, contributes to self-regulation and serves as an indicator for depressive psychopathology in adolescence. To answer this question, three complementary studies were conducted, each focusing on a different dimension of cardiac vagal regulation: (1) resting state activity as a tonic index of self-regulatory capacity, (2) phasic responses to challenges as indicators of adaptive flexibility, and (3) the coupling between vagal and immune regulation as a marker of neurovisceral-immunological integration.

Based on the NIM, which conceptualizes self-regulation as an emergent property arising from reciprocal inhibitory circuits connecting the PFC, limbic structures and autonomic outputs (Thayer & Lane, 2000), this thesis extends the model by incorporating immune function via the cholinergic AIR and developmental dimensions of regulatory capacity. To recapitulate, the NIM posits that vmHRV reflects the functional integrity of the CAN, which forms a hierarchical and recursive system controlling autonomic, emotional, and executive functions. In this system, higher vmHRV indicates effective prefrontal control over subcortical activity and thus functions as a psychophysiological proxy for the functional integrity of self-regulation systems (Thayer & Lane, 2000; Thayer & Lane, 2009). Adolescence represents a sensitive developmental phase in which substantial reorganization of the CAN occurs, making it a particularly relevant phase for studying emerging patterns of dysregulation (Casey et al., 2008; Koenig, 2020). The three manuscripts, incorporated in this thesis, address depressive symptoms during this period from complementary physiological perspectives, tonic, phasic and immunoregulatory, through different methodological

approaches, providing a comprehensive, multidimensional analysis of regulatory function and dysfunction.

The first manuscript investigated the association between depressive symptoms and vagal activity as indicated by resting-state vmHRV in children and adolescents. Empirical studies were identified through a systematic search process, following the PRISMA statement (Page et al., 2021). The resulting meta-analysis confirmed that children and adolescents with clinically significant depression exhibit significantly reduced resting-state vmHRV compared to healthy controls. This result might align well with the proposed framework of the NIM: Relatively lower values of resting-state vmHRV indicate diminished vagal activity, associated with impaired physiological and psychological adaptability and self-regulatory capacity (Koenig, 2020; Thayer & Lane, 2000, 2009), resulting in depressive symptoms. In contrast, in the studies that exclusively examined these measures dimensionally, no correlation between vmHRV and depressive symptoms was found. Note that in most of these studies, samples with subclinical depressive symptoms were examined rather than clinical populations. Possibly, in non-clinical samples, autonomic alterations may be more subtle and depend more strongly on moderating factors such as sex, pubertal status, or hormonal changes. These influences may lead to heterogeneous effects across studies, that impede detections of consistent associations at the group level. This consideration is addressed in more detail in the following section on *Contextual Modulators of HRV*. It should be noted that although the average age of the included total population was 13.59 years, the age range was between 3.06 and 16.65 years, extending beyond the definition of adolescence. Therefore, conclusions about adolescent-specific mechanisms should be interpreted with caution.

The second manuscript expanded upon the resting-state vagal activity by focusing on phasic aspects of autonomic regulation in response to an orthostatic challenge with additional consideration of vmHRV reactivity and recovery in the context of internalizing symptoms in a

sample of healthy adolescents. Participants reporting higher levels of depressive symptoms displayed blunted vmHRV reactivity as well as delayed recovery, whereas anxiety levels showed no independent effect on vmHRV reactivity but did contribute uniquely to impaired recovery. These effects were more pronounced in male subjects. These findings extend the NIM's emphasis on tonic vagal activity as a marker of self-regulation by showing that impaired adaptability may indicate dysregulation, thus complementing findings from the first manuscript on reduced tonic with impaired phasic vmHRV associated with depressive symptoms in adolescence. The discovery of symptom- and sex-specific effects suggests that the original model could be refined by taking into account dynamic flexibility on the one hand, but also context-specific developmental trajectories on the other. These subjects again are discussed in more detail in the following section on *Contextual Modulators of HRV*.

The third study aimed to clarify the relationship between the ANS and immune regulation in female adolescents engaging in NSSI compared to healthy control subjects, with a particular focus on the interaction between the two systems. Based on how these are conceptualized in the NIM and AIR, changes in vmHRV and proinflammatory markers (leukocytes, CRP, IL-6) were investigated in relation to the severity of depressive symptoms across conditions. Results showed that the associations between vmHRV and inflammatory markers were generally attenuated. Depression severity was positively correlated with the inflammatory markers leukocytes and CRP and correlated negatively with vmHRV. Likewise, vmHRV correlated negatively with leukocytes and CRP. Mediation analysis indicated that the association between lower vmHRV and higher inflammatory markers was statistically accounted for by higher depression severity. In line with the NIM, the observed inverse relationship between vmHRV and depression severity again suggests disrupted neurovisceral integration in adolescents exhibiting higher depressive symptoms. The findings also substantiate the AIR concept: The positive associations of depression severity with

proinflammatory markers, particularly leukocytes and CRP, combined with the negative correlations between vmHRV and these inflammatory markers imply that diminished vagal regulation contributes to heightened systemic inflammation in the examined population of adolescents. However, since mediation paths were calculated across conditions, these results do not allow conclusions about group-specific differences between adolescents with NSSI and healthy controls. Thus, the AIR-related dysfunction observed here could represent either a general correlate of depression in adolescents or a characteristic feature of the NSSI phenotype.

Taken together, the three manuscripts provide consistent evidence that reduced vmHRV as an index of vagal activity is associated with depressive symptoms in adolescence, both at rest and under challenge, and that these associations also extend to altered immune regulation according to the AIR concept. Observed effects vary substantially depending on modifying factors such as sex, developmental stage, and comorbid symptom dimensions. Differences in diagnostic status, sex composition, and assessment context across the distinct adolescent samples further complicate cross-population synthesis of vmHRV - symptom - immune relationships, limiting the generalizability of findings to all phenotypic presentations of adolescent depression. Such heterogeneity indicates that vmHRV does not function as a uniform biomarker of depression but rather reflects a multidimensional regulatory phenotype whose expression is modulated by demographic and clinical variables. Accounting for these moderating influences is crucial for refining the explanatory scope of the NIM and AIR frameworks and for accurately evaluating the utility of vmHRV in identifying depression in adolescents. These factors are therefore discussed in detail in the following section.

Contextual Modulators of vmHRV: Sex, Transdiagnostic Dimensions, and Developmental Pathways

Sex differences emerged as a recurring factor in the three studies comprising this thesis. In the meta-analysis, sex moderated the association between vmHRV and depressive symptoms, suggesting sex-specific variability in the link between diminished vmHRV at rest and elevated depression severity, which appears to be more pronounced in adolescent girls. Epidemiologically, adolescent girls are more likely to exhibit depressive symptoms than boys (Costello et al., 2006; Shorey et al., 2022; Nolen-Hoeksema & Girgus, 1994), and during puberty, diagnoses of depression in females nearly double (Angold et al., 1998). Regardless of cultural context, female adolescents appear to be more susceptible to developing depressive symptoms, primarily due to biological vulnerabilities (e.g., genetic factors, hormonal differences) as well as psychological and cultural factors (Chentsova-Dutton et al., 2014; Liu et al., 2015; Nolen-Hoeksema & Girgus, 1994). At the physiological level, healthy women generally exhibit higher vmHRV at rest, reflecting greater parasympathetic activity, while males typically display lower resting vmHRV, characterized by relative sympathetic dominance (Koenig & Thayer, 2016). In contrast, meta-analytic evidence displays that sex differences in vagal regulation in healthy children and adolescents are characterized by lower resting vmHRV in girls compared to boys (Koenig, Rash, et al., 2017). Findings from the present meta-analysis indicate sex-specific differences in the association between vmHRV and clinically significant depression in adolescence and complement existing evidence showing that vmHRV reductions associated with depressive symptoms are more pronounced, directionally different, or even exclusive in women compared to men (Dietrich et al., 2011; Koenig et al., 2017; Kuang et al., 2019; Tobaldini et al., 2020). While these existing studies have largely focused on adult samples, the importance of considering sex differences in children and adolescents in future research on this topic is emphasized. Potential mechanisms

underlying adolescent sex differences in vagal regulation have been discussed in the literature. As Koenig, Rash, et al., (2017) argue, hormonal changes during puberty could contribute significantly to the observed differences between boys and girls and favour the shift in the direction of the association. Levels of the female sex hormones estrogen and progesterone are associated with cardiac autonomic modulation (Du et al., 1994) and fluctuations in those levels during the menstrual cycle are associated with fluctuations in cardiac vagal regulation, with higher vagal activity observed during phases with low estrogen and progesterone levels (Bai et al., 2009; Hirshoren et al., 2002; Tenan et al., 2014; Vallejo et al., 2005). However, the present meta-analysis found that clinically significant depression in girls is accompanied by a significant reduction in vmHRV. This suggests a loss of the advantage conferred by a theoretically higher self-regulatory capacity in a subgroup typically characterized by higher resting vagal activity. In the second study, which investigated phasic aspects of vmHRV in a group of healthy adolescents, the associations between anxiety symptoms and particularly relevant here, depressive symptoms and vmHRV reactivity were stronger in boys, while levels of anxiety showed a unique association with reduced vmHRV recovery in male adolescents. These results highlight that, beyond resting-state vagal activity, altered reactivity and recovery under orthostatic challenge may represent important additional markers of dysregulation. In line with the NIM, the findings underscore that not solely static vagal tone, but also its dynamic flexibility appears to be central for self-regulation. The discovery of sex differences in autonomic response patterns represents an additional extension beyond the scope of the original model. The distinct associations of anxiety and depression with vmHRV parameters in girls compared to boys suggest that the CAN exhibits sex-specific developmental and functional patterns that extend beyond the general predictions of the model. Specifically, the finding that anxiety was uniquely associated with reduced recovery of vmHRV in boys, indicates that neurovisceral integration mechanisms may function differently between the

sexes, especially in the course of pubertal development. These findings support an expanded conceptualization of the framework that incorporates not only static network function but also dynamic adaptability and sex-specific developmental aspects of neurovisceral integration. This is particularly relevant for understanding how the CAN develops and functions during adolescence (Koenig, 2020). Importantly, vmHRV associations with symptoms of depression and anxiety are not mutually exclusive but frequently overlap (Henje Blom et al., 2010; Kemp et al., 2012; Yaroslavsky et al., 2013). Nevertheless, a focused examination of each aspect offers added value for the multidimensional interpretation of the link between vagal regulation and internalizing psychopathology. As in the second study, which examined phasic vagal processing, the distinction in contrast to tonic vagal regulation is systematically captured within the Vagal Tank Theory (VTT; Laborde et al., 2018). The theory builds on the NIM by conceptualizing vagal function as a reservoir that can be indexed at three levels: (a) resting or baseline HRV as an indicator of available capacity, (b) HRV reactivity as the extent to which this capacity is mobilized under stress, and (c) HRV recovery as the efficiency of resource replenishment after exposure to stress. According to Laborde et al., 2018, considering these three components jointly provides a more comprehensive account of how vagal regulation supports adaptive self-regulation. This consideration complements the NIM by explicitly highlighting the dynamic interaction between capacity, reactivity, and recovery.

The third study on immunological integration included only female adolescents with and without engagement in NSSI, which precluded direct comparisons of sex but provided an opportunity to examine vagal-immunological associations in a clinically relevant group. With regard to the autonomic-immune integration, two previous studies reported significant sex differences in the association between HRV and inflammatory markers, suggesting that the effect may be greater in women than in men (Thayer & Fischer, 2009; Von Känel et al., 2009). This finding has been interpreted as evidence of a potentially stronger vagal-immunological

coupling in women, which could contribute to their increased susceptibility to internalizing disorders. However, this interpretation is preliminary, as the underlying mechanisms are not yet fully understood and the evidence is still limited: The broader literature emphasizes that the relationship between depression and inflammation is complex and bidirectional, with no evidence of a single causal pathway (Fried et al., 2020). Nevertheless, chronic increases in cytokine levels may contribute to depressive phenotypes by altering monoaminergic, glutamatergic, and neurotrophic signalling pathways (Felger & Lotrich, 2013). Taking together, these findings suggest that sex differences in autonomic activity and vagus nerve-immune system coupling may influence vulnerability to depression but are unlikely to fully account for the observed sex differences in depression prevalence. There is a lack of studies investigating autonomic-immune integration in adolescents, which seems particularly relevant given the extent of susceptibility to internalizing disorders in this developmental phase on the one hand (Kessler et al., 2005), and on the other hand considering the formerly described shift from lower resting-state vmHRV in adolescent females to increased vmHRV in women compared to their male counterparts. Building on that, the present study displayed that NSSI, a transdiagnostic phenomenon often associated with depressive symptoms (Hankin & Abela, 2011; Kindler et al., 2022; Marshall et al., 2013), is linked to lower baseline vmHRV and its immunological integration via the AIR (elevated leukocytes/CRP, with effects mediated by depression severity). This suggests that vagal dysregulation is not limited to depression or anxiety but may also capture broader self-regulation deficits that manifest behaviourally in the form of self- injury.

By integrating these strands, the present findings support a multidimensional conceptualization of vmHRV: rather than being a uniform marker of psychopathology, vmHRV reflects gender-specific and symptom-related processes. Conceptually, these findings refine the explanatory scope of the NIM by highlighting the different informational value of

tonic and phasic indices, consistent with the VTT's emphasis on baseline, reactivity, and recovery as complementary dimensions of vagal function, and is complemented by the AIR concept by showing that the coupling of vagal regulation and the immune system during adolescence may contribute to self-regulation demands. These considerations suggest that vmHRV should not be viewed as an isolated indicator of depression but rather as a reflection of broader self-regulatory processes that manifest differently depending on sex and symptom dimensions. Together, these findings point to an integrative view of vmHRV as a dynamic marker of self-regulation shaped by autonomic and immunological processes. This perspective refines existing models by highlighting the developmental and sex-specific pathways through which vagal function relates to depressive symptomatology in adolescence.

Methodological and Theoretical Limitations

Despite the valuable insights into vagal regulation in adolescent depression provided by the three studies that comprise this thesis, there are some limitations that must be taken into consideration. There are several methodological issues that need to be addressed, which could be crucial not only for a qualified interpretation of the respective results, but also for the conduct of future studies. To this end, a critical examination of the theoretical framework of the NIM and the concept of the AIR in this context also appears necessary.

The first methodological limitation to consider concerns the interpretation of vmHRV as a proxy for vagal activity based on cross-sectional studies. In adult patients, it has been shown that cardiac activity not only correlates with neural dysregulation in clinical depression but also contributes significantly to general physiological dysregulation (Mather & Thayer, 2018). This is supported by the results of longitudinal population-based studies (Jandackova et al., 2016) and twin studies (Huang et al., 2018) conducted in adults, which suggest that a reduction in vmHRV precedes the onset of depressive symptoms, suggesting a suppressed vmHRV as a risk marker for depression rather than a consequence. Even though existing

evidence suggests that children and adolescents are at risk of developing psychopathology (Koenig et al., 2016), supported by findings of the presented meta-analysis, most analyses regarding vmHRV and depressive symptoms in children and adolescents are based on cross-sectional data, which precludes causal inferences regarding the directionality of observed associations. The lack of evidence of causal associations especially in adolescent and child populations is compounded by methodological problems in cross-sectional studies. Cross-sectional designs are limited in their ability to distinguish age-related differences from intra-individual developmental changes and are susceptible to cohort effects. Longitudinal approaches, on the other hand, provide stronger evidence for temporal trajectories and allow for the modelling of intra-individual variability over time, thereby offering more valid insights into developmental processes (Singer & Willett, 2003). Moreover, the measurement of HRV is strongly confounded by additional third variables (Laborde et al., 2017). These include individual variables like, as mentioned above, sex, pubertal status and menstrual cycle (e.g., Koenig, Rash, et al., 2017) or level of physical activity (e.g., Gutin et al., 2005), but also measurement-related variables such as the measurement method, the time of day of the measurement, etc. (Chen et al., 2023). These issues seem particularly important to investigate longitudinally from a developmental perspective and need to be elaborated in light of normative changes. Although conducted cross-sectionally, efforts were made in all three included manuscripts to control for potential confounders of vmHRV. In the meta-analysis (Manuscript #1), study-level moderators such as age, sex, and clinical status were systematically examined, and inclusion was restricted to studies that applied established HRV guidelines. In the orthostatic stress study (Manuscript #2), analyses were statistically controlled for relevant covariates such as age, sex, and body mass index, while participants were instructed to refrain from consuming substances (e.g., caffeine, nicotine) prior to testing. The immunological integration study (Manuscript #3) was controlled for sex due to sample

selection, and the considered group comparisons accounted for severity of depression to ensure that correlations between vmHRV and inflammatory markers were not solely attributable to underlying symptom burden, even though the latter is not relevant to the present research question. Nevertheless, several confounding factors highlighted in the existing guidelines, such as puberty status, menstrual cycle phase, respiration, or physical activity, were not consistently assessed, which limits comparability and may have led to residual bias (Laborde et al., 2017; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The absence of longitudinal studies limits the ability to track developmental trajectories and establish temporal relationships between variables: If long-term studies demonstrated that early changes in vmHRV precede the development of depression in children and adolescents, vmHRV could be used and interpreted as a reliable biological marker for early risk of depression genesis. Larger, longitudinal and experimental designs would be necessary to clarify causality and developmental processes for this specific population.

A further limitation concerns the generalizability of the presented results. This is due to the statistical significance and sample size of the studies, two issues that are closely related: With smaller samples, the probability of detecting true effects decreases, and estimates become less reliable. Many psychological and neuroscientific studies are underpowered, often achieving only 30–40% power rather than the conventionally aspired 80% (Brysbaert & Stevens, 2018; Button et al., 2013; Cohen, 1962). Consistent with this, the meta-analysis presented in this thesis showed that many included studies exhibited insufficient power. The moderate sample sizes of the other presented studies similarly limit the detection of smaller effects and generalizability. Although larger and more representative samples are clearly needed in this field of research (Quintana, 2017), the recruitment of sufficiently large clinical and developmental cohorts remains challenging and resource-intensive, reinforcing the

importance of rigorous design and transparent reporting in smaller-scale studies in order to render results as comprehensible and interpretable as possible. Another limitation to the generalizability of the results is the fact that although the meta-analysis provides valuable evidence for reduced vmHRV in adolescents with clinically significant depression, the wide age range (3.06–16.65 years) limits the developmental specificity. Future meta-analytic studies should distinguish between prepubertal and adolescent samples in order to clarify age-related trajectories of vagal regulation in depressive psychopathology.

Finally, a critical view at the theoretical framework of the NIM used in this thesis is warranted. First, alternative models of autonomous regulation exist, which were not systematically examined in the manuscripts presented, but could contribute additional explanatory value. For example, *Polyvagal Theory* emphasizes the hierarchical organization of the autonomic nervous system with different vagal pathways that support social interaction, mobilization, and immobilization, and highlights neural circuits that regulate adaptive behavioural strategies in response to safety and threat (Porges, 2007). Looking at the limitations of the NIM, one key concern is its generalization. The model suggests that a shared central control network, especially structures like the medial prefrontal cortex, anterior cingulate cortex (ACC), and insula, controls both vmHRV and executive and emotional self-regulation (Thayer & Lane, 2000, 2009). Empirically, there are indeed associations between resting HRV and prefrontal activity as well as cognitive performance (Jennings et al., 2015; Thayer et al., 2012). However, in a large sample, Jennings et al. (2015) showed that although HRV was associated with regional cerebral blood flow and cognitive measures, these correlations could not be explained by a uniform neural control system, thus calling into question the strong formulation of the model. This is closely related to the interpretive limitations of correlational findings. The vast majority of studies to date are based on cross-sectional data, the findings of which do not allow causal conclusions to be drawn: it remains

unclear whether low HRV reflects impaired prefrontal control or whether third variables such as fitness, stress, hormonal states, or inflammatory processes influence both variables (Beauchaine & Thayer, 2015; Smith et al., 2017). As already acknowledged, from a methodological point of view, it remains questionable to interpret HRV as a direct and exclusive index of prefrontal control, since HRV is modulated by a variety of factors, including respiratory rate, baroreflexes, and the interaction of sympathetic and parasympathetic activity (Billman, 2013; Laborde et al., 2017). Despite these theoretical limitations and the potential explanatory contribution of alternative models, the NIM remains a very appropriate framework for this thesis. This is primarily due to its theoretical plausibility and its wide empirical support. Unlike more metaphorical or selectively oriented models, such as the somewhat controversial (Walz & Grossman, 2024) Polyvagal Theory appears to be , the NIM enables precise, verifiable connections between autonomic function, executive control, and affective regulation (Thayer et al., 2012). However, the generalization that a uniform control network always explains HRV and cognitive and emotional regulation at the same time is not sufficiently supported by empirical evidence. Rather, the evidence points to context-dependent and multifactorial relationships (Jennings et al., 2015; Smith et al., 2017).

Considering these methodological and theoretical limitations, the need to apply longitudinal and experimental designs in future research is emphasized, to include more diverse and representative samples, to refine and extend existing theoretical models, and to further validate the clinical applicability of autonomic and immune markers in adolescent psychopathology. These considerations form the basis for the following implications and recommendations for future research and clinical practice.

Implications and Future Research Directions

As previously explained by the heterogeneity of the effects and the dependence of vmHRV on various modifying factors presented here, vmHRV cannot be considered a disorder-specific biomarker for depression, but rather a transdiagnostic index for self-regulation ability. The implications of this perspective for future research and clinical transition are twofold: On the one hand, it informs the refinement of theoretical models and concepts such as the NIM and AIR. On the other hand, it holds possibilities for clinical application, ranging from early identification of at-risk populations to the evaluation and enhancement of treatment strategies. Interventions that target vagal regulation directly represent promising approaches for improving self-regulatory capacity. Moreover, vmHRV could serve as a transdiagnostic biomarker not only for prevention but also for monitoring treatment response in clinical populations.

To build on the implications for the treatment of depressive symptoms in adolescents: A promising therapeutic approach represents non-invasive vagus nerve stimulation (tVNS). It delivers mild electrical stimulation, for example, via the auricular branch of the vagus nerve, which is typically applied to the tragus or cymba conchae of the outer ear. Through afferent projections to the nucleus tractus solitarii and subsequent connections to the locus coeruleus and prefrontal regions, tVNS can modulate autonomic and cognitive-affective circuits (He et al., 2013; Komisaruk & Frangos, 2022). It is used in a variety of clinical settings in adults, for example in the treatment of epilepsy (Stefan et al., 2012), post-traumatic stress disorder (Gurel et al., 2020), as well as symptoms of clinically-significant depression (Hein et al., 2013; Rong et al., 2016). There is increasing evidence of the effectiveness of tVNS treatment (Farmer et al., 2021) along with good safety and tolerability (Redgrave et al., 2018), however the existing literature is also accompanied by inconsistencies around reporting of methodological detail (Farmer et al., 2021). In children and adolescents, studies examining

tVNS as treatment option in the context of different physical and psychopathological conditions in children and adolescents are emerging (Sigrist et al., 2023) and preliminary evidence supports influences of tVNS on vagal activity in adolescents (Höper et al., 2022). Although the early stages of tVNS evaluation for psychopathological treatment in adolescent population, its non-invasive nature and favourable side effect profile make it particularly promising.

Beyond direct treatment intervention, vmHRV may be useful as a marker for treatment monitoring and prognosis in depression. Because vagal indices respond to both symptom severity and recovery dynamics, they may provide an objective physiological parameter for tracking treatment progress and detecting early signs of relapse. Preliminary results even support the assumption that vmHRV itself can serve as a direct treatment target under tVNS. In adolescents, tVNS has been shown to increase vmHRV compared to sham stimulation, while simultaneously increasing oxygenation of the PFC. Importantly, a greater increase in vmHRV was associated with greater PFC activation, directly confirming the visceral and neurovagal interactions described in the NIM (Höper et al., 2022). This suggests that vmHRV may not only indicate risk and treatment response but may also reflect the physiological mechanisms through which interventions such as tVNS exert their therapeutic effects. Together, these applications demonstrate how vmHRV-related research can influence clinical practice in depression by both informing the development of new complementary interventions and providing a physiological marker for monitoring treatment response. Although the present results also point to relevance for anxiety disorders and NSSI, in line with the subject focus of this thesis, the outlined implications concern only the treatment of depressive symptoms.

The present findings also contribute to theoretical models of autonomic regulation and psychopathology. The NIM provides a valuable framework for understanding HRV as an

index of prefrontal autonomic regulatory circuits. The results suggest that its explanatory scope can be refined by systematically distinguishing between tonic and phasic indices, in line with the VTT (Laborde et al., 2018), which distinguishes between baseline capacity, reactivity, and recovery. Furthermore, the observed associations between HRV and immune markers in adolescent girls highlight the role of the AIR and suggest that vagal-immunological interactions may represent an additional pathway linking autonomic regulation to depressive symptoms and associated behaviours. Together, these perspectives underscore that vmHRV should not be conceptualized as a uniform biomarker, but rather as a multidimensional index embedded in broader neurovisceral and neuroimmune systems. Future theoretical work could benefit from integrating these perspectives to better capture how vagal regulation contributes to the onset and maintenance of depression in adolescence.

The present work also points to several methodological priorities for future research on vmHRV in the context of adolescent depression. A key implication is the need for developmentally sensitive, longitudinal designs that address vmHRV at the onset, persistence, and remission of depressive psychopathology in adolescence. Such designs are necessary to determine under which developmental conditions vmHRV can serve as a risk marker for the course of the disease rather than as a simultaneous correlate. They might be most informative if they incorporate confounding variables such as pubertal status and sex hormone changes, as well as contextual risk factors such as early life stress and adversity exposure, to allow for more comprehensive models of vulnerability to depression (Koenig, 2020). In addition, progress will require larger and more diverse samples, including different sexes and individuals from different cultural and socioeconomic backgrounds. This is crucial for disentangling sex-specific trajectories and for establishing the generalizability of findings beyond Western populations. Future work should also move toward multimodal designs, integrating HRV with neural, endocrine, and immune markers, as well as with ecological

momentary assessment. Such designs can capture the interplay between autonomic regulation, central processes, and environmental influences in real time. Methodologically, multimodal approaches (e.g., combining HRV, neuroimaging, inflammation assays, ecological momentary analysis) can capture the dynamic and context-sensitive nature of self-regulation under realistic conditions. Improved control and standardization of confounding factors such as breathing, physical activity, and substance use are essential for increasing validity, and future studies should consistently adhere to established guidelines (Task Force, 1996; Laborde et al., 2017). In addition, larger and more diverse samples with balanced representation of sexes are needed to disentangle sex-specific trajectories and improve generalizability.

The sex differences observed across the three studies also carry translational significance. They resonate with emerging approaches in personalized and stratified psychiatry, which emphasize tailoring prevention and treatment to inter-individual variability in biology and context (Kendler, 2016; National Research Council et al., 2011; Stephan et al., 2016; Tamminga, 2014). This perspective has been reinforced by precision medicine initiatives (Terry, 2015) and by the *Research Domain Criteria* framework, which seeks to redefine psychiatric nosology based on neurobiological mechanisms (Cuthbert & Kozak, 2013; Insel, 2014). In that light, interventions targeting vagal regulation, as outlined above, may not be equally effective across sexes but could have differential value. Although this is yet to be confirmed in clinical interventional studies, strategies that strengthen phasic adaptability may be particularly beneficial for boys, whereas approaches addressing tonic dysregulation or autonomic–immune coupling may hold more promise for girls. Taken together, these considerations highlight the need to stratify preventive and therapeutic interventions by sex and developmental stage rather than applying uniform approaches.

Finally, the present work emphasizes that the investigation of the complex autonomic regulatory processes by one single marker will be insufficient for advancing a mechanistic

understanding. Rather, a combination of several markers indicating different states of ANS activity (Prinsloo et al., 2014; Walker et al., 2017), as well as the integration of various markers that capture autonomic, immunological, and affective regulation throughout development, appears to be necessary to disentangle normative from deviant trajectories (Koenig, 2020; Pozzato et al., 2019). This integrative perspective also provides the conceptual bridge toward the concluding considerations of this thesis.

Conclusion

The present thesis set out to examine the extent to which vagal regulation and its immunological integration are related to self-regulation and manifestations of depressive psychopathology during adolescence. Across the three complementary manuscripts, the findings converge on the conclusion that alterations in cardiac vagal regulation mark impairments in self-regulatory capacity that are central to adolescent depression.

The results of the meta-analysis support the view that adolescents with clinically significant depression exhibit reduced vagal activity at rest, consistent with the findings in adults. It reinforces the view that tonic cardiac vagal regulation serves as a physiological marker of impaired self-regulation. Beyond resting-state measures, the experimental study demonstrated that reduced reactivity and delayed recovery of vmHRV under orthostatic stress are also characteristic of depressive symptoms, particularly in boys. The dynamic flexibility is therefore essential for adaptive regulation with developmental and gender-specific factors shaping these patterns. In female adolescents, reduced vmHRV was additionally associated with elevated inflammatory markers, consistent with the framework of the autonomic AIR. Although these effects were mediated by depression severity, this finding indicates that vagal–immune coupling constitutes an additional pathway through which self-dysregulation may manifest in adolescence.

To conclude, examining the central question of this study has yielded valuable insights: Changes in vmHRV accompany depressive symptoms in adolescence, particularly in clinically significant cases, but their broader significance lies in reflecting transdiagnostic self-regulation deficits that span a multidimensional regulatory phenotype encompassing tonic, phasic, and immunological processes. This perspective refines the theoretical framework of the NIM by incorporating developmental aspects and points to clinical applications of HRV as a tool for risk identification and treatment optimization of depression, particularly in combination with developmental, gender-specific, and immunological considerations. Ultimately, this conceptualization advances the understanding of adolescent self-regulation within psychopathology and underlines the importance of interdisciplinary approaches integrating psychiatry and neurophysiology.

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