Premenstrual symptoms as a function of altered central autonomous nervous activity

A neurovisceral integration perspective on premenstrual syndrome

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Cumulative dissertation for the attainment of the degree of

DOCTOR PHILOSOPHIAE

(Dr. phil.)

Submitted to the Faculty of Human Sciences, University of Potsdam

Institute for Psychology

by

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Date of Submission: 02.01.2024

1st reviewer: Prof. Dr. Mathias Weymar
2nd reviewer: Prof. Dr. Sarah Schumacher

Published online on the
Publication Server of the University of Potsdam:
https://doi.org/10.25932/publishup-64597
https://nbn-resolving.org/urn:nbn:de:kobv:517-opus4-645970

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Summary

The experience of premenstrual syndrome (PMS) affects up to 90% of individuals with an active menstrual cycle and involves a spectrum of aversive physiological and psychological symptoms in the days leading up to menstruation (Tschudin et al., 2010). Despite its high prevalence, the precise origins of PMS remain elusive, with influences ranging from hormonal fluctuations to cognitive, social, and cultural factors (Hunter, 2007; Matsumoto et al., 2013).

Biologically, hormonal fluctuations, particularly in gonadal steroids, are commonly believed to be implicated in PMS, with the central factor being varying susceptibilities to the fluctuations between individuals and cycles (Rapkin & Akopians, 2012). Allopregnanolone (ALLO), a neuroactive steroid and progesterone metabolite, has emerged as a potential link to PMS symptoms (Hantsoo & Epperson, 2020). ALLO is a positive allosteric modulator of the $GABA_A$ receptor, influencing inhibitory communication (Rupprecht, 2003; Andréen et al., 2006). Different susceptibility to ALLO fluctuations throughout the cycle may lead to reduced GABAergic signal transmission during the luteal phase of the menstrual cycle.

The GABAergic system's broad influence leads to a number of affected physiological systems, including a consistent reduction in vagally mediated heart rate variability (vmHRV) during the luteal phase (Schmalenberger et al., 2019). This reduction in vmHRV is more pronounced in individuals with high PMS symptoms (Baker et al., 2008; Matsumoto et al., 2007). Fear conditioning studies have shown inconsistent associations with cycle phases, suggesting a complex interplay between physiological parameters and PMS-related symptoms (Carpenter et al., 2022; Epperson et al., 2007; Milad et al., 2006).

The neurovisceral integration model posits that vmHRV reflects the capacity of the central autonomous network (CAN), which is responsible for regulatory processes on behavioral, cognitive, and autonomous levels (Thayer & Lane, 2000, 2009). Fear learning, mediated within the CAN, is suggested to be indicative of vmHRV's capacity for successful

regulation (Battaglia & Thayer, 2022). Given the GABAergic mediation of central inhibitory functional connectivity in the CAN, which may be affected by ALLO fluctuations, this thesis proposes that fluctuating CAN activity in the luteal phase contributes to diverse aversive symptoms in PMS.

A research program was designed to empirically test these propositions. Study 1 investigated fear discrimination during different menstrual cycle phases and its interaction with vmHRV, revealing nuanced effects on acoustic startle response and skin conductance response. While there was heightened fear discrimination in acoustic startle responses in participants in the luteal phase, there was an interaction between menstrual cycle phase and vmHRV in skin conductance responses. In this measure, heightened fear discrimination during the luteal phase was only visible in individuals with high resting vmHRV; those with low vmHRV showed reduced fear discrimination and higher overall responses.

Despite affecting the vast majority of menstruating people, there are very limited tools available to reliably assess these symptoms in the German speaking area. Study 2 aimed at closing this gap, by translating and validating a German version of the short version of the Premenstrual Assessment Form (Allen et al., 1991), providing a reliable tool for future investigations, which closes the gap in PMS questionnaires in the German-speaking research area.

Study 3 employed a diary study paradigm to explore daily associations between vmHRV and PMS symptoms. The results showed clear simultaneous fluctuations between the two constructs with a peak in PMS and a low point in vmHRV a few days before menstruation onset. The association between vmHRV and PMS was driven by psychological PMS symptoms.

Based on the theoretical considerations regarding the neurovisceral perspective on PMS, another interesting construct to consider is attentional control, as it is closely related to

functions of the CAN. Study 4 delved into attentional control and vmHRV differences between menstrual cycle phases, demonstrating an interaction between cycle phase and PMS symptoms. In a pilot, we found reduced vmHRV and attentional control during the luteal phase only in participants who reported strong PMS.

While Studies 1-4 provided evidence for the mechanisms underlying PMS, Studies 5 and 6 investigated short- and long-term intervention protocols to ameliorate PMS symptomatology. Study 5 explored the potential of heart rate variability biofeedback (HRVB) in alleviating PMS symptoms and a number of other outcome measures. In a waitlist-control design, participants underwent a 4-week smartphone-based HRVB intervention. The results revealed positive effects on PMS, with larger effect sizes on psychological symptoms, as well as on depressive symptoms, anxiety/stress and attentional control.

Finally, Study 6 examined the acute effects of HRVB on attentional control. The study found positive impact but only in highly stressed individuals.

The thesis, based on this comprehensive research program, expands our understanding of PMS as an outcome of CAN fluctuations mediated by $GABA_A$ receptor reactivity. The results largely support the model. These findings not only deepen our understanding of PMS but also offer potential avenues for therapeutic interventions. The promising results of smartphone-based HRVB training suggest a non-pharmacological approach to managing PMS symptoms, although further research is needed to confirm its efficacy.

In conclusion, this thesis illuminates the complex web of factors contributing to PMS, providing valuable insights into its etiological underpinnings and potential interventions. By elucidating the relationships between hormonal fluctuations, CAN activity, and psychological responses, this research contributes to more effective treatments for individuals grappling with the challenges of PMS. The findings hold promise for improving the quality of life for those affected by this prevalent and often debilitating condition.

Zusammenfassung

Das prämenstruelle Syndrom (PMS) betrifft bis zu 90% aller Personen mit einem aktiven Menstruationszyklus und umfasst ein Spektrum aversiver physiologischer und psychologischer Symptome in den Tagen vor der Menstruation (Tschudin et al., 2010). Trotz der hohen Prävalenz bleiben die genauen Ursachen von PMS weitgehend unklar, wobei Einflüsse von hormonellen Schwankungen bis hin zu kognitiven, sozialen und kulturellen Faktoren reichen (Hunter, 2007; Matsumoto et al., 2013).

Von einer biologischen Perspektive werden hormonelle Schwankungen insbesondere in den Geschlechtshormonen häufig mit PMS in Verbindung gebracht. Dabei gelten individuelle und zyklusabhängige Anfälligkeiten gegenüber der hormonellen Schwankungen als zentraler Faktor (Rapkin & Akopians, 2012). Allopregnanolon (ALLO), ein neuroaktives Steroid und ein Progesteronmetabolit, hat sich als potenzielle Verbindung zu PMS-Symptomen herausgestellt (Hantsoo & Epperson, 2020). ALLO ist ein positiver allosterischer Modulator des $GABA_A$-Rezeptors, der die inhibitorische Kommunikation beeinflusst (Rupprecht, 2003; Andréen et al., 2006). Eine unterschiedliche Anfälligkeit für ALLO-Schwankungen im Verlauf des Menstruationszyklus kann zu einer verminderten GABAergen Signalübertragung während der Lutealphase führen.

Der breite Einfluss des GABAergen Systems führt zu einer Vielzahl von betroffenen physiologischen Systemen, einschließlich einer konstanten Reduktion der vagal vermittelten Herzfrequenzvariabilität (vmHRV) während der Lutealphase (Schmalenberger et al., 2019). Diese Reduktion der vmHRV ist bei Personen mit starken PMS-Symptomen stärker ausgeprägt (Baker et al., 2008; Matsumoto et al., 2007). Studien zur Furchtkonditionierung haben inkonsistente Assoziationen mit den Zyklusphasen gezeigt, was auf ein komplexes Zusammenspiel zwischen physiologischen Parametern und PMS-spezifischen Symptomen hindeutet (Carpenter et al., 2022; Epperson et al., 2007; Milad et al., 2006).

Das neuroviszerale Integrationsmodell postuliert, dass die vmHRV die Kapazität des zentralen autonomen Netzwerks (CAN) widerspiegelt, das für regulatorische Prozesse auf Verhaltens-, kognitiver und autonomer Ebene verantwortlich ist (Thayer & Lane, 2000, 2009). Das innerhalb des CAN vermittelte Furchtlernen wird als Indikator für die Fähigkeit der vmHRV zur erfolgreichen Regulation betrachtet (Battaglia & Thayer, 2022). Angesichts der GABAergen Vermittlung der zentralen inhibitorischen funktionellen Konnektivität im CAN, die durch ALLO-Schwankungen beeinflusst werden kann, postuliert diese Arbeit, dass eine fluktuierende CAN-Aktivität in der Lutealphase zu den vielfältigen aversiven Symptomen des PMS beiträgt.

Ein Forschungsprogramm wurde konzipiert, um diese Annahmen empirisch zu überprüfen. Studie 1 untersuchte die Furchtdiskriminierung während verschiedener Menstruationszyklusphasen und deren Wechselwirkung mit vmHRV. Dabei wurden nuancierte Effekte auf den akustischen Schreckreflex und die Hautleitfähigkeitsreaktion aufgedeckt. Während eine gesteigerte Furchtdiskriminierung in akustischen Startlereaktionen bei Teilnehmenden in der Lutealphase festgestellt wurde, zeigte sich in den Hautleitfähigkeitsreaktionen eine Wechselwirkung zwischen Menstruationszyklusphase und vmHRV. In dieser Variable war eine erhöhte Furchtdiskriminierung während der Lutealphase nur bei Personen mit hoher Ruhe-vmHRV sichtbar; Personen mit niedriger vmHRV zeigten eine verringerte Furchtdiskriminierung und insgesamt stärkere Reaktionen.

Trotzdem PMS die Mehrzahl aller menstruierender Personen betrifft, gibt es im deutschen Sprachraum wenige Instrumente, die die Symptomatik reliabel erfassen. Um diese Lücke zu schließen, übersetzte und validierte Studie 2 eine deutsche Version der Kurzversion der Premenstrual Assessment Form (Allen et al., 1991), wodurch ein reliables Instrument für zukünftige Untersuchungen bereitgestellt wurde. Dieses schließt eine Lücke in PMS-Fragebögen in der deutschen Forschungslandschaft.

Studie 3 verwendete ein Tagebuchstudienparadigma, um tägliche Zusammenhänge zwischen vmHRV und PMS-Symptomen zu erforschen. Die Ergebnisse zeigten klare simultane Fluktuationen zwischen den beiden Konstrukten mit einem Höhepunkt in PMS und einem Tiefpunkt in vmHRV einige Tage vor Beginn der Menstruation. Die Assoziation zwischen vmHRV und PMS wurde hautsächlich durch psychologische PMS-Symptome verursacht.

Basierend auf den theoretischen Überlegungen zur neuroviszeralen Perspektive auf PMS, ist ein weiteres interessantes zu betrachtende Konstrukt Aufmerksamkeitskontrolle, da diese eng mit Funktionen des CAN zusammenhängt. Studie 4 untersuchte Aufmerksamkeitskontrolle und Unterschiede in der vmHRV zwischen der Luteal- und Follikelphase des Menstruationszyklus und zeigte eine Wechselwirkung zwischen Zyklusphase und PMS-Symptomen. In einer Pilotstudie fanden wir eine reduzierte vmHRV und Aufmerksamkeitskontrolle während der Lutealphase ausschließlich bei Teilnehmenden, die starke PMS-Symptome berichteten.

Während die Studien 1-4 Evidenz für die Mechanismen hinter PMS lieferten, untersuchten Studien 5 und 6 Kurz- und Langzeitinterventionsprotokolle zur Verbesserung der PMS-Symptomatik. Studie 5 untersuchte den Effekt von Herzratenvariabilitätsbiofeedback (HRVB) auf PMS-Symptome und einer Reihe anderer Outcomemaße. In einem Wartelisten-Kontroll-Design durchliefen die Teilnehmenden eine 4-wöchige Smartphone-basierte HRVB-Intervention. Die Ergebnisse zeigten positive Effekte auf PMS, mit größeren Effektstärken in psychologischen Symptomen, sowie bei depressiven Symptomen, Ängstlichkeit/Stress und Aufmerksamkeitskontrolle.

Schließlich untersuchte Studie 6 die akuten Effekte von HRVB auf Aufmerksamkeitskontrolle. Die Studie zeigte positive Effekte, jedoch nur bei stark gestressten Personen.

Die vorliegende Dissertation erweitert auf Grundlage dieses umfassenden Forschungsprogramms unser Verständnis von PMS als Ergebnis von Fluktuationen im zentralen autonomen Netzwerk (CAN), vermittelt durch die Reaktivität des $GABA_A$-Rezeptors, vor. Die Ergebnisse unterstützen größtenteils das Modell. Diese Erkenntnisse vertiefen nicht nur unser Verständnis von PMS, sondern bieten auch potenzielle Ansätze für therapeutische Interventionen. Die vielversprechenden Ergebnisse des Smartphone-basierten HRVB-Trainings stellen einen nicht-pharmakologischen Ansatz zur Bewältigung von PMS-Symptomen vor, obwohl weitere Forschung erforderlich ist, um die Wirksamkeit zu bestätigen.

Zusammenfassend beleuchtet diese Dissertation das komplexe Geflecht von Faktoren, die zu PMS beitragen, und liefert wertvolle Einblicke in seine ätiologischen Grundlagen und mögliche Interventionen. Durch die Aufklärung der Beziehungen zwischen hormonellen Fluktuationen, CAN-Aktivität und psychologischen Reaktionen trägt diese Forschung zu effektiveren Behandlungen für Menschen bei, die mit den Herausforderungen von PMS kämpfen. Die Ergebnisse versprechen, die Lebensqualität der Betroffenen von diesem weit verbreiteten und oft belastenden Zustand zu verbessern.

List of abbreviations

(vm)PFC	(ventromedial) prefrontal cortex
ALLO	Allopregnanolone
ANOVA	analysis of variance
ANT-R	revised attention network test
CAN	central autonomic network
CeA	central nucleus of the amygdala
CS-	conditioned stimulus not paired with unconditioned stimulus
CS+	conditioned stimulus paired with unconditioned stimulus
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	electrocardiography
EDA	electrodermal activity
fMRI	functional magnetic resonance imaging
GABA	γ-Aminobutyric acid
HR	heart rate
HRV	heart rate variability
HRVB	heart rate variability biofeedback
ICD-10	International Classification of Diseases, 10^{th} edition
NVI	neurovisceral integration model
NVI-f	neurovisceral integration model of fear
PAF20/10	premenstrual assessment form, short version
PMDS	premenstrual dysphoric disorder
PMS	premenstrual syndrome
PMSIS	Premenstrual Symptoms Impact Survey
RMSSD	root mean square of successive differences
RSA	respiratory sinus arrythmia
RVLM	rostral ventrolateral medulla
SEV	saccadic eye velocity
UCS	unconditioned stimulus
vmHRV	vagally mediated heart rate variability

1 Theoretical background

1.1 Premenstrual symptoms and their relevance

During the late luteal phase of the menstrual cycle, which occurs right before menstruation, nearly all menstruating individuals regularly experience a range of symptoms. These symptoms can be broadly categorized into two types: physiological and psychological. On the physiological side, individuals may contend with discomfort such as back pain, acne, and water retention. Simultaneously, psychological symptoms like irritability and anxiousness can also manifest during this phase. The symptoms emerge in the premenstrual phase and dissipate within a few days after menstruation onset. However, the impact of these symptoms can vary significantly both within and between individuals. The intensity can range from experiencing mild water retention with minimal disruption to one's daily life to enduring severe episodic symptoms of depression, leading to high levels of debilitation. When this symptom complex presents itself with a certain level of regularity and noticeable impact, it is commonly referred to as premenstrual syndrome (PMS) (Ryu & Kim, 2015).

There is no consistent agreement on when premenstrual symptoms qualify as PMS, leading to a wide variation in reported prevalence rates. A meta-analysis conducted by Direkvand-Moghadam et al. (2014) revealed a pooled prevalence of 47%, with original studies reporting prevalences ranging from 10% to 98%. Interestingly, newer publications tend to report higher prevalences, although this trend is not statistically significant. This variability is likely due to the lack of a consistent definition for diagnosing PMS (Direkvand-Moghadam et al., 2014). In a representative study of nearly 4000 menstruating individuals in Switzerland, Tschudin et al. (2010) found that at least one regular premenstrual symptom was reported by 91% of all participants, highlighting the high relevance of the topic.

PMS can affect individuals of all ages between menarche and menopause. The results regarding association of symptom intensity and age have been inconsistent. Some studies find no association of symptom intensity to age (Potter et al., 2009), while some research indicates that the intensity of symptoms tends to follow an inverted U-shaped curve with the highest symptomatology typically experienced during the late 20s and early 30s (Freeman et al., 1995). Dennerstein et al. (2011) found different symptom course pattern over life span, indicating increases over time, no changes or U shapes with peaks at either around 35 or five to ten years later. That study may be indicative of why often no associations with age are found. Symptom intensity courses, the same as symptom profile, intensity, and consistency, seem to be highly individual.

Cases of PMS with severe affective symptoms are diagnosed as premenstrual dysphoric disorder (PMDD), following clear diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, American Psychiatric Association, 2013) and the International Classification of Diseases (ICD-10, World Health Organization [WHO], 1993). According to the DSM-V, PMDD falls under the category of depressive disorders and requires the presence of at least 5 symptoms during the week preceding menstruation, with improvement within a few days after menstruation begins, and minimal or absent symptoms during other menstrual cycle phases. Among these symptoms, there must be at least one affective symptom (e.g., irritability, dysphoria, anxiety) and at least one non-affective symptom (e.g., concentration difficulty, feeling overwhelmed, physical symptoms). These symptoms should be present in most cycles over one year, causing significant distress and interference with daily life. To diagnose PMDD, daily symptom tracking for at least two symptomatic cycles is necessary. PMDD affects approximately 1-2% of individuals with an active menstrual cycle (American Psychiatric Association, 2013).

In a review of the burden of illness associated with PMS and PMDD, Rapkin and Winer (2009) highlight that, even though there are little studies on the topic, premenstrual syndromes have a substantial impact on various aspects of individuals' lives. The authors found that PMS reduces quality of life (in all domains, see Victor et al., 2019), impairs work and school productivity, and affects social life. Additionally, PMS carries a significant economic burden, primarily due to decreased productivity and work absenteeism. On average, individuals experiencing PMS miss 1.2 more days of work per month compared to those without PMS. Rapkin and Winer's (2009) analysis also suggests that the burden of PMDD is comparable to that of conditions such as type 2 diabetes, arthritis, or hypertension.

Despite the high relevance and prevalence of the topic, there is currently limited research on premenstrual symptoms (Zehravi et al., 2023). While the number of publications related to PMS saw a gradual increase per year since the 1970s, there has been a plateau from 2008 to 2018, with approximately 100-120 publications annually (Gao et al., 2021). In contrast, research publications related to terms like 'depression' or 'anxiety' have been increasing exponentially, with current numbers reaching around 30,000 per year (search on PubMed as of 17.10.23). The existing research primarily focuses on the clinical presentation of PMDD (Gao et al., 2021). However, even though there are significant inter- and intraindividual differences in symptom experiences (Potter et al., 2009), premenstrual symptoms, including at subclinical levels, affect nearly all menstruating individuals, which constitute about 26% of the global population. Given the substantial burden and the vast number of affected individuals, it is crucial to increase research into the etiology, mechanisms, and potential treatments.

1.2 Etiology of premenstrual syndrome

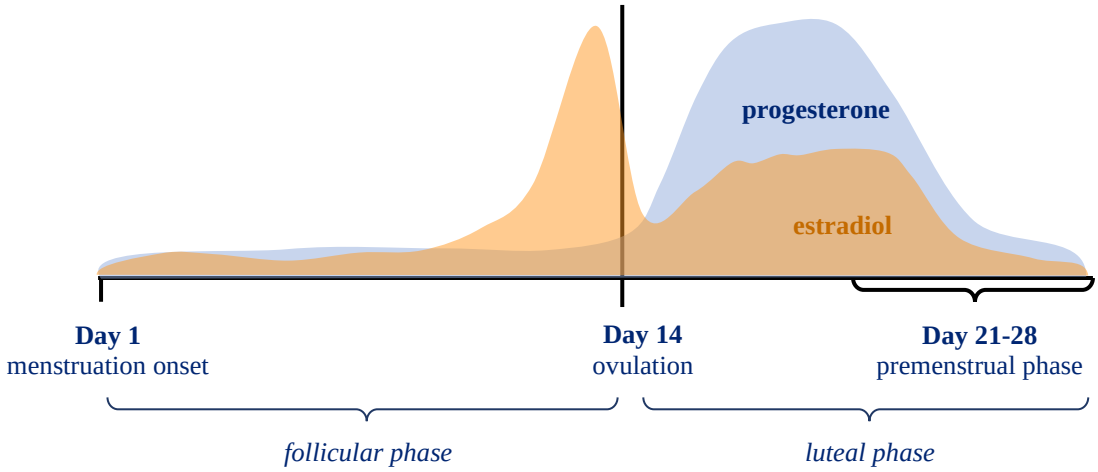
The menstrual cycle is a complex process consisting of distinct phases, each characterized by specific hormonal fluctuations and physiological changes. This cycle typically lasts around 28 days, although there can be considerable variation in cycle length among individuals (Schmalenberger et al., 2021).

- Menstruation (Days 1-5): The menstrual cycle begins with menstruation, which is the shedding of the uterine lining. During this phase, overall hormone levels are relatively low.
- Follicular Phase (Days 1-13): With the menstruation onset, the follicular phase commences. This phase is marked by the ripening of a follicle in the ovary, where the egg is stored. The length of this phase is highly variable.
- Ovulation (Around Day 14): Approximately one week before ovulation, estrogen levels rise, reaching their peak one or two days before the release of the egg. This surge in estrogen triggers the release of a mature egg from the follicle. The egg is then transported into the fallopian tube, where it can potentially be fertilized by sperm.
- Luteal Phase (Days 15-28): Ovulation marks the onset of the luteal phase, which consistently lasts 14-15 days. During this phase, there is a significant increase in progesterone levels. Progesterone peaks around the middle of this phase and then gradually declines until menstruation begins if fertilization has not occurred.
- Premenstrual Phase (3-7 days before menstruation onset): Premenstrual symptoms, often experienced during the latter part of the luteal phase, also called the premenstrual phase, coincide with the drop in progesterone and estradiol levels.

A visualization of an idealized menstrual cycle can be found in Figure 1.

Figure 1

Fluctuations in progesterone and estradiol during an idealized menstrual cycle



Note. The figure depicts an idealized menstrual cycle of 28 days with typical fluctuations in progesterone (P4, shown in blue) and estradiol (E2, shown in orange). The y-axis shows schematic changes in serum levels of gonadal steroids, and the x-axis represents time from one menstruation onset to the next. Visible is the characteristic peak of estradiol a few days before menstruation and the stark continuous increase in progesterone in the first half of the luteal phase, followed by an analogous decline in the second half of the luteal phase.

While the co-appearance of premenstrual symptoms with hormonal fluctuations might suggest a direct causal relationship, scientific investigations have not confirmed this straightforward connection. Studies have failed to find significant and consistent differences in serum hormone levels between individuals with severe and mild premenstrual symptoms or between symptomatic and asymptomatic menstrual cycles during different cycle phases (Rapkin & Akopians, 2012; Thys-Jacobs et al., 2008).

Different models have therefore proposed an interplay of social, cognitive, emotional, biological, and even cultural factors in the etiology of premenstrual symptoms. Examples include the biopsychosocial models proposed by Matsumoto et al. (2013) and Hunter (2007). While a solid body of research has identified that PMS experience is heavily influenced by cultural and social factors (American Psychiatric Association, 2013) as well as genetics

(Jahanfar et al., 2011), the focus in this thesis will be on potential physiological and neuroendocrine factors in the development of symptoms.

As a biological factor, the literature has long assumed differential susceptibility to hormonal fluctuations (Nappi et al., 2022; Rapkin & Akopians, 2012), as there are no evident differences in the hormonal fluctuations themselves. This assumption is based, among other factors, on early research that did not find differences in hormone levels but still found associations with hormonal exposure. For example, Schmidt et al. (1998) found that ovarian suppression with an agonist analogue of gonadotropin-releasing hormone makes symptoms disappear in women who usually experience PMS. Progesterone and estradiol replacement then reinstates symptoms only in PMS, not in asymptomatic women. The mechanisms of this differential sensitivity are not clear, but recent research suggests a vital role for a progesterone metabolite, which will be discussed below.

1.3 The role of Allopregnanolone in premenstrual symptoms

Progesterone has two primary metabolites that it readily converts into, which can cross the blood-brain barrier and exert central nervous effects: pregnanolone and allopregnanolone (ALLO) (Freeman et al., 1993). Among these, ALLO has been gaining more attention in the PMS literature because of its potential role in the etiology of premenstrual symptoms (Nappi et al., 2022).

ALLO exerts an allosteric effect on the γ-Aminobutyric acid $(GABA)_A$ receptor, which is the primary inhibitory receptor in the central nervous system (Rupprecht, 2003). Through its binding to the receptor, the neuroactive steroid enhances the effects of GABA on the receptor, by increasing the chloride ion flux when GABA attaches to the receptor complex (Majewska et al., 1986). At a certain concentration, ALLO is even believed to directly open the chloride channels (Belelli & Lambert, 2005). Consequently, acute exposure to ALLO has direct anxiolytic effects and may even produce sedative and anesthetic effects which are comparable to those of benzodiazepines (Freeman et al., 1993; Schüle et al., 2014). ALLO plays a crucial role in the autonomous nervous system by influencing the Hypothalamic-Pituitary-Adrenal (HPA) axis. It provides negative feedback, helping to dampen the stress response and restore homeostasis (Bali & Jaggi, 2014).

The effects of ALLO on mood and aversive symptoms, however, are somewhat paradoxical. Bäckström et al. (2011) describe how while ALLO is typically a positive modulator of the $GABA_A$ receptor, inducing calming effects, under certain circumstances, ALLO exposure can lead to anxiety and irritability. This effect is not unique to ALLO. Benzodiazepines and alcohol, which similarly have an allosteric effect on $GABA_A$ receptors, have been documented to induce agitation and, in some individuals, even aggression rather than the sedative effect typically observed at certain dosages (Bäckström et al., 2011). In the case of ALLO, there appears to be a U-shaped dosage-effect relationship. A study of post-

menopausal women taking exogenous oral progesterone found that exposure to both low and high ALLO doses was associated with more positive effects, while medium concentrations were associated with a negative mood (Andréen et al., 2006). Interestingly, the concentrations that were observed to be associated with a negative mood are similar to those typically observed during the luteal phase of the menstrual cycle (Bäckström et al., 2011).

Furthermore, Turkmen et al. (2011) elaborate on how chronic exposure to ALLO can lead to tolerance building. The authors argue that this tolerance is linked to the increased expression of specific subunits of the $GABA_A$ receptor, resulting in reduced sensitivity to ALLO and other positive modulators. Specifically, the $GABA_A$ receptor consists of five different subunits from various subunit classes, making the individual composition of the receptors rather heterogeneous. In acute high or chronic ALLO exposure, the α4 subunit expression is upregulated. A receptor containing this unit, rather than, for example, the α1 or α3 unit, is only sensitive to large concentrations of ALLO and is thus unresponsive to low amounts, leading to tolerance effects (Turkmen et al., 2011).

Research investigating ALLO concentrations throughout the cycle in PMS has yielded inconclusive results. Studies comparing individuals suffering from PMS/PMDD with those having low or no symptoms found varying ALLO levels, showing lower levels (Rapkin et al., 1997), higher levels (Girdler et al., 2001), and no difference (Bičíková et al., 1998) during the luteal phase. Additionally, some studies found lower levels during the follicular phase (Bičíková et al., 1998), while others found no difference (Girdler et al., 2001). The results regarding the ratio between ALLO and progesterone have also been mixed (Bičíková et al., 1998; Girdler et al., 2001; Rapkin et al., 1997). Although one study found no differences in the metabolic processing of progesterone in individuals suffering from PMDD after ovulation suppression (Nguyen et al., 2017), blocking the conversion from progesterone to ALLO reduced some core symptoms of PMDD sufferers in a clinical trial conducted over three cycles

(Martinez et al., 2016). Similarly, ALLO levels have been noted to decrease regardless of the menstrual cycle phase after the successful treatment of PMDD with antidepressants (Freeman et al., 2002). In summary, these studies paint a heterogenous picture concerning the role of ALLO concentrations on premenstrual symptoms.

The crucial aspect in ALLO's role in premenstrual symptoms may not be the total concentrations, but rather the sensitivity to fluctuations in ALLO availability throughout the menstrual cycle (Hantsoo & Epperson, 2020). The variations in ALLO levels closely correspond to the rise and fall of progesterone during the menstrual cycle. Progesterone increases during the luteal phase and then rapidly declines, coinciding with the onset of premenstrual symptoms (see to Figure 1). Hantsoo and Epperson (2020) suggest that premenstrual symptoms may emerge as withdrawal symptoms from ALLO exposure. The authors suggest that this is mediated through the tolerance building of $GABA_A$ receptors to ALLO (Bäckström et al., 2011; MacKenzie & Maguire, 2014), which, in turn, stand in relation to the expression of its subunits (Bäckström et al., 2011). Lovick et al. (2017) observed a rapid decline in ALLO concentrations in the late luteal phase in individuals with high premenstrual symptoms, while those with low or no symptoms exhibited a more gradual change. Hantsoo and Epperson (2020) suggest that while $GABA_A$ receptors typically adapt to fluctuations in ALLO levels, more pronounced changes might intensify the 'withdrawal' in the system.

Evidence for this can be found in studies using saccadic eye velocity (SEV). Measurements of changes in SEV are an established method to measure $GABA_A$ receptor-mediated sedation, as SEV is indirectly proportional to $GABA_A$ receptor activity (Bixo et al., 2018). In a study by Timby et al. (2016), individuals with PMDD exhibited atypical responses in SEV following exogenous ALLO exposure. While healthy controls showed slightly lower SEV reactivity to ALLO during the luteal phase, in PMDD participants, the SEV reaction was significantly stronger during the luteal phase compared to the follicular phase. The authors

concluded from this finding that the tolerance-building response to the increased ALLO levels during the luteal phase may be reduced in individuals with PMDD.

Similar results also suggest altered reactivity to other $GABA_A$ modulators, although the effects are not consistent. When administered benzodiazepines, participants with high PMS showed reduced SEV responses compared to controls only in the follicular phase (Sundström et al., 1997), while pregnanolone injection led to reduced SEV responses in PMS sufferers only in the luteal phase (Sundström et al., 1998). In measurements of SEV without the administration of exogenous neuroactive substances, participants had significantly decreased SEV, with lower velocities the closer menstruation onset was compared to the follicular phase, and to non-PMS sufferers (Sundström & Bäckström, 1998).

In summary, ALLO plays a pivotal role in the development of premenstrual symptoms by impacting GABAergic signaling during the luteal phase. It has been suggested that altered reactivity to ALLO in symptomatic cycles and individuals creates "withdrawal" symptoms in response to the strong ALLO fluctuations in this phase (Hantsoo & Epperson, 2020). The resulting reduced GABAergic transmission may be a pathogenetic factor in premenstrual symptoms, making it a subject of ongoing research.

1.4 Physiological markers associated to the menstrual cycle and premenstrual symptoms

As is expected when influencing a complex system like the GABAergic neurotransmitter system, the menstrual cycle, especially in association with PMS, is characterized by fluctuations in several physiological markers. Some of these relevant markers will be discussed in the following.

One marker consistently found to be covarying with the menstrual cycle phase is the cortisol level. In a meta-analysis, Klusmann et al. (2022) found lower cortisol levels in the luteal compared to the follicular phase, as well as lower cortisol levels during the premenstrual compared to the menstrual phase. This is congruent with the unintuitive, abide consistent findings of lower cortisol levels in psychopathological states (Yehuda & Seckl, 2011). Cortisol, being one of the major players in managing stress responses, appears to be a likely candidate to mediate some of the associations between ALLO and PMS. However, in a review of the association between cortisol and PMS/PMDD, Kiesner and Granger (2016) found no consistent associations between cortisol levels/fluctuations and premenstrual symptoms.

Another marker that is worth exploring is the acoustic startle response. The startle response is a reflexive reaction to sudden and unexpected stimuli, often used as an indicator of fear processing (Lonsdorf et al., 2017). The extent of this startle reflex indicates the current subcortical fear levels and is mediated through the amygdala (Wendt et al., 2023). In laboratory settings, this reflex is measured by playing loud, unexpected sounds and recording electromyographic (EMG) data from the muscularis orbicularis oculi, which shows a short reflexive activation due to the startle blink reflex. Larger amplitudes indicate stronger subcortical fear processing. While it is glutamate that primarily processes the startle response, GABA has direct inhibitory effects on this response (M. Koch, 1999), and a reduction in GABAergic activity during the luteal phase can alter this process. Indeed, Armbruster et al. (2018) found higher overall startle magnitudes during the luteal phase compared to the

follicular phase. Critically, this difference is especially pronounced in participants suffering from PMDD compared to low-symptom controls (Epperson et al., 2007).

An interesting concept to consider when examining acoustic startle is that of fear discrimination. Startle magnitude is often used to investigate fear conditioning, a paradigm in which a neutral stimulus is either paired (conditioned stimulus CS+) or not paired (CS-) with an aversive stimulus (unconditioned stimulus UCS). Typically, the startle response is potentiated during CS+ trials (Lonsdorf et al., 2017). The difference in response between CS+ and CS- is then termed fear discrimination, indicating how well the respondent can differentiate between safe and dangerous environments. In a review on the effect that the menstrual cycle has on fear conditioning, Merz et al. (2018) did not come to a direct conclusion. Fear discrimination in acoustic startle magnitude has been found to be higher during the luteal phase of the menstrual cycle (Glover et al., 2013) and specifically during the premenstrual period in the luteal phase (van der Molen et al., 1988). While associations with premenstrual symptoms have not been investigated, this finding suggests a possible role of fear processing in premenstrual symptoms.

Another measure commonly employed in fear conditioning paradigms is skin conductance response (SCR). SCR refers to the change in electrodermal activity (EDA) in response to a stimulus. It is measured as the difference between peak EDA after stimulus onset and EDA pre-stimulus (Lonsdorf et al., 2017). SCR is the most commonly employed measurement in fear conditioning, as it consistently shows a higher response to the conditioned stimulus (CS+) than to the unconditioned stimulus (CS-) (Lonsdorf et al., 2017). Interestingly, while acoustic startle magnitude exhibits menstrual phase effects, no significant differences in SCR have been observed between menstrual cycle phases (Lonsdorf et al., 2015; Milad et al., 2006) or in fear discrimination across these phases (Carpenter et al., 2022; Milad et al., 2006).

Both SCR and acoustic startle response which are used in fear conditioning paradigms, are associated to activity in the amygdala. SCR is commonly viewed as a marker of sympathetic nervous system activity. In contrast, the startle blink reflex is proposed as an indicator of subcortical fear processing within fear-provoking situations, as it is directly controlled by the amygdala (Lonsdorf et al., 2017; Wendt et al., 2023). Looking directly at the amygdala in regard to menstrual cycle phases yields conflicting results. While there is increased (dorsal left) amygdala volume in the late luteal phase, linked to stress-induced negative affect (Ossewaarde et al., 2013), Derntl et al. (2008) observed lower amygdala activation during the luteal phase during an emotion recognition task.

In a small review on physiological correlates of PMDD, Sundström Poromaa (2014) identified a number of other markers that show divergence in individuals diagnosed with PMDD such as event-related potentials in electroencephalography, prepulse inhibition and vagally mediated heart rate variability (vmHRV). The physiological marker most relevant to this thesis, showing associations with menstrual phase and premenstrual symptoms, is vmHRV. Heart rate variability (HRV) is defined as the variation in the time intervals between successive heartbeats and serves as a marker for autonomic nervous activity. Specifically, vagally mediated HRV, as a marker for parasympathetic activity, has received increased attention due to its correlations with a wide range of outcomes, from cognitive functions (Holzman & Bridgett, 2017; Zahn et al., 2016) to psychopathology (Heiss et al., 2021). While various parameters can be extracted from the heartbeat series, not all can be clearly interpreted. The two HRV parameters that have been shown to reflect vagal contributions to cardiac activity, and thus serve as a proxy for the quantification of parasympathetic activity, are the root mean square of successive differences (RMSSD) and the high-frequency component of power spectral analysis (HF), encompassing oscillations in the normal ventilation frequencies (Appelhans & Luecken, 2006).

A meta-analysis and systematic review by Schmalenberger et al. (2019) examined 38 studies with a total of over 1,000 participants. They consistently reported small decreases in vmHRV from the follicular to the luteal phase with a medium effect size (d = -0.39). Additionally, the authors noted reduced vmHRV when comparing the premenstrual phase to the menstrual or mid/late-follicular phases.

A handful of studies have explored the connection between the phasic reduction in vmHRV and premenstrual symptoms. The majority of these studies have observed that premenstrual symptoms moderate the vmHRV reductions during the luteal phase. This effect is such that groups with severe PMS show larger reductions during the luteal phase, while low-symptom groups either exhibit smaller reductions than high-symptom groups (Zambotti et al., 2013) or no reductions at all (Baker et al., 2008; Matsumoto et al., 2007). Matsumoto et al. (2007) also included a group diagnosed with PMDD, which showed reduced vmHRV compared to the PMS and low-symptom groups in both cycle phases. The studies finding this effect employ short-term resting vmHRV measures like the RMSSD or the HF component of power spectral analysis. These measures, assessed during rest, are consistently linked to psychopathological (Heiss et al., 2021) and cognitive outcomes (Holzman & Bridgett, 2017; Zahn et al., 2016) and widely accepted as markers for cardiac vagal control (Appelhans & Luecken, 2006; Laborde et al., 2017). The associations with psychopathological outcomes are so consistent that Beauchaine and Thayer (2015) have proposed resting short-term vmHRV as a transdiagnostic marker of psychopathology.

However, not all studies investigating vmHRV in relation to PMS find effects in the same direction. A study that measured vmHRV continuously over a 24-hour period found no vmHRV changes between menstrual cycle phases, both in a high PMS group and in a low-symptom control group (Landén et al., 2004). In a different approach using an unconventional vmHRV measurement, which calculates the difference between the longest and shortest R-

peak to R-peak intervals during slow-paced breathing, another study observed the opposite effect in relation to symptom intensity. In this case, the high PMS group showed smaller decreases from the follicular to the luteal phase compared to a control group (Kulshreshtha et al., 2013). These two studies assessed heart rate variability in a manner that has a less clear interpretation.

While some studies have reported more significant reductions in vmHRV during the luteal phase in groups characterized by severe PMS, it is essential to acknowledge that there are no clear criteria for distinguishing PMS from non-PMS. The spectrum of symptoms should be viewed as a continuous phenomenon, considering that fewer than 10% of menstruating individuals remain entirely symptom-free (Tschudin et al., 2010). To date, no study has examined premenstrual symptoms as a continuous variable in this context. Nevertheless, the apparent connection between vmHRV and PMS prompts the proposal of an association, a theoretical basis for which will be elaborated upon in the following sections.

1.5 Neurovisceral integration model and neurovisceral integration model of fear

A theoretical framework for interpreting vmHRV is provided by Thayer and Lane's (2000) neurovisceral integration model (NVI). In this model, vmHRV is considered an indicator of functional connectivity within, as well as a reciprocal part of, a network of interconnected neuronal structures that coordinate affective, cognitive, and physiological regulatory processes. This network, referred to as the central autonomic network (CAN, Benarroch, 1993), integrates information about internal and external demands, allowing for flexible and adaptive responses.

One of the key concepts within the NVI is the automated default threat response. Thayer and Lane (2000) suggest that when individuals encounter novel or ambiguous stimuli, their neuronal system defaults to a stress response. This response is coordinated by the central nucleus of the amygdala (CeA), resulting in sympathetic activation and, consequently, reduced vmHRV. This subcortically organized, sympatho-excitatory response, centered around the CeA, can lead to a high allostatic load (i.e. cumulative physiological burden of continued states of stress, Guidi et al., 2021) when chronically or frequently triggered. Furthermore, the authors propose that in modern human life, only a few challenges require this fight-or-flight response.

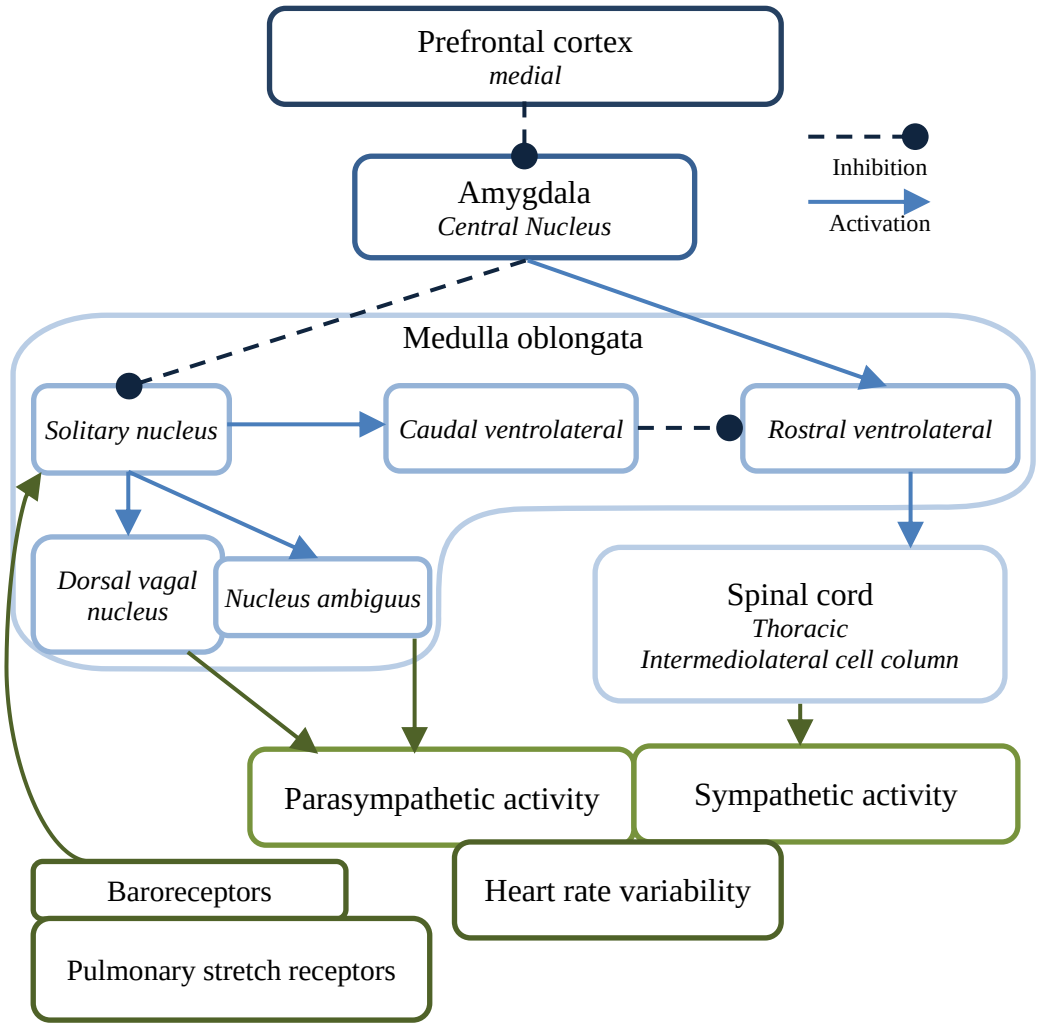
Instead, the authors suggest that a life marked by successful adaptation hinges on cognitive abilities like thoughtful reflection, conflict resolution, and the capacity to delay gratification. These abilities are associated with the suppression of automatic, reflexive processes orchestrated by subcortical structures, including the threat response initiated by the amygdala (Thayer & Lane, 2000). Specifically, the activity of the amygdala is tonically inhibited by GABAergic projections originating from the medial prefrontal cortex (mPFC, Thayer, 2006). Through this functional inhibitory connection, the mPFC can regulate the automatic sympatho-excitatory default response to novel situations.

Gee et al. (2013) demonstrated that functional connectivity between the mPFC and the amygdala is present in both children and adults. However, they found that this connectivity develops a specifically negative coupling, indicating an inhibitory quality, during adolescence. The study also revealed a negative correlation between the strength of this functional connectivity and amygdala activity, underscoring the mPFC's distinct role in dampening amygdala activity. Strong connectivity allows for greater inhibition, leading to reduced amygdala activity. For instance, damage to the mPFC, as shown by Buchanan et al. (2010), can result in the perception of (social) situations as more threatening, as the default threat appraisal mechanism fails to be attenuated.

VmHRV holds a central role in Thayer and Lane's (2009a) theory as it is considered a peripheral indicator of the inhibitory capacity of the mPFC over the default stress response. In addition to the CeA and the mPFC, Thayer et al. (2009) describe several other neuronal structures involved in the CAN, as first described by Benarroch (1993). These structures include the anterior cingulate cortex, insular cortex, orbitofrontal prefrontal cortex, as well as various brainstem structures such as the nucleus of the solitary tract and the nucleus ambiguous. The principal output of this network influences the sinoatrial node both sympathetically, through the stellate ganglia, and parasympathetically, via the vagus nerve (refer to Figure 2 for a visualization of specific pathways). VmHRV is primarily driven by a phenomenon called respiratory sinus arrhythmia (RSA). While the sinoatrial node, which controls the heart rate (HR), receives tonic sympathetic input that elevates HR, phasic parasympathetic input during exhalation temporally decreases heart rate (Penttilä et al., 2001). This results in sinus-like fluctuations in HR, referred to as RSA. The quantification of the extent of RSA is, thus, largely vagally mediated and commonly referred to as vmHRV.

Figure 2

Pathways of heart rate variability cardiac control



Note. The chart shows pathways of possible autonomic nervous activity modulation in the central nervous system which influence the heart rate. For simplification, the connections are visualized unidirectionally and top-down. The medial prefrontal and orbitofrontal cortex inhibit the central nucleus of the amygdala (CeA). The activity in the CeA decreases parasympathetic activity. The amygdala activity inhibits tonic activity of baroreceptive neurons in the solitary nucleus which receive additional input from slow adapting pulmonary stretch receptors. This decrease inhibits activity in the dorsal vagal motor nucleus and the nucleus ambiguous, both of which contain preganglionic parasympathetic neurons that innervate the heart. A decreased activity in the solitary nucleus additionally may cut down the inhibitory input the caudal ventrolateral medulla gives to the tonically active rostral ventrolateral medulla (RVLM). Saha (2005) suggests a direct excitatory projection from the CeA to the RVLM. The RVLM projects to sympathetic preganglionic neurons in the intermediolateral cell column of the thoracolumbar spinal cord innervating among others the stellate ganglion. Through these two pathways, the CeA increases sympathetic activity. Figure adapted from Saha (2005) and Thayer and Lane (2009).

Given that vmHRV is both directly and indirectly influenced by the interplay between the PFC and the amygdala, Thayer and Lane (2000) argue that it serves as an indicator of the extent to which higher processing structures like the vmPFC influence brainstem and autonomic activity. This also mirrors the organism's ability to effectively self-regulate, meaning it can overcome the presumed default threat reaction and other automatic conditioned responses and instead adapt flexibly to environmental demands. Support for this idea can be found in various brain imaging studies, showing among others a correlation between vmHRV and mPFC activity (Lane et al., 2009) and associations between vmHRV and the functional connectivity between mPFC and amygdala (Sakaki et al., 2016).

Battaglia and Thayer (2022) expand upon this model in their Neurovisceral Integration Theory of Fear (NVI-f). Within this framework, Battaglia and Thayer (2022) emphasize the role of the described inhibitory connectivity between the mPFC and CeA. as well as that of vmHRV as its peripheral indicator, in fear processing. The authors describe how the mPFC assesses the level of danger or safety in a situation through information integration. This assessment can either suppress the default limbic fear response in safe situations or enhance it in dangerous ones. VmHRV can then be viewed as an indicator for both fear responses and ability to discriminate between safe and dangerous environments (Ruiz-Padial et al., 2003).

Both the NVI and NVI-f theories are grounded in a substantial body of research that consistently associates reduced vmHRV with increased psychopathological symptomatology, such as anxiety (Chalmers et al., 2014) and depression (C. Koch et al., 2019), as well as with decreased cognitive self-control parameters (Holzman & Bridgett, 2017; Zahn et al., 2016).

1.6 Premenstrual symptoms as fluctuations in central autonomic network

In this thesis, I propose that premenstrual symptoms arise as a consequence of fluctuations in signal transmission within the CAN. As previously explained, a probable source of PMS can be traced to the reactivity of the $GABA_A$ receptor to the phasic changes in ALLO levels during the luteal phase (Hantsoo & Epperson, 2020). This reactivity may result in reduced GABAergic signal transmission during this phase. At the core of the CAN, as outlined in the NVI and NVI-f, lies the GABAergic inhibition of amygdala activity by the mPFC (Battaglia & Thayer, 2022; Thayer & Lane, 2009a). This inhibitory connectivity enables the system to modulate its response to various situations, suppressing the automatic sympathetic response orchestrated within the amygdala, and instead responding flexibly and appropriately to internal and external demands (Thayer & Lane, 2000).

If the potency of GABAergic information transmission is diminished due to altered subunit composition of the $GABA_A$ receptor in the luteal phase, the functional connectivity between the mPFC and the amygdala is disrupted. This disruption can lead to an increased frequency and intensity of physiological stress responses, thus elevating allostatic load. Additionally, it may reduce the system's ability to inhibit negative affect. The overarching idea is that the dysregulation of GABAergic signaling during the luteal phase has profound implications for the CAN, influencing how it manages stress and emotions during this particular phase of the menstrual cycle. The theoretical perspective is particularly based on research showing reductions in vmHRV during the luteal phase when premenstrual symptoms are present (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013).

Reduced vmHRV, which is presumed to indicate a reduced inhibitory capacity of the CAN, is consistently linked to symptom complexes resembling those observed in PMS. These symptoms include increased stress, anxiety, and depression (Laborde et al., 2023). The support for the NVI perspective on PMS symptoms is evident in the detailed associations between

menstrual phases, premenstrual symptoms, and physiological indicators discussed in the NVI and NVI-f models, such as vmHRV (Matsumoto et al., 2007) and fear processing markers such as acoustic startle response (Epperson et al., 2007). Additionally, premenstrual symptoms exhibit high comorbidity with anxiety and affective disorders (Yonkers & McCunn, 2007), implying a shared etiological relationship.

Brain imaging research provides further evidence for the origins of premenstrual symptoms in the CAN. In a functional magnetic resonance imaging (fMRI) study, Protopopescu et al. (2008) observed a higher amygdala response to neutral vs. negative stimuli in a PMDD group compared to a low symptom control group. Notably, PMDD participants did not exhibit the expected increased response in the mPFC when viewing negative compared to neutral pictures. The NVI postulates that this heightened mPFC response is an adaptive mechanism to limit a maladaptive stress/fear reaction (Thayer & Lane, 2000). Additionally, a study by Ossewaarde et al. (2010) found increased amygdala activation in response to neutral stimuli during the late luteal phase compared to the follicular phase, while there was reduced amygdala activation in response to stress induction. Similar effects were also found by Protopopescu et al. (2005). Although premenstrual symptoms were not assessed in this study, the authors found that this effect was mediated by ALLO levels, implying an association with PMS. These results further support the argument that premenstrual symptoms are related to processes in the CAN.

In summary, certain evidence and theoretical considerations support the perspective of premenstrual symptoms in the context of the NVI. ALLO, an allosteric $GABA_A$ receptor modulator, fluctuates during the luteal phase of the menstrual cycle. These fluctuations cause changes in the subunit composition of the $GABA_A$ receptor, making it less sensitive to similar steroids and potentially reducing GABAergic signal transmission, which could contribute to the development of PMS. The NVI and NVI-f integrate a substantial body of research that

demonstrates reduced vmHRV in psychopathology and negative associations with cognitive functions like attention. These theories elaborate on how inhibitory functional connectivity between the mPFC and the amygdala allows for effective self-regulation on emotional, cognitive, and physiological levels. This GABAergic connectivity may be compromised under specific circumstances during the luteal phase of the menstrual cycle, affecting systems associated with CAN functionality and leading to the wide range of psychological and physiological symptoms observed in PMS (Halbreich et al., 1982).

1.7 Heart rate variability biofeedback

Treatment options for PMS remain limited. While a range of potential alleviations has been identified in the areas of diet supplementation (Sultana et al., 2022) and lifestyle adaptations (Rapkin, 2003), the effect sizes are small, and practical application is sparce. Recommendations for treatment and applied treatments in practice are largely limited to symptom-specific pharmacological treatments such as hormonal cycle suppression and antidepressants (Tiranini & Nappi, 2022). These treatments, however, are well-known to be associated to strong side effects (Price et al., 2009; Robinson et al., 2004; Skovlund et al., 2016).

A potential intervention that has not been investigated in relation to PMS is heart rate variability biofeedback (HRVB). In this intervention, vmHRV is learned to be increased through slow-paced breathing (SPB) in combination with visual feedback of current vmHRV (Lehrer & Gevirtz, 2014).

Practicing this technique daily over a couple of weeks has been proven to improve a wide range of outcomes, including mental health, physical health, and performance enhancements in sports (Lehrer et al., 2020). Specifically, psychopathological outcomes such as anxiety, stress (Goessl et al., 2017), and depression (Pizzoli et al., 2021) consistently show improvements with HRVB, with the largest effect sizes observed in the area of stress management. The following section will explain how HRVB is able to unfold its various effects.

The primary mechanism behind HRVB is a resonance phenomenon involving the synchronization of breathing, heart rate, and blood pressure at the utilized breathing frequency (Sevoz-Couche & Laborde, 2022). In the phenomenon known as RSA, heart rate increases during inhalation and decreases during exhalation, resulting in sinus-like fluctuations in heart rate that are synchronized with the breathing pattern. This mechanism has been proposed by

Lehrer and Gevirtz (2014) to enhance the efficiency of gas exchange, ensuring that heart rate and blood flow are at their maximum when the lungs are filled with air and oxygen is abundant for metabolism. HR correlates with fluctuations in blood pressure; when blood pressure drops, HR increases. This coordination is achieved through baroreceptors in the arteries that relay current pressure levels to brainstem nuclei which in turn sends regulatory information to the sinoatrial node, which controls heart rate and is called the baroreflex (Lehrer & Gevirtz, 2014).

The relationship between breathing and the cardiovascular system can be seen as a double oscillatory system. Such a system has a natural intrinsic frequency at which oscillations of the dependent oscillating system — in this case, HR — reach a local maximum. This frequency is known as the resonance frequency and is dependent on the amount of blood carried by the cardiovascular system, which is related to a person's body size (Vaschillo et al., 2006). In most individuals, the resonance frequency at which RSA oscillation amplitude is maximized is around 0.1 Hz, equivalent to approximately 6 breathing cycles per minute (Vaschillo et al., 2006). In a recent review, Sevoz-Couche and Laborde (2022) identified the reason for the maximization of RSA at that specific frequency in optimal timing allowing for complete acetylcholine release during exhalation and ensuing hydrolysis in vagal efferents.

The RSA is driven by the phasic inhibitory vagal input into the sinoatrial node during exhalation (Berntson et al., 1993; Eckberg, 1983). VmHRV is largely determined by this phasic input, and, in simple terms, quantifies RSA (Grossman & Taylor, 2007; Karemaker, 2022). When RSA is maximized during HRVB, there is a strong increase in vagal input into the sino-atrial node and consequently in vmHRV (Laborde et al., 2022). Over time, this trains the baroreflex and habitually increases baroreflex gain and therefore RSA and vmHRV at rest (Lehrer et al., 2003).

As outlined by Thayer and Lane (2000) in their NVI, vmHRV is not just a peripheral indicator of regulatory capacity within the CAN, but also a reciprocal part of the system. This implies that bottom-up effects of HRVB can enhance higher processing levels.

Some pathways discussed in relation to the bottom-up effects of HRVB involve direct input from baroreceptors into the nucleus of the solitary tract, which is then connected to higher limbic and cognitive areas (see Figure 2) (Henderson et al., 2004). Furthermore, slow-adapting pulmonary stretch receptors in the lungs have been found to activate during prolonged inhalation, as occurs during the SPB employed in HRVB, and increase sympathetic activity (Noble & Hochman, 2019). Similar to the baroreceptor input, these receptors communicate with higher brain structures through pathways that pass through the nucleus of the solitary tract, from where connections branch out to all structures of the CAN (Henderson et al., 2004). Additionally, Lehrer and Gevirtz (2014) discuss potential meditative effects during conscious breathing. Further potential pathways involve the enhancement of slow cortical potentials through direct pathways associated rhythmic airflow in the olfactory bulb during slow nasal breathing (Zaccaro et al., 2018). One of the most important pathways, however, through which HRVB can improve CAN function is the vagal afferent pathway, which has been proposed to be the mechanistic pathway behind the many positive effects of contemplative practices (Gerritsen & Band, 2018).

While the effect of HRVB on adjacent symptom etiologies such as anxiety, stress, and depressive symptoms is well-researched (Goessl et al., 2017; Pizzoli et al., 2021), PMS symptoms have not been investigated in this context. In this thesis, I propose that PMS symptoms result from phasic fluctuations in signal transmission within the CAN. Based on this, there are three different ways through which HRVB may alleviate PMS symptoms.

One pathway involves stress reduction. HRVB has been shown to effectively reduce stress (Goessl et al., 2017). PMS symptoms are consistently linked to stress (e.g., Lee & Im,

2016; Potter et al., 2009; Tschudin et al., 2010). Increased stress exposure within the cycle, which is associated with ALLO release responses (Bali & Jaggi, 2014), may be responsible for the specific response of $GABA_A$ receptors to ALLO during the luteal phase of the menstrual cycle in symptomatic cycles and individuals (Hantsoo & Epperson, 2020). By reducing stress levels, HRVB may help mitigate the impact of hormonal fluctuations on GABAergic neurotransmission and therefore prevent symptoms.

Another potential mechanism is the enhancement of CAN function. HRVB is assumed to enhance the capacity of the CAN by specifically bolstering the functional inhibitory connectivity between the mPFC and amygdala (Schumann et al., 2020; Schumann et al., 2021). By increasing the overall functional capacity, HRVB may enhance resilience and make it possible to maintain stability even in the presence of momentary reductions in GABAergic transmission during the luteal phase. By strengthening this regulatory system, HRVB might help prevent GABAergic transmission in amygdala response inhibition from dropping below a threshold that triggers high-impact PMS symptoms.

Furthermore, HRVB can enhance attentional control (Tinello et al., 2022), a function associated with the CAN. During the luteal phase, momentary reductions in GABAergic transmission may lead to heightened attention to physical discomfort, contributing to affective PMS symptoms. HRVB might alleviate negative affect and psychological symptoms by phasically increasing attentional control. This heightened attentional control may counteract the increased focus on physical discomfort and reduce at least some of the psychological symptoms associated with PMS. Reduced ability to concentrate (i.e., allocate attention to desired stimuli) is a commonly experienced symptom during PMS, which may also be directly targeted by the intervention.

2 Research questions and objectives

Building on the assumption that premenstrual symptoms are caused by reduced GABAergic signal transmission within the CAN during the luteal phase, which effectively reduces functional connectivity in the network, several empirical implications can be derived and tested. In the following section, I will outline the research questions and objectives that will be addressed within the framework of this thesis.

In the NVI-f, Battaglia and Thayer (2022) propose that fear processing primarily occurs within the aforementioned CAN. Fear conditioning serves as a laboratory model for anxiety and is used to study fear processes (Beckers et al., 2023). While some studies have explored the effects of menstrual cycle phases on the two primary outcome measures in fear conditioning — acoustic startle response and SCR — the results have been inconsistent (Carpenter et al., 2022; Epperson et al., 2007; Glover et al., 2013; Milad et al., 2006; van der Molen et al., 1988). Assuming that PMS symptoms arise from fluctuations in CAN activity, with vmHRV serving as a peripheral marker, investigating the interaction between cycle phase and current resting vmHRV may provide further insight into phase-related effects in fear processing measures. This is one of the research objectives.

In the German-speaking region, there are currently only three validated questionnaires for assessing PMS. One of these questionnaires evaluates the impairment caused by PMS (Kues et al., 2016), while another one examines DSM-IV criteria (Bentz et al., 2012). However, these assessments do not capture the wide range of symptoms experienced in the premenstrual phase to quantify the extent of PMS. The third instrument, the translated Premenstrual Tension Syndrome Scale (Bergant et al., 2004), does assess a wider variety of symptoms. Nonetheless, it only determines the presence of symptoms, without quantifying the intensity of each. In contrast, the English-speaking research landscape offers a multitude of different instruments that assess up to 200 symptoms (Haywood et al., 2002). Clinical studies often adhere to the

DSM-V criteria and employ daily symptom tracking to establish PMS or PMDD diagnoses. However, this approach places a significant burden on both participants and researchers, potentially contributing to the limited research in the field of PMS.

While some evidence suggests that retrospective symptom recall may introduce a bias towards higher symptom reporting, the reported symptoms mostly overlap (Matsumoto et al., 2021). Furthermore, there is evidence indicating that tracking symptoms over a period of time can exacerbate symptom severity (MacKrill et al., 2020), which supports the use of retrospective assessments. Currently, there is a lack of a translated and validated instrument in German that can comprehensively capture a wide range of symptoms and their intensity retrospectively. Therefore, one of the research objectives was to translate and validate a suitable instrument for effectively assessing premenstrual symptoms in laboratory and intervention studies, namely the short version of the premenstrual assessment form (Allen et al., 1991).

The empirical relationship between vmHRV and cognitive self-regulation abilities is well-established (Holzman & Bridgett, 2017; Zahn et al., 2016). However, limited research has explored the connection between PMS symptoms and cognitive self-regulation processes, which presumably are largely CAN functions. In a review, Le et al. (2020) shed light on cognition and PMS, revealing contradictory and inconclusive findings regarding the association between cognitive processes and PMS. One of the key research questions aims to identify the specific cognitive constructs related to PMS. Among these cognitive outcomes, those more strongly associated with and influenced by HRV are in the realm of attentional control (Holzman & Bridgett, 2017; Tinello et al., 2022). As such, the investigation focuses on whether attentional control fluctuates across menstrual cycle phases and whether these fluctuations are linked to premenstrual symptoms.

The association between vmHRV and PMS is clearer in the existing literature. However, only a handful of studies have examined vmHRV fluctuations throughout the

menstrual cycle in relation to PMS symptoms (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013). All studies in this field worked with a PMS and control group. As previously elaborated, PMS affects nearly all menstruators (Tschudin et al., 2010) and should, therefore, be viewed as a dimensional construct, with the degree of symptomatology as a continuous variable rather than binary. Furthermore, previous studies tested each participant only once during the luteal and follicular phases. This study design does not allow to observe the actual course of the presumably co-varying fluctuations of vmHRV and PMS. The objective of this thesis is to further investigate the relationship between PMS and HRV, using study designs that address some of these limitations.

In the treatment of PMS and PMDD, the clinical practice and research continue to prioritize the use of hormonal ovulation suppression and antidepressants to improve physical and psychological symptoms (Ryu & Kim, 2015). However, due to the well-documented emotional and physical side effects associated with hormonal contraceptives (Robinson et al., 2004; Skovlund et al., 2016) and prescribed antidepressants (Price et al., 2009), the search for alternative treatment options has a long-standing tradition (Maharaj & Trevino, 2015; Stevinson & Ernst, 2001). According to current research, forms of cognitive-behavioral therapy (Kancheva Landolt & Ivanov, 2020) appear particularly promising, albeit they are resource-intensive in terms of cost and time.

A biofeedback training aimed at increasing vmHRV has been meta-analytically shown to have a substantial effect in reducing anxiety, stress (Goessl et al., 2017), and depression (Pizzoli et al., 2021), which symptomatically resemble or are associated with PMS. Additionally, the theoretical considerations laid out previously give rise to the assumption that tackling stress experience and CAN functional connectivity may improve PMS symptoms. However, the influence of HRVB training on PMS symptoms, as planned in this dissertation,

has not yet been investigated. Whether or not an easily accessible smartphone-based HRVB is suitable to alleviate symptoms is another research question of this thesis.

HRVB interventions are typically conducted over several weeks, and their acute effects have been explored in only a few pilot studies (Pagaduan et al., 2021; Prinsloo et al., 2013). The present study aims to build upon this research. One of the suggested mechanisms through which HRVB may improve psychological PMS symptomatology is through the bolstered ability to redirect attention from physical discomfort experienced during the luteal phase. This pathway, however, only poses a possibility if HRVB is indeed able to acutely increase attentional control. Testing the hypothesis that HRVB has acute beneficial effects on attentional control is a final aim of this thesis.

3 Summary of studies

3.1 *Study 1*: Menstrual phase dependent fluctuations in fear conditioning and their association to heart rate variability

3.1.1 Research Goal

The first concept which was investigated as evidence for reduced CAN activity during the luteal phase is that of fear conditioning, specifically the two physiological markers of SCR and acoustic startle response and their interaction with vmHRV. Fear learning processes are dependent on some of the central functions of complex interplay between central and autonomic nervous system, as highlighted in Battaglia and Thayer's (2022) NVI-f. Fluctuations of ALLO concentrations throughout the cycle may therefore affect fear learning, specifically with heightened amygdala activity during the luteal phase. This is a likely prediction, as many individuals report increased anxiety during the luteal phase of their cycle (Allen et al., 1991). VmHRV is considered a biomarker for the inhibition of amygdala activity and shows consistent reductions during the luteal phase (Schmalenberger et al., 2019). Fear conditioning paradigms, focusing on the amygdala's role in affective processing, provide valuable insights. Previous studies present conflicting findings but suggest higher startle magnitude and fear discrimination during the luteal phase. This study investigates startle magnitude and SCR as fear discrimination measures, and potential interactions with vmHRV in individuals in the follicular and luteal phases. By deepening our understanding of menstrual cycle effects on fear processing, this study aims to unravel the complex relationship between the menstrual cycle, fear responses, and autonomic processes.

3.1.2 Methods

The study involved healthy participants who took part in a larger biofeedback intervention study. A total of 58 participants with a regular active menstrual cycle and no

hormonal contraception usage were included in the analysis. The participants underwent a resting state vmHRV measurement and a fear conditioning paradigm.

During the fear conditioning protocol, participants were exposed to conditioned stimuli (CS+) and control stimuli (CS-) in the form of geometric shapes displayed on a computer screen. The CS+ was partially reinforced (50%) with an unpleasant electro-tactile stimulus, while a startle stimulus in the form of white noise was presented after each stimulus.

Startle magnitude and SCR were recorded as dependent measures during the fear acquisition phase of the experiment. The menstrual cycle phase of the participants was assessed through self-report (forward-count method). Linear mixed models were used to analyze the data. The trials from the instructed acquisition phase were utilized for the analysis and were clustered by participants. The independent variables considered in the analysis included trial conditions (CS+, CS-, intertrial interval / unconditioned stimulus), menstrual phase, and their interaction. Additionally, resting vmHRV and its interactions were taken into account.

3.1.3 Results

In the study, 58 individuals were included in the analysis, with 36 in the follicular phase and 22 in the luteal phase of their menstrual cycles. There were no significant differences in age between the groups.

The startle response analysis showed no overall effect of menstrual cycle phase on startle magnitude, but there was a significant interaction effect between condition and cycle phase. An inspection of the interaction effect revealed a higher fear discrimination in individuals tested during the luteal phase. This was mainly driven by a higher startle magnitude in response to the CS+ but not to the CS- or intertrial interval.

The SCR analysis revealed no main effect of cycle phase, but a significant interaction effect between cycle phase and condition. Additionally, the interaction effect was further moderated by heart rate variability. Critically, the interaction between cycle phase and

condition only revealed itself once the 3-way interaction with vmHRV was included in the analysis. The direction of the effect indicates a similarly higher fear differentiation in startle measures during the luteal phase, but only in individuals with a high vmHRV. Low vmHRV participants showed less fear discrimination than high vmHRV individuals in the luteal phase and also than participants tested during the follicular phase. Additionally, low vmHRV individuals showed a higher overall skin conductance response during the luteal phase to all conditions (CS+, CS- and unconditioned stimulus).

3.1.4 Discussion

In this study, the effects of menstrual cycle phase and vmHRV on fear conditioning were investigated. The results showed differential effects on SCR and acoustic startle measures. While no main effect of menstrual cycle phase was found on startle magnitude, there was higher fear differentiation during the luteal phase, specifically in response to the conditioned stimulus (CS+). This effect was consistent across participants, regardless of their resting vmHRV. In terms of SCR, individuals with high vmHRV exhibited increased fear differentiation between CS+ and CS- during the luteal phase, whereas those with low vmHRV showed lower fear differentiation and higher overall electrodermal activity (EDA). The interaction between phase and condition in skin conductance was only evident when vmHRV was included in the analysis. The findings suggest that individuals with a drop in vmHRV during the luteal phase may experience higher sympathetic activation and less differentiation in their fear responses, which is in line with the NVI-f. However, more research is needed to understand the relationship between vmHRV, menstrual cycle phases, and symptom experience. The study concludes that the menstrual cycle should be considered in fear conditioning paradigms to better understand individual experiences of premenstrual symptoms.

3.2 *Study 2*: Validation of a German questionnaire to quantify premenstrual symptoms

3.2.1 Research Goal

The first study investigated cycle-dependent CAN functionality fluctuations, providing initial evidence of reduced fear discrimination (i.e., CAN capacity) in one of the two measures, only in individuals with reduced vagally mediated heart rate variability (vmHRV) during the luteal phase. The hypothesis is that those individuals experience higher PMS during the luteal phase. However, we did not assess PMS symptoms in that study. To efficiently assess premenstrual symptoms in laboratory settings in their full range, we decided to close the gap in the German research landscape by translating and validating a suitable PMS questionnaire in the next study.

The PMS describes a range of psychological and physiological symptoms that occur before menstruation and disappear afterward. PMS affects 50% of menstruating individuals, with 90% experiencing at least one symptom (Tschudin et al., 2010). PMS is poorly understood and has received limited research attention compared to other symptom complexes affecting such a big group of people like anxiety and affective disorders. To improve understanding, specific research and suitable instruments are needed.

Currently, there are only three validated instruments in German for assessing premenstrual changes. However, these instruments have limitations. One focuses solely on clinical diagnoses (Bentz et al., 2012), another assesses a range of symptoms without quantifying their extent (Bergant et al., 2004), and the third measures the impact of symptoms rather than the symptoms themselves (Kues et al., 2016). A comprehensive assessment that quantifies the full range and intensity of experienced symptoms, providing variance for research studies and representing symptoms beyond clinical relevance, is lacking in the German research landscape.

The Premenstrual Assessment Form (PAF) is a comprehensive English instrument capturing a wide range of symptoms (Halbreich et al., 1982). More concise versions, PAF20 and PAF10, have been developed (Allen et al., 1991). Assessing the severity of premenstrual symptoms is important, and the PAF20 quantifies both the presence and intensity of symptoms. Closing the gap in German instruments, the PAF20 was translated and validated on a non-clinical sample.

3.2.2 Methods

The study aimed to translate and validate the PAF20 questionnaire. The translation process involved five steps, including initial translations by two German native speakers, comparison and discussion of discrepancies, independent evaluation by a third person, and pretesting with feedback.

The translated questionnaire was then validated in an online study with 147 participants. The study collected demographic data and assessed the internal consistency and convergent validity of the PAF20 questionnaire with the PMS-Impact Questionnaire (Kues et al., 2016) and the diagnostic criteria for PMS or PMDD in the DSM-V (American Psychiatric Association, 2013). It also examined its divergent validity by comparing it with the Brief Symptom Inventory-18 (Spitzer et al., 2011).

3.2.3 Results

Both the PAF20 and PAF10 scales demonstrated good internal consistency, with Cronbach's alpha coefficients of .93 and .87, respectively. Good convergent validity was demonstrated through an analysis of variance (ANOVA), which revealed significant variance explanation in PAF20 and PAF10 scores based on group assignment using DSM-V criteria, as well as high correlations with the PMS-I. The overall mean values for PAF20 and PAF10 were found to be 46.24 (±20.93) and 22.89 (±10.81), respectively. The PAF20 sum score demonstrated a significantly higher correlation with PMS-Impact Score than with the general symptom score of the Brief Symptom Inventory-18, indicating satisfactory divergent validity.

A factor analysis revealed a two-factor structure in both the PAF20 and PAF10, with items clearly loading on a physical symptom or a psychological symptom scale. The sum scores of PAF10 and PAF20 exhibited a high correlation ($r = .96$, $p < .001$). Lastly, the optimal cut-off value for PAF20 to differentiate groups with and without suspected diagnoses was determined to be 53, with a sensitivity of .72 and a specificity of .73.

3.2.4 Discussion

The German translation of the PAF20 and PAF10 demonstrated good internal consistency and convergent validity. The PAF total scores were highly associated with PMS-I scores and showed significant group differences based on suspected diagnoses according to DSM-V criteria. The instrument's values were comparable to the original English version, and a two-factor structure representing psychological and physiological symptomatology was identified. Cut-off values for clinical relevance were determined. The translated PAF20/10 offers a valid and reliable tool for retrospective assessment of premenstrual symptoms, making it suitable for research purposes. Further studies are needed to explore its applications in diary formats and during different phases of the menstrual cycle.

3.3 *Study 3*: Covarying fluctuations in vagally mediated heart rate variability and premenstrual symptoms over the whole cycle in an ambulatory assessment diary study

3.3.1 Research goal

Equipped with a suitable and flexible instrument to assess premenstrual symptomatology after study 2, we decided to delve deeper into the association between PMS and vmHRV, which was presumed in study 1. VmHRV reflects cardiac vagal control and has been linked to various psychological and cognitive outcomes. Studies have consistently shown reduced vmHRV during the luteal phase compared to the follicular phase of the menstrual cycle (Schmalenberger et al., 2019), with larger effects in individuals experiencing stronger PMS (Baker et al., 2008; Matsumoto et al., 2007; Schmalenberger et al., 2023; Zambotti et al., 2013).

While the direction of this vmHRV-PMS association is consistent, previous research has typically involved single measurements during each cycle phase, making it challenging to track potential parallel fluctuations of symptoms and vmHRV. To gain a better initial understanding of this relationship and assess feasibility, a pilot diary study was initiated, involving three participants who provided daily assessments of premenstrual symptoms (measured with the PAF10 from study 2) and resting vmHRV measurements throughout their menstrual cycles.

3.3.2 Methods

Three participants were recruited, meeting criteria outlined by Laborde et al. (2017), ensuring that they were not on medication affecting vmHRV, had no chronic diseases, and were not pregnant. The testing protocol involved daily measurements with an online questionnaire assessing premenstrual symptoms (PAF20, adapted for daily symptom assessment) and conducted 5-minute resting electrocardiography (ECG) measurements with mobile ECG devices. Participants provided daily assessments over a full menstrual cycle, including luteal and follicular phases.

Statistical analyses evaluated the association between premenstrual symptoms and RMSSD over the menstrual cycle. Pearson correlations were calculated individually for each participant, examining both the physiological and psychological subscales of the PAF20 in relation to RMSSD. A linear mixed model predicting PMS symptoms and including fixed effects of RMSSD and a number of control variables was also conducted.

3.3.3 Results

Figure 3 visually illustrates the symptom progression and RMSSD trends for all three participants. Negative correlations of medium to large effect sizes between log-transformed RMSSD and daily symptom scores were identified for each participant. Notably, stronger correlations were observed between RMSSD and psychological symptoms compared to physiological symptoms. For all three participants, there were no significant associations between RMSSD and physiological symptoms. The association remains intact when including a number of control variables known to be associated to PMS (substance consumption, stress, sport, sleep quality).

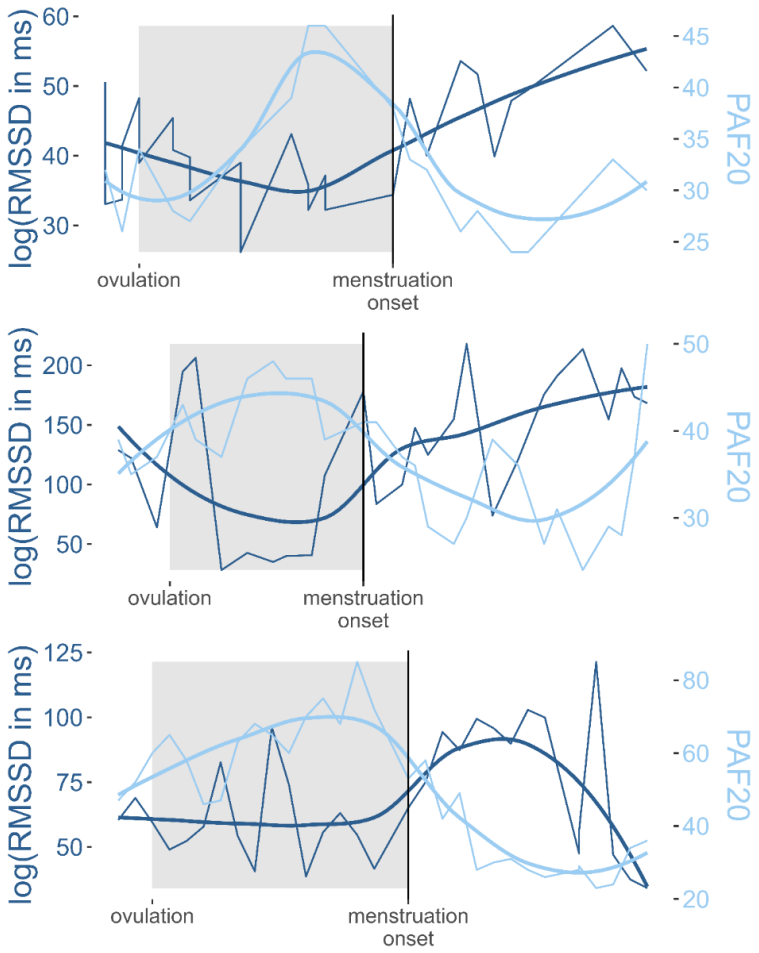
3.3.4 Discussion

This pilot study aimed to explore the simultaneous variations in premenstrual symptoms and vmHRV reductions during the menstrual cycle's luteal phase, assessing the feasibility of daily ambulant assessments. By collecting daily data on vmHRV and premenstrual symptoms from three participants, we uncovered a consistent pattern of PMS symptoms and vmHRV changes over one menstrual cycle. These findings support the idea of vmHRV playing a role in PMS, echoing previous research. Notably, the association between vmHRV and PMS was more pronounced for psychological symptoms than physiological ones, aligning with the link between vmHRV and psychopathological outcomes. Decreases in vmHRV may mediate increased negative affect and stress during the luteal phase, affecting top-down regulation. These results shed light on cyclic menstrual changes and validate our research design's

feasibility, paving the way for future studies to delve into interindividual differences and underlying mechanisms.

Figure 3

Course of vagally mediated heart rate variability and premenstrual symptoms over a menstrual cycle



Note. The plots show the covarying vagally mediated heart rate variability and premenstrual symptom scores over one cycle for participants 1-3 (top to bottom). Grey shading indicates the luteal phase, which is marked by increases in symptoms and decreases in vagally mediated heart rate variability. The thin lines show the raw values, while the thicker lines indicate trend lines using the LOESS (locally estimated scatterplot smoothing) method. RMSSD – root mean square of successive differences, PAF20 – sum score of short form of the premenstrual assessment form.

3.4 *Study 4*: Menstrual phase dependent fluctuations of heart rate variability and attentional control and their association with premenstrual syndrome

3.4.1 Research Goal

Building on the evidence supporting the hypothesis of PMS symptoms being associated with fluctuations in the CAN from study 1 and study 3, the next study gathers more evidence for the proposed relations and investigates a further marker closely related to CAN activity—attentional control. Attentional control has consistently been linked to vmHRV (Holzman & Bridgett, 2017; Zahn et al., 2016) and is assumed to be a core functionality within CAN capacity as an aspect of cognitive self-regulation (Thayer et al., 2009).

As elaborated above, PMS symptoms may be associated with altered fluctuations in ALLO, an anxiolytic progesterone metabolite and neuropeptide. ALLO binds to GABA receptors, increasing inhibitory GABA activity in the central nervous system. During the second half of the luteal phase, a sudden reduction in ALLO availability may impair GABAergic activity and thus contribute to premenstrual symptoms (Hantsoo & Epperson, 2020).

This decrease in GABA activity can affect the inhibitory connections between the amygdala and the mPFC, which are important for adaptive self-regulation in the CAN as proposed in Thayer and Lane's (2000) NVI. VmHRV is suggested as a marker for the CAN's inhibitory capacity. VmHRV typically decreases from the follicular to the luteal phase (Schmalenberger et al., 2019), particularly in individuals with PMS symptoms (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013).

The relationship between PMS, cycle phases and cognitive self-regulation, which is closely linked to the CAN's functional capacity, is not well-established due to inconsistent results (Le et al., 2020). Attentional control tasks, such as the Executive and Orienting Network score of the revised attention network test (ANT-R), consistently correlate with resting vmHRV, reflecting the core functioning of the CAN.

This study aimed to explore the connections between HRV, PMS, and attentional control. The primary goal was to replicate the observed decrease in HRV and test the hypothesized decline in attentional control performance during the luteal phase particularly in individuals that report strong premenstrual symptoms.

3.4.2 Methods

Ninety-five participants were recruited from the Universities of Greifswald and of Potsdam. Exclusion criteria were applied based on previous HRV studies (Laborde et al., 2017), resulting in a sample of 65 individuals with an active menstrual cycle.

The procedure involved measuring vmHRV with an ECG, completing a modified version of the attention network test (ANT-R), and filling out questionnaires to assess the menstrual cycle phase and premenstrual symptom impact. VmHRV measurements were taken at rest for 5 minutes. The RMSSD and HF components of power spectral analysis were calculated as measures of vmHRV.

The trustANT, a modified version of the ANT-R (Fan et al., 2009), was administered. It involved reacting to a target arrow surrounded by flankers, with spatial cues indicating the likely location of the target. Trustworthiness cues were added to assess potential affective cueing effects.

Cycle phase, premenstrual symptoms, and control variables were assessed through questionnaires. The impact of premenstrual symptoms was measured using the Premenstrual Symptoms Impact Survey (PMSIS, Wallenstein et al., 2008). Age and study program information were collected as control variables.

Statistical analyses were conducted using linear mixed models and linear regression models in R. The models included various predictors to test hypotheses related to reaction times and HRV fluctuations.

3.4.3 Results

The PMSIS scores exhibited non-normal distribution with floor effects. To overcome this, a median split was applied to create high and low PMS groups. Age and hormonal contraception use differed between the groups, so they were included as control variables in further analyses.

A mixed model was used to analyze reaction times, indicating no differences in the Orienting Network between cycle phases and PMS impact groups. However, there was a significant interaction between PMS impact, flanker condition, and cycle phase for the Executive Network. High PMS individuals in the luteal phase had slower reaction times in incongruent flanker trials compared to high PMS individuals in the luteal phase, which translates to lower Executive Functioning Scores of attentional control. No such difference was observed in the low PMS group.

For RMSSD analysis, the final model also included the interaction between PMS impact group and cycle phase. High PMS individuals in the luteal phase had lower RMSSD values compared to high PMS individuals in the follicular phase. However, the post-hoc analysis did not reveal significant differences between individual groups.

The HF component of power spectral analysis did not show any significant predictors. Although it is highly correlated with RMSSD, the larger variance in the HF component data might have obscured the effect in the statistics.

3.4.4 Discussion

The study aimed to explore connections between menstrual cycle phases, premenstrual syndrome symptomatology, attentional control, and vagally mediated heart rate variability. The hypothesis anticipated reduced attentional control and heart rate variability in individuals with high premenstrual syndrome during the luteal phase compared to the follicular phase. The results supported this hypothesis, revealing diminished attentional control in the Executive Network and lower heart rate variability during the luteal phase in high premenstrual syndrome

individuals. Interestingly, low premenstrual syndrome individuals did not show such variations in attentional control or heart rate variability between phases. Despite promising findings, limitations include age and contraceptive use disparities between high and low premenstrual syndrome groups and the study's reliance on the forward/backward-count method for cycle phase determination. In conclusion, the study supports the perspective of compromised central autonomous network activity during the luteal phase in individuals with heightened premenstrual syndrome symptoms.

3.5 Study 5: Effect of smartphone-based heart rate variability biofeedback on premenstrual and depressive symptoms and attentional control

3.5.1 Research goal

The previous studies (1, 2, 4) provided evidence for the hypothesized neurovisceral integration perspective on the occurrence of premenstrual symptoms and offered a flexible research instrument to efficiently assess premenstrual symptomatology in a way that reflects a wide range of experiences. This study proposes and carries out an initial implementation of an intervention based on the hypothesis and the evidence provided in this thesis, while employing the translated questionnaire. HRVB has been shown to increase not only vmHRV (Laborde et al., 2022) but also functional connectivity within the CAN (Schumann et al., 2020). Therefore, we tested its effects on PMS in a pilot study.

HRVB has demonstrated effectiveness in diverse areas, from reducing anxiety and depression to improving sleep and sports performance (Lehrer et al., 2020). However, practical implementation has been limited due to cost and specialized equipment requirements. Smartphone apps that measure heart rate through the camera offer a promising solution. This study aims to validate smartphone-based HRVB for alleviating depression and explores its application for premenstrual symptoms.

PMS is a condition associated with vmHRV fluctuations. PMS symptoms often relate to stress and may be grounded in affected GABAergic signaling, potentially affecting the CAN's inhibitory network.

Smartphone-based HRVB has shown promise, but studies utilizing the capacity to measure HR through the camera are lacking. In this study, we investigate a 4-week smartphone-based HRVB intervention using photoplethysmography (PPG) to alleviate PMS. We also assess its impact on depressive symptoms, anxiety, stress, attentional control, and vmHRV.

3.5.2 Methods

In this study, 29 participants were recruited from the University of Potsdam. Eligibility criteria included increased premenstrual symptoms, depressive symptoms, or both. Exclusion criteria comprised factors suggested by Laborde et al. (2017) like pregnancy, chronic diseases, and medication. Participants underwent a 4-week smartphone-based HRVB intervention. They practiced HRVB daily, received online coaching, and attended laboratory sessions before and after the intervention. Half of the sample was included in a waitlist group, which was additionally tested in a laboratory session four weeks before the start of the intervention.

Outcome measures included premenstrual symptoms (PAF20, Blaser et al., 2023), depressive symptoms (Beck's Depression Inventory II, Richter et al., 1998), anxiety, stress (Depression Anxiety and Stress Scales, Henry & Crawford, 2005), and attentional control (ANT-R, Fan et al., 2009). VmHRV (RMSSD) was also assessed. A smartphone app provided by the company Kenkou GmbH was used for both biofeedback and home vmHRV measurements. The statistical analysis employed linear mixed models. Post-treatment data from a waiting-list control group were included in the analyses. The study aimed to investigate the effects of HRVB on these various measures with the waitlist period as a control.

3.5.3 Results

We found improvements during the HRVB intervention period, but not during the waitlist period, in premenstrual, depressive, stress, and anxiety symptoms, as well as the Executive Functioning component of the ANT-R. However, we did not find improvements in RMSSD and the Orienting component of the ANT-R.

3.5.4 Discussion

The positive effects on premenstrual, depressive, anxiety, and stress symptoms highlight the feasibility and effectiveness of this smartphone-based HRVB intervention. Visual feedback on respiratory sinus arrhythmia can assist users and enhance their engagement with the app. HRVB is easily learned, with minimal side effects, making it highly accessible.

We found a significant improvement in premenstrual symptoms following HRVB practice, suggesting a potential link between the intervention and the ALLO/GABA system. Further studies are needed to understand the mechanism of action and the optimal timing in the menstrual cycle for the intervention's effectiveness.

The effects on depressive symptoms, anxiety, and stress align with previous research, although our effect sizes were slightly smaller due to our inclusion criteria. We didn't observe the anticipated improvements in vmHRV, which might be related to our small sample size.

The effects on attentional control were mixed, with improvements in the Executive Score but not in the Orienting Score. More research is needed to understand the impact of HRVB on cognitive outcomes.

Limitations include a small sample size and a passive control group. Future studies should address these limitations and standardize criteria for participant selection.

In summary, smartphone-based HRVB shows promise for self-managing premenstrual symptoms and improving emotional and cognitive well-being, without the need for external devices. However, further research is needed to establish its credibility as a treatment for PMS.

3.6 *Study 6*: Acute effects of a single-session heart rate variability biofeedback on attentional control

3.6.1 Research goal

After finding positive effects of HRVB on PMS, the last study delved into a more basic research problem, namely an exploration of the mechanistic pathways of HRVB. Several ways in which HRVB can unfold its various effects have already been proposed in the literature (Lehrer & Gevirtz, 2014). In light of the previous findings within this thesis, namely the association of PMS with attentional control (study 4) and the finding that specifically psychological PMS symptoms fluctuate with vmHRV (study 3) and respond more strongly to the HRVB (study 5), a proposed pathway may be the following. Physiological changes throughout the cycle are part of normal biological processes (Schmalenberger et al., 2019). A large proportion of suffering from PMS, however, stems from psychological symptoms, which appear more closely related to CAN functionality, potentially due to reduced attentional control and thus more attentional resources allocated to physical discomfort. One mechanism through which HRVB may alleviate this is by momentarily increasing attentional control in the critical phases when it is compromised. As an add-on to the research program, this study, therefore, investigates whether or not HRVB is able to acutely increase attentional control.

Long-term HRVB training has shown cognitive and emotional benefits (Lehrer et al., 2020), while immediate effects remain unclear. Immediate effects may include stress reduction and cognitive improvement, especially in individuals with high stress levels. These findings suggest that stress levels may moderate the impact of HRVB on attentional control.

To explore the acute effects of HRVB on attentional control and the moderating role of stress, we conducted a HRVB study measuring vmHRV, attentional control, and stress levels. We hypothesized that vmHRV would increase during HRVB, that resting vmHRV would correlate with attentional control, and that HRVB would enhance the Orienting Network score

of the ANT-R compared to a normoventilation control condition. Additionally, we expected stress levels to moderate the effects of HRVB on attentional control.

3.6.2 Methods

Sixty participants aged 18 to 30 were recruited, and various exclusion criteria according to Laborde et al. (2017) were applied to ensure a homogeneous sample. During two testing sessions, participants completed the ANT-R and underwent vmHRV assessments. VmHRV measurements focused on RMSSD as an indicator of vagal activity. In one of the sessions, each participant received a 5-minute HRVB training session followed by the ANT-R. During the other session, each participant completed a normoventilation control condition before the ANT-R. Before the first session, participants completed an online questionnaire in which their current stress levels were assessed through self-report (perceived stress scale; Klein et al., 2016).

We then compared the attentional control measures after the HRVB and control condition using linear mixed models. Additionally, we tested for an interaction with current stress levels.

3.6.3 Results

The analysis revealed that HRVB increased RMSSD significantly compared to normoventilation. Moreover, the relationship between RMSSD baseline and reaction time in the Orienting Network was explored. Results showed that individuals with higher RMSSD baseline scores had faster reaction times in trials with invalid cues, indicating better Orienting Network Scores. However, the anticipated improvement in Orienting Network performance after HRVB was not supported, as no significant enhancement was observed.

A significant three-way interaction involving self-reported stress, condition, and cue indicated that HRVB had a more beneficial effect on Orienting Network performance in individuals reporting higher stress levels, compared to those with lower stress levels. This

effect was primarily driven by differences in invalid cue trials between the biofeedback and normoventilation conditions.

3.6.4 Discussion

This study aimed to investigate the immediate impact of HRVB on attentional control. Results demonstrated that HRVB effectively increased vmHRV during the intervention, albeit temporarily. While the intervention improved vmHRV during slow-paced breathing, this effect did not persist, potentially due to the cognitive task engagement or the natural short-term nature of vmHRV improvements.

Moreover, the relationship between vmHRV baseline and attentional control, specifically the Orienting Score in the ANT-R, was observed. A higher vmHRV baseline was associated with better top-down goal-directed attentional control. However, despite these associations, the HRVB intervention did not significantly improve attentional control across all participants.

Interestingly, the study identified an interaction effect between self-reported stress levels and the intervention condition, indicating that highly stressed individuals showed slightly improved attentional control after the biofeedback condition compared to the control condition.

These findings suggested that short-term HRVB had varying effects on attentional control, with stressed individuals benefitting more. However, the overall effect was relatively small, highlighting the need for further research in this area.

4 General discussion

4.1 Summary of results

The research in this thesis offers a comprehensive understanding of the intricate relationship between the menstrual cycle, PMS and various facets of menstruators' physical and emotional well-being, specifically in relation to CAN activity.

In Study 1, we observed that during the luteal phase, fear discrimination in acoustic startle responses is notably heightened. In SCR to fear discrimination, there was an interaction with vmHRV, where high vmHRV was associated with increased fear discrimination and low vmHRV correlated with reduced fear discrimination during the luteal phase in comparison to the follicular phase.

Study 2 made a significant contribution to the field by translating a reliable economic tool for retrospective assessment of PMS symptoms. This standardized assessment tool ensures more consistent and comparable evaluations in subsequent studies.

Studies 3 and 4 revealed a compelling relationship between PMS symptoms and vmHRV fluctuations. It became evident that high PMS symptoms, particularly during the luteal phase, parallel a phasic reduction in vmHRV. This observation highlights a potential physiological underpinning for the emotional and physical changes experienced by individuals with PMS. Furthermore, Study 4 unveiled that individuals with high PMS symptoms exhibit lower attentional control (conflict resolution) during the luteal phase, underscoring the far-reaching impact of PMS on cognitive functions associated to CAN activity.

Additionally, Study 5 introduced an innovative approach, utilizing smartphone-based HRVB training, which exhibited promising results in alleviating PMS symptoms over one menstrual cycle. Lastly, in Study 6, we explored potential mediators of symptom improvement, suggesting that the positive effects of HRVB training on PMS symptoms may be partially mediated through momentary heightened attentional control, although the evidence was

considered weak. These findings enhance our comprehension of the menstrual cycle's influence on emotional and cognitive aspects and offer insights into non-pharmacological interventions for PMS symptom management.

4.2 Discussion

This thesis proposes that PMS symptoms are intricately linked to alterations in CAN activity during the luteal phase. The presented evidence provides substantial support for the hypothesis that PMS is associated with a phasic reduction in CAN functional capacity, primarily due to diminished GABAergic transmission resulting from receptor adaptations to fluctuations in the neuroactive steroid, ALLO. The markers of CAN activity examined throughout this thesis showed associations with menstrual cycle phases and with PMS symptomatology.

Namely, vmHRV, assumed to be a peripheral marker for the functional capacity of the CAN, has previously been identified as reduced during the luteal phase (Schmalenberger et al., 2019). We found initial evidence for parallel fluctuations of PMS symptoms and vmHRV throughout the cycle (study 3) and the reduction of vmHRV in the luteal phase is dependent on PMS intensity, in line with previous research (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013). Despite being a small pilot conducted on only a handful of individuals, the methodology used provides a better understanding of how vmHRV and PMS are connected. While previous studies (as well as study 4 of this thesis) have found reductions in vmHRV during the luteal phase (Baker et al., 2008; Matsumoto et al., 2007; Schmalenberger et al., 2023; Zambotti et al., 2013), comparing one measurement to one measurement during the follicular phase, Figure 3 shows that within each individual, the rise and fall of vmHRV and PMS symptoms are highly associated. This speaks for common underlying mechanisms as the one proposed in this thesis and offers a new perspective. A larger study with a similar daily assessment design can help differentiate between within- and between-subject associations in

this regard. It is interesting that the PMS and vmHRV associations within each subject were significantly larger than the associations over all participants together. This finding highlights the subjectiveness of these physiological and affective processes.

Additionally, we observed that one aspect of attentional control (conflict resolution) shows a similar association with cycle phase and PMS, indicating reduced capacity during the luteal phase, specifically in high PMS sufferers (study 4). Attentional control is one of the domains consistently linked to vmHRV and is assumed to be a function of the specific inhibitory capacity within the CAN.

While cognitive self-regulation tasks, specifically within the attention domain, show consistent associations with vmHRV, the effect sizes are on average rather small and depend heavily on the specific task (Holzman & Bridgett, 2017; Zahn et al., 2016). The association of cognitive functions with menstrual cycle phases, on the other hand, is extremely inconsistent (Le et al., 2020). In this thesis, I proposed that the common underlying network – the CAN – is responsible or involved in both concepts. The attentional task examined, the ANT-R, contains two components that have shown relatively high associations with vmHRV (Quintana et al., 2017; Ramírez et al., 2015; Sørensen et al., 2019), and when observed more closely, contain the specific moments of cognitive inhibition assumed to be the central part of the CAN in the NVI and may thus be more strongly related to PMS than other tasks. One of the two components, the Executive Function component, measured in a flanker task and therefore reflecting conflict resolution capacity, showed both associations with PMS and improvements after the HRVB. This finding contributes to the existing literature by identifying a specific cognitive function that is both related to vmHRV and PMS. Being exposed to salient stimuli, such as physical discomfort, and having a reduced ability to allocate attention to less salient but more relevant interoceptive stimuli might be central in giving rise to affective PMS

symptoms. The improvement of the Executive Function component after the HRVB may thus contribute to alleviating symptom burden.

In the NVI-f, the authors propose that another process mediated in the CAN (Battaglia & Thayer, 2022) is fear learning, which would imply that it is affected during the luteal phase. The two fear discrimination measures we investigated (SCR and acoustic startle response) yielded conflicting results. In acoustic startle, there was higher fear discrimination during the luteal phase compared to the follicular phase. This increase was not associated with resting vmHRV. Presumably, a lowered vmHRV during this phase indicates reduced CAN capacity, which may contribute to PMS symptoms. However, in the case of SCR, the phase-dependent fear discrimination was moderated by vmHRV during the luteal phase. The direction of the effect suggested that reduced vmHRV during the luteal phase (presumably associated with PMS) was linked to decreased fear discrimination and higher overall SCR. This finding aligns with the hypothesis of this thesis. SCR is considered a marker of sympathetic activity. Reduced fear discrimination in the luteal phase among individuals with low vmHRV indicates a stress response, regardless of the "safety" of the situation, which is consistent with the hypothesized reduced top-down inhibition of default amygdala reactivity (Battaglia & Thayer, 2022). The reason why the startle data did not support the model remains unclear and may require investigation in future studies.

Building upon the assumption that PMS is a result of altered CAN activity and the supporting evidence presented so far, we tested an intervention aimed at improving PMS symptoms by targeting functional connectivity. HRVB has been found to increase resting vmHRV (Laborde et al., 2022), enhance mental health outcomes (Lehrer et al., 2020), and partially improve attentional control (Tinello et al., 2022), all of which are associated with PMS. Furthermore, the intervention has been shown to increase functional connectivity within the CAN (Schumann et al., 2020). In study 5, we found initial evidence suggesting that this

user-friendly intervention can alleviate PMS symptoms. While there were some methodological limitations, this result provides further evidence for the perspective that PMS has etiological roots in the CAN.

It is noteworthy that both physiological and psychological symptoms were improved by the intervention, although the effects were more pronounced in the psychological symptom domain. This result aligns with the proposed mechanisms of HRVB in the literature, involving bottom-up effects through the brain stem originating in baroreceptors (Lehrer & Gevirtz, 2014), slow-adapting pulmonary stretch receptors (Noble & Hochman, 2019), and a vagal route (Lehrer & Gevirtz, 2014) reaching limbic areas. To elucidate the specific mechanistic pathways through which HRVB positively affects PMS symptoms, I proposed three potential mechanisms.

The first way is based on the assumption that the $GABA_A$ reactivity to ALLO fluctuations, which leads to reduced GABAergic transmission in the luteal phase, is at least partly caused by stress (Girdler et al., 2001). This assumption is grounded in the consistent associations between PMS and stress (Lee & Im, 2016), as also identified in study 3. HRVB is known to reduce stress levels (Goessl et al., 2017), and our findings in study 5 showed improved stress symptoms after the smartphone-based HRVB. Reducing stress levels throughout the cycle may alleviate the burden on the ALLO system and prevent PMS symptoms from developing.

The second potential pathway involves the enhancement of CAN functional capacity (Schumann et al., 2020), ensuring that phasic reductions during the luteal phase do not fall below a threshold that produces symptoms. The alleviating effects of HRVB on PMS symptoms may provide evidence for either of these pathways, though differential assessments cannot be made and may require distinct research designs.

The last proposed mechanism involves the acute increase in attentional control. This proposal is rooted in the observation of reduced attentional control during the luteal phase in individuals with high PMS symptoms (as identified in study 4). Enhanced attentional control may enable individuals to effectively redirect their focus from physical discomfort and, at the very least, reduce affective symptomatology. To validate this pathway, it is essential to demonstrate that HRVB can acutely improve attentional control. In our study (study 6), we found limited evidence for acute improvements in attentional control through HRVB. However, this effect was primarily visible in highly stressed individuals, and the magnitude of the effect was relatively small. Given the high association between PMS and stress (Lee & Im, 2016; also discovered in study 3), this finding does not rule out the possibility of this pathway. It must be noted, however, that the attentional control components identified throughout this thesis — specifically, the one found to fluctuate in PMS (Executive Functioning Score of ANT-R, study 4) and the one acutely affected by HRVB (Orienting Score of ANT-R, study 6) — are different. This warrants further in-depth research in this area. Nevertheless, the acute improvement in attentional control in highly stressed individuals aligns with previous research (Hoffmann et al., 2019; Laborde et al., 2019; Prinsloo et al., 2011; Sherlin et al., 2010) and improves our understanding of HRVB effects.

In this thesis, I propose a novel perspective on the etiology of PMS as an outcome of altered GABAergic transmission in the CAN, as proposed in Thayer and Lane's (2000, 2009) NVI. In a series of studies, I collected substantial evidence for this perspective. I then used this newfound knowledge and brought it to application by implementing an intervention based on the theory, the success of which provides further evidence for the assumptions. The research program added to the current understanding of physiological underpinnings of PMS by building on state-of-the-art theoretical models (i.e., the role of ALLO and $GABA_A$ receptor modulation) and extending them to close a gap in the argument and explain a wider range of

premenstrual changes. Furthermore, I brought these new understandings into application in a modern digital health format by showing first evidence for symptom alleviation through a smartphone-based biofeedback intervention.

4.3 Limitations

The present doctoral thesis, while offering valuable insights into the intricate relationship between PMS, the menstrual cycle, physiological responses, and psychological factors, is not without its limitations. It is crucial to acknowledge these limitations as they provide context for the interpretation of the study results and guide directions for future research.

First, a notable limitation in this research is the low sample size in both the smartphone-based HRVB intervention study (study 5) and the studies investigating the association between vmHR and PMS symptoms (studies 3, 4). The restricted sample sizes may affect the generalizability of the findings. Another limitation pertains to the selective nature of the samples used in these studies, which consisted predominantly of students. This selectivity may also restrict the generalizability of the findings to a broader population, as students do not represent the full spectrum of people experiencing PMS and related symptoms. Expanding the participant pool to include a more diverse demographic would enhance the external validity of the results.

Additionally, none of the studies incorporated clinical assessments for PMDD. While the primary aim of the research was not to assess clinical diagnoses but rather to look at premenstrual symptoms in their whole range, it could be intriguing to explore whether the observed effects align with ones observed in clinically diagnosed PMDD. For example, Matsumoto et al. (2007) found that in PMDD, vmHRV is reduced in both cycle phases, rather than exhibiting the characteristic drop in the luteal phase. Clinical assessments could provide

a more comprehensive understanding of how these findings relate to individuals experiencing severe premenstrual symptoms.

Furthermore, in the fear discrimination study, PMS symptoms were not assessed. This absence of PMS symptom assessment limits our ability to draw direct connections between the observed fear discrimination effects and PMS symptomatology. Incorporating PMS symptom assessments in future research could offer a more comprehensive understanding of the interplay between fear processing and PMS.

Two of the studies in this research assessed cycle phases solely through the forward-count method. While this method is commonly used, it may not be the most reliable way to determine cycle phase. The recommended approach involves a combination of forward and backward counting, along with hormonal assessments (Schmalenberger et al., 2021).

Another noteworthy limitation relates to the retrospective assessment of PMS symptoms. Some evidence suggests that cultural influences may lead to overestimations of PMS symptoms in retrospective assessments (Matsumoto et al., 2021). This cultural influence on the perception of PMS symptoms warrants consideration in the interpretation of the results.

In the intervention study (study 5), it was not feasible to incorporate participants' cycle phases due to the research design. While the idealized menstrual cycle length is typically considered to be 28 days, in reality, there are considerable intra- and interindividual variations (Schmalenberger et al., 2021). Future studies could benefit from standardizing the recruitment phase of participants and specifying the number of cycles over which interventions, such as the smartphone-based HRVB, are practiced. This approach would help account for the variability in menstrual cycle length and enhance the reliability of the results. Lastly, the intervention study lacked an active control group. Comparing the effects of the smartphone-based HRVB intervention with an active control group, such as another stress-reducing technique or a

pharmacological treatment, would have provided a more robust basis for evaluating the intervention's efficacy.

4.4 Outlook

The current research provides a solid foundation for understanding PMS under a NVI perspective. However, several crucial avenues for future research should be pursued to expand our knowledge in this field.

First and foremost, it is essential to recognize that the research in this thesis does not establish causal effects. To address this, further research is warranted to investigate the associations of GABA reactivity levels and other neurobiological markers in conjunction with the constructs examined in this study.

To reinforce the neuroendocrine basis of the neurovisceral PMS model proposed in this thesis, it is imperative to conduct neuroimaging and pharmacological blockade studies. These studies will offer a more direct and concrete understanding of the physiological underpinnings of the associations observed in our research. By pinpointing the neural and hormonal pathways involved, we can gain deeper insights into the mechanisms that drive changes in emotional and physiological responses throughout the menstrual cycle, thus enhancing our understanding of PMS etiology.

According to the hypothesis that PMS symptoms arise from a 'withdrawal' of ALLO in the last week of the menstrual cycle (Hantsoo & Epperson, 2020), effects may not be expected in the first half of the luteal phase, when ALLO levels rise. However, some individuals experience PMS symptoms throughout the entire luteal phase, with a peak often occurring a few days before the onset of menses (see Figure 3). Our studies (1 and 3) typically compared the last 10 days of the cycle to the follicular phase. To gain a better understanding of how fluctuations in ALLO affect various functions of the CAN, it may be worthwhile to explore the effects in the early, mid, and late luteal phases.

Furthermore, to expand our knowledge of how the menstrual cycle influences emotional and physiological processes in association with PMS, future research should delve into the interactions between fear discrimination in SCR and acoustic startle, vmHRV, and premenstrual symptomatology over the menstrual cycle. Understanding the complexities inherent in these relationships can open new avenues for research and may eventually lead to more effective interventions and treatments for individuals affected by PMS and related conditions.

A further promising path for future research lies in conducting a diary study similar to the design of Study 3 but on a larger scale. Such an extensive diary study can provide a deeper understanding of the temporal course of PMS and the dynamic fluctuations in vmHRV across different menstrual cycles. This approach will allow for a more comprehensive exploration of intra- and interindividual differences in PMS symptoms, vmHRV patterns, and the factors associated with these variations. By capturing real-time data over multiple cycles, we can better appreciate the complexity of these interactions, ultimately contributing to a more nuanced understanding of PMS etiology.

Additionally, it is essential to confirm the effectiveness of smartphone-based HRVB in a larger-scale study, ideally incorporating an active control group for comparison. By conducting a study with a larger sample and an active control group, we can provide more robust evidence regarding the specific benefits and efficacy of HRVB as a non-pharmacological intervention for alleviating PMS symptoms. This approach ensures a more comprehensive evaluation of the intervention's impact and can help guide its potential implementation in clinical settings.

4.5 Conclusion

In summary, this thesis has embarked on a journey to unravel the intricate web of factors contributing to PMS by proposing a novel theoretical model. I postulated that PMS symptoms could be an outcome of fluctuations in CAN activity mediated through $GABA_A$ receptor reactivity, shaped by the neuroactive steroid ALLO. Through a series of studies, we explored the associations of various factors, such as vmHRV, fear discrimination, and attentional control, known to be related to CAN activity, with menstrual cycle phase and/or PMS symptoms. The results largely provide substantial support for the hypothesis. These investigations not only provided valuable insights into the underlying mechanisms of PMS but also illuminated potential avenues for future research.

Furthermore, a pilot study was conducted to test an intervention based on the theoretical model. This pioneering approach, focusing on smartphone-based HRVB training, offered a new perspective on alleviating PMS symptoms. While the results were promising, the thesis acknowledges the need for further research to confirm the intervention's efficacy and explore its potential as a non-pharmacological treatment.

Ultimately, the findings from this thesis contribute to a deeper understanding of PMS symptomatology, offering a fresh perspective on its etiological underpinnings and potential therapeutic interventions. By shedding light on the intricate relationships between hormonal fluctuations, CAN activity, and psychological responses, this research paves the way for more effective treatments and support for the hundreds of millions of individuals facing the challenges of PMS. These insights not only enhance our comprehension of this complex phenomenon but also hold the promise of improving the quality of life for those affected by it.

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Appendix A: Manuscripts

Manuscript 1: Blaser, B. L., Hufenbach, M. C., Ventura Bort, C., Weymar, M., & Wendt, J. (submitted). Fear acquisition across the menstrual cycle: The moderating role of vagally mediated heart rate variability. Preprint available. https://doi.org/10.22541/au.169516750.01875818/v1

Manuscript 2: Blaser, B. L., Weymar, M., & Wendt, J. (2023). Ökonomische Erhebung prämenstrueller Symptomatik – Deutsche Übersetzung der Kurzversion der Premenstrual Assessment Form und deren psychometrische Überprüfung [Efficient assessment of premenstrual symptoms - German translation of the shortened Premenstrual Assessment Form and its psychometric evaluation]. *Psychotherapie, Psychosomatik, medizinische Psychologie*. Advance online publication. https://doi.org/10.1055/a-2136-6941

Manuscript 3: Blaser, B. L., Weymar, M., & Wendt, J. (unpublished). Associations between fluctuations in premenstrual symptoms and vagally mediated heart rate variability in daily assessments throughout the menstrual cycle: a feasibility study. Preprint available. https://doi.org/10.22541/au.170000985.55376250/v1

Manuscript 4: Blaser, B. L., Weymar, M., & Wendt, J. (submitted). Premenstrual syndrome is associated with differences in heart rate variability and attentional control throughout the menstrual cycle: a pilot study.

Manuscript 5: Blaser, B. L., Weymar, M., & Wendt, J. (submitted). Smartphone-based heart rate variability biofeedback training improves premenstrual and depressive symptoms as well as anxiety/stress symptoms and attentional executive control: a pilot study. Preprint available. https://doi.org/10.22541/au.170000973.36600989/v1

Manuscript 6: Blaser, B. L., Weymar, M., & Wendt, J. (2023). The effect of a single-session heart rate variability biofeedback on attentional control: Does stress matter? *Frontiers in Psychology*, 14. https://doi.org/10.3389/fpsyg.2023.1292983

A.1 Manuscript 1

Fear acquisition across the menstrual cycle: The moderating role of vagally mediated heart rate variability

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submitted

Fear acquisition across the menstrual cycle: The moderating role of vagally mediated heart rate variability

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Running head: Fear acquisition and menstrual cycle

Keywords: fear potentiation, human fear conditioning, menstrual cycle, vagal tone, heart rate variability, startle, skin conductance

Abstract

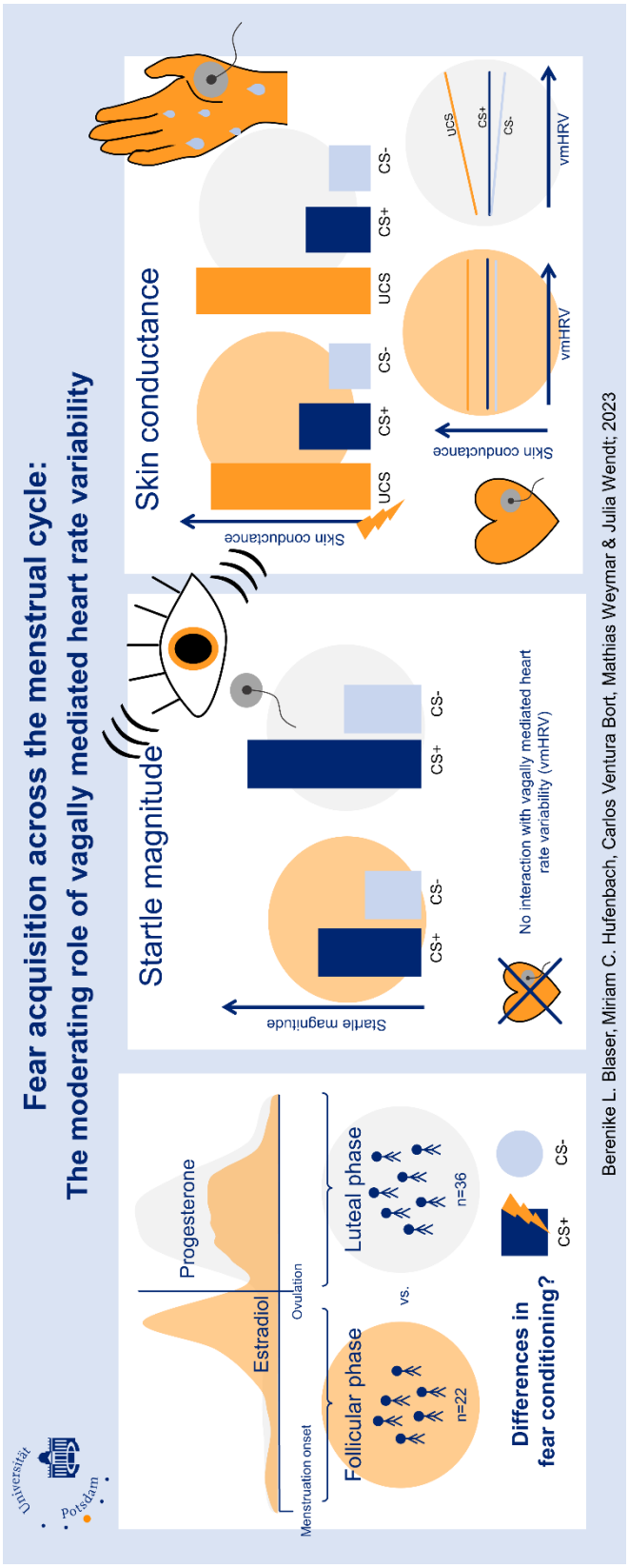
The luteal phase of the menstrual cycle is accompanied by diminished vagally mediated heart rate variability (vmHRV). VmHRV is consistently linked to anxiety, a commonly experienced symptom during the luteal phase. However, fear conditioning, a laboratory model of anxiety, has received limited attention in the context of menstrual cycle fluctuations. This study therefore aims to explore the influence of menstrual cycle phases on instructed fear conditioning and its interactions with vmHRV.

In this study, 58 healthy individuals with regular menstrual cycles, currently in the luteal or follicular phase, participated in a fear conditioning paradigm. During this experiment, two geometric figures were either paired (CS+) or not paired (CS-) with an electric shock. Linear mixed models were used to analyze the modulatory effects of the menstrual cycle phase on the startle magnitude and skin conductance responses (SCRs) to these conditioned stimuli.

Results revealed higher fear differentiation (CS+ vs. CS-) during the luteal phase in the startle magnitude, driven by a startle potentiation to the conditioned stimulus (CS+). In terms of SCR, interacting effects with vmHRV revealed that individuals with high vmHRV exhibited a similar increased fear differentiation during the luteal phase, while low vmHRV individuals showed less fear differentiation.

These findings suggest that during the luteal phase, individuals exhibit stronger fear-related differentiation, a pattern that is partly modulated by vmHRV. These insights shed light on potential origins of varying symptom experiences like increased anxiety during the luteal phase. However, further research is required to investigate associations between these fluctuations and symptomatology.

Graphical abstract



Introduction

During the luteal phase of their menstrual cycle, most menstruating individuals experience aversive physical and affective symptoms [1]. These symptoms might be linked to cycle phase-dependent neurophysiological and autonomic processing, such as changes in neurotransmitter systems [2] and a decrease in parasympathetic activity [3]. Heightened anxiety is a frequently reported symptom during this phase [4]. Notably, anxiety is consistently associated with reduced vagally mediated heart rate variability (vmHRV) (Chalmers et al., 2014), such that vmHRV fluctuations likely contribute to the mood and affect fluctuations observed during the menstrual cycle [5].

VmHRV is an indicator of autonomic processing and is associated with the inhibitory functional connectivity between the medial *prefrontal cortex* (PFC) and the amygdala [6]. In the neurovisceral integration model of fear, the authors [7] propose that vmHRV serves as a relevant biomarker for studying inter- and intraindividual differences in fear learning. This is attributed to the fact that vmHRV is considered a peripheral indicator of the interplay among crucial brain structures involved in fear acquisition and processing, with one of the primary regions being the amygdala. Notably, vmHRV is consistently found to be reduced during the luteal phase of the menstrual cycle [3]. There is also evidence that suggests that stronger reductions in vmHRV are accompanied by a higher degree of aversive symptoms, including anxiety-related symptomatology, during the late luteal phase, known as premenstrual symptoms [5]. This may indicate that the heightened aversive symptoms during the luteal phase are linked to reduced amygdala inhibition, as reflected by lower vmHRV.

A research paradigm that serves as a laboratory model for anxiety [8] and in which the amygdala has consistently been found to be involved [9,10] is fear conditioning. Fear conditioning paradigms, therefore, may provide valuable insights into the relationship between anxiety-related symptomatology and cycle-related fluctuations. One of the most commonly used fear

conditioning paradigms is the differential conditioning procedure in which neutral stimuli are either paired (CS+) with an aversive unconditioned stimulus (UCS) or not (CS-) [11]. The CS+/UCS association (fear acquisition takes place) leads to conditioned responses to the CS+. Additionally, an association between CS- and the absence of UCS is formed, giving the CS- the quality of a safety signal. The difference in reactions to the sole presentation of CS+ and CS- is then termed fear discrimination, representing how effectively the individual distinguishes between the "dangerous" and "safe" conditions. This process of differential fear and safety acquisition can be enhanced by providing verbal instructions about the pairings [12]. Two of the most commonly used physiological outcome measures of fear acquisition are skin conductance response (SCR) and the startle blink reflex (i.e., fear-potentiated startle), characterized by larger responses to the CS+ compared to the CS-. SCR is typically interpreted as an indicator of sympathetic activity, while the startle blink reflex is suggested as an indicator of subcortical fear processing in fear-inducing contexts because it is directly mediated by the amygdala [11,13].

A recent review [14] highlighted the potential relevance of menstrual cycle-related fluctuations in fear conditioning paradigms. However, the evidence presented by the authors is inconclusive, and there is little further research on this topic. One study observed a trend for overall higher startle magnitude in the luteal phase[15]. This effect is especially pronounced in persons experiencing strong affective premenstrual symptoms[16]. Critically, another study showed higher startle magnitudes for CS+ compared to CS- (i.e., fear discrimination), during the luteal than the follicular phase[17]. In skin conductance measures, however, previous studies showed no overall effects between menstrual phases in SCR [18,19], as well as no differential fear discrimination effect [19,20]. A small study of 31 naturally cycling individuals compared those who were currently in the last week of the luteal phase (premenstrual phase) to those in

all other phases (including early and mid-luteal) and found higher fear discrimination in SCR in premenstrual individuals (n = 8) [21].

Overall, despite the potential impact of the menstrual cycle on anxiety-related mechanisms [14], the existing research on the relationship between fear acquisition and the menstrual cycle has been rather scarce and characterized by the use of unimodal indicators of fear acquisition, leading to heterogeneous findings. To deepen our understanding of the impact of the menstrual cycle on fear processing, we therefore investigated fear conditioning measures of startle magnitude and SCR in individuals in the follicular phase and individuals in the luteal phase of their menstrual cycle. Furthermore, extending previous findings, we will also investigate the potential interacting role of vmHRV as one of the most relevant modulators of the relationship between anxiety symptomatology and the cycle phase.

Methods

Participants

We tested healthy participants who took part in a larger biofeedback intervention study [22]. Participants were recruited through postings at the Universities of Potsdam and Greifswald, online platforms, and through posts on social networks. Exclusion criteria included having a body mass index lower than 18.5 kg/m² or higher than 30 kg/m², cardiovascular, neurological, or respiratory diseases, impaired hearing or color vision, claustrophobia, pregnancy, and the use of medications that alter the normal functions of the autonomic nervous system. A total of 128 participants were tested. Of the tested participants, 58 were included in the data analysis who reported a regular active menstrual cycle (with regular changes in length of no more than 4 days), no hormonal contraception and were currently either in the luteal or follicular phase of their cycle. All participants gave informed consent and were compensated with course credit or money. The data were collected between June 2020 and October 2022 and the project was approved by the Ethics Committee of the University Medicine Greifswald and in accordance with the Declaration of Helsinki.

Procedure and fear conditioning

The testing took place in the context of a large intervention study described elsewhere [22] which investigates the effects of heart rate variability biofeedback on extinction learning in healthy individuals. The focus of this report is on data from the acquisition phase of the fear conditioning paradigm that was used in this project.

After the introduction to the study, participants were led to a darkened experimental room where sensors were attached to measure the physiological signals. Participants went through a 6-minute electrocardiogram (ECG) measurement with closed eyes, followed by a fear acquisition protocol.

For the fear paradigm, a blue square and an orange circle served as conditioned stimuli. The stimuli were displayed on a black background in the center of the computer screen, each with a duration of 6 seconds. The intertrial intervals (ITI) varied in length between 14, 15, and 16 seconds. The stimulus presentation was realized using Presentation software (Version 20.3, Neurobehavioral Systems, Inc.).

The assignment of the CS+ and CS- stimulus was counterbalanced across participants. The CS+ was partially (50%) reinforced by an electro-tactile stimulus for a 1ms duration (UCS). The intensity was individually adjusted for each participant before training to a level judged to be "very unpleasant but not painful." (M = 6 mA, SD = 3.7, Range [1.3; 21.0]). The CS- was never accompanied by an electro-tactile stimulus. The stimulation electrode was placed on the inside of the right leg, approximately 3 cm above the ankle. Electrical stimulation was controlled using a DS7A Constant Current Stimulator (Digitimer, Hertfordshire, UK) in Potsdam and an S-48K stimulator (Grass Instruments, West Warwick, RI, USA) in Greifswald.

Bursts of white noise (duration of 50 ms duration, 95 dB volume) served as startle acoustic startle probes and were delivered binaurally through headphones (Potsdam: Audio-Technica ATH-PRO700MK2, Greifswald: AKG K 66). The startle stimuli were administered 4.5 or 5.5 seconds after each CS onset and in half of the ITI (i.e., 16 times) 7.5 seconds after CS offset.

The conditioning phase consisted of 16 trials (8 CS+, 8 CS-) of uninstructed acquisition, followed by a slide informing the participants which of the geometric figures was associated with the aversive stimulus. Then 16 trials of instructed acquisition followed. Before and after the acquisition protocol, participants rated the stimuli on valence and arousal using a 9-point visual analog scale ranging from 1 (valence: highly unpleasant, arousal: calm) to 9 (valence: very pleasant, arousal: exciting).

Startle magnitude, skin conductance and heart rate variability

All physiological recordings were performed using a BIOPAC MP160 amplifier system and AcqKnowledge 5.0.2 software (BIOPAC Systems, Inc., Goleta, CA, USA). All data were sampled at a rate of 2,000 Hz and filtered at various sample rates (see below). A silicon grounding electrode (TerniMed) was attached to the participant's left upper arm.

For the ECG, two Ag/AgCl electrodes (10mm contact surface diameter; Schuler Medizintechnik GmbH) filled with electrode paste (CareFusion) were applied on the right forearm (approximately 2 cm below the elbow) and the left leg (approximately 2 cm proximal to the ankle). The ECG data was digitally sampled at a rate of 400 Hz. The processing of the ECG data was executed using Kubios HRV Software (University of Eastern Finland, Kuopio, Finland) following the recommendations of the Task Force of the European Society of Cardiology [23]. The root mean square of successive differences (RMSSD) was used as a vmHRV measure due to its robustness to breathing rate influences, which were not controlled for in the present study [24].

For the Electrodermal Activity (EDA) recording, the non-dominant hand of the participants was used. Two Ag/AgCl sintered biopotential electrodes (8mm contact surface diameter, Easycap GmbH) were filled with isotonic electrode contact gel (0.5% NaCl, GEL101, BIOPAC Systems, Inc.) and then attached palm-side using double-sided adhesive rings over the hypothenar muscles. The EDA was recorded using an EDA100C module (BIOPAC Systems, Inc.), employing a constant voltage method (0.5V). The EDA data were passed through a 10 Hz low-pass filter.

The startle response was measured using electromyography (EMG) of the Orbicularis Oculi muscle. For this purpose, two electrodes (Ag/AgCl electrodes, 5mm contact surface diameter; Schuler Medizintechnik GmbH) were filled with electrode contact paste (CareFusion) and positioned under the left eye of the participant, with the first electrode located approximately 0.5 to 1 cm below the eye vertically aligned with the pupil, and the second electrode placed laterally adjacent to it (parallel to the eyelid contour) approximately 1 cm from the outer corner of the eye. The EMG signal was recorded using the EMG100C module (BIOPAC Systems, Inc.). The EMG data was digitally sampled at a rate of 1,000 Hz and filtered using 30 Hz high pass, 400 Hz low pass and 50 Hz notch-filter.

The startle magnitude and EDA data were preprocessed using MATLAB.

SCRs were analyzed using the trough-to-peak method (TTP) in Ledalab Version 3.4.9 [25]. In the TTP method, the SCR amplitude is defined as the difference between the skin conductance at the peak of the response and its preceding trough in a determined time window. Adhering to the guidelines [26], the response window was set from 1 to 4 seconds after CS onset. The startle magnitude procedure adhered to recommendations [27]. Blink response onset and peak were automatically identified within 20-120 ms after probe onset, with a peak before 150 ms, employing a algorithm described elsewhere [28]. In a subsequent visual inspection, trials without blinks were scored as zero, and trials with excessive background activity or artifacts were

considered missing. As our emphasis was on interindividual variability in startle magnitude, we decided to use raw data instead of T-transformed data [29].

Menstrual cycle phase

Cycle phases were assessed through self-report using the forward-count method [30]. The follicular phase was assigned when participants reported being in days 1-11 of their cycle. To determine the luteal phase window, 11 days were subtracted from the reported average cycle length. If participants were between these phases or if their cycle day or average cycle length could not be reliably assessed, they were excluded from the analysis.

Statistical analyses

All analyses were conducted in R version 4.2.2. Linear mixed models were calculated, using SCR and startle magnitude from instructed acquisition trials as dependent variables respectively. Participant intercepts were introduced as random effects to cluster the trials by participant. Predictor variables included trial condition (CS+, CS- or ITI/UCS, contrast-coded), menstrual phase (follicular or luteal, dummy-coded) and their interaction. RMSSD and its interaction with trial condition as well as participants' age (control variable) were included if they improved the model fit as indicated by Likelihood Ratio Tests.

Results

Sample description

Out of the 58 individuals included in the analysis, 36 reported being in the follicular phase, while 22 reported being in the luteal phase. The difference in group sizes is attributed to the higher reliability of reporting the follicular phase using the forward-count method, resulting in more individuals currently in the luteal phase being excluded from the analysis. The groups did not differ significantly in terms of age (M_{luteal} = 22.7, SD_{luteal} = 2.3, $M_{follicular}$ = 24.0, $SD_{follicular}$ = 2.9).

Startle response

The results of the model can be viewed in Table 1. There was no significant main effect of the cycle phase, $t(63) = 1.54$, $p = .13$., indicating no differential overall startle magnitude between phases. The interaction effect of Condition x Cycle Phase yielded significant terms in the model, $t(1296) = -2.58$, $p = .010$ (CS+ vs. CS-), $t(1296) = -2.68$, $p = .007$ (CS+ vs. ITI).

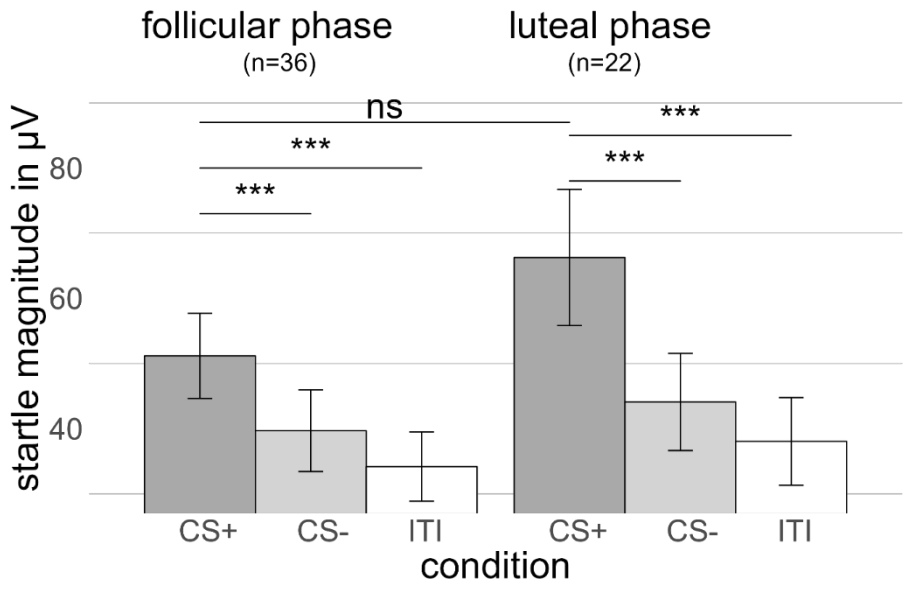
Table 1 Results of mixed model predicting startle magnitude

Predictors	*Estimates*	*CI*	*p*
(Intercept)	51.16	39.28 – 63.04	**<.001*** **
condition [CS-]	-11.38	-16.43 – -6.33	**<.001*** **
condition [ITI]	-17.06	-22.15 – -11.98	**<.001*** **
phase [lut]	15.19	-4.11 – 34.48	.12
condition [CS-] × phase [lut]	-10.78	-18.98 – -2.57	**.010***
condition [ITI] × phase [lut]	-11.24	-19.47 – -3.02	**.007****
Observations	1358		
Marginal R^2 / Conditional R^2	0.045 / 0.582		

Note. The final model had the following structure: startle magnitude ~ condition * phase + (1|participant). CS+ – stimulus paired with unconditioned stimulus; CS- – stimulus not paired with unconditioned stimulus; ITI – intertrial interval; lut – luteal phase.

A visualization of the interaction effect, including significance levels from post-hoc contrast testing, can be seen in Figure 1. Although CS+ trials evoked higher startle magnitudes compared to CS- and ITI trials in both the follicular and luteal phases, the disparity between CS+ and the other trials was more pronounced during the luteal phase, indicating heightened fear discrimination. Post-hoc contrast testing, however, showed no significant difference between startle responses to the CS+ in the follicular and the luteal phase group, $t(63) = -1.54$, $p = .13$. Adding the RMSSD as a main effect or interaction to the model did not change the results. Age was not included as it did not improve the model fit.

Figure 1 Startle magnitude by condition and menstrual cycle phase.



Note. The figure shows a significant interaction effect. Bar plots indicate group means and whiskers standard errors. CS+ – stimulus paired with unconditioned stimulus; CS- – stimulus not paired with unconditioned stimulus; ITI – intertrial interval. ns – not significant; ***: p<.001.

Skin conductance response

A Box-Cox analysis indicated the necessity of logarithmic transformation of the SCR data due to left skewness. Therefore, the analyses were conducted using the log-transformed data (log(1+SCR)). In 4 participants, null reactions in UCS trials amounted to more than 50%, which led to their exclusion from the analysis [31].

The results of the model predicting SCR are presented in Table 2. The inclusion of a three-way interaction term (Cycle Phase x Condition x RMSSD) significantly improved the model fit, as evidenced by a Likelihood Ratio Test, χ^2 (2, N = 58) = 8.42, p = .015. Adding age or RMSSD as main effects did not improve the model. There was no main effect of the menstrual cycle phase in the final model, $t(76) = 0.82$, p = .42, indicating no overall differential skin conductance levels between the phases.

Table 2 Results of mixed model predicting skin conductance

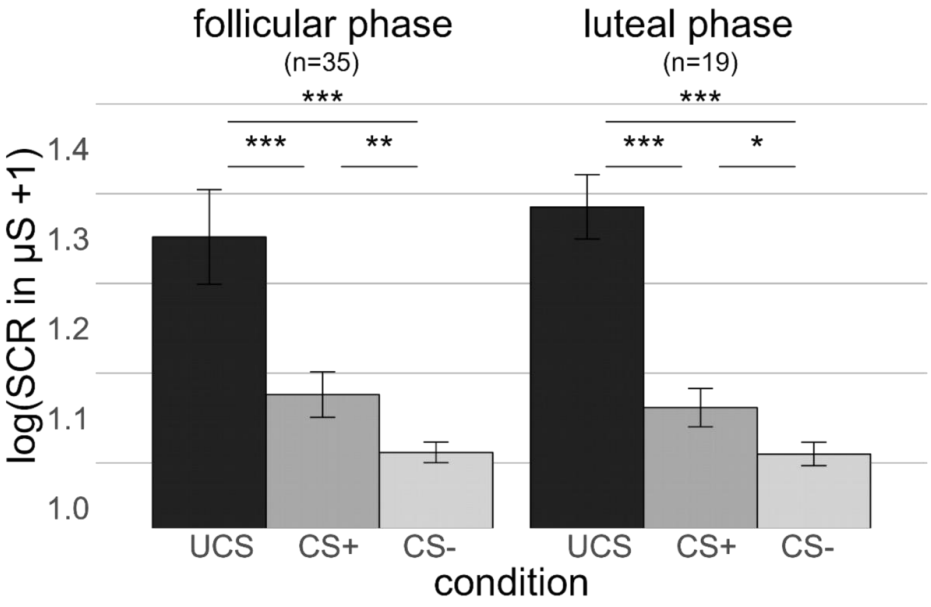
Predictors	*Estimates*	*CI*	*p*
(Intercept)	1.06	1.02 – 1.10	**<.001*** **
condition [CS+]	0.06	0.03 – 0.09	**<.001*** **
condition [UCS]	0.24	0.20 – 0.28	**<.001*** **
phase [lut]	0.14	-0.20 – 0.47	.41
condition [CS+] × phase [lut]	-0.16	-0.42 – 0.10	.22
condition [UCS] × phase [lut]	-0.42	-0.74 – -0.11	**.009** **
Condition [CS-] × phase [lut] × log(RMSSD)	-0.04	-0.13 – 0.05	.40
condition [CS+] × phase [lut] × log(RMSSD)	0.00	-0.09 – 0.09	.96
condition [UCS] × phase [lut] × log(RMSSD)	0.09	-0.02 – 0.19	**.096+**
Observations	1080		
Marginal R^2 / Conditional R^2	0.178 / 0.365		

Note. The final model had the structure: log(skin conductance response) ~ condition * phase + log(RMSSD):condition:phase + (1|participant). CS+ – stimulus paired with unconditioned stimulus; CS- – stimulus not paired with unconditioned stimulus; UCS – unconditioned stimulus; RMSSD – root mean square of successive differences; lut – luteal phase.

However, a two-way interaction of Cycle Phase x Condition (UCS vs. CS-) yielded a significant effect (see Figure 2 for visualization including significance levels from post-hoc contrast testing), $t(1020) = -2.63$, $p = .009$. The effect mirrors the interaction observed in the startle response, albeit less distinctly pronounced. During the luteal phase, a heightened SCR is evident specifically in response to the UCS (unconditioned stimulus) compared to the follicular phase. Although the visual inspection confirms that this difference drives the

interaction effect, post-hoc testing did not find a significant difference between the UCS values in the follicular phase group and the luteal phase group, $t(126) = -1.08$, $p = .28$.

Figure 2 Skin conductance by condition and menstrual cycle phase

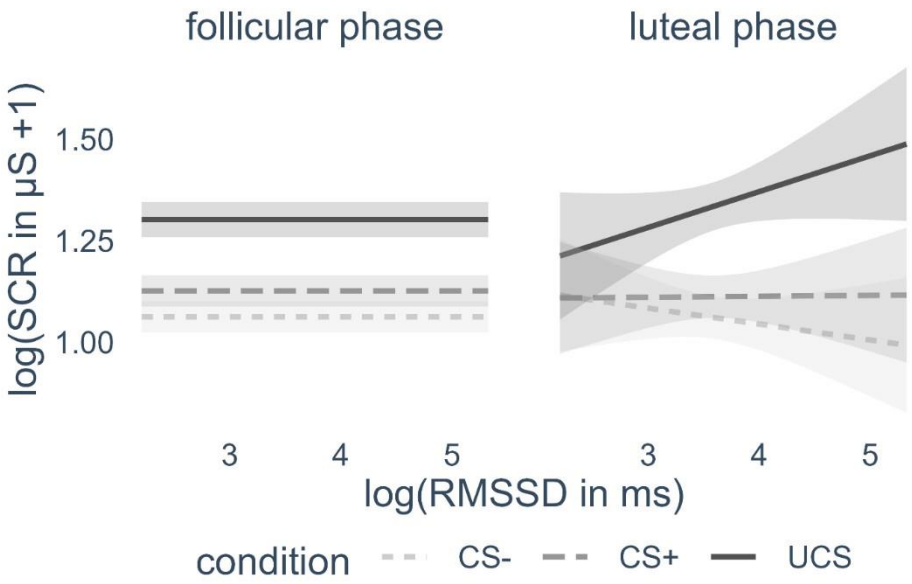


Note. The figure shows a significant interaction effect. Bar plots indicate group means and whiskers standard errors. CS+ – stimulus paired with unconditioned stimulus; CS- – stimulus not paired with unconditioned stimulus; UCS – unconditioned stimulus; SCR – skin conductance response. *: p<.05; **: p<.01; ***: p<.001.

Furthermore, an additional three-way interaction term with RMSSD indicated that this effect was moderated by vagally mediated heart rate variability. While the interaction term was only marginally significant, $t(126) = 1.67$, $p = .098$, adding the effect significantly improved the overall model fit, indicating a relevant explanation of the data through the three-way interaction. Figure 3 depicts the three-way interaction, illustrating the effect when all other effects are held constant. It revealed that greater fear discrimination during the luteal phase (resulting in a larger difference between UCS and CS-, as well as CS+ and CS-) is associated

with higher vmHRV. Conversely, individuals with very low vmHRV in the luteal phase exhibit less distinction than those in the follicular phase. Post-hoc testing for the beta weights of the interaction showed that this effect is driven by the difference in slopes of the CS- and the UCS in the luteal phase group, $t_{ratio}(1018) = 2.90$, $p = .044$. While the standardized UCS slope in this phase is 0.40, the slope for the CS- is -0.18. This indicates that for each standard deviation (SD) lower vmHRV during the luteal phase, there is a corresponding decrease of 0.4 SDs in the SCR response to the UCS and an increase of 0.2 SDs in the SCR response to the CS-. During the follicular phase, the level of fear discrimination is not linked to resting vmHRV.

Figure 3 Skin conductance by condition, menstrual cycle phase and vagally mediated heart rate variability



Note. The figure shows a significant interaction effect when all other effects are held constant. RMSSD – root mean square of successive differences; SCR – skin conductance response; CS+ – stimulus paired with unconditioned stimulus; CS- – stimulus not paired with unconditioned stimulus; UCS – unconditioned stimulus.

Discussion

In the present study, we investigated the effects of the menstrual cycle phase and vagally mediated heart rate variability (vmHRV) on instructed fear conditioning. We found that the menstrual cycle modulated fear discrimination in both startle magnitudes and the SCR. Specifically, an enhanced CS+ vs. CS- differentiation was seen in startle responses in individuals during the luteal phase compared to individuals in the follicular phase. This enhanced discrimination was driven by larger responses particularly to CS+ stimuli. In skin conductance response (SCR) measurements, we observed reduced fear and safety discrimination during the luteal phase in individuals with low resting vmHRV compared to individuals with high vmHRV during the luteal phase and those in the follicular phase.

Firstly, our results indicate higher fear differentiation in startle magnitude during the luteal phase, specifically showing a higher fear-potentiated startle response to the conditioned stimulus (CS+) but not to the unconditioned stimulus (CS-) and intertrial interval (ITI). This finding replicates previous research [17], which similarly observed increased fear discrimination in startle measures during the luteal phase. Importantly, this effect was consistent across all participants, regardless of their resting vmHRV. However, we did not find a significant main effect of the menstrual cycle phase on startle magnitude. This contrasts with previous results [15], which reported higher overall startle magnitudes during the luteal phase compared to the follicular phase.

With regard to skin conductance, we observed that individuals with high vmHRV show the same increased fear differentiation between CS+ and CS- (and UCS) in the luteal phase while low vmHRV individuals showed less fear differentiation. In contrast, during the follicular phase, there were no differences in skin conductance fear responses based on vmHRV. Although this three-way interaction term between condition, cycle phase, and vmHRV was only marginally significant, adding it to the model significantly improved the

model fit. This indicates a notable enhancement in the explanation of variance in SCR through this interaction. The two-way interaction between phase and condition was not evident until vmHRV was included in the model, which may be the reason why it was not found in previous studies [19,20]. These results emphasize the importance of considering moderating variables that may interact with the menstrual cycle to gain a better understanding of the underlying physiological and psychological changes.

The heightened fear differentiation observed in startle measures across all individuals and in skin conductance in individuals with high vmHRV could potentially be linked to increased estrogen levels during the luteal phase. While some studies have observed increased fear discrimination in individuals with elevated estradiol levels, as seen in skin conductance [32] and activation of the amygdala and hypothalamus [33], other studies have not replicated this effect [34]. In these studies, however, the interpretation of the relation to menstrual cycle phases is limited due to the absence of cycle phase assessment or its exclusion from the analysis, and the reliance on simple median splits of participants' current estradiol levels for group comparisons. It is important to note that high estradiol levels can be observed both during the second half of the follicular phase and throughout the majority of the luteal phase, with a peak during the mid-phase. Consequently, some of the results may be confounded or diluted by including individuals in different phases or predominantly in the luteal phase. To disentangle the effects of the menstrual cycle phase and estradiol and validate the role of estradiol in the amplified fear discrimination during the luteal phase, subsequent studies incorporating evaluations of both phase and hormonal levels would be essential.

We found a positive association of SCR fear discrimination and vmHRV during the luteal phase. Why this association is evident only during the luteal phase of the cycle remains unclear. It is hypothesized that certain individuals possess a lower neuroendocrine reactive threshold to the fluctuating expression of gonadal steroids across the menstrual cycle,

contributing to aversive symptomatology during the luteal phase [2]. The connection between reduced vmHRV and diminished fear discrimination in skin conductance measures among select participants could potentially reflect this susceptibility. While a meta-analysis [3] reported a general slight decrease in vmHRV during this phase, evidence suggests that this reduction in vmHRV is specifically associated with premenstrual symptoms. Persons who reported high premenstrual symptoms showed the characteristic drop in vmHRV from the follicular to the luteal phase, whereas individuals who did not experience premenstrual symptoms also did not exhibit these fluctuations [5]. Commonly reported premenstrual symptoms encompass anxiety, irritability, and heightened stress sensitivity [4]. These symptoms align with the less distinct sympathetic reactivity observed in individuals with low vmHRV during the luteal phase in our study, as similar affective states to those experienced during PMS, such as clinical anxiety, have previously been associated with reduced fear discrimination [35]. Furthermore, decreased vmHRV is well-known to also be associated with anxiety and anxious states [36].

The Generalized Unsafety Theory of Stress presents a framework for these findings [37]. The authors argue that prolonged stress responses, even in the absence of stressors (such as chronic anxiety), result from a perceived lack of safety even in ostensibly secure environments. Similar to the Neurovisceral Integration Model of Fear, the authors propose the existence of a default stress response, which, in healthy individuals, is inhibited in safe environments. VmHRV serves as an indicator of this inhibitory capacity. Evidence supporting this theory can be observed in the negative association between vmHRV and SCR in individuals during the luteal phase, as identified in this study (β = -0.18). The lower an individual's vmHRV was during this phase, the stronger their SCR response to CS- cues, which signal safety. It's noteworthy that all participants were explicitly informed, as part of the instructed fear acquisition paradigm, that there would be no aversive stimuli associated with this symbol. The reduction of vmHRV during the luteal phase accompanied by the altered skin conductance

responses may thus be indicative of the origination of premenstrual symptoms in a phasic reduction of this inhibition of the default stress response. This assumption, however, would have to be verified in a paradigm that additionally assesses symptomatology.

In a similar way, our results could also be interpreted within the neurovisceral integration theory of fear [7], which is rooted in the broader neurovisceral integration theory [38]. This theory highlights the significance of the interplay between the central and autonomic nervous systems in fear processing. This process occurs via a network of interconnected brain structures that facilitate the regulation of a system known as the central autonomic network. A pivotal idea here is that, in healthy individuals, the PFC adeptly gauges the safety or danger of a situation. Through an inhibitory functional connection with limbic structures like the amygdala, fear responses are then dampened in safe scenarios while becoming more pronounced in hazardous assessments. Subsequently, the autonomic nervous system orchestrates the appropriate response, which could manifest as fear or a lack thereof.

The authors emphasize the importance of vmHRV in this context. It may serve as both a real-time indicator of ongoing responses and an index of the strength of the connectivity between the PFC and amygdala on a trait level [6]. This connection, indicated by resting vmHRV, determines an individual's capacity to regulate behaviour effectively and adequately. Battaglia and Thayer (2022) propose that individuals with low resting vmHRV may experience reduced abilities to sufficiently modulate fear responses [39,40].

Our findings partially corroborate this assumption, revealing a connection between vmHRV and effective fear discrimination during the luteal phase of the menstrual cycle. However, this association is only evident in skin conductance and not in startle measures, which partly contradicts the neurovisceral integration theory of fear [7].

Some limitations must be considered when interpreting the results. The main limitation is the self-report assessment of menstrual cycle phase. It is recommended to support self-report

with hormonal assessments or another form of physiological ovulation confirmation [30]. The second limitation is the between-subject design, which is less sensitive to potential cycle-related effects [30]. That effects were still found, however, speaks to the strength of the observed effects. Lastly, we included the ITI values in the analysis of acoustic startle and the UCS in the analysis of the skin conductance measures. This reduces comparability between the analyses of the two measures and was done to gain a first understanding of the interaction of menstrual cycle phase, vmHRV, and fear acquisition. The results need to be replicated in a study design that addresses these shortcomings to allow final interpretability.

Conclusion

In summary, the menstrual cycle does have an overall effect on instructed fear conditioning, but the effects vary depending on the outcome measure and covariates. While there is a higher differentiation during the luteal phase in startle response, skin conductance shows this differentiation only in individuals with high vmHRV during this phase. Low vmHRV individuals show decreased differentiation in this measure during the luteal phase. These findings may provide valuable insights into the origin of the differential intra- and interindividual experience of premenstrual symptoms. Although in the current study, we did not directly assess whether these fluctuations are directly related to the experience of symptoms, our results clearly suggest that the menstrual cycle phase should be considered in fear conditioning paradigms.

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Acknowledgements

Berenike Blaser was supported by a PhD scholarship from the University of Potsdam (Potsdam Graduate School) with fundings from the Graduate Fund of the State of Brandenburg (Germany). The project was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - Projektnummer 491466077 and WE5873/1-2. A preprint of the manuscript is available under doi.org/ 10.22541/au.169516750.01875818/v1 [41].

Author contributions

BB: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. MH: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – review & editing. CV: Conceptualization, Methodology, Software, Data curation, Writing – review & editing. MW: Resources, Writing – review & editing. JW: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Data availability statement

The da**t**asets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author(s) declare no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 3.5 in order to increase readability of the text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

A.2 Manuscript 2

Ökonomische Erhebung prämenstrueller Symptomatik – Deutsche Übersetzung der Kurzversion der Premenstrual Assessment Form und deren psychometrische Überprüfung

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Psychotherapie, Psychosomatik, medizinische Psychologie

2023

Ökonomische Erhebung prämenstrueller Symptomatik - Deutsche Übersetzung der Kurzversion der Premenstrual Assessment Form und deren psychometrische Überprüfung

Efficient assessment of premenstrual symptoms – German translation of the shortened Premenstrual Assessment Form and its psychometric evaluation

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Schlüsselwörter: Prämenstruelles Syndrom, Prämenstruelle dysphorische Störung, Fragebogen, Gütekriterien, Menstruation

Key words: premenstrual syndrome, premenstrual dysphoric disorder, questionnaire, psychometric properties, menstruation

Zusammenfassung

Prämenstruelle Symptomatik ist eine weitverbreitete und dennoch wenig beforschte Problematik. Im deutschen Sprachraum existiert bislang kein Instrument zur Erhebung des breiten Spektrums an möglichen Symptomen und deren Ausprägung. Aus diesem Grund wurden die Kurzversionen der Premenstrual Assessment Form mit 20 und 10 Items übersetzt und an einer Stichprobe von N = 147 menstruierenden Personen validiert.

Die internen Konsistenzen der 20er und 10er Item-Versionen sind hoch (Cronbachs α_{PAF20} = .93 und α_{PAF10} = .88) und vergleichbar mit den Originalversionen. Eine Faktorenanalyse identifizierte zwei Skalen, die psychologische und physiologische Symptomatik erfassen. Konvergente Validität wird durch den Zusammenhang mit dem PMS-Impact Questionnaire (r_{PAF20} = .66, p < .001) belegt. Dieser ist signifikant höher (z = 2.67, p = .004) als der Zusammenhang mit dem Brief Symptom Inventory-18 (r_{PAF20} = .50, p > .001), wodurch die divergente Validität als gegeben angenommen wird. Es wurden außerdem Cut-Off Werte für Verdachtsdiagnosen auf Basis der Diagnosekriterien des DSM-V für beide Kurzformen berechnet.

Die übersetzte Premenstrual Assessment Form ist ein valides, reliables, ökonomisches und flexibel einsetzbares Instrument. Es eignet sich zur Quantifizierung prämenstrueller Symptomatik in der Forschung.

Abstract

Premenstrual symptomatology is a widespread and yet under-researched problem. To date, there is no German instrument for assessing the broad spectrum of possible symptoms and their degree of expression. For this reason, the short versions of the Premenstrual Assessment Form with 20 and 10 items were translated and validated in a sample of 147 menstruating persons. The internal consistencies of the 20-item and 10-item versions are high (Cronbach's α_{PAF20} = .93 and α_{PAF10} = .88, respectively) and comparable to the original versions. Factor analysis identified two scales that assess psychological and physiological symptoms. Convergent validity was demonstrated by a correlation with the PMS Impact Questionnaire (r_{PAF20} = .66, $p < .001$). This association was higher than the correlation with the Brief Symptom Inventory-18 (r_{PAF20} = .50, $p > .001$), which verifies divergent validity. Additionally, cut-off values for suspected diagnoses based on DSM-V diagnostic criteria for both short forms were calculated.

The translated Premenstrual Assessment Form is a valid, reliable, and parsimonious instrument that can be used flexibly. It is suitable for quantifying premenstrual symptomatology in research.

Einleitung

Das Prämenstruelle Syndrom (PMS) beschreibt eine Reihe heterogener psychischer und physiologischer Symptome (z.B. depressive Verstimmung, Reizbarkeit, Wassereinlagerungen und Schmerzen), die prämenstruell vorhanden sind und nach Einsatz der Menstruation wieder verschwinden. Die Prävalenz in der Bevölkerung ist ausgesprochen hoch: 50% aller menstruierenden Personen leiden unter dem PMS [1] und 90% erleben regelmäßig wenigstens ein Symptom [2]. Die *Prämenstruelle Dysphorische Störung* (PMDS) bezeichnet eine sehr starke Ausprägung vorwiegend der psychischen Symptomatik und ist als affektive Störung klassifiziert [3]. Für die Diagnosestellung nach dem Diagnostischen und Statistischen Manual Psychischer Störungen der fünften Auflage (DSM-V) müssen mindestens 5 von insgesamt 11 genannten Symptomen in der Woche vor Beginn der Menses auftreten und anschließend abklingen. Davon muss mindestens ein Symptom aus der Kategorie der affektiven Symptome (z.B. deutliche Affektlabilität, depressive Verstimmung, Angst) kommen. Zusätzlich müssen die Symptome mit klinisch relevantem Leiden oder Beeinträchtigung in mindestens einem Lebensbereich einhergehen.

Die Konstrukte des PMS und der PMDS sind wenig verstanden und kaum beforscht [4]. Nach einem initialen Anstieg der prämenstruellen Forschung in den 80er Jahren steigen die PMS-bezogenen Publikationen pro Jahr nur noch leicht. Von etwa 130 Veröffentlichungen pro Jahr Ende der 80er Jahre ist die durchschnittliche Anzahl im Zeitraum von 2019 bis 2021 lediglich auf 160 gestiegen (Suche bei PubMed zum Stichwort „premenstrual AND (symptom OR syndrome OR distress OR dysphoric)“ vom 18.05.22). Im Vergleich dazu steigen Publikationen zu den Stichworten „Depression“ oder „Angst“ exponentiell mit aktuellen Zahlen, die um die 30.000 Publikationen pro Jahr liegen.

Um das Verständnis und den Umgang mit der extrem weit verbreiteten Symptomatik zu verbessern, ist spezifische Forschung erforderlich. Dafür notwendig sind geeignete Instrumente, die die Ausprägung von prämenstrueller Symptomatik abbilden. Zur klinischen

Diagnostik eines PMS oder einer PMDS sind laut dem DSM-V Symptomtagebücher über mindestens zwei symptomatische Zyklen nötig [3]. Dies ist ein Aufwand, der außerhalb von groß angelegten klinischen Studien in der Forschung kaum umsetzbar ist. Des Weiteren gibt es Hinweise darauf, dass das tägliche Verfolgen von prämenstruellen Symptomen zu einem Anstieg der berichteten Symptome führt [5]. Sparsame, ökonomische Fragebögen zur Erfassung der Ausprägung prämenstrueller Symptome sind deshalb unerlässlich zur dringend notwendigen Erforschung der Hintergründe und Prozesse der PMS und PMDS.

Im deutschen Sprachraum gibt es aktuell lediglich drei validierte Instrumente zur Erfassung prämenstrueller Veränderungen. Das „Screening-Instrument für prämenstruelle Symptome“ (SIPS) dient der Identifikation von Personen, die aufgrund ihrer Symptome möglicherweise einen Behandlungsbedarf aufweisen [6]. Das zweite validierte Instrument ist der „PMS-Impact Questionnaire“ (PMS-I), welcher die Beeinträchtigung durch Prämenstruelle Veränderungen quantifiziert [7]. Das dritte Instrument, die deutsche Übersetzung der „Premenstrual Tension Syndrome Observer and Self-Rating Scale“ [8], erfasst ein breiteres Spektrum an Symptomen, die allerdings nur als vorhanden oder nicht vorhanden angegeben werden können. Ein Spektrum von prämenstruellen Symptomen und deren Ausprägung wird mit keinem der drei Fragebögen erhoben. Im englischen Sprachraum hingegen existiert eine Vielzahl von Instrumenten zur Erhebung prämenstrueller Symptomatik, die bis zu 100 verschiedene Symptome umfassen [9], was die Heterogenität und Variationsbreite des PMS widerspiegelt [10]. Eine der meistverwendeten Skalen ist die Premenstrual Assessment Form (PAF) [11], auf deren Items diverse weitere Instrumente basieren [9]. Der Fragebogen besteht aus 95 Items, die eine weite Bandbreite an symptomatischen Veränderungen während der prämenstruellen Phase abbilden.

Zwei sparsamere Kurzversionen der PAF wurden auf Basis der 20 meistberichteten Items (PAF20) und der 10 am eindeutigsten auf drei gefundenen Komponenten Affekt, Schmerzen und Wasserrückhalt (Einlagerung von Flüssigkeit im Körpergewebe; engl. water

retention) ladenden Items (PAF10) erstellt [12]. Die Kurzversionen zeigen gute psychometrische Gütekriterien, die mit denen der Langform vergleichbar sind. Sowohl die PAF20 als auch die PAF10 weisen eine interne Konsistenz von .95 auf. Die Test-Retest Reliabilität für beide Kurzversionen (sowie die Skalen) wird mit .6-.7 berichtet.

Da bis zu 90% aller Personen mit aktivem Menstruationszyklus prämenstruelle Veränderungen erleben [13], ist prämenstruelle Symptomatik als dimensionales Konstrukt anzusehen. In den meisten Fällen führen die Veränderungen zu keinem klinisch relevanten Leiden. Die Erforschung der Veränderungen ist jedoch auch außerhalb des klinischen Bereichs relevant. Die PAF20 erhebt im Vergleich zum SIPS ein Spektrum von psychischer und physischer Symptomatik, welches nicht auf psychopathologische, affektive Veränderungen und klinische Diagnostik der PMDS fokussiert ist. Entsprechend richtet sich die PAF20 anders als der SIPS an eine nicht-klinische Zielgruppe.

Zur Quantifizierung von prämenstrueller Symptomatik ist nicht nur die Abfrage breit aufgefächerter Symptome wichtig, sondern auch die Erhebung ihrer Ausprägungen. Die Premenstrual Tension Syndrome Skalen fragen lediglich das Vorliegen oder Nicht-Vorliegen von Symptomen ab. Die PAF20 hat im Gegensatz dazu den Vorteil, auch die Stärke der vorliegenden Symptome zu quantifizieren. Dies wird nicht nur dem Erleben der Symptomatik gerechter, sondern erzeugt auch mehr Varianz, was die wissenschaftliche Untersuchung der Phänomene erleichtert.

In Abgrenzung zur PMS-I erhebt die PAF20 die eigentliche prämenstruelle Symptomatik statt der Beeinträchtigung durch die Symptome. Beide Konstrukte sind bei der Erforschung prämenstrueller Veränderungen von Bedeutung, allerdings differenziert zu betrachten.

Um die Lücke an deutschsprachigen Instrumenten zur Erfassung prämenstrueller Symptomatik zu schließen, soll nun die Kurzversion der PAF übersetzt und an einer nicht-klinischen Stichprobe validiert werden.

Material und Methoden

Übersetzungsprozess

Die PAF20 wurde mit Erlaubnis einer der Hauptautorinnen übersetzt und validiert. Der Übersetzungsprozess bestand dabei aus fünf Schritten.

1) Im ersten Schritt wurden die Items von zwei deutschen Muttersprachlerinnen mit C2-Englisch-Niveau übersetzt.
2) Im zweiten Schritt wurden die beiden Übersetzungen gegeneinander verglichen und Items hervorgehoben, die eine Diskrepanz aufwiesen.
3) Die entsprechenden Formulierungen wurden im nächsten Schritt von den beiden Übersetzerinnen diskutiert, bis ein Konsens über das jeweilige Item zustande kam.
4) Anschließend folgte eine unabhängige Bewertung der Übersetzung einer dritten Person (C2-Englisch-Niveau, Psychologische Psychotherapeutin).
5) Abschließend erfolgte eine Prätestung mit Feedback von drei Personen, die der Zielgruppe des Fragebogens (Personen mit aktivem Menstruationszyklus) angehören. Die Testenden füllten den übersetzten Fragebogen dabei einmal aus und gaben anschließend Feedback bezüglich der Verständlichkeit der Items und Format des Fragebogens.

Die Vorgehensweise basiert auf den in einer Übersichtsarbeit als am wichtigsten identifizierten Schritten bei der interkulturellen Adaptation von Fragebögen [14].

Validierung

Die finale Version der übersetzten PAF wurde anschließend in einer Online-Studie validiert. Auf Basis eines Subject-To-Item-Verhältnisses von 7, wie in der Literatur zur Prüfung der internen Konsistenz vorgeschlagen [15], wurde eine Stichprobe von 140 Personen angestrebt. Da der Fragebogen nicht zur Diagnostik bestimmt ist, wurde keine klinische Stichprobe erhoben. Das Ausfüllen des Fragbogens dauerte etwa 10 Minuten und wurde mit dem Online-Fragebogen Tool SoSciSurvey auf dem Server der Universität Potsdam

implementiert. Eingeschlossen wurden Personen über 18 Jahren mit aktiven Menstruationszyklen, d.h. Personen, die angaben, regelmäßige oder auch unregelmäßige Monatsblutungen zu erleben. Dieses Kriterium wurde auf der ersten Seite der Online-Erhebung im Selbstbericht abgefragt. Wurde dies verneint, endete die Online-Studie vor dem Ausfüllen der Fragebögen. Die Rekrutierung erfolgte über die Studienrekrutierungsplattform SONA der Universität Potsdam, von wo aus Teilnehmende direkt zur Online-Umfrage weitergeleitet wurden. Die Versuchspersonen wurden für ihre Teilnahme mit Versuchspersonenstunden im Rahmen des Studiums vergütet oder nahmen ohne Vergütung teil. Die Erhebung lief im Zeitraum von Februar bis Oktober 2022. Das Studienprotokoll wurde von der Ethikkommission der Universität Potsdam genehmigt (Ethikvotum Nr. 30/2022).

Verwendete Instrumente

Premenstrual Assessment Form

Der PAF20 Fragebogen besteht aus 20 Items mit Symptomen, für die jeweils retrospektiv angeben wird, wie stark die Ausprägung der letzten prämenstruellen Phase erlebt wurde. Das Antwortformat ist eine 6-Punkt-Likert Skala, welche von 1- „nicht vorhanden oder keine Veränderung vom Normalzustand“ bis hin zu 6-„extreme Veränderung, vielleicht sogar bemerkbar für flüchtig Bekannte“ reicht. Am Ende wird ein Summenwert von 0-100 errechnet. Die Bearbeitung dauert 2-3 (PAF20) bzw. 1-2 (PAF10) Minuten. Der übersetzte Fragebogen befindet sich im Zusatzmaterial.

Kontrollvariablen

Als Kontrollvariablen wurden soziodemographische Daten erhoben (Alter, Bildungsabschluss, Geschlechtsidentität, Beruf/Studium), sowie Körpergröße und -gewicht zur Berechnung des Body-Mass-Indexes (BMI). Ebenfalls erhoben wurden Informationen zur Regelmäßigkeit des Menstruationszyklus, der aktuellen Zyklusphase (durchschnittliche Länge des Zyklus, Tage seit Beginn der letzten Menstruation) sowie zur Nutzung hormoneller Kontrazeptiva.

Konvergente Validität

Der PMS-I [7] besteht aus 18 Items, die auf zwei Skalen die funktionale (z.B. „Wegen meiner PMS-Symptome gehe ich weniger Freizeitaktivitäten nach.“) und psychologische (z.B. „Wegen meiner PMS-Symptome kann ich schlechter mit Stress umgehen.“) Beeinträchtigung aufgrund prämenstrueller Veränderungen abfragen. Die beiden Skalen zeigen jeweils eine gute interne Konsistenz von $\alpha = .9$. Das Instrument zeigt gute diskriminante und konvergente Validität [7].

Des Weiteren wurden die Kriterien zur Diagnose eines PMS oder einer PMDS nach dem DSM-V erhoben. Dabei wurden Items aus den Formulierungen der Symptome des DSM-V erstellt. Die Versuchspersonen wurden dann gebeten, für jedes der zwölf Symptome anzugeben, wie stark sie dieses normalerweise einige Tage vor der Menstruation erleben. Das Antwortformat wurde hier vom SIPS [6] übernommen, bei welchem im Gegensatz dazu die Items aus den DSM-IV Kriterien bestehen. Zudem gaben die Teilnehmenden an, wie stark sie unter den genannten Symptomen leiden und Einschränkungen in den in den DSM-V Kriterien angegebenen Lebensbereichen erleben. Die Symptome und Einschränkungen wurden mit Hilfe einer 4-stufigen Likert-Skala (1- „gar nicht“ bis 4- „stark“) erhoben. Auf Basis der Antworten wurden die Teilnehmenden nach den DSM-V Kriterien in die Verdachtsdiagnose-Gruppen „PMDS“, „PMS“ und „ohne Verdachtsdiagnose“ aufgeteilt. Die Verdachtsdiagnose „PMDS“ wurde vergeben, wenn mindestens 5 der 11 Symptom-Items mit einem Wert ≥ 3 beantwortet wurden, davon mindestens eins mit vier und jeweils ein Item aus der Gruppe der Kern- und der Zusatzsymptome nach DSM-V Klassifikation. Zusätzlich musste in mindestens einem Lebensbereich eine starke Beeinträchtigung angegeben werden. Die Einteilung in diese Gruppe ist analog zur Diagnosestellung nach dem DSM-V. Zur Gruppe „PMS“ wurden angelehnt an das SIPS Personen gezählt, die die Kriterien für die Gruppe „PMDS“ nicht erfüllten, aber in mindestens fünf Symptomen und einem Bereich der Beeinträchtigung einen Wert ≥ 3 angaben.

Divergente Validität

Es wurde zur Erhebung der divergenten Validität außerdem das Brief Symptom Inventory-18 (BSI-18) [16] eingesetzt. Das BSI-18 besteht aus 18 Items, die aktuelle psychische Symptomatik auf den Skalen Angst, Depression und Somatisierung misst. Die Skala zeigt trotz ihrer Sparsamkeit gute psychometrische Gütekriterien.

Die PAF erfasst Zyklus-bezogen physiologisches und psychisches Unwohlsein, einschließlich Angst und Traurigkeit. Das BSI-18 umfasst ebenfalls Items, die sowohl körperliches (Skala Somatisierung) als auch psychisches Unwohlsein (Skalen Ängstlichkeit und Depressivität) erfassen, dies allerdings unabhängig vom Menstruationszyklus (Beispielitem aus dem BSI-18: Wie sehr litten sie in den vergangenen 7 Tagen unter… Furchtsamkeit; Beispielitem aus der PAF20: Wie stark erlebten Sie in der prämenstruellen Phase ihres letzten Zyklus… sich ängstlich(er) fühlen). Zum Nachweis der divergenten Validität soll gezeigt werden, dass die PAF spezifisch prämenstruelle und nicht generelle Symptomatik erhebt. Zusammenhänge zwischen PAF und BSI-18 werden jedoch trotzdem erwartet, da Komorbiditäten mit unipolaren affektiven und Angststörungen beim PMS und der PMDS häufig auftreten [17].

Trotz der hohen inhaltlichen Nähe in den Itemformulierungen zwischen PAF und BSI-18 und den beschriebenen Komorbiditäten wird erwartet, dass die PAF eindeutig Zyklus-spezifische und nicht die generelle Symptomatik erfasst. Daher wird eine signifikant niedrigere Korrelation zwischen PAF und BSI-18 als zwischen der PAF und dem PMS-I erwartet. Denn obwohl der PMS-I nicht direkt die PMS-Symptome, sondern deren Auswirkungen auf verschiedene Lebensbereiche erfasst, wird basierend auf der Zyklusspezifität eine höhere gemeinsame erklärte Varianz erwartet. Damit wäre im Sinne einer divergenten Validität nachgewiesen, dass in der PAF eindeutig prämenstruelle Symptomatik erfasst wird und nicht die angrenzende, aber getrennt zu betrachtende generelle psychopathologische Symptomatik.

Statistische Analysen

Alle Analysen wurden mit R Version 4.1.2 durchgeführt. Zur Gewährleistung der Annahme der Normalverteilung wurden die intervallskalierten Variablen bei Bedarf BoxCox transformiert. Die Hypothesen wurden mit einer 5%igen Fehlerwahrscheinlichkeit überprüft.

Um den Einfluss der erhobenen Kontrollvariablen auf die PAF-Werte zu untersuchen und mögliche Verzerrungen aufzudecken, wurde eine lineare Regression mit den Prädiktoren BMI, Alter und Zyklusphase (Dummy-kodiert) auf den PAF-Summenwert gerechnet. Der Einfluss hormoneller Verhütung wurde mit einem t-Test (PAF-Summenwert) und einem Chi-Quadrat-Test (Kategorie nach Verdachtsdiagnosen DSM-V Kriterien) überprüft.

Für das Gütekriterium der Reliabilität wurde jeweils für die 20-Item und 10-Item Version der übersetzten PAF ein Cronbachs-Alpha-Wert berechnet, wobei $\alpha \geq .7$ als akzeptabel, $\alpha \geq .8$ als gut und $\alpha \geq .9$ als exzellent interpretiert wird [18]. Die konvergente Validität wurde durch zwei Berechnungen überprüft. Die erste Berechnung beinhaltete eine Korrelation zwischen dem PAF-Summenwert und dem PMS-I Summenwert. Für die Zusammenhänge zwischen prämenstrueller Symptomatik und Beeinträchtigung durch die Symptomatik werden sehr hohe Korrelationen von bis .8 beobachtet [19]. Aus diesem Grund erwarten wir hier hohe Korrelationen >.5. In einer einfaktoriellen ANOVA wurde zusätzlich überprüft, ob die Varianz der PAF-Summenwertes signifikant durch die Einteilung der Versuchspersonen in die Gruppen „PMDS“, „PMS“ und „ohne Verdachtsdiagnose“ nach den DSM-V Kriterien zu erklären ist. Im zweiten Schritt wurde bei signifikantem Ergebnis überprüft, ob der Effekt in die erwartete Richtung geht, die PAF-Werte der PMDS-Gruppe demnach im Mittel signifikant höher als die der PMS-Gruppe sind und die Werte der PMS-Gruppe wiederum signifikant höher liegen als die der Gruppe ohne Verdachtsdiagnose.

Für die divergente Validität wurden bivariate Korrelationen des PAF-Summenwertes mit dem Global Severity Index (GSI) des BSI-18 gerechnet. Es wurden signifikant niedrigere Zusammenhänge als mit dem PMS-I Summenwert erwartet (einseitige Testung). Die Literatur

zeigt Korrelationskoeffizienten zwischen .4 und .5 für die Assoziation von PMS-Symptomatik und psychopathologischer Symptomatik wie Angst und Depression [19]. Wir erwarten hier Zusammenhänge mit ähnlichen Effektstärken, die eindeutig niedriger liegen als der Zusammenhang zur Beeinträchtigung durch die prämenstruelle Symptomatik.

Für die Überprüfung der faktoriellen Validität wurde eine Faktorenanalyse mit Varimax-Rotation angewendet. Zur Bestimmung der idealen Faktorenanzahl wurde ein Scree-Plot erstellt und nach der sogenannten „Knickmethode“ die Anzahl der Faktoren bestimmt. Wenn kein eindeutiger Knick identifiziert werden konnte, wurde die Faktorenzahl sekundär nach Eigenwertmethode identifiziert. Der gleiche Prozess wurde jeweils für die 10-Item und die 20-Item Version durchgeführt.

Um Annäherungen für Cut-Off Werte möglicher klinischer Relevanz zu erhalten, wurden die Teilnehmenden in zwei Gruppen eingeteilt, die zum einen Personen beinhaltete, die nach den selbstberichteten DSM-V Kriterien einen Verdacht auf PMS oder PMDS zeigten, und zum anderen Personen enthielt, die keinen Verdacht zeigten. Es wurde anschließend nach dem optimalen Cut-Off Wert zur Differenzierung der Gruppen gesucht. Dafür wurde mittels einer ROC-Analyse der Punkt mit der maximalen Summe von Spezifität und Sensitivität ermittelt.

Ergebnisse

Übersetzungsprozess

Die beiden unabhängigen Übersetzungen zeigten eine hohe inhaltliche Übereinstimmung. Es traten lediglich geringfügige Differenzen bzgl. der Itemformulierungen auf, die in den Schritten 3 (Diskussion der Übersetzerinnen bis zum Konsens) und 4 (Bewertung und Überarbeitung durch dritte Person) des Prozesses behoben wurden. Aufgrund des Feedbacks der Testenden in Schritt 5 wurden keine Veränderungen mehr an der finalen Version des Fragebogens vorgenommen.

Stichprobe

Die Stichprobe bestand aus 147 menstruierenden Personen im Alter von 18 bis 48 Jahren, wobei das Durchschnittsalter bei 24.9 Jahren lag. Die Geschlechtsidentität wurde vom Großteil (138 Personen, 93.9%) als weiblich angegeben, von drei Personen als divers, weiteren drei Personen als nicht-binär und drei Personen wollten keine Angabe zu ihrer Geschlechtsidentität machen. Alle bis auf zwei Versuchspersonen gaben an, sich aktuell im Studium zu befinden. 79.6% (n = 117) der Personen gaben einen regelmäßigen Zyklus an. 21.1% (n = 31) gaben eine Verwendung hormoneller Kontrazeptiva an, wobei 22 Personen eine Verhütungspille einnahmen, sechs eine Hormonspirale und drei einen Verhütungsring verwendeten.

Zum Zeitpunkt des Ausfüllens befanden sich nach der forward-count Methode 44.2% (n = 65) in der Follikelphase (Tag 1-12 des Zyklus), 41.5% (n = 61) in der Lutealphase (durchschnittliche Zykluslänge-12 Tage) und 12.2% (n = 18) in der Zyklusmitte. Bei drei Personen fehlten Angaben zur Berechnung der Phase.

Einfluss von Kontrollvariablen

Bei Personen, die hormonell verhüten (n = 31 / 21.09%, m_{PAF20} = 40.77 ±22.16), gab es im Vergleich zu natürlich zirkulierenden Personen (n = 116 / 78.91%, m_{PAF20} = 47.71 ±20.44) keinen signifikanten Unterschied in der Symptomatik (t = -1.85, p = .07). Ein Chi-Quadrat-Test zeigte, dass es ebenfalls keine signifikanten Verteilungsunterschiede der Verdachtsdiagnosen basierend auf den DSM-V Kriterien nach Verhütung gibt (χ^2 = 2.94, p = 0.23). Eine lineare Regression zeigte keinen signifikanten Einfluss von aktueller Zyklusphase (Luteal- vs. Follikelphase, Dummy-kodiert: β = -0.07, p = .46; Ovulation vs. Follikelphase: β = 0.09, p = .31), Alter (β = .10, p = .26) oder Body-Mass-Index (β = .10, p = .24) auf die berichtete Symptomatik. Da keine der Kontrollvariablen einen signifikanten Einfluss auf die prämenstruelle Symptomatik zeigte, wurden sie nicht in die späteren Analysen einbezogen.

Validität und Reliabilität

Sowohl die PAF20 als auch die PAF10 zeigten gute interne Konsistenzen von $\alpha_{PAF20} = .93$ und $\alpha_{PAF10} = .87$. Eine einfaktorielle ANOVA zeigt eine signifikante Varianzerklärung des PAF20 ($F = 27.75$, $p < .001$) wie auch des PAF10 ($F = 25.05$, $p < .001$) Summenwerts durch die Gruppenzuordnung auf Basis der DSM-V Kriterien. Dabei geht der Effekt in die erwartete Richtung, wobei der PAF-Summenwert bei der Verdachtsdiagnose „PMDS“ ($n = 27$ / 18.37%, $m = 63.08 \pm 18.04$) höher ist als bei „PMS“ ($n = 34$ / 23.13%, $m = 55.26 \pm 14.78$) und Personen mit der Verdachtsdiagnose „PMS“ im Durchschnitt wiederum einen höheren Wert aufzeigen als Personen ohne Verdachtsdiagnose ($n = 84$ / 57.14%, $m = 36.99 \pm 18.87$) (für Signifikanzniveaus der Mittelwertvergleiche siehe Abbildung 1). Der Gesamtmittelwert liegt bei $m_{PAF20} = 46.24$ (± 20.93) bzw. $m_{PAF10} = 22.89$ (± 10.81).

Des Weiteren wurde eine Korrelation von $r_{PAF20} = .66$ ($p < .001$) bzw. $r_{PAF10} = .62$ ($p < .001$) des PAF-Summenwertes mit dem PMS-I Summenwert gefunden. Der GSI des BSI-18 hingegen zeigt eine Korrelation von $r_{PAF20} = .50$ ($p < .001$) bzw. $r_{PAF10} = .47$ ($p < .001$). Die Korrelation von PAF20 mit PMS-I ist signifikant größer als die Korrelation mit dem GSI ($z = 2.67$, $p = .004$).

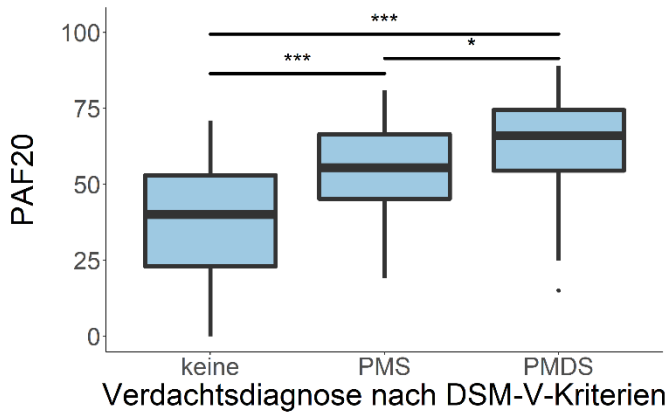

Abb. 1: Summenwert der Premenstrual Assessment Form 20 nach Verdachtsdiagnosen basierend auf selbstberichteten DSM-V Kriterien. PMS – Prämenstruelles Syndrom; PMDS – Prämenstruelle Dysphorische Störung. Gruppe „keine“ n = 85, „PMS“ n = 34, „PMDS“ n = 27. Boxplots visualisieren Mediane und Quartile der Verteilungen. * $p < .05$; ** $p < .01$; *** $p < .001$

Faktorenstruktur

Zur Bestimmung der Anzahl der zu extrahierenden Faktoren wurde ein Scree-Plot für die PAF20 erstellt. Es zeigte sich ein leichter Knick bei einer 2-Faktoren-Struktur (Eigenwerte Komponenten 1: 10.74; 2: 2.42; 3: 1.34; 4: 1.22; 5: 1.03). Im Scree-Plot der PAF10 war ein klarer Knick bei zwei Komponenten erkennbar (Eigenwerte Komponenten 1: 5.37; 2: 1.73; 3: 0.99; 4: 0.78). Die Ladungen der Items der beiden Versionen auf den beiden Faktoren können Tabelle 1 entnommen werden. Die orthogonale Varimax-Rotation wurde zur Vergleichbarkeit mit der Methodik des Originalinstruments [12] verwendet. Da allerdings korrelierte Faktoren stark anzunehmen sind, wurde zusätzlich eine oblique Promax-Rotationsanalyse durchgeführt. Hierbei ist das Faktorenladungsmuster identisch mit dem der orthogonalen Rotation.

Die Summenwerte der beiden auf den Faktorenladungen basierenden Skalen korrelieren zu .59 ($p < .001$) bei der PAF20 und zu .51 ($p < .001$) bei der PAF10. Die Summenwerte von PAF10 und PAF20 zeigen eine Korrelation von .96 ($p < .001$).

Cut-Off Werte

Der optimale Cut-Off Wert der PAF20 zur Differenzierung der Gruppen mit und ohne Verdachtsdiagnose, bei dem gleichzeitig Sensitivität und Spezifität maximiert werden, liegt bei 53. Dieser Cut-Off zeigt eine Sensitivität von .72 und eine Spezifität von .73. Die entsprechende ROC-Kurve ist in Abbildung 2 zu sehen.

Bei der PAF10 liegt der optimale Cut-Off Wert ebenfalls etwa in der Mitte des zu erreichenden Werts bei 23 (Sensitivität = .82, Spezifität = .61).

	PAF20		**PAF10**	
	Faktorladungen		Faktorladungen	
	1	2	1	2
Fehlen von Energie	.58			
Ängstlichkeit	.60			
Unwohlsein	.61	.40		
Überforderungsgefühl	.70		.72	
Nörgeln	.75			
Unzufriedenheit mit Aussehen	.56	.45		
Weinen	.73			
Gestresstheit	.85		.90	
Stimmungsschwankungen	.78			
Gereiztheit	.77		.70	
Traurigkeit	.82		.82	
Intoleranz	.52			
Brustschmerzen		.62		.60
Rückenschmerzen		.57		.56
Gewichtzunahme		.68		.70
Unterleibsschmerzen		.63		.61
Schwellungen		.61		.63
Aufgeblähtheit		.71		.69
Sexuelles Verlangen		.41		
Hautprobleme		.43		

Tab. 1: Faktorenladungen der übersetzten Premenstrual Assessment Form Items der 20er und 10er Version. Es werden alle Ladungen ≥.4 angegeben. Grau hinterlegte Items sind in der 10er Version enthalten. Faktor 1 wird als psychologische Symptomatik und Faktor 2 als physiologische Symptomatik benannt

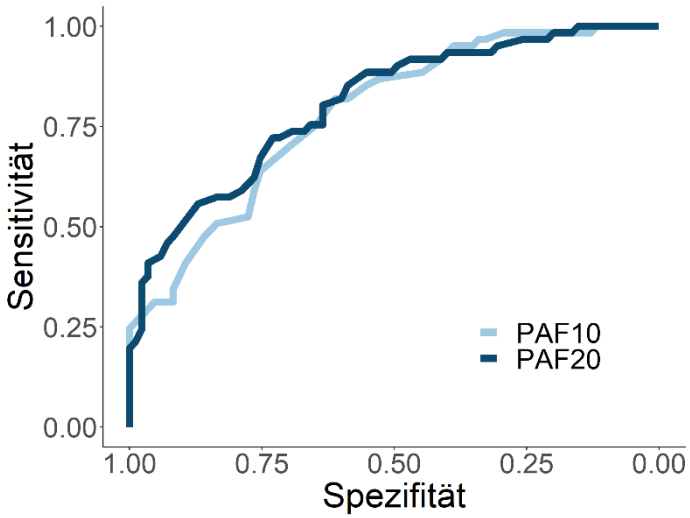

Abb. 2: ROC-Kurven der PAF20 und PAF10 als Prädiktor einer prämenstruellen Verdachtsdiagnose basierend auf selbstberichteten DSM-V Kriterien.

Diskussion

Die Übersetzung der Kurzversion der Premenstrual Assessment Form wurde an einer nicht-klinischen Stichprobe von 147 menstruierenden Personen validiert. Dabei wurden sowohl die Version mit 20 als auch mit 10 Items betrachtet. Beide Versionen zeigen sehr gute interne Konsistenzen. Eine hohe Assoziation von PAF-Summenwerten mit den PMS-I Werten sowie nachgewiesene Gruppenunterschiede in den PAF-Summenwerten nach Verdachtsdiagnosen basierend auf den DSM-V Kriterien belegen eine gute konvergente Validität. Die Assoziation mit dem GSI des BSI-18 liegt aufgrund von Komorbidität von PMS und Angst-/Depressionssymptomatik im erwarteten Bereich. Dennoch ist die Korrelation mit der Zyklus-unspezifischen Symptomatik signifikant niedriger als die Assoziation mit dem PMS-I. Dadurch wird belegt, dass die PAF20 eindeutig Zyklus-spezifische Symptomatik und nicht generelle psychische Belastung abbildet. Die divergente Validität wird aus diesem Grund als gegeben angenommen. Die Werte der übersetzten PAF20 sind vergleichbar mit denen der

englischen Originalversion ($m_{PAF20,\ original} = 43.0 \pm 20.8$, $m_{PAF20,\ Übersetzung} = 46.2 \pm 20.9$), während die Werte der PAF10 etwas höher liegen ($m_{PAF10,\ original} = 17.4 \pm 10.9$, $m_{PAF10,\ Übersetzung} = 22.9 \pm 10.8$). Es wurde eine 2-Faktoren-Stuktur gefunden, wobei die beiden Faktoren eindeutig psychologische und physiologische Symptomatik abbilden. Es wurden außerdem Cut-Off Werte für die Verdachtsdiagnosen „PMS“ oder „PMDS“ nach den DSM-V Kriterien identifiziert (PAF20: 53 / 100; PAF10: 23 / 50).

Die Autorinnen des Originalinstruments [12] fanden eine 3-Faktorenstruktur, bei der die Faktoren mit Affekt, Schmerzen und Wasserrückhalt betitelt wurden. Unsere Daten der übersetzten Version unterstützen jedoch am wahrscheinlichsten ein 2-Faktorenmodell, wobei die beiden Faktoren inhaltlich auf physiologischer und psychologischer Symptomatik basieren. Warum der physiologische Faktor nicht wie im Originalinstrument in Schmerz und Wasserrückhalt aufgegliedert ist, ist nicht ganz klar. Allerdings laden auch in der Originalversion die Items inhaltlich nicht eindeutig auf diesen Faktoren. Die Items „Unzufriedenheit mit dem eigenen Aussehen“ und „Gefühl von Unwohlsein“ beispielsweise sind den Faktoren nicht eindeutig zuordbar. Zusätzlich besteht die dritte Komponente „Wasserrückhalt“ aus der Originalversion auch aus Items wie „Hautunreinheiten“ und „verringerte Energie“. Die Autorinnen des Originalinstruments [12] berichten zudem nicht, nach welchem Kriterium die Komponentenzahl ausgewählt wurde. Es ist denkbar, dass die Faktorenstruktur äquivalent zu der aus dieser Studie ist, aber durch das Eigenwertkriterium eine Entscheidung für drei Faktoren getroffen wurde, was zu vergleichsweise niedrigen Ladungen auf den letzten Faktor und einem unklaren Ladungsmuster führte. Die 2-faktorielle Struktur jedoch hat eine hohe Augenscheinvalidität und liefert eine gute Grundlage zur Differenzierung der körperlichen und psychischen Ebene der Symptomatik.

Die identifizierten Cut-Off Werte für eine klinische Relevanz liegen in etwa bei der Hälfte des möglichen Wertespektrums. Hier liegen 46.3% der Befragten über dem Cut-Off,

was passend zu dem Befund ist, dass etwa die Hälfte aller Menstruierenden unter dem Vollbild des PMS leidet. In einer Meta-Analyse epidemiologischer Studien mit einer Gesamtstichprobe von N = 18803 zeigte sich eine gepoolte Prävalenz von 47.8% für das Vollbild des PMS [1]. Es weist ebenfalls darauf hin, dass die PAF das gesamte Varianzspektrum der Symptome abbildet und wenig Deckeneffekte aufweist.

Die erhobene Stichprobe besteht fast ausschließlich aus Studierenden mit einem Altersdurchschnitt von 25 Jahren. Damit ist sie jünger und gebildeter als repräsentativ für die Bevölkerung wäre. Die Verteilung der Verdachtsdiagnosen auf Basis der DSM-V Kriterien ist allerdings vergleichbar zu der Verteilung in repräsentativen Erhebungen [1], was dafürspricht, dass es zu wenig Verzerrung gekommen ist. Zwar zeigen sich im PAF10-Summenwert in der vorliegenden Stichprobe höhere Werte als im Originalinstrument, allerdings weisen die beiden Stichproben auch systematische Unterschiede auf. Es handelte sich in der Validierung der Originalversion um Personen, die an einer klinischen Interventionsstudie zur Raucherentwöhnung teilnahmen und einen deutlich höheren Altersdurchschnitt aufwiesen (m = 38 ±6.49). Die Schwere der berichteten PMS-Symptomatik nimmt mit dem Alter ab [20], was eine mögliche Erklärung für die Unterschiede in den Summenwerten ist.

Ein Punkt, der gegen die retrospektive Erhebung von prämenstrueller Symptomatik spricht, sind Befunde, die darauf hinweisen, dass PMS-Symptome im Vergleich zur prospektiven Erhebung überschätzt werden [21]. Basierend darauf wäre zu erwarten, dass Personen, die sich aktuell in der späten Lutealphase oder kurz danach befinden, realistischere Einschätzungen geben können und somit niedriger ausgeprägte Symptomatik berichten. Da allerdings in den vorliegenden Daten keine Unterschiede der berichteten Symptomstärke in Abhängigkeit der aktuellen Zyklusphase zu sehen sind, gehen wir davon aus, dass die retrospektive Erhebung keine systematische Verzerrung hervorruft.

Limitationen. Die erhobene Stichprobe ist nicht repräsentativ für die Grundgesamtheit der menstruierenden Personen. Dass die Verteilung der Symptomatik allerdings ähnlich wie in

repräsentativen Studien ist, deutet darauf hin, dass es hierdurch zu wenigen Verzerrungen gekommen ist. Außerdem fand keine klinische Diagnostik statt, um die Cut-Off-Werte für die klinische Relevanz der Symptomatik zu verifizieren. Falls das Instrument zu klinischen Screeningzwecken eingesetzt werden soll, ist eine weitere Studie mit einer repräsentativen Stichprobe und klinischer Diagnostik notwendig.

Schlussfolgerung

Zusammenfassend betrachtet bietet die deutsche Übersetzung der PAF20 und der PAF10 ein valides und reliables Instrument zur retrospektiven Erfassung prämenstrueller Symptomatik. Vor allem in Erhebungen, in denen Symptomtagebucherhebungen nicht realisierbar sind, bietet sich die Verwendung an. Das Instrument eignet sich daher, um notwendige Forschung zum besseren Verständnis des Konstrukts PMS im Deutschsprachigen Raum voranzutreiben. Durch einfache Anpassung der Zeitangabe in den Instruktionen eignen sich die beiden ökonomischen Kurzversionen auch zur Erhebung im Tagebuchformat oder zur mehrfachen Erhebung während verschiedener Zyklusphasen. Diese Einsatzmöglichkeiten des Instruments müssen jedoch in weiteren Studien konzipiert und validiert werden.

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Zusatzmaterial: Übersetzte Premenstrual Assessment Form 20 (PAF20)

Premenstrual Assessment Form 20 (PAF20)

Wählen Sie für jedes der untenstehenden Symptome bitte die Zahl, die am ehesten der Intensität Ihrer prämenstruellen Symptome **während Ihres letzten Zyklus** entspricht. Diese Phase fängt ungefähr sieben Tage vor der Menstruationsblutung (oder sieben Tage vor Ihrer Periode) an und endet ungefähr, wenn die Blutung beginnt. Beurteilen Sie jedes Item auf dieser Liste auf einer Skala von 1 (nicht vorhanden oder keine Veränderung vom Normalzustand) bis 6 (extreme Veränderung, vielleicht sogar bemerkbar für flüchtig Bekannte).

- Verringerte Energie haben oder dazu neigen, schneller zu ermüden
- Sich ängstlich(er) fühlen
- Ein Gefühl von Unwohlsein haben
- *Schmerzen, Druckempfindlichkeit, Vergrößerung oder Schwellungen der Brüste haben
- *Sich von alltäglichen Anforderungen überfordert fühlen
- Zum Nörgeln neigen oder über Kleinigkeiten streiten
- Unzufrieden mit eigenem Aussehen sein
- Dazu neigen, sich weinerlich zu fühlen oder zu weinen
- *Sich gestresst fühlen
- Stimmungsschwankungen haben
- *Anfälle von Gereiztheit oder schlechte Laune haben
- *Sich traurig oder niedergeschlagen fühlen
- *Dazu neigen, Rücken-, Gelenk-, oder Muskelschmerzen oder -steifheit zu haben
- *An Gewicht zunehmen
- Dazu neigen, intolerant oder ungeduldig zu sein oder die Fähigkeit zu verlieren, die Fehler oder Bedürfnisse von anderen zu verstehen oder darauf zu reagieren

- *Relativ stabiles Gefühl von Schwere, Beschwerden oder Schmerzen im Unterleib haben
- Erhöhtes sexuelles Verlangen oder Interesse haben
- Hautprobleme haben so wie Akne, Pickel, usw.
- *Ödeme, Schwellungen oder Wassereinlagerungen haben oder sich aufgedunsen fühlen
- *Sich aufgebläht fühlen

** Markierte Items sind Teil der PAF10.*

Auswertung:

- Gesamtsummenwert: Summe aller Antworten – 20 (Wert zwischen 0 und 100)
- Physiologische Subskala: Items 4*, 13*, 14*, 16*, 17, 18, 19*, 20*
- Psychische Subskala: Items 1, 2, 3, 5*, 6, 7, 8, 9*, 10, 11*, 12*, 15

Der Fragebogen steht zur freien Verwendung zur Verfügung.

A.3 Manuscript 3

Associations between fluctuations in premenstrual symptoms and vagally mediated heart rate variability in daily assessments throughout the menstrual cycle: a feasibility study

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Unpublished manuscript, preprint available

Associations between fluctuations in premenstrual symptoms and vagally mediated heart rate variability in daily assessments throughout the menstrual cycle: a feasibility study

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Running head: Heart rate variability and premenstrual symptoms

Keywords: heart rate variability, vagal tone, premenstrual syndrome, premenstrual symptoms, menstrual cycle, ambulatory assessment

Abstract

Introduction

Premenstrual syndrome (PMS) affects up to 90% of individuals with an active menstrual cycle. Several studies have observed reduced vagally mediated heart rate variability in a single assessment during the luteal phase compared to an assessment during the follicular phase, especially in participants experiencing strong PMS. The aim of this investigation was to initially assess the relationship between premenstrual symptoms and vagally mediated heart rate variability throughout the menstrual cycle, as well as to examine the feasibility of conducting a large-scale study to verify this association.

Methods

Three participants completed daily ambulatory assessments of resting vagally mediated heart rate variability using mobile electrocardiographs and typical PMS symptoms. We calculated correlations between these measurements for each participant.

Results

PMS symptoms and vagally mediated heart rate variability showed medium to high correlations in each of the participants throughout the cycle. These associations were primarily driven by the relationship between vagally mediated heart rate variability and psychological symptoms rather than physiological symptoms. Visual inspection of the fluctuations confirmed the concurrent occurrence of a phasic reduction in vagally mediated heart rate variability parallel to the increases in PMS symptoms experienced during the mid to late luteal phase in each participant.

Discussion

The results support the notion of an association between PMS symptoms and vagally mediated heart rate variability. An ambulatory daily assessment paradigm proves to be feasible. Studies with larger samples are necessary to provide deeper insights into inter- and intra-individual differences as well as stronger knowledge on the mechanistic pathways of PMS.

Introduction

Premenstrual syndrome (PMS) encompasses a heterogeneous collection of symptoms that typically manifest in the week preceding menstruation, during the luteal phase of the menstrual cycle, and dissipate within a few days after menstruation begins. These symptoms can be of a physiological nature, such as bloating and water retention, or psychological, including feelings of stress, anxiety, or irritability. It is noteworthy that as many as 90% of menstruating individuals regularly experience at least one symptom associated with PMS (Tschudin et al., 2010).

The etiology of PMS remains unclear. A common hypothesis is that varying sensitivities to fluctuations in gonadal hormones throughout the menstrual cycle play a role (Rapkin & Akopians, 2012). This differential sensitivity may involve several systems, including the Gamma-Aminobutyric Acid (GABA) and serotonin systems (Nappi et al., 2022; Rapkin & Akopians, 2012). Vagally mediated heart rate variability (vmHRV) serves as a potential physiological marker that could contribute to our understanding of PMS. VmHRV is regarded as a marker for cardiac vagal control (Laborde et al., 2023), and research has linked it to a wide range of psychopathological states (Heiss et al., 2021) and cognitive outcomes (Holzman & Bridgett, 2017; Zahn et al., 2016). The associations are so consistent, that Beauchaine and Thayer (2015) have proposed vmHRV as a transdiagnostic biomarker for psychopathology.

In a meta-analysis conducted by Schmalenberger et al. (2019), consistent reductions in vmHRV of medium effect size were identified during the luteal phase when compared to measurements during the follicular phase. A limited number of studies, however, have explored the relationship between this vmHRV reduction and PMS.

The fluctuations in vmHRV are found to be moderated by the extend of premenstrual symptomatology (Schmalenberger et al., 2023). The observed effect indicates that high PMS

groups experience more substantial reductions in vmHRV during the luteal phase, whereas control groups show either smaller fluctuations (Zambotti et al., 2013) or no discernible difference (Baker et al., 2008; Matsumoto et al., 2007) in vmHRV between the follicular and luteal phases.

The consistent direction of the association between vmHRV and PMS is noteworthy, but it is important to acknowledge that all previous studies on this topic have involved only a single measurement during each cycle phase. Consequently, it is challenging to ascertain whether symptoms and vmHRV fluctuate in parallel throughout the menstrual cycle. In an effort to shed more light on the relationship between vmHRV and PMS and to assess feasibility, we therefore initiated a pilot diary study involving three participants. This study aimed to gather daily assessments of premenstrual symptoms alongside measurements of resting vmHRV to follow the course of their association.

Methods and Materials

Participants

We tested three participants of different ages ($age_{participant\ 1} = 44$, $age_{participant\ 2} = 27$, $age_{participant\ 3} = 20$) who were recruited within our department. These participants provided informed consent and received either course credit or no compensation for their participation. In line with the guidelines suggested by Laborde et al. (2017), the participants did not take medication that could affect vmHRV, had no chronic diseases, and were not pregnant.

Testing protocol

Each participant received an introduction on how to use the mobile electrocardiography (ECG) device and a document with written instructions outlining the procedure. Measurements were taken each day at the same time, between 7 and 8 pm. The participants began by completing an online questionnaire assessing premenstrual symptoms, recording their last menstrual period, and responding to a number of control variables. Following the questionnaire, the ECG measurement was conducted. Participants attached the ECG device to their chest, set a timer for 6 minutes, initiated the ECG recording, and closed their eyes while the resting vmHRV measurement was taken. This measurement was performed with participants in a sitting position.

Participants were requested to complete the assessments daily over 1.5 menstrual cycles to ensure the inclusion of one complete cycle. We employed the backward- and forward-counting method to assess the cycle phase (Schmalenberger et al., 2021). We included two weeks before a reported menstruation onset (luteal phase) and two to three weeks (depending on reported average cycle length) after a reported menstruation onset (follicular phase) for the analysis.

Heart rate variability

Vagally mediated heart rate variability was assessed using a mobile 1-channel ECG device, the Bittium Faros 180. The device electrodes were attached to the chest, and data were collected at a sampling rate of 1000 Hz. Data preprocessing was performed using the Faros Software, which generated R-R interval and R peak timestamp series. The first and last 30 seconds of each measurement were removed, resulting in a 5-minute interval, to avoid artifacts caused by participant movement, as participants initiated and concluded the measurement themselves.

The root mean square of successive differences (RMSSD) was derived from the time series as measurement of vmHRV. The time series were analyzed in R (version 4.2.2) using the RHRV package (https://rhrv.r-forge.r-project.org/), following the package documentation. We chose this measurement over the high-frequency component of power spectral analysis due to its robustness to breathing rate and its clearer indication of parasympathetic activity (Chapleau & Sabharwal, 2011).

Premenstrual symptoms

Premenstrual symptoms were assessed with the German version of the shortened Premenstrual Assessment Form (PAF20) (Allen et al., 1991; Blaser et al., 2023b). The questionnaire comprises the 20 most endorsed items from the long form PAF, which includes nearly 100 items in total. Each item represents a specific symptom, and participants are asked to rate how strongly they experienced each symptom during the last premenstrual phase using a 6-point Likert scale, ranging from “not at all/no change from normal” to “extreme change from normal”. The German version of this questionnaire has demonstrated good validity and reliability and loads onto two distinct factors, creating psychological and physiological symptom scales. For this study, we adapted the questionnaire to a diary format, where participants reported how strongly they experienced each symptom in the previous 24 hours.

Control variables

The daily online questionnaire included several control variables that are known to influence vmHRV or PMS. Participants were asked to provide retrospective assessments of these variables for the last 24 hours. The control variables encompassed substance intake (alcohol, caffeine, nicotine), a one-item rating of the level of stress experienced that day on a Likert scale ranging from 1 to 9, a one-item rating of sleep quality on a 1-9 Likert scale, and reports of any physical health symptoms related to acute diseases, such as respiratory symptoms.

Analysis

All statistical analyses were conducted with R (version 4.2.2). To assess the association between premenstrual symptoms and RMSSD over the menstrual cycle, we conducted Pearson correlations between the two measurements for each participant individually. Furthermore, separate correlations were calculated for the physiological and the psychological subscale of the PAF20 with the RMSSD.

To test the association between PAF20 and RMSSD for all three participants, independently of the control variables, we conducted a linear mixed model predicting PAF20 sum scores. Participant intercepts were modeled as random effects to account for nesting of the data. The RMSSD and control variables were introduced as fixed effects.

Results

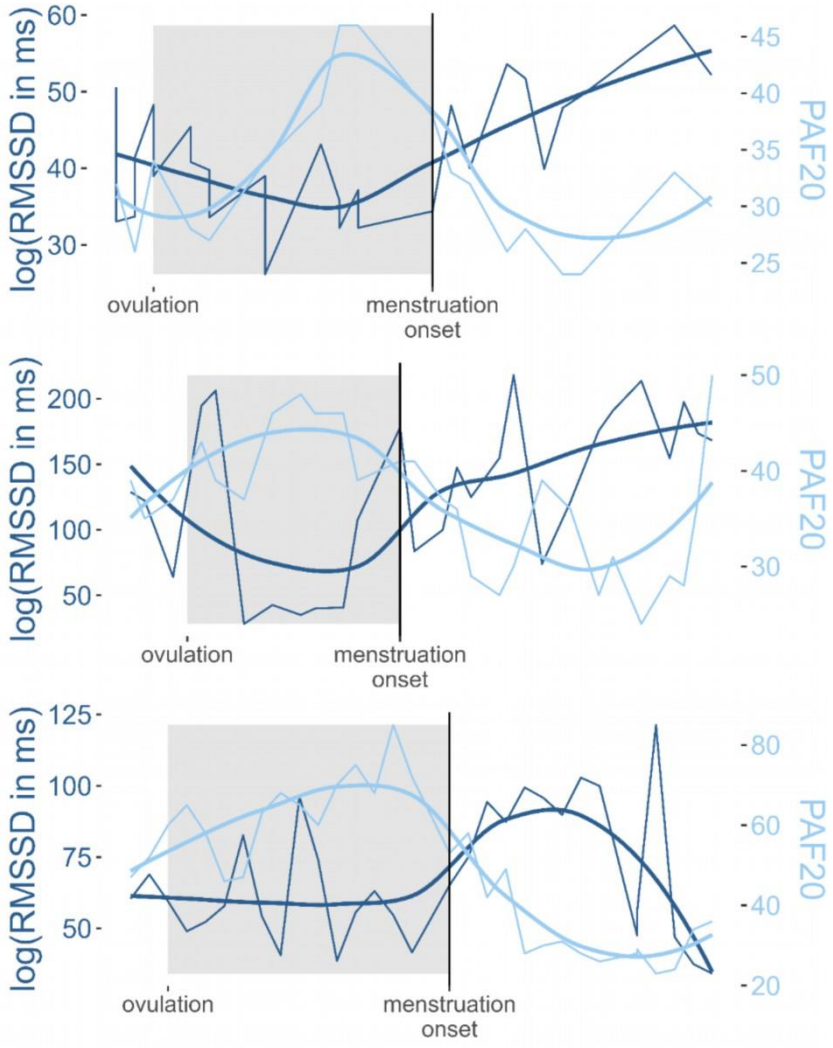
The RMSSD values were subjected to a log transformation to approximate a normal distribution, aligning with the conventions of other vmHRV research (Laborde et al., 2017). A visual representation of the symptom course and RMSSD for each of the three participants is presented in Figure 1. Pearson correlations between log-transformed RMSSD and daily symptom scores were moderate to high, $r_{participant1}(25) = -.41$, $p < .05$, $r_{participant\ 2}(35) = -.48$, $p < .01$, $r_{participant\ 3}(29) = -.43$, $p < .05$. The correlations were consistently higher in the psychological subscale than the physiological subscale (see Table 1). The associations between RMSSD and physiological symptoms were not significant in all three participants.

Table 1. Pearson correlations of vagally mediated heart rate variability and premenstrual symptom scores

		Psychological symptoms			Physiological symptoms		
		r	df	p	r	df	p
log(RMSSD)	Participant 1	-.50	25	**.008**	-.25	25	.21
	Participant 2	-.57	35	**<.001**	-.07	35	.68
	Participant 3	-.46	29	**.010**	-.31	29	.093

Notes. The symptom scores are the sum scores of the psychological and physiological subscale of the daily ratings of the short form of the premenstrual assessment form (PAF20). RMSSD – root mean square of successive differences; df – degrees of freedom.

Figure 1. Course of vagally mediated heart rate variability and premenstrual symptoms over a menstrual cycle



Note. The plots show the covarying vagally mediated heart rate variability and premenstrual symptom scores over one cycle for participants 1-3 (top to bottom). Grey shaded area indicates the luteal phase, which is marked by increases in symptoms and decreases in vagally mediated heart rate variability. The thin lines show the raw values, while the thicker lines indicate trend lines using the LOESS (locally estimated scatterplot smoothing) method. RMSSD – root mean square of successive differences, PAF20 – sum score of short form of the premenstrual assessment form.

For the control variables, stress ratings were log-transformed to approximate a normal distribution. Nicotine usage was not included due to the absence of variance. Sport and alcohol consumption were both recategorized as factors with three levels (sport: no sport, <60 min, >60 min; alcohol: no consumption, one drink, >one drink).

The results of the linear mixed model predicting PAF sum scores are presented in Table 2. After introducing all control variables, RMSSD remained a significant predictor of premenstrual symptoms with a standardized regression weight of -0.28.

Table 2. Results of linear mixed model predicating premenstrual symptoms.

	PAF sum score		
Predictors	*β*	*CI*	*p*
(Intercept)	0.05	-0.87 – 0.97	0.919
sleep	0.10	-0.06 – 0.25	0.210
stress	0.46	0.30 – 0.63	<0.001
caffein	0.13	-0.15 – 0.41	0.363
alcohol [one drink]	-0.35	-0.81 – 0.11	0.134
alcohol [more drinks]	-0.77	-1.30 – -0.25	0.004
sport [1-60min]	0.38	-0.05 – 0.82	0.085
sport [<60min]	-0.40	-0.88 – 0.08	0.102
log(RMSSD)	-0.28	-0.49 – -0.07	0.011
Random Effects			
σ^2	0.47		
$\tau_{00\ vpn}$	0.61		
ICC	0.57		
$N_{\ vpn}$	3		
Observations	95		
Marginal R^2 / Conditional R^2	0.288 / 0.693		

Note. Participant intercepts were introduced as random effects. Bold p-values indicate significant predictors. PAF – premenstrual assessment form short version; RMSSD – root mean square of successive differences.

Discussion

In this pilot study, our aim was to gain a better understanding of the co-occurrence of premenstrual symptoms and vmHRV reductions during the luteal phase of the menstrual cycle and to assess feasibility of daily ambulant assessments. Through daily measurements of vmHRV and premenstrual symptoms in three participants, we discovered parallel fluctuations of PMS symptoms and vmHRV over one menstrual cycle. The PMS symptoms and vmHRV were negatively correlated, with medium to high associations, indicating that the characteristic peak of premenstrual symptoms a few days before menstruation onset is accompanied by a dip in vmHRV.

These findings highlight and support the notion of vmHRV being involved in PMS, which is consistent with previous research (Baker et al., 2008; Matsumoto et al., 2007; Schmalenberger et al., 2023; Zambotti et al., 2013). Importantly, the association between vmHRV and PMS was primarily driven by the psychological symptoms in the PMS questionnaire. The sum score of the physiological symptom scale did not show significant associations with vmHRV in any of the participants. This finding aligns with previous research that consistently associates vmHRV with psychopathological outcomes (Beauchaine & Thayer, 2015). VmHRV has, therefore, been suggested as a peripheral indicator for top-down regulation responsible for flexible attention allocation and inhibiting stress responses to internal and external stimuli (Thayer & Lane, 2000). Decreases in vmHRV, indicative of decreases in this capacity, may have a mediating role by increasing negative affect and stress in response to physiological changes during the luteal phase.

The association between vmHRV and PMS symptoms remains consistent when controlling for variables known to influence PMS. The results also confirm the established association between PMS symptomatology and stress (e.g., Lee & Im, 2016).

The results provide a first exploration of the cyclic changes of vmHRV and symptoms faced during a menstrual cycle in every-day life using daily ambulatory assessment. The findings suggest that conducting an extensive study on this relationship could yield crucial insights into the mechanisms underlying the course of premenstrual symptoms. Such a study appears not only feasible with the current technical resources but also has the potential to open up new approaches for PMS treatment through the regulation of vmHRV.

Acknowledgements

The first author was partly supported by a PhD scholarship from the University of Potsdam (Potsdam Graduate School) with fundings from the Graduate Fund of the State of Brandenburg (Germany). Open access costs were funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – project number 491466077.

During the preparation of this work, the first author utilized ChatGPT 3.5 to enhance the text's readability. Prompts used were aimed at tasks such as “check grammar and spelling in this paragraph.” After employing this tool/service, the author reviewed and edited the content as necessary and assumes full responsibility for the publication's content.

A preprint of this manuscript is available under doi.org/10.22541/au.170000985.55376250/v1 (Blaser et al., 2023a).

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A.3 Manuscript 4

Premenstrual syndrome is associated with differences in heart rate variability and attentional control throughout the menstrual cycle: a pilot study

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Submitted

Premenstrual syndrome is associated with differences in heart rate variability and attentional control throughout the menstrual cycle: a pilot study

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Running head: PMS, HRV and attentional control

Keywords: cognition; self-regulation; attentional control; attention; executive functions; premenstrual syndrome; premenstrual changes; menstrual cycle; heart rate variability; vagal tone

Highlights:

- Menstrual cycle fluctuations in attentional control and HRV depend on PMS severity
- Lower HRV during luteal phase only among high PMS individuals
- Lower attentional control during luteal phase only among high PMS individuals

Abstract

Introduction

Most persons with an active menstrual cycle suffer from a range of aversive symptoms (e.g. reduced ability to concentrate) in the days before their menstruation – the premenstrual syndrome (PMS). Biological and cognitive mechanisms of PMS are poorly understood. It has been shown that vagally mediated heart rate variability (vmHRV), a physiological marker of self-regulation, decreases during the PMS-affected cycle phase (luteal phase) only in individuals with high PMS symptomology. This study investigates the specific associations between vmHRV, PMS symptomology and cognitive self-regulation (attentional control).

Methods

In this between-subject study, participants completed an vmHRV baseline measurement through electrocardiography, a reaction time paradigm to measure attentional control (modified attention network test revised, ANT-R) and filled out a questionnaire regarding impact of PMS as well as current menstrual phase.

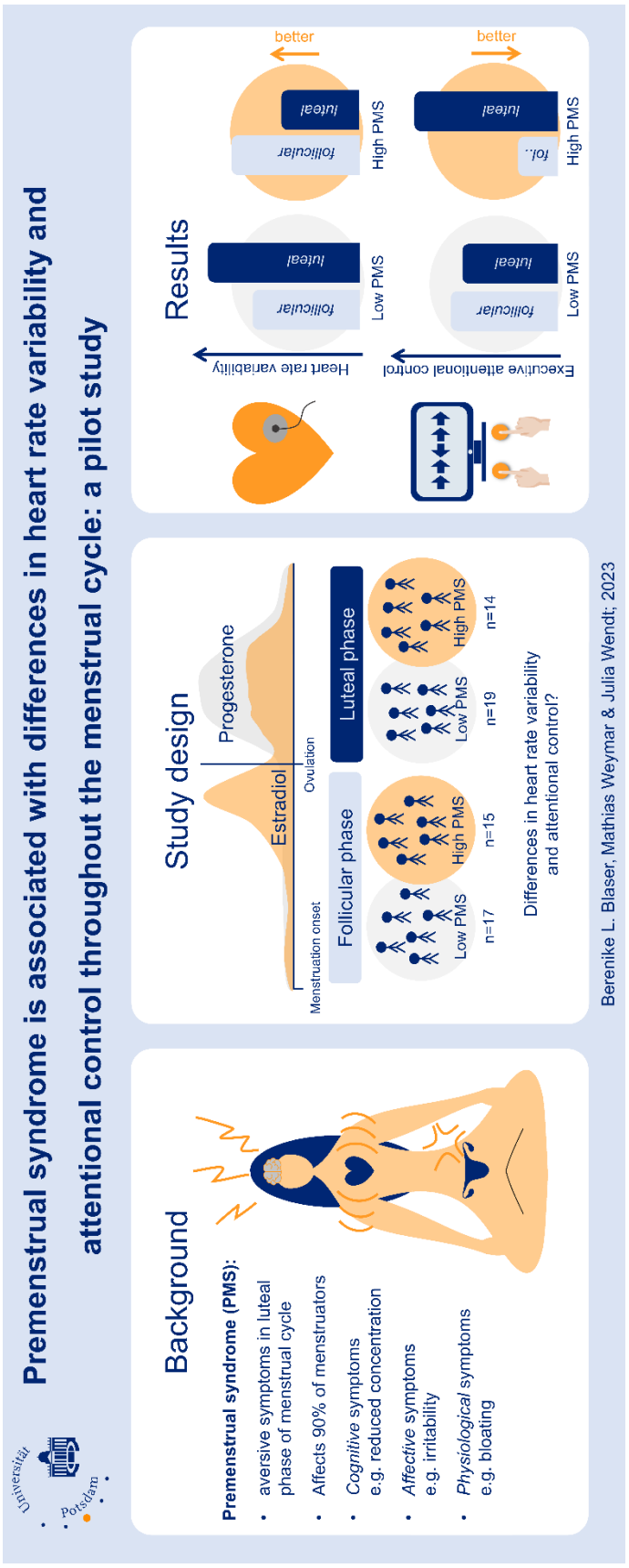
Results

Mixed Model analysis showed interactions effects in the hypothesized direction. VmHRV was decreased during the luteal phase only in individuals with higher PMS. Analogously, performance in the Executive Functioning of the ANT-R task was reduced in the luteal compared to the follicular phase only in individuals with increased PMS symptoms. No effects were found in the Orienting Network Score.

Discussion

The results point in the direction of associations between vmHRV, PMS and self-regulation. This could hint at common underlying mechanisms. Further research, however, must be conducted to examine causal pathways to confirm these associations.

Graphical Abstract



Introduction

Premenstrual syndrome (PMS) is a common and distressing condition that affects up to 90% of individuals with a menstrual cycle ((Tschudin et al., 2010). PMS symptoms can be both physical and psychological in nature, manifesting as breast tenderness, abdominal heaviness, depressive mood, anxiety, irritability, or reduced ability to concentrate during the late luteal phase of the menstrual cycle. These symptoms can persist for up to a week after menstruation onset, significantly impacting an individual's daily functioning and quality of life (Victor et al., 2019) from social life to work performance (American Psychiatric Association, 2013).

The etiology of PMS is unclear so far but due to the definitional relationship of symptoms to the menstrual cycle, a strong link to cycle-dependent hormonal changes has been made in etiological models (Nappi et al., 2022). Progesterone and estradiol are the hormones that show the strongest fluctuations throughout the menstrual cycle. However, there are no systematic differences in progesterone and estradiol serum levels between individuals with and without symptoms (Rapkin & Akopians, 2012). Therefore it is a common assumption that individuals with stronger symptomatology have a higher sensitivity of the central nervous system to these fluctuations in gonadal steroids (Nappi et al., 2022). Below, we will elaborate on how premenstrual syndromes are related to altered activity of inhibitory neurotransmitters and how this relationship may explain the cycle-dependent changes in autonomic nervous system activity and attentional control.

Rapkin and Akopians (2012) present a potential mechanism of differential sensitivity to hormonal fluctuations that may give rise to premenstrual symptomatology. The authors describe how progesterone metabolites, specifically the neuropeptide Allopregnanolone (ALLO) bind to γ-aminobutyric acid (GABA) receptors. GABA is the main inhibitory neurotransmitter in the central nervous system. ALLO's allosteric modulatory effect increases the $GABA_A$ receptor excitability and consequently leads to higher inhibitory GABA activity

(Rupprecht, 2003). ALLO is typically released in response to acute stressors and reduces the activation of the HPA-axis as part of a negative feedback loop and results in an anxiolytic effect (Bali & Jaggi, 2014). Rodent models have shown that chronic exposure to ALLO leads to increased expression of the $GABA_A$ α4-subunit, which is sensitive only to very high amounts of ALLO (Smith et al., 1998). The effect can be viewed as tolerance building towards the anxiolytic effect of ALLO (Turkmen et al., 2011). ALLO withdrawal after prolonged exposure thus renders the modulatory ALLO effects less effective and leads to reduced overall GABAergic activity and enhanced anxiety (Smith et al., 1998).

The menstrual cycle is marked by a distinct increase of expression of progesterone and its readily reduced metabolites such as ALLO in the first half of the luteal phase followed by a dramatic decrease in the week before menstruation onset. Hantsoo and Epperson (2020) suggest that premenstrual symptomatology arises from altered $GABA_A$ reactivity to the ALLO fluctuations throughout the cycle where the symptoms specifically present as a consequence of ALLO withdrawal in the second half of the luteal phase. Evidence for this mechanism stems from studies using saccadic eye movement velocity as an indicator for GABAergic activity (Sundström & Bäckström, 1998), which suggest lowered GABAergic activity in individuals with stronger premenstrual symptoms.

One of the many inhibitory GABAergic pathways in the central nervous system, that is affected by the reduced GABA activity during the late luteal phase in PMS, is the inhibitory functional connectivity of the amygdala and the medial prefrontal cortex (mPFC) (Thayer & Lane, 2009). This functional connectivity is proposed by Thayer and Lane (2000) to be the central mechanism of the central autonomous network (CAN), which mediates general self-regulation, in their model of neurovisceral integration (Thayer & Lane, 2000, 2009). Critically, this network is responsible for the functional inhibition of automated default threat response patterns. Specifically, amygdala activity is related to conditioned behavior patterns (Quirk &

Gehlert, 2003) and triggers automated “threat responses”, which lead to increased sympathetic activity. The mPFC inhibits these dominant patterns in favor of a wider range of deliberate, adequate responses. Importantly, Thayer et al. (2009) propose vagally mediated heart rate variability (vmHRV) as a peripheral marker for the functional capacity of inhibition within this network. This theory is based on a wide variety of research showing consistent associations between vmHRV and behavioral self-regulation measures (Holzman & Bridgett, 2017; Zahn et al., 2016).

GABA is the main inhibitory neurotransmitter within the CAN (Shouman & Benarroch, 2021). Inadequate reactivity to the fluctuation of progesterone and ALLO levels, which alter $GABA_A$ receptor activity (Hantsoo & Epperson, 2020), can therefore render the inhibitory neuronal pathway, which counteracts salient, conditioned behavior patterns, less effective. Additionally, decreased binding in the $GABA_A$ receptor can be found in relevant prefrontal areas in anxiety (Thayer & Friedman, 2002), which is often an integral symptom of PMS. Premenstrual symptoms are also empirically associated to constructs of self-regulation like reward sensitivity (Hou et al., 2020), emotion regulation (Eggert et al., 2017; Eggert et al., 2016; Wu et al., 2016) and stress reactivity (Liu et al., 2017), especially in emotional conflict (Hoyer et al., 2013),

Based on the accumulating evidence, we suggests that the functional capacity of the CAN and vmHRV as proxy measure might be compromised during the symptomatic phase in individuals who experience strong PMS. Indeed, a meta-analysis by Schmalenberger et al. (2019) showed that vmHRV decreases from the follicular to the luteal phase. In individuals, who show PMS symptomatology, these cyclic fluctuations have been found to be more pronounced (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013), whereas individuals with very high emotional premenstrual burden showed decreased vmHRV in both

cycle phases compared to control groups with no or low symptoms (Landén et al., 2004; Matsumoto et al., 2007).

If PMS symptomology is at least partly based on a distinct decrease of GABAergic activity, which leads to a lower engagement of inhibitory control to automated response patterns as proposed by Thayer and Lane's (2009) model of neurovisceral integration, an acute decrease in behavioral capacity for self-regulation should be convergent with the presence of PMS symptoms. Whereas the empirical association between vmHRV and cognitive self-regulation is well researched (Holzman & Bridgett, 2017; Zahn et al., 2016), the association of PMS and cognitive self-regulation is less clear. In a systematic review, Le et al. (2020) found contradicting and unclear results with regard to the association between PMS and behavioral paradigms assessing cognitive performance parameters. The authors report a trend towards reduction in performance in some cognitive tasks for very symptomatic individuals during the luteal phase. Nonetheless, no single cognitive task has consistently shown these associations and the authors point out a severe lack in methodologically sound studies.

Meta-analyses show that the effect size of the association of vmHRV and behavioral laboratory self-regulation tasks are rather small, although slightly higher in the attentional control domain (Holzman & Bridgett, 2017; Zahn et al., 2016). The Executive and Orienting Network score of the attention network test revised (Fan et al., 2009), however, have consistently shown medium to large associations to resting vmHRV (Quintana et al., 2017; Ramírez et al., 2015; Sørensen et al., 2019). We therefore assume that they are closely related to the core activity of the CAN. Further support for this stems from functional imaging studies showing activation in central structures of the CAN such as the mPFC and the anterior cingulate cortex during the flanker conflict solution of the Executive Network task and the suppression of incorrect spatial cueing information of the Orienting Network task (Petersen & Posner, 2012). If the functional capacity of the CAN is compromised (due to the ALLO withdrawal) in

the late luteal phase in high PMS individuals, as hypothesized, fluctuations in the performance in attentional control, namely the ANT-R Executive and Orienting score, throughout the cycle should be observed.

We conducted a pilot study to address the hypothesized associations between vmHRV, PMS and attentional control. Firstly, we aimed to replicate the findings that show a distinct decrease of vmHRV in individuals with high premenstrual symptomatology from the follicular to the symptomatic luteal phase, but not in individuals with low symptomatology. We hypothesized the same pattern in the attentional control tasks of the ANT-R. We further expected both the Orienting and the Executive Network performance to be lower in the luteal phase compared to the follicular phase in individuals suffering from strong PMS, but not in individuals with low PMS.

Material and methods

Sample

Ninety-five participants were recruited from the student populations of the University of Potsdam and the University of Greifswald. Each individual provided written informed consent for a protocol approved by the ethics committee of the University of Potsdam (proposal No 30/22), which is consistent with the Declaration of Helsinki.

Exclusion criteria were adapted from those proposed by Laborde et al. (2017) regarding vmHRV studies (medication or illnesses affecting autonomic functions, competitive athleticism, pregnancy, 30 < BMI or < 18). As the session was introduced as a screening for a larger study protocol, which is described elsewhere (Hufenbach & Wendt, 2022), an active menstrual cycle was no primary inclusion criterion. Of the recruited individuals, 81 reported an active menstrual cycle. Thirteen participants were excluded because their current cycle phase could not be assessed with satisfactory accuracy, or the participant was currently in the ovulatory phase. Three further participants had to be excluded because their accuracy in the

reaction time task was <.85 (Fan et al., 2009). Thus, the final sample included in the analyses consisted of 65 individuals (12 reported hormonal ovulation suppression). The participants had a mean age of 23.06 (±3.74) years.

Procedure

Participants were tested in a laboratory setting. Each individual had their vmHRV measured with an electrocardiogram (ECG), completed a modified version of the ANT-R, and filled out questionnaires to determine the menstrual cycle phase and PMS symptom impact. The total duration of the session was approximately 30 min.

Heart rate variability measurement

VmHRV was measured at rest through ECG for 5 minutes (Laborde et al., 2017). Participants were sitting and instructed to close their eyes during the measurement. The ECG was conducted with hard- and software from BioSign ("HRV-Scanner"; Biosign®, D-85570, Ottenhofen, Germany) through a one-lead ECG at a sampling rate of 500 Hz with a 16-bit resolution. The R-peak detection was completed in a two-step process using the HRV-Scanner software. In the first step, the software automatically detected peaks and highlighted areas of unlikely R-R interval sequences. The second step involved manual evaluation of the highlighted areas followed by the correction of incorrectly identified R-peaks and removal of artifacts and areas including ectopic heartbeats.

Both the root mean square of successive differences (RMSSD in ms) and the high frequency (HF) component of power spectral analysis (in ms^2) as measures of vmHRV were then calculated for the corrected measurements within the BioSign software.

The trustANT

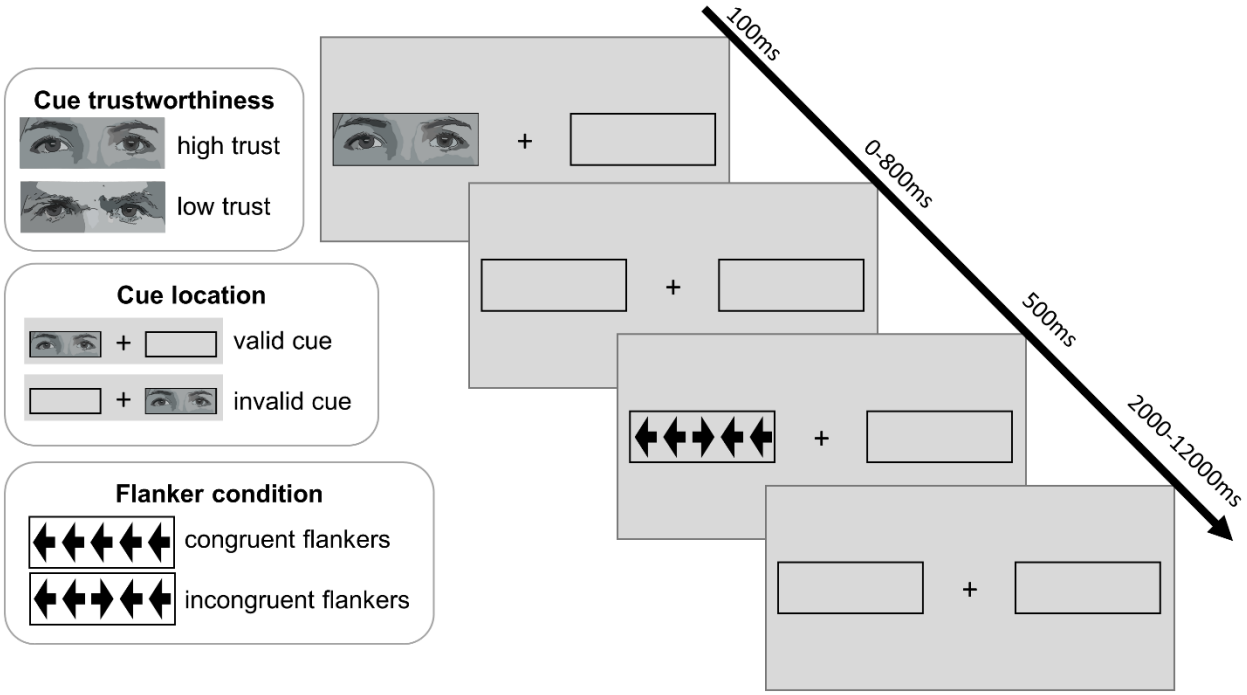
After the first vmHRV assessment, participants completed a modified version of the attention network test revised (ANT-R, Fan et al., 2009) – the trustANT (see Figure 1). In this test, participants have to react to a target arrow and decide in which direction the arrow points.

The target is flanked by two further arrows on each side which either point in the same (valid flankers) or the opposite direction (invalid flankers). The target and flankers appear in a rectangle either on the right or the left side of the screen. A valid (same location as target) or invalid spatial cue indicates on which side the target is likely to appear (valid in 75% of the trials).

In the modified version, this cue consisted of pairs of eyes that were cut from faces of the set by Lischke et al. (2018) to fit the dimensions of the boxes in which the target and flanker later appeared. In a pre-study, the eye images were rated for trustworthiness and the 12 images with the highest and the 12 lowest ratings were used as cues in a 1:1 ratio of trustworthiness. We included this emotional modification of trustworthiness to find potential differential effects of affective cueing (Cohen et al., 2011). We expected a moderation effect of trustworthiness such that the expected decreased attentional control in high PMS during the luteal phase would be potentiated in trials with cues that had been rated low in trustworthiness.

The original ANT-R additionally includes temporal cueing indicating the Alerting Network Score (Fan et al., 2009). For this score, trials with no or double (both boxes flash simultaneously) cues are included in the task. As we did not expect any effects in the Alerting Network, we excluded no and double cue trials from the trustANT. Trials with incorrect responses and reaction times <100ms and >1500ms were excluded from the analysis (Fan et al., 2009).

Figure 1. Schematic of the modified attention network test-revised



Note. During each trial, the target (center arrow) appeared with incongruent or congruent flankers on each side for 500ms. The target presentation was preceded by a pair of trustworthy or untrustworthy eyes flashing for 100ms in one of two spatial cue conditions (valid or invalid cues), followed by a duration of 0, 400 or 800ms. The participant made a response within 1700ms after the onset of the target. The period between the offset of the target and the onset of the new trial varied between 2000 to 12000ms. Due to copywrite reasons, the depicted trustworthiness stimuli were schematics and not original stimuli.

Cycle phase, premenstrual symptoms, and control variables

After the completion of the trustANT, participants completed an online questionnaire on a tablet, assessing the current cycle phase and the impact of premenstrual symptoms. The cycle phase was assessed using the forward-count method, supplemented in part of the sample (n = 10) with the backward-count method. That means that in the session, the participants indicated the first day of their last menses and the average length of their menstruation cycles. From that day, days are counted forward to the testing session to approximate the current cycle phase. Days 1-10 of the cycle were interpreted as the follicular phase (Schmalenberger et al.,

2021). For the luteal phase, the reported average cycle length was subtracted by 10. If the participant was tested during these last 10 days of their cycle, the cycle phase was interpreted as the luteal phase (Schmalenberger et al., 2021). Any test sessions that took place outside of these two phases were excluded from the analysis. If participants reported regular fluctuations in their cycle length of more than 5 days and were not currently in the follicular phase, they were also excluded from the analysis.

The impact of premenstrual symptoms was quantified with a German translation of the Premenstrual Symptoms Impact Survey (PMSIS, Wallenstein et al., 2008). The questionnaire consists of six items assessing the impact of premenstrual symptoms during the last premenstrual phase (e.g. In your last premenstrual phase, how often did your symptoms limit your ability to concentrate?). Participants respond on a 5-point Likert scale from “never” to “always”. The questionnaire shows good convergent validity with the diagnostic criteria of the DSM-IV and excellent internal consistency. The sum score of the items was translated to a scale score ranging from 0 to 100, as proposed by Wallenstein et al. (2008).

The online questionnaire also included the control variables age and study program. Furthermore, information regarding hormonal contraceptive (HC) usage was provided by each participant.

Statistical analyses

All statistical analyses were conducted in R version 4.2.2. BoxCox transformations as well as visual inspections of the distributions were applied to all continuous variables to ensure normal distribution.

Hypotheses regarding reaction times were tested using linear mixed models. In these models, data points were clustered per participant by introducing participant intercepts as random effects. In an iterative model selection process, predictors were consecutively added to the model. Each model was then compared for data fit to the respective simpler model using

an analysis of variance (ANOVA). A predictor was kept for the model if it significantly improved the fit with an error probability of less than .05. If two models were equal regarding degrees of freedom, better model fit was indicated by a lower Akaike information criterion (primary) and Bayesian information criterion (secondary). Predictors included CUE VALIDITY, FLANKER CONGRUENCE, CUE TRUSTWORTHINESS, MENSTRUAL PHASE, PREMENSTRUAL IMPACT SCORE and their interactions, as well as AGE and HORMONAL CONTRACEPTIVE USAGE as control variables. The PMS x CYCLE PHASE x CUE/FLANKER interactions were used to test the main hypotheses. If a three-way interaction was significant and included in the final model, the direction of the effect was verified in post-hoc analysis and visual inspection of the effects.

To test the hypothesis regarding vmHRV fluctuations, a similar linear regression model approach was used. In a hierarchical model selection process, the predictors MENSTRUAL PHASE, PMSIS-SCORE, the MENSTRUAL PHASE x PMSIS interaction, AGE, and HC (control variables) were added to the model. Each model was then compared to the next simpler model. If the total explained variance improved, the more complex model was kept. To prove the hypothesis, the PHASE x PMSIS interaction had to be a significant predictor in the final model. The direction of the effect was then verified through post-hoc comparisons and visual inspection.

Results

BoxCox analyses (Box & Cox, 1964) indicated logarithmic transformations of the vmHRV data (both RMSSD and HF power). For the PMSIS scores, the λ-value of the BoxCox transform indicated no necessary transformation. However, a visual inspection showed non-normal distribution with an accumulation of values at the lower end of the scale, indicating floor effects. To be able to still conduct the analyses with the PMSIS scores, a median split was applied creating a high PMS (n = 29) and a low PMS (n = 36) group. The group factor was dummy-coded for the analyses.

Comparability of the groups. A Chi-square test revealed no significant deviations from chance of the distribution of the group sizes high PMS/ follicular phase, high PMS/ luteal phase, low PMS/ follicular phase, and low PMS/ luteal phase, $\chi^2(1, N = 65) = 0.01$, $p = .91$. Age and HC use, however, differed between the groups. An ANOVA showed older participants in the high PMS group, $F(1, 63) = 10.16$, $p = .002$, and in the group that was tested during the luteal phase, $F(1, 63) = 4.75$, $p = .03$. Although a Cochran-Mantel-Haenszel test showed no statistically significant dependence of the factors cycle phase and PMS group with HC use, $\chi^2(1, N = 65) = 3.58$, $p = .059$, the usage varied strongly between the groups (see Table 1). Therefore, AGE and HC USE were included as control variables in further analyses.

Table 1. Characterization of the four groups

	Cycle phase	n	Age in years	HC usage	log(RMSSD in ms)	log(HF in ms^2)	Executive Network Score in ms	Orienting Network Score in ms
Low PMS	**Follicular**	17	21.18 ± 3.43	41.2%	3.47 ± 0.50	6.25 ± 1.14	136.04 ± 67.05	97.86 ± 50.23
	Luteal	19	22.53 ± 3.42	15.8%	3.92 ± 0.66	6.87 ± 1.51	131.38 ± 35.78	100.38 ± 51.56
High PMS	**Follicular**	15	23.20 ± 3.53	6.6%	3.75 ± 0.35	6.56 ± 0.91	108.46 ± 31.39	103.02 ± 63.00
	Luteal	14	25.93 ± 3.29	7.1%	3.49 ± 0.79	5.93 ± 1.69	151.15 ± 46.57	99.14 ± 45.63

Note. The table shows means and standard deviations of the measured parameters in the four groups. PMS - premenstrual syndrome; HC - hormonal contraception; RMSSD - root mean square of successive differences; HF - high frequency component of spectral analysis.

Reaction time analysis. The analysis of reaction times yielded the following final mixed model:

Reaction time ~ FLANKER + CUE + PMS GROUP + MENSTRUAL PHASE +

PMS GROUP : FLANKER : MENSTRUAL PHASE + (1 | participant) .

The results are displayed in Table 2. The PMS GROUP X CUE X MENSTRUAL PHASE interaction was not included in the final model. This indicates that there are no differences in the Orienting Network score between cycle phases and PMS impact groups.

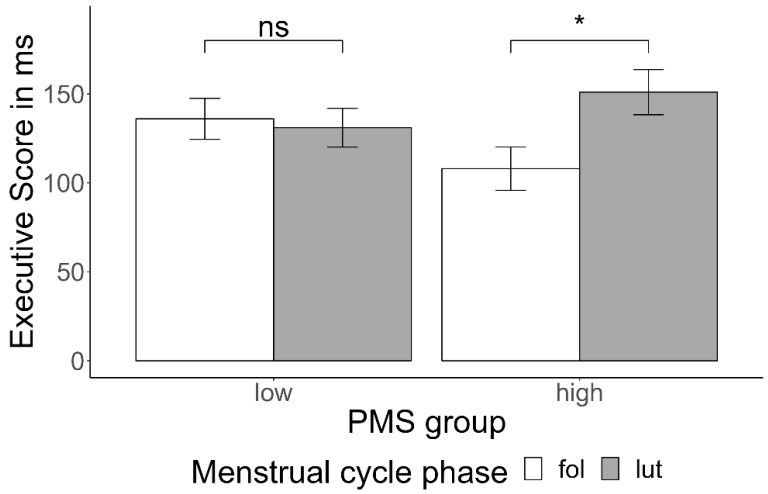
The model, however, included the PMSIS GROUP X FLANKER X MENSTRUAL PHASE interaction. The interaction was a significant predictor in the final model, $t(5893) = 3.99$, $p < .001$) indicating a difference in the Executive Network score depending on PMS impact and cycle phase. Post-hoc contrast analysis and visual inspection of the effect (see Figure 2) confirmed that the effect was in the expected direction. Individuals in the high PMS group, who were currently in the luteal phase, were slower in incongruent flanker trials than high PMS individuals in the follicular phase, $t_{ratio}(61) = 2.43$, $p < .05$. In the low PMS group, individuals in the follicular and luteal phase showed no such difference in the incongruent flanker trials, $t_{ratio}(61) = -0.30$, $p = .77$.

Table 2. Results of the final linear mixed model predicting reaction time

	Reaction time		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	552.49	520.35 – 584.63	**<0.001**
PMS group	-9.62	-41.50 – 22.25	0.554
phase	-44.76	-89.75 – 0.23	0.051
Flanker	105.71	96.98 – 114.43	**<0.001**
Cue	87.21	78.05 – 96.37	**<0.001**
flanker × cue	32.31	19.05 – 45.57	**<0.001**
(PMS group [low] × flanker) × phase	9.77	-3.49 – 23.03	0.149
(PMS group [high] × flanker) × phase	29.87	15.18 – 44.55	**<0.001**
Random Effects			
σ^2	12447.87		
$\tau_{00\ vpn}$	8275.60		
ICC	0.40		
N_{vpn}	65		
Observations	5933		
Marginal R^2 / Conditional R^2	0.227 / 0.536		

Note. PMS – premenstrual syndrome.

Figure 2. Interaction effect of menstrual phase and premenstrual symptoms on the Executive Network Score of the ANT-R



Note. The high/low PMS groups were created by conducting a median split on the Premenstrual Syndrome Impact Scores. For visualization purposes, the Executive Network composite Score was calculated. ANT-R – revised attention network test; PMS - premenstrual syndrome; fol - follicular phase; lut - luteal phase.

CUE TRUSTWORTHINESS did not appear as a main effect or in any interaction term of the final model, nor was it a significant predictor of reaction time in any iteration.

Heart rate variability analysis. The final model predicting the RMSSD included only the PMS GROUP X CYCLE PHASE interaction, as well as the main effects. The results can be found in Table 3. None of the factors AGE, HC USAGE and interactions of AGE with PMS GROUP / CYCLE PHASE and of HC USAGE with PMS GROUP / CYCLE PHASE significantly improved the explained variance of the model. As the final model only included the interaction of the contrast-coded factor CYCLE PHASE and the dummy-coded factor PMS GROUP, the result was verified in an ANOVA, $F(2, 62) = 3.341$, $p = 0.042$. Visual inspection of this effect (see Figure 3a) confirmed the expected direction. Individuals in the high PMS group who were tested in the luteal phase had lower vmHRV than high PMS individuals in the follicular phase. Low PMS individuals showed similar vmHRV levels in both phases. Post-hoc analysis, however, showed that none of the individual group differences were significant, which indicates that the

significant interaction term is driven by the difference in slope coefficients. A marginal trend analysis comparing the phase difference slopes for both groups revealed, that the slope from the follicular to the luteal phase was significantly more negative in the high than the low PMS group, with a difference in slopes of -0.36, $t_{ratio}(62) = -2.40$, $p < .05$.

With regard to the HF component of power spectral analysis, none of the tested independent variables and their interaction terms constituted significant predictors. This is somewhat surprising, as the HF component and the RMSSD are both viewed as indicators of respiratory sinus arrythmia, which are usually highly correlated. Indeed, the correlation coefficient was extremely high in this sample, $r_{\log(RMSSD),\, \log(HF)}(63) = .92$, $p < .001$. For comparison reasons, the results for a model predicting the HF component equivalent to the model predicting the RMSSD can be found in Table 4. Plotting of the data showed that there is a similar effect as in the RMSSD data, but the variance was slightly larger (see Figure 3b), which might hide the effect in the statistics and lead to an only marginally significant interaction effect. A trend analysis showed that the slope between follicular and luteal phase was marginally more negative in the high compared to the low PMS group with a slope difference of -0.63, $t_{ratio}(62) = -1.86$, $p = .067$.

Table 3. Results of the final linear mixed model predicting the RMSSD

	log(RMSSD)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	3.66	3.51 – 3.80	**<0.001**
PMS group	-0.05	-0.26 – 0.16	0.615
Phase	0.05	-0.10 – 0.20	0.512
PMS group × phase	-0.25	-0.46 – -0.04	**0.020**
Observations	65		
R^2 / R^2 adjusted	0.101 / 0.057		

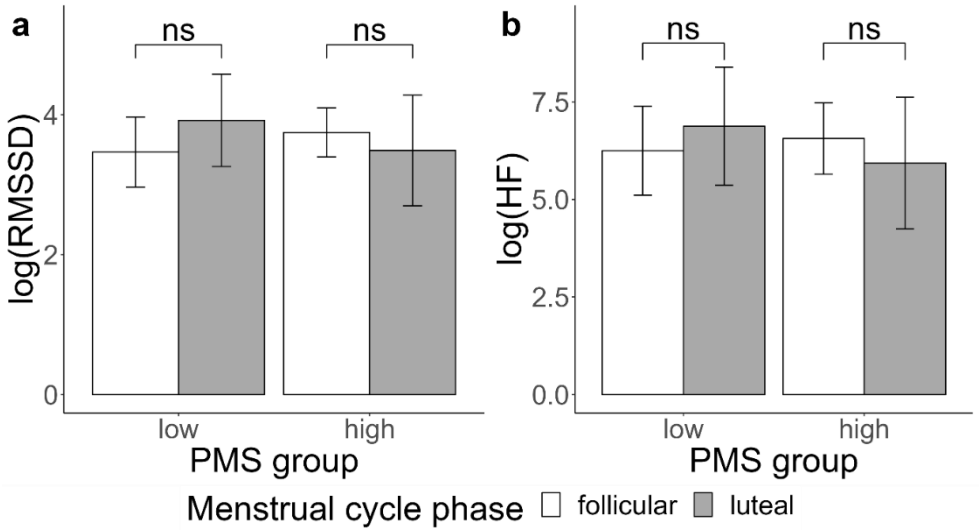
Note. RMSSD – root mean square of successive differences; PMS – premenstrual syndrome.

Table 4. Results of the final linear mixed model predicting the HF Power

	log(HF power)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	6.40	6.07 – 6.74	**<0.001**
PMS group]	-0.22	-0.70 – 0.25	0.352
Phase	-0.00	-0.34 – 0.34	0.997
PMS group × phase	-0.44	-0.92 – 0.03	0.067
Observations	65		
R^2 / R^2 adjusted	0.068 / 0.022		

Note. HF – high frequency component of spectral analysis; PMS – premenstrual syndrome.

Figure 3. Heart rate variability by cycle phase and premenstrual symptom impact



Note. PMS groups were created through a median split of the Premenstrual Syndrome Impact Score. The boxplots show mean values; the whiskers show standard deviations. PMS - premenstrual syndrome; RMSSD - root mean square of successive differences; HF - high frequency component of power spectral analysis.

Discussion

The goal of the present study was to investigate associations between menstrual cycle phase, PMS symptomatology and attentional control as well as vmHRV. We hypothesized reduced attentional control and vmHRV in individuals with high PMS in the luteal phase compared to high PMS individuals in the follicular phase. We also expected no difference in attentional control in low PMS individuals in both phases. We found this reduced attentional control during the luteal phase in high PMS individuals in the luteal compared to high PMS individuals in the follicular phase in the Executive Network of attention (flanker task) but not in the Orienting Network (spatial cueing task). The factor trustworthiness did not moderate the present results. We also found a significant interaction term, indicating a reduced RMSSD in the luteal compared to the follicular phase only in high PMS individuals. The post-hoc comparison yielded no significant group differences in the RMSSD but different slopes in the

expected direction. In the HF component, the interaction term was only marginally significant, but the same trend was also visible when plotting the data.

The significant interaction term of group and phase in RMSSD and the marginally significant interaction term in the HF component is consistent with the effects found in previous studies (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013). The post-hoc testing of the interactions did not reveal significant subgroup differences. This is likely not due to the effect not being there, but rather the small sample. The effect sizes between the phases in the high PMS group were medium (d_{RMSSD} = .44 and d_{HF} = .49). To confirm these effects in post-hoc testing in a between-subject study, a G*Power (Faul et al., 2007) analysis revealed a necessary sample size of n = 65 (compared to our samples of about 15) in each group to find the effect with a power of .8. However, we did find significant differences in slopes between the two phases. When visually inspecting the effect, it is noticeable that this effect was not only driven by lower vmHRV in high PMS individuals in the luteal phase compared to individuals in the follicular phase, but also by slightly higher vmHRV values in low PMS individuals in the luteal compared to the follicular phase. A meta-analysis showed overall lower values in vmHRV during the luteal phase (Schmalenberger et al., 2019). Some previous studies already show evidence that this reduction is driven mostly by symptomatic individuals and/or cycles (Baker et al., 2008; Schmalenberger et al., 2023; Zambotti et al., 2013). In this between-subject design, the higher vmHRV found in low PMS individuals is difficult to interpret, but the results do, however, support previous research by showing a clear contrast in vmHRV fluctuations between high and low PMS individuals. The results offer further evidence for the perspective of compromised CAN activity during the luteal phase in PMS affected individuals/cycles.

We were able to find clear reaction time effects in the expected directions in the ANT-R in one of the two measures. The results indicated reduced performance in the Executive Network in high PMS individuals during the luteal phase compared to high PMS individuals

in the follicular phase. There was no difference between low PMS individuals in the luteal vs. the follicular phase. We were able to find this effect due to the higher power offered by the mixed model approach allowing us to include each trial in the analysis. It is unclear why the domain of Executive attentional control, but not Orienting attentional control was affected by cycle phase and PMS impact interaction. In their meta-analysis, Le et al. (2020) found similar cycle phase effects in about half of the included studies investigating cognitive effects. The findings are somewhat surprising, since the Orienting Score of the ANT-R has previously shown larger associations with vmHRV, which is considered a peripheral marker for CAN activity (Thayer et al., 2009), than the Executive Function Score (Ramírez et al., 2015; Sørensen et al., 2019), although both measures require a point of targeted inhibition and are thus considered to be associated to CAN activity. Further research into the mechanisms and courses of action is necessary to unravel the effects that the menstrual cycle and premenstrual symptoms have on cognitive functions.

All in all, both the effect in one attentional control domain and in vmHRV support our hypothesis of a compromised function of the self-regulatory functions within the CAN during the luteal phase in individuals who suffer more from PMS symptoms.

Despite the promising results, some limitations need to be considered. One limitation of the study is that the individuals in the high PMS groups were older than those in the low PMS groups and had lower contraceptive use percentages. Although neither of these control variables explained a significant amount of variance in the models, some of the group effects might be due to these variables and could thus have produced redundancy in the data. Additionally, the forward/backward-count method without physiological confirmation to determine current cycle phases is not the best way to assess the phases (Schmalenberger et al., 2021). While the luteal phase is somewhat constant in length, the follicular phase length varies strongly both inter- and intra-individually, which could affect predicting the onset of the next

menses. Lastly, menstrual cycle changes inherently represent individual within-subject changes. Therefore, it was suggested that studying the menstrual cycle (e.g. (Schmalenberger et al., 2021) using within-subject designs would be more optimal.

Conclusion. Taken together, we have proposed that premenstrual symptoms are a function of fluctuating capacity within the central autonomous network, as described in the neurovisceral integration model. In this pilot study, we observed lower attentional control in one of two measurements among high PMS individuals in the luteal phase compared to high PMS individuals in the follicular phase, with no such difference among low PMS individuals in both phases. A similar trend was noticeable, with lower vmHRV during the luteal phase observed only in high PMS individuals, supporting previous research (Baker et al., 2008; Matsumoto et al., 2007; Zambotti et al., 2013). Both of these findings align with the neurovisceral integration perspective on PMS. However, the study design has some limitations that need to be addressed in future studies.

Acknowledgements

Berenike Blaser was supported by a PhD scholarship from the University of Potsdam (Potsdam Graduate School) with fundings from the Graduate Fund of the State of Brandenburg (Germany). The project was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) [grant numbers 491466077, WE5873/1-2].

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A.5 Manuscript 5

Smartphone-based heart rate variability biofeedback training improves premenstrual and depressive symptoms as well as anxiety/stress symptoms and attentional executive control: a pilot study

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Under review in Frontiers in Digital Health

Smartphone-based heart rate variability biofeedback training improves premenstrual and depressive symptoms as well as anxiety/stress symptoms and attentional executive control: a pilot study

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Running head: Smartphone-based Heart Rate Variability Biofeedback for PMS

Keywords: smartphone photoplethysmography, mHealth, heart rate variability, biofeedback, premenstrual syndrome, stress, depression, attentional control

Abstract

Introduction

Heart rate variability biofeedback (HRVB) is a well-studied intervention known for its positive effects on emotional, cognitive, and physiological well-being, including relief from depressive symptoms. However, its practical use is hampered by high costs and a lack of trained professionals. Smartphone-based HRVB, which eliminates the need for external devices, offers a promising alternative, albeit with limited research. Additionally, premenstrual symptoms are highly prevalent among menstruating individuals, and there is a need for low-cost, accessible interventions with minimal side effects. With this pilot study, we aim test, for the first time, the influence of smartphone-based HRVB on depressive and premenstrual symptoms, as well as anxiety/stress symptoms and attentional control.

Methods

Twenty-seven participants with above-average premenstrual or depressive symptoms underwent a 4-week photoplethysmography smartphone-based HRVB intervention using a waitlist-control design. Laboratory sessions were conducted before and after the intervention, spaced exactly 4 weeks apart. Assessments included resting vagally mediated heart rate variability (vmHRV), attentional control via the revised attention network test (ANT-R), depressive symptoms assessed with the BDI-II questionnaire, and stress/anxiety symptoms measured using the DASS questionnaire. Premenstrual symptomatology was recorded through the PAF questionnaire if applicable. Data analysis employed linear mixed models.

Results

We observed improvements in premenstrual, depressive, and anxiety/stress symptoms, as well as the Executive Functioning Score of the ANT-R during the intervention period but not during the waitlist phase. However, we did not find significant changes in vmHRV or the Orienting Score of the ANT-R.

Discussion

These findings are promising, both in terms of the effectiveness of smartphone-based HRVB and its potential to alleviate premenstrual symptoms. Nevertheless, to provide a solid recommendation regarding the use of HRVB for improving premenstrual symptoms, further research with a larger sample size is needed to replicate these effects.

Introduction

Heart rate variability biofeedback (HRVB) is a well-researched intervention that has demonstrated effectiveness in a wide range of areas (Lehrer et al., 2020), including relieving anxiety and stress (Goessl et al., 2017), ameliorating depression (Pizzoli et al., 2021), improving sleep (Stein & Pu, 2012), alleviating asthma symptoms (Lehrer et al., 2004), and even enhancing sports performance (Jiménez Morgan & Molina Mora, 2017). However, despite its potential, this user-friendly method has seen limited practical implementation. This can be attributed, in part, to the high costs associated with necessary stationary and mobile electrocardiography (ECG) devices, as well as the required training and expertise of staff members entrusted with its administration, which further strains healthcare systems. Encouragingly, smartphone apps capable of assessing heart rate through the device's camera, without additional equipment, are promising to yield similar results (Yuda et al., 2020). Nevertheless, empirical validation of smartphone-based HRVB applications remains limited. This study aims to validate the effectiveness of an HRVB intervention applied through smartphones, specifically targeting the alleviation of depressive symptoms, a well-documented outcome of conventional HRVB. Additionally, we explore a novel application of HRVB for premenstrual symptoms.

HRVB is a method in which vagally mediated heart rate variability (vmHRV), an indicator of parasympathetic activity (Laborde et al., 2023; Penttilä et al., 2001), is systematically increased through slow, controlled breathing and visual feedback of heart rate oscillations. The primary driving mechanism involves slow-paced breathing at 0.1 Hz or an individual resonance frequency (Laborde, Allen, Borges, Iskra, et al., 2022). It is believed to exert its various beneficial effects through bottom-up modulation of a neural network described by Thayer and Lane (2000) in their neurovisceral integration model.

This model delineates a network of interconnected structures known as the central autonomic network (CAN), responsible for integrating information and regulating appropriate responses. At the core of this regulatory network, Thayer and Lane (2009) propose an inhibitory connectivity between the medial prefrontal cortex (mPFC) and the amygdala. The stronger this connectivity, the greater an individual's capacity to downregulate a presumed default stress response and deliver a precise and personalized reaction to internal and environmental demands. VmHRV is considered both a peripheral index for this capacity and a reciprocal element within this network (Thayer et al., 2009). This theory is grounded in a substantial body of evidence linking low vmHRV to psychopathology (Heiss et al., 2021) and reduced performance in cognitive self-control tasks (Holzman & Bridgett, 2017; Zahn et al., 2016).

When practiced over several weeks, HRVB enhances the capacity of the CAN through coherence phenomena involving the synchronization of breathing rate, blood pressure, and heart rate oscillations (Sevoz-Couche & Laborde, 2022). These phenomena contribute to several bottom-up routes. The most crucial of these routes involve input into the CAN through baroreceptors via the nucleus of the solitary tract, stretch receptors in the lungs, and a vagal afferent pathway (Lehrer & Gevirtz, 2014; Noble & Hochman, 2019; Sevoz-Couche & Laborde, 2022).

HRVB interventions have demonstrated the potential to improve various affective and cognitive outcomes associated with CAN capacity, including depression (Pizzoli et al., 2021) and anxiety (Goessl et al., 2017). Our study aims to expand these effects in the context of a smartphone-based intervention. While vmHRV is reliably associated with cognitive outcomes, particularly executive functions, the impact of HRVB on these variables is less clear (Tinello et al., 2022). In a systematic review, Tinello et al. (2022) found that existing effects are primarily observed in the domain of attentional control and are often found in patient

populations or individuals experiencing high levels of stress. Given that attention is strongly linked to vmHRV, we also investigate the effect of HRVB on attentional control using the revised Attention Network Test (ANT-R, Blaser et al., 2023a; Fan et al., 2009).

Expanding on these replications, we further investigate HRVBs impact on premenstrual syndrome (PMS), a highly prevalent condition characterized by a diverse collection of psychological and physiological symptoms. These symptoms typically manifest in individuals with active menstrual cycles during the week leading up to menstruation and tend to subside shortly after. As many as 90% of menstruating individuals regularly encounter at least one symptom of PMS (Tschudin et al., 2010). Commonly reported symptoms encompass heightened stress reactivity, anxiety, depressive mood, breast tenderness, and abdominal pain (Allen et al., 1991).

As a component of the gender data gap, premenstrual syndrome (PMS) remains significantly under-researched (Zehravi et al., 2023). Even today, treatment options remain limited, primarily centered on addressing specific psychological or physiological symptoms through hormonal cycle suppression or antidepressant medication in both clinical practice and research (Ryu & Kim, 2015). Both of these approaches are associated with substantial adverse side effects (Price et al., 2009; Robinson et al., 2004; Skovlund et al., 2016).

Premenstrual symptoms have been linked to cyclic fluctuations in vagally mediated heart rate variability (vmHRV) (Schmalenberger et al., 2019). Individuals who experience more severe symptoms tend to exhibit a pronounced reduction in vmHRV during the luteal phase of their menstrual cycle, coinciding with the experience of these symptoms (Matsumoto et al., 2007). Matsumoto et al. (2007) have suggested a potential causal relationship in this regard.

One possible explanation for this phenomenon lies in a metabolite of progesterone, one of the main fluctuating gonadal steroids during the menstrual cycle. Sundström-Poromaa et al.

(2003) have identified this metabolite, namely Allopregnanolone (ALLO), an allosteric Gamma-Aminobutyric Acid (GABA) receptor modulator as a likely cause of the experience of premenstrual symptoms (Hantsoo & Epperson, 2020). As ALLO operates on the GABAergic system, the proposed CAN in the neurovisceral integration theory (Thayer & Lane, 2000, 2009) might also be affected. In this theory, successful adaptation relies on inhibitory connectivity between the mPFC and the amygdala. The strength of these connections, which are part of the central nervous system's inhibitory GABAergic network, are influenced by GABA levels in the mPFC (Delli Pizzi et al., 2017). Compromised inhibition in this circuit due to ALLO withdrawal and/or maladaptive ALLO responses may lead to a compromised self-regulatory capacity of the organism on both affective and physiological levels, as observed in PMS.

Following this line of reasoning, HRVB is a promising candidate to counteract some of these effects through two mechanisms. Firstly, the most pronounced effects of HRVB are observed in stress management (Goessl et al., 2017). If stress throughout the cycle causes irregularities in the ALLO system during the premenstrual phase, reducing stress throughout the cycle may prevent some of the symptom development. Existing evidence already suggests that various relaxation techniques can positively impact PMS (Jose et al., 2022). Secondly, HRVB is assumed to increase the inhibitory capacity of the mPFC over the amygdala and, as a result, enhance the inhibition of the default stress response (Schumann et al., 2021). Although GABAergic transmission may be compromised during the premenstrual phase, boosting the baseline inhibitory strength between these two brain structures could raise inhibition levels. This might make it less likely for a sudden drop to cross the threshold to trigger symptoms that cause significant distress.

Initial studies have already provided evidence of the effectiveness of HRVB for mental health outcomes when administered through smartphones. Previous studies that utilized smartphone-based HRVB interventions to improve outcomes like depressive or anxiety

symptoms, however, have typically relied on external devices connected to the smartphone via Bluetooth. These devices include wearable ECG-measuring breast straps (Chung et al., 2021; Herhaus et al., 2022; Lin, 2018; Schumann et al., 2022; Schumann et al., 2021) or earlobe-clip pulse measuring devices (Economides et al., 2020; Minen et al., 2021; Schuman et al., 2023). Acquiring a wearable device presents a significant obstacle for potential HRVB users.

Smartphone cameras can now measure heart rate when the user places a finger on the camera. An application activates the camera flash and analyzes the red-to-green ratio in the image at high frequency, generating pulse curves. This process is known as photoplethysmography (PPG) and closely resembles the process behind the optical sensors that emit infrared or green light in commonly used pulse measurement devices. Yuda et al. (2020) suggest that the heart rate variability indicator used in smartphone apps, which they term 'pulse rate variability' as measured through PPG, may contain distinct information compared to its ECG-measured counterpart. Nevertheless, recent research has demonstrated very high correlations between HRV parameters measured through ECG and PPG of over .9 (van Dijk et al., 2023), even though the reliability is somewhat dependent on sampling rate of the device (Guede-Fernández et al., 2020). Moreover, the associations with mental health outcomes are also evident when assessing vmHRV via PPG using the smartphone camera (Liu et al., 2020). This supports the use of PPG as a foundation for HRVB.

In this study, we investigated the novel application of a 4-week smartphone-based HRVB intervention using PPG via smartphone camera instead of an external device for alleviating depressive and premenstrual symptoms. Our sample comprised young adults who either exhibited above-average PMS or depressive symptoms. Additionally, we examined the impact of the intervention on various other outcomes, including anxiety and stress symptoms, attentional control, and vmHRV.

Methods

Participants

A G*Power analysis revealed that a sample size of 40 was necessary to detect an effect size of .4, based on a meta-analytic effect of HRVBFB on depressive symptoms reported by Pizzoli et al. (2021), with a power of .8 and a one-tailed alpha error probability of .05. However, due to recruitment difficulties and resourcing issues by the company providing the app during the extended recruitment period, we were unable to reach our target of 40 participants.

Twenty-nine participants were recruited from the student population of the University of Potsdam for this study. Recruitment was carried out via the online recruiting platform for study participants of the cognitive sciences (Sona Systems, https://www.sona-systems.com) of University Potsdam as well as via flyers on campus and advertisement in university mailing lists. Inclusion criteria required participants to have either above-average premenstrual symptomatology (short version Premenstrual Assessment Form, PAF20 $\geq$ 50), depressive symptoms that indicate at least minimal depression (Beck's Depression Inventory, BDI-II $\geq$ 9), or both. Participants who exceeded a BDI-II score of 14 received a consultation with a clinical psychologist to discuss possible necessary treatment prior to study participation.

Exclusion criteria included factors proposed by Laborde et al. (2017) such as pregnancy, heart rate-altering chronic diseases or medication. We additionally excluded competitive athletes to avoid ceiling effects, since this population has systematically increased vmHRV (Da Silva et al., 2015). Participants currently in any treatment or planning significant lifestyle changes during the period of study participation were also excluded. In addition, participants were required to be at least 18 years of age.

All participants provided informed consent prior to their inclusion for a study protocol approved by the ethics committee of the University of Potsdam (No. 30/2022). Participants

who met the inclusion criteria were eligible for study participation and received either course credits or monetary compensation.

Procedure

The study protocol was preregistered on Open Science Framework (osf.io/68fzq). The study procedure began with an online screening questionnaire to determine eligibility based on inclusion and exclusion criteria, as well as to assess sociodemographic factors such as age, gender, study program, and BMI. Participants were also required to provide information about their menstrual cycle to ensure that the appropriate questionnaires were administered. Additionally, participants were asked to provide their email address for communication throughout the study.

All eligible participants took part in a 4-week biofeedback intervention during which they practiced smartphone-based HRVB for at least 5 minutes every day. After the first and second week, participants additionally received an online coaching session to improve their technique and address any technical or other difficulty they encountered.

Before and after the 4-week intervention, participants completed laboratory sessions that were scheduled at the same time, exactly 4 weeks apart (T1 and T5). During these sessions, various measures were collected, including vagally mediated heart rate variability by ECG, attentional control using the reaction time paradigm ANT-R (Fan et al., 2009), and self-reported symptoms of depression, premenstrual syndrome (PMS), and anxiety/stress via questionnaires.

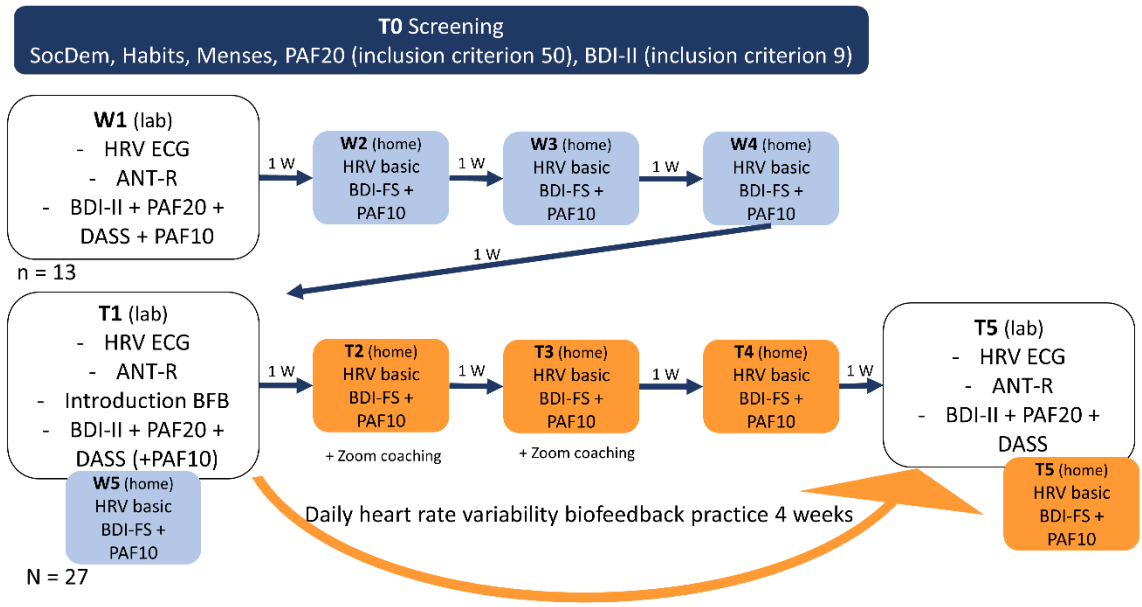
To ensure balanced allocation of participants to the waitlist group, half of the participants within each group of inclusion criteria (depression, PMS, or both) were pseudo-randomly assigned to the waitlist group. The waitlist group additionally completed a laboratory session four weeks prior to study inclusion, during which the same parameters were assessed (W1).

Throughout the study, participants completed short versions of the depressive and premenstrual symptom questionnaires and underwent a photoplethysmography based HRV measurement at home using the biofeedback app, each week on the same day and at the same time that they chose (W2-W4 and T2-T4). Participants received automated email reminders and a link to the respective questionnaire to ensure compliance. The results of these measurements are not analysed and reported in this report. Figure 1 provides an overview of the study procedure.

All participants received an introduction to smartphone-based HRVB during T1. The waitlist group received a tutorial on conducting vmHRV measurements at home with the app during W1, while the intervention-only group received this tutorial during T1.

Since PMS occurs only once during each menstrual cycle, and cycle lengths can vary significantly both between and within individuals, we included a follow-up measurement of the online questionnaire 4 weeks after T5. If a participant reported no new menstruation onset during the last two weeks of the intervention, indicating no new premenstrual phase, we used the PMS values reported in the follow-up measurement as the post-intervention values, describing the next premenstrual phase after completing the intervention.

Figure 1. Study procedure



Note. SocDem – sociodemographic information, PAF10 – premenstrual assessment form 10 item version; PAF20 – premenstrual assessment form 20 item version; BDI-II – Beck's Depression Inventory; BDI-FS – Beck's Depression Inventory short version; ANT-R – attention network test-revised; DASS – Depression Anxiety Stress Scale; HRV ECG – heart rate variability measurement in lab (electrocardiography); HRV basic – measurement at rest at home on phone (photoplethysmography); W – week.

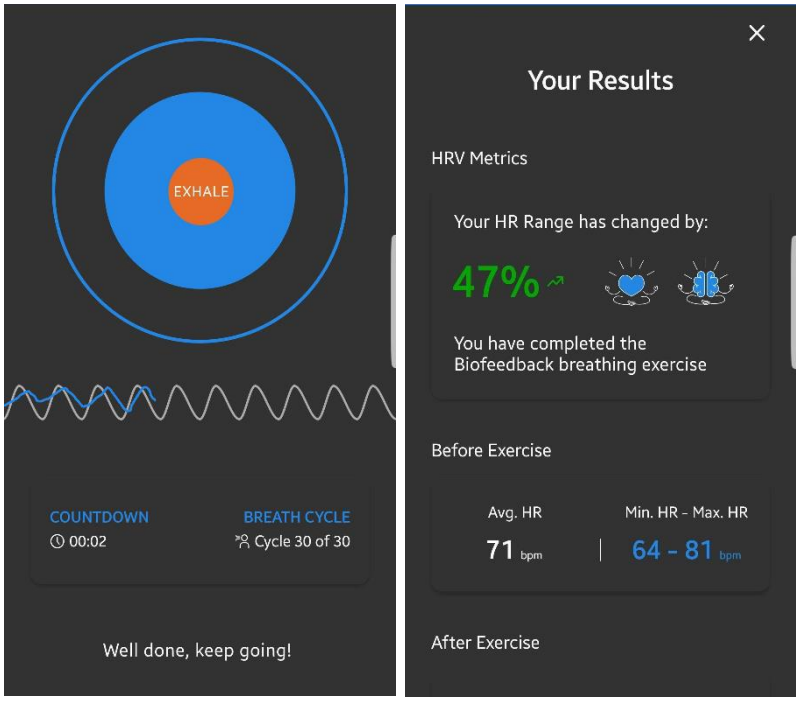
Smartphone-based heart rate variability biofeedback

The HRVB intervention used in this study was app-based and built with the software development kit (SDK) provided by Kenkou GmbH. The app measured HRV via photoplethysmography (PPG), whereby participants placed their index finger on the camera lens and a flash was used to illuminate the tissue. The camera measured the intensity of blood flow, and a peak detection algorithm was used to detect heartbeats.

Before each biofeedback session, participants underwent a 1-minute baseline measurement to assess their current state, which allowed the feedback to be adjusted

accordingly. During the biofeedback session, participants saw a growing and shrinking circle indicating the breathing rhythm at 0.1 Hz. A fixed sinus-like wave was also displayed at the frequency of the paced breathing, and the pulse rate over time was mapped on top of this. Participants were instructed that the two waves would converge more as they relaxed. After the HRVB exercise, the user was given feedback on HRV improvement during the exercise to increase motivation. Screenshots of the app can be seen in Figure 2.

Figure 2. Screenshots of the HRVB application



Note. For the biofeedback, the current respiratory sinus arrhythmia, measured through photoplethysmography using the device's integrated camera, was represented as a blue line. A dynamic expanding and contracting circle visually represented the paced breathing rhythm at a frequency of 0.1 Hz. This frequency was further depicted by gray sinusoidal waves in the background, behind the measured heart rate oscillations.

The experimenter provided approximately 15 minutes of instructions to participants on how to use the app and how the biofeedback worked. Participants were coached on how to

engage in relaxed slow-paced breathing. They were instructed to practice at least 5 minutes daily for the next 4 weeks, with the option to practice for longer periods of time if desired. Participants were also informed that more practice would likely lead to greater benefits.

Three participants encountered technical difficulties while running the application on their devices. To ensure their participation in the intervention, they were provided with an alternative mobile HRVB system ('Qiu' by Biosign®, D-85570, Ottenhofen, Germany).

Outcome measures

Premenstrual Assessment Form (short form)

The short form of the Premenstrual Assessment Form (PAF20) is a retrospective instrument that assesses PMS symptoms during the last premenstrual phase (Allen et al., 1991). It was derived from the 20 most endorsed items of the long form PAF, which includes almost 100 items (Halbreich et al., 1982). Each item represents one premenstrual symptom, for which the participant must indicate how strongly they experienced it during the last cycle on a 6-point Likert scale from 1 (not at all/no change) to 6 (extreme change). The German translation of the PAF-20 shows good internal consistency and reliability and loads on two factors, indicating a psychological and physiological subscale (Blaser et al., 2023b).

The 10-item version (PAF-10) was constructed using the items with the highest factor loadings and shows a very high correlation with the PAF-20 (Blaser et al., 2023b). To assess the fluctuations of symptoms throughout the cycle and approximate a prospective assessment, the participants filled out the PAF-10 once a week with altered instructions, asking for a report of the 10 symptoms during the last week.

Becks Depression Inventory

The Beck Depression Inventory II (BDI-II) is a widely used questionnaire that assesses the severity of depressive symptoms. It consists of 21 items, each containing four statements about depressive symptoms ranging from 0 (normal) to 3 (most severe). The total maximum score is 63. The BDI-II has good psychometric properties, including high internal consistency, test-retest reliability, and concurrent and discriminant validity. Additionally, the questionnaire has been translated into multiple languages and is widely used in clinical and research settings to assess depression severity, monitor treatment progress, and evaluate outcomes. Previous studies have also shown that the BDI-II has good discrimination between patients with varying degrees of depression and accurately reflects changes in depression intensity over time (Beck et al., 1988; Richter et al., 1998).

The Fast Screen Version of the Becks Depression Inventory (BDI-FS) was developed as a short form to allow for parsimonious screenings, e.g., in research settings. It includes seven items and is based on the DSM-5 criteria for depression, clinical importance, and factor loadings (Beck et al., 2000).

Depression Anxiety Stress Scale

The German version of the Depression Anxiety and Stress Scale (DASS), developed by Henry and Crawford (2005) and based on the original version by Lovibond and Lovibond (1995), was employed for data collection. The DASS-21, a shortened version of the scale, consists of 21 statements that assess three distinct subscales: depression, anxiety, and stress.

Participants were asked to rate the extent to which each statement applied to them during the designated period using Likert scales ranging from 0 to 3. Higher scores on the DASS-21 indicate elevated levels of depressive symptoms, anxiety, and stress.

The internal consistency of the DASS-21 was found to be satisfactory, with a Cronbach's α coefficient of 0.89 (Bibi et al., 2020). The DASS-21 was selected as an outcome

measure in this study based on its consistent effects in biofeedback interventions, as demonstrated in prior research (Goessl et al., 2017).

Vagally mediated heart rate variability

Resting vmHRV was determined using the BioSign software and hardware ("HRV-Scanner"; Biosign®, D-85570, Ottenhofen, Germany). Participants had been sitting down for at least 15 minutes before the measurement. The measurement was taken in a sitting position. Participants were instructed to sit comfortably, place their feet side by side on the floor, close their eyes, and were told that they didn't have to pay attention to anything in particular. Following the recommendations by Laborde et al. (2017), the measurement had a duration of 5 minutes.

HRV was measured by a one-lead electrocardiogram (ECG) through two surface sensors attached to the right and left wrists of the participant. The device worked with a sampling rate of 500 Hz and a 16-bit resolution. Artifacts and abnormal beats were filtered in a two-step process following the software documentation (BioSign GmbH, 2023). First, the HRV Scanner software automatically marked areas of the heart rate curve that included implausible changes in heart rate (through the division of the heart rate curve into small segments and a subsequent scan of each segment). This process was based on an algorithm patented by the BioSign company that identifies outliers in a Poincaré plot, where each RR interval is plotted against the previous RR interval.

Working with these recognized areas of possible disturbances, in the second step, the R-spike recognition was manually assessed and corrected, and artifacts (e.g., due to movement) were removed. After the two-step process, the data quality was excellent, with less than 0.1% artifacts per measurement on average.

Participants additionally conducted short resting vmHRV measurements through the app using PPG, as described above, once a week. These measurements lasted one minute, and

participants were instructed to take these measurements each week on the same day, at the same time, and in the same place, ensuring they would not be disturbed. They were also instructed to sit comfortably and close their eyes during the measurement, similar to the way they were during the ECG measurement in the laboratory.

We used the root mean square of successive differences (RMSSD) as a measure for vagally mediated heart rate variability. This choice was due to its indication of parasympathetic output and robustness to influences of breathing rate (Chapleau & Sabharwal, 2011).

Attentional network test revised

We employed the ANT-R, developed by Fan et al. (2009), as a measure of attentional control. This task is reaction time task and was designed as a combination of the Eriksen flanker task (Eriksen & Eriksen, 1974) and the Posner cueing task (Posner, 1980).

During the ANT-R, participants were presented with a grey background and a black horizontal arrow. Their task was to indicate the direction of the arrow by pressing the corresponding button with their left or right index finger.

The ANT-R task consists of a total of 288 trials, divided into two identical runs of 144 trials each. The duration of the entire test is approximately 30 minutes. Previous studies have demonstrated good split-half reliability in the Executive ($r = .74$) and Orienting network scores ($r = .70$) (Greene et al., 2008). To reduce participant burden, only one run was completed per session.

The task was administered using the Presentation® software (Neurobehavioral Systems, Inc.) on a 24-inch screen positioned 80 cm away from the participants. Before the main task, participants completed 6 practice trials with feedback and 32 practice trials without feedback. Written and visual instructions were provided prior to the practice trials.

During the main task, participants were required to achieve a minimum accuracy of 80%. On average, participants reached an accuracy rate of 95% in the main task block.

Statistical analysis

All analyses were conducted using R (version 4.2.2). A linear mixed model was calculated for each target variable, with data points clustered per participant by introducing participant intercepts as random effects. When applicable, items were also included as random effects. The fixed effects included in the model were TIME point, TREATMENT, the TREATMENT * TIME interaction, and control variables (AGE, GENDER, BMI, RMSSD), along with exploratory three-way interactions involving potential mediators of the main TREATMENT * TIME effect.

A model selection process was applied to each analysis, with predictors being consecutively added to the model. Likelihood Ratio Testing compared the goodness of fit of each model to the next simpler one, and predictors were retained if they improved the model's fit.

The main hypotheses were tested with TREATMENT * TIME interactions in the respective model. The hypothesis was considered accepted if the interaction term was included in the final model, a significant predictor, and the effect aligned with the expected direction. Post-hoc comparisons and plots of the interaction effects were used to verify the expected direction of the effects.

As this study was a randomized controlled trial (RCT) with a waiting-list control group, the analyses included post-treatment data from the control group. Therefore, the post-treatment data points of the control group were classified into the post-treatment intervention group.

The same procedure was applied for reaction time data, involving three-way interactions instead of two-way interactions. These three-way interactions included TREATMENT, TIME, and FLANKER or CUE condition for the Executive and Orienting Network performance, respectively.

Results

Descriptive Statistics

Out of the 29 participants initially included in the study, 27 attended at least the first session and were included in the analyses. However, an additional 3 participants dropped out after the first and before the last session, resulting in 24 participants who completed the study entirely. Table 1 provides a description of the groups that underwent only the intervention and those who completed both the waitlist and intervention protocols.

Table 1. Sample description

	Group waitlist (n = 13)		Group only intervention (n = 14)	
	Mean ± SD	Range	Mean ± SD	Range
Age	25.3 ± 7.0	18-37	22.6 ± 2.8	19-27
BMI in kg/m^2	22.9 ± 4.5	18.3-32.2	22.9 ± 3.6	18.4-29.4
Gender	12f, 1m		14f	
Active menstrual cycle	11 yes, 2 no		14 yes	
HC usage	36.4%		42.9%	
PAF sum	54.7 ± 13.4	23-70	57.4 ± 20.2	19-93
BDI-II sum	12.9 ± 7.2	0-27	13.4 ± 8.0	2-30
Inclusion criterium	4 BDI, 4 PAF, 5 both		4 BDI, 4 PAF, 6 both	
DASS sum	34.1 ± 7,1	27-54	40.5 ± 8.3	25-50
RMSSD in ms	37.0 ± 10.9	19.6-51.5	41.9 ± 30.1	18.7-128.9
ANT-R Executive in ms	148.1 ± 56.8	76.7-291.3	129.2 ± 39.1	80.8-194.9
ANT-R Orienting in ms	85.0 ± 37.3	36.3-149.6	120.6 ± 35.1	46.7-183.8

Note. The DASS, RMSSD, and ANT-R values were obtained during the first laboratory session of each participant. All other values were assessed during the screening. SD – standard deviation; BMI – body-mass-index; HC – hormonal contraceptives; PAF – premenstrual assessment form; BDI-II – Becks Depression Inventory; DASS – depression anxiety stress scales; RMSSD – root mean square of successive differences; ANT-R – revised attention network test.

Premenstrual Symptoms

Out of 21 PAF20 post values recorded for the T5 measurement, 9 were replaced with the follow-up measurements. This occurred because there was either no premenstrual phase during the intervention period or the premenstrual phase occurred during the first two weeks of the intervention phase.

The final model for predicting premenstrual symptoms incorporated the TREATMENT and TIME variables along with their interaction. Furthermore, it included the SCALE of the PAF20 questionnaire to which each symptom belonged (psychological vs. physiological symptoms) and its interaction with the TREATMENT * TIME interaction (see Table 2). The final model was:

Value ~ treatment*time + scale + treatment:time:scale + (1|vpn) + (1|item).

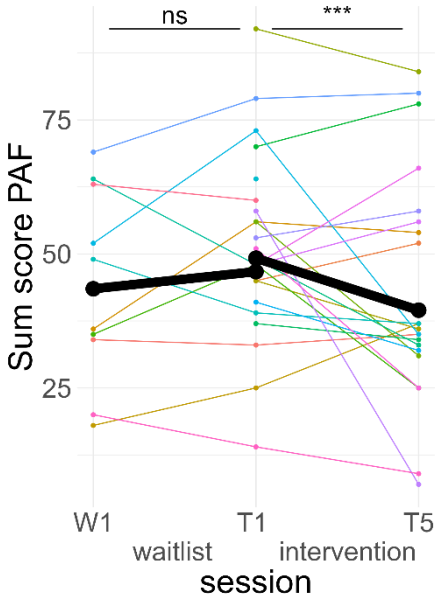
Post-hoc Tukey testing of the two-way interaction TREATMENT * TIME revealed a significant improvement in the intervention group, d = -0.30, $t_{ratio}(1258) = -5.89$, $p < .001$, whereas there was no significant pre-post difference in the waitlist group, $d = 0.10$, $t_{ratio}(1252) = 1.35$, $p = .18$ (see Figure 3). When SCALE was included in the interaction, it showed that the improvement in the intervention group was larger for psychological scale items (d_{psych} = -0.42) than for physiological scale items (d_{physio} = -0.19), with both improvements being significant. Detailed post-hoc testing results for the TIME * TREATMENT * SCALE interaction can be found in Table 3.

Table 2. Results of a linear mixed model predicting premenstrual symptoms

	value PAF20 item		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	2.92	2.44 – 3.40	<0.001
group [W]	-0.28	-0.50 – -0.07	0.010
time	-0.30	-0.54 – -0.07	0.012
scale [psy]	1.08	0.61 – 1.56	<0.001
group [W] * time	0.40	0.03 – 0.78	0.034
(group [I] * time) * scale [psy]	-0.36	-0.65 – -0.06	0.017
(group [W] * time)* scale [psy]	0.13	-0.26 – 0.51	0.520
Random Effects			
σ^2	1.40		
$\tau_{00\ participant}$	0.58		
$\tau_{00\ item}$	0.24		
ICC	0.37		
$N_{\ participant}$	24		
$N_{\ item}$	20		
Observations	1300		
Marginal R^2 / Conditional R^2	0.116 / 0.442		

Note. The random effect structure includes participant intercepts and item intercepts. PAF20 – premenstrual assessment form short version; group – treatment (biofeedback vs. waitlist); W – waitlist; I – intervention (biofeedback); psy – psychological symptoms.

Figure 3. Course of premenstrual symptoms



Note. Colored lines indicate individual participants. Black lines indicate the predicted interaction effect based on the mixed effect model depicted in Table 2. The waitlist period occurred between sessions W1 and T1, while the heart rate variability biofeedback intervention period took place between T1 and T5. PAF – premenstrual assessment form; *** – p<.001; ns – not significant.

Table 3. Post-Hoc Tukey effects of time*treatment*scale interaction term predicting premenstrual symptoms

	Scale	Diff	*p*
Waitlist	Physio	0.06	.54
	Psych	0.14	.11
Intervention	Physio	-0.19	**.012**
	Psych	-0.42	**<.0001**

Note. Diff – standardized pre-post treatment difference; psych – psychological symptoms; physio – physiological symptoms.

Depressive Symptoms

The final model predicting depressive symptoms included only TREATMENT and TIME, as well as their interaction as fixed effects (see Table 4). The model was the following:

Value ~ treatment*time + (1|vpn) + (1|item).

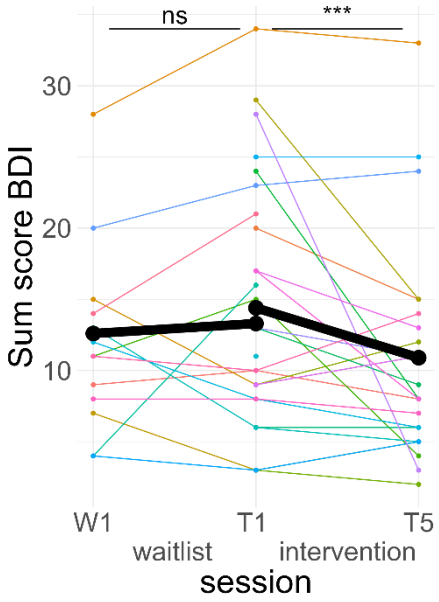
A post-hoc Tukey test of the interaction showed that symptom scores significantly improved in the intervention period, d = -0.25, $t_{ratio}(1576) = -4.71$, $p < .001$, but not in the wait-list period, d = 0.05, $t_{ratio}(1567) = 0.73$, $p = .46$ (see Figure 4).

Table 4. Results of a linear mixed model predicting depressive symptoms

	value BDI item		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	1.69	0.54 – 0.83	<0.001
group [W]	-0.09	-0.18 – 0.00	0.054
time	-0.17	-0.24 – -0.10	<0.001
group [W] * time	0.21	0.09 – 0.33	0.001
Random Effects			
σ^2	0.34		
$\tau_{00\ participant}$	0.10		
$\tau_{00\ item}$	0.03		
ICC	0.27		
$N_{\ participant}$	27		
$N_{\ item}$	21		
Observations	1617		
Marginal R^2 / Conditional R^2	0.010 / 0.281		

Note. The random effect structure includes participant intercepts and item intercepts. BDI – Beck's Depression Inventory II; group – treatment (biofeedback vs. waitlist); W – waitlist.

Figure 4. Course of depressive symptoms



Note. Colored lines indicate individual participants. Black lines indicate the predicted interaction effect based on the mixed effect model depicted in Table 4. The waitlist period occurred between sessions W1 and T1, while the heart rate variability biofeedback intervention period took place between T1 and T5. BDI – Beck's Depression Inventory II; *** – p<.001; ns – not significant.

Stress and Anxiety

The best model predicting DASS values included the RMSSD and the DASS SCALE (anxiety, stress or depression) on top of TREATMENT, TIME and their interaction (see Table 5). There was no three-way interaction of TREATMENT * TIME * SCALE. The model was:

Value ~ treatment*time + scale + RMSSD + (1|vpn) + (1|item).

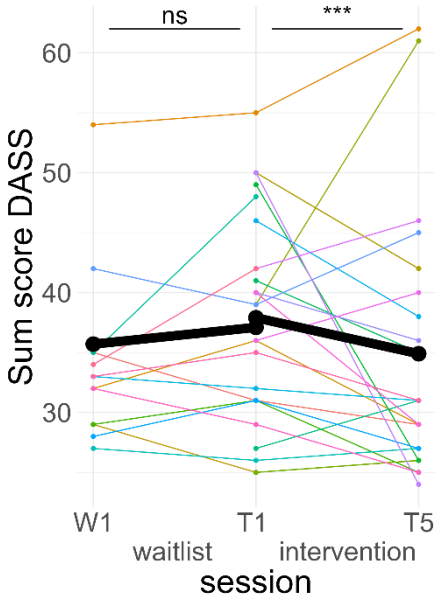
Post-hoc Tukey testing of the TREATMENT * TIME interactions showed a significant improvement in the intervention period, d = -0.19, $t_{ratio}(1573) = -3.88$, $p < .001$, but not in the waitlist period, d = 0.09, $t_{ratio}(1567) = 1.37$, $p = .17$ (see Figure 5).

Table 5. Results of a linear mixed model predicting stress/anxiety symptoms

	value DASS item		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	1.12	0.64 – 1.60	<0.001
time	-0.14	-0.22 – -0.07	<0.001
group [W]	-0.11	-0.20 – -0.01	0.023
scale [D]	0.11	-0.19 – 0.40	0.466
scale [S]	0.44	0.15 – 0.74	0.003
rmssd	0.14	0.03 – 0.26	0.015
time * group [W]	0.21	0.09 – 0.34	0.001
Random Effects			
σ^2	0.35		
$\tau_{00\ participant}$	0.14		
$\tau_{00\ item}$	0.07		
ICC	0.39		
$N_{\ participant}$	27		
$N_{\ item}$	21		
Observations	1617		
Marginal R^2 / Conditional R^2	0.074 / 0.432		

Note. The random effect structure includes participant intercepts and item intercepts. DASS – Depression Anxiety and Stress Scale; group – treatment (biofeedback vs. waitlist); W – waitlist; D – depression scale; S – stress scale; RMSSD – root mean square of successive differences.

Figure 5. Course of Anxiety/Stress symptoms



Note. Colored lines indicate individual participants. Black lines indicate the predicted interaction effect based on the mixed effect model depicted in Table 5. The waitlist period occurred between sessions W1 and T1, while the heart rate variability biofeedback intervention period took place between T1 and T5. DASS – Depression Anxiety and Stress Scales; *** – p<.001; ns – not significant.

Heart rate variability

The RMSSD was log-transformed to approximate a normal distribution, aligning it with the methodology used in other vmHRV research studies. Two participants had to be excluded from the post measurement, as they had acute respiratory tract infections.

The final model predicting the log(RMSSD) included only TREATMENT, TIME and the TREATMENT * TIME interaction as fixed effects (see Table 6).

Value ~ treatment*time + (1|vpn) + (1|item).

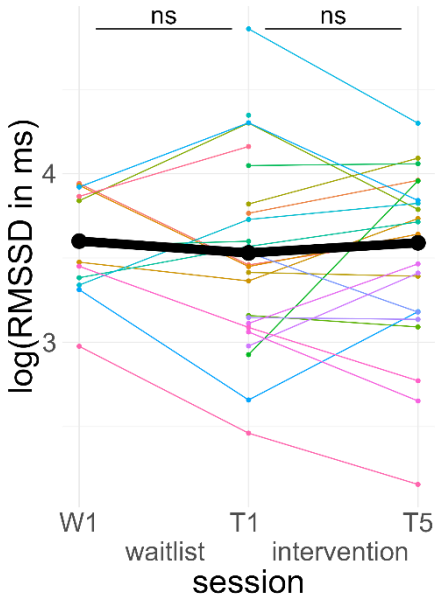
None of the fixed effects were significant predictors. A post-hoc Tukey test of the interaction confirmed no significant improvement in the intervention group, $d = 0.11$, $t_{ratio}(44) = 0.66$, $p = .51$, and no significant pre-post difference in the waitlist group, $d = -0.14$, $t_{ratio}(43) = 0.61$, $p = .55$ (see Figure 6).

Table 6. Results of a linear mixed model predicting vagally mediated heart rate variability

	log(RMSSD in ms)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	3.53	3.32 – 3.75	<0.001
group [W]	0.07	-0.15 – 0.29	0.546
time	0.06	-0.12 – 0.23	0.509
group [W] * time	-0.13	-0.42 – 0.16	0.381
Random Effects			
σ^2	0.08		
$\tau_{00\ participant}$	0.21		
ICC	0.71		
$N_{\ participant}$	25		
Observations	71		
Marginal R^2 / Conditional R^2	0.003 / 0.711		

Note. The random effect structure includes participant intercepts. RMSSD – root mean square of successive differences; group – treatment (biofeedback vs. waitlist); W – waitlist.

Figure 6. Course of vagally mediated heart rate variability



Note. Colored lines indicate individual participants. Black lines indicate the predicted interaction effect based on the mixed effect model depicted in Table 6. The waitlist period occurred between sessions W1 and T1, while the heart rate variability biofeedback intervention period took place between T1 and T5. RMSSD – root mean square of successive differences; ns – not significant.

Attentional control

The reaction time prediction model included main effects for TIME, TREATMENT, CUE, and FLANKER. Additionally, two three-way interactions were included – TREATMENT * TIME * CUE and TREATMENT * TIME * FLANKER. Both of these three-way interactions revealed significant terms in the model (see Table 7).

Reaction Time ~ treatment:time:cue + treatment:time:flanker + time + treatment + cue + flanker + (1|vpn) + (1|item).

We used linear trend estimates from the emmeans package (v1.8.8) to compare valid vs. invalid (cue) and congruent vs. incongruent (flanker) slopes in each pre-post comparison. This approximated the original score calculations. Significant differences in slopes indicate changes in the Orienting Score (invalid vs. valid cue trials) or Executive Score (incongruent vs. congruent flanker trials) between pre and post-assessment.

In the TIME * TREATMENT * CUE interaction, there were no significant differences in pre-post slopes between valid and invalid trials during both the intervention period, d = -0.03, z_{ratio} = -0.67, p = .91, and the waitlist period, d = 0.00, z_{ratio} = 0.03, p = 1, (see figure 7a).

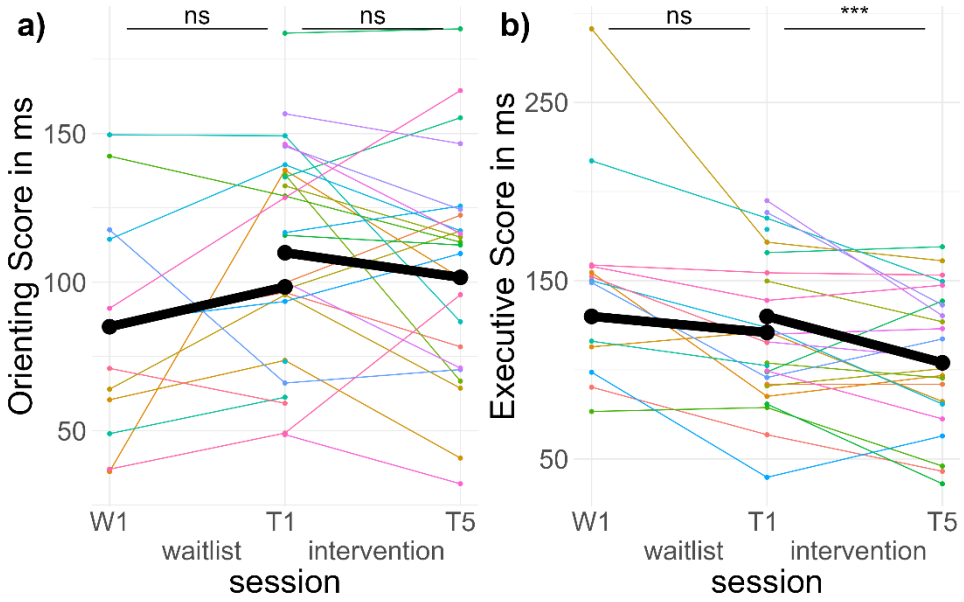
In the TIME * TREATMENT * FLANKER interaction, there was a significant difference in pre-post slopes between congruent and incongruent trials during the intervention period, d = -0.18, z_{ratio} = -4.60, p < .001, but no difference in the waitlist period, d = -0.06, z_{ratio} = -1.34, p = .54. The effect in the intervention period indicated less difference between valid and invalid trials post-treatment compared to pre-treatment, equivalent to better Executive Scores (see figure 7b).

Table 7. Results of a linear mixed model predicting attentional control

	Reaction time		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	600.31	574.20 – 626.41	<0.001
time	-37.63	-49.22 – -26.05	<0.001
group [W]	39.00	31.02 – 46.99	<0.001
flanker [incongruent]	130.14	123.20 – 137.08	<0.001
cue [valid]	-98.44	-106.51 – -90.37	<0.001
time × group [I] × cue [invalid]	45.56	28.15 – 62.97	<0.001
time × group [W] ×cue [invalid]	-0.22	-16.33 – 15.89	0.978
time × group [I] × cue [valid]	41.09	27.57 – 54.61	<0.001
time × group [I] × flanker [incongruent]	-26.57	-37.90 – -15.25	<0.001
time × group [W] × flanker [incongruent]	-9.44	-23.31 – 4.43	0.182
Random Effects			
σ^2	11369.21		
$\tau_{00\ participant}$	4325.41		
ICC	0.28		
$N_{\ participant}$	27		
Observations	7040		
Marginal R^2 / Conditional R^2	0.267 / 0.469		

Note. The model predicts trial-based prediction times of the revised attention network test. The random effect structure includes participant intercepts. Group – treatment (biofeedback vs. waitlist); W – waitlist; I – intervention (biofeedback).

Figure 7. Course of attentional control



Note. Colored lines indicate individual participants. Black lines indicate the predicted interaction effect based on the mixed effect model depicted in Table 5. The waitlist period occurred between sessions W1 and T1, while the heart rate variability biofeedback intervention period took place between T1 and T5. a) Orienting Score – (reaction time $_{\text{incongruent spatial cues}}$ - reaction time $_{\text{congruent spatial cues}}$); b) Executive Score – (reaction time $_{\text{invalid flankers}}$ - reaction time $_{\text{valid flankers}}$). *** – p<.001; ns – not significant.

Discussion

In this study, we investigated the impact of a 4-week photoplethysmography smartphone-based HRVB intervention on premenstrual and depressive symptoms using a waitlist-control design. Additionally, we assessed its effects on stress symptoms, vmHRV, and attentional control. Our findings revealed improvements in premenstrual, depressive, and stress symptoms following the intervention, with no significant changes observed during the waitlist period. However, we did not observe any effects on vmHRV, and the results for attentional control were mixed.

The positive effects on premenstrual, depressive, anxiety, and stress symptoms found in our study highlight the feasibility and effectiveness of a smartphone-based HRVB intervention without the need for external devices. Laborde, Allen, Borges, Iskra, et al. (2022) reported similar effects of a slow-paced breathing intervention, whether or not visual feedback on current HRV was provided. This suggests that slow-paced breathing is the primary driver of the intervention's effectiveness. However, learning the technique of abdominal slow-paced breathing, which allows for a relaxed resonance frequency activation, can be challenging. The drastically slowed-down breathing can be uncomfortable and may even lead to hyperventilation (Szulczewski & Rynkiewicz, 2018). Providing visual feedback on respiratory sinus arrhythmia can assist users in correctly employing the method at home without extensive training. Moreover, this biofeedback feature can enhance user engagement with the app, as it offers immediate visual results of the breathing intervention, providing a sense of immediate gratification. Essentially, this form of feedback incorporates a simplified version of gamification into the intervention, which can increase motivation and engagement (Johnson et al., 2016).

Our primary objective was to investigate whether HRVB could help alleviate PMS symptoms. We observed a significant improvement in the premenstrual phase following 2-4

weeks of HRVB practice compared to the preceding cycle in which no HRVB was practiced. The effect size we observed is approximately 0.3, with a slightly larger effect of 0.4 in the psychological symptom scale. In this context, the effect size is similar to the moderate effect size found in meta-analyses of depressive symptoms (Pizzoli et al., 2021). This finding supports the notion that PMS may result from an altered reactivity within the ALLO/GABA system (Hantsoo & Epperson, 2020), affecting the CAN as proposed by Thayer and Lane (2000). Consequently, interventions designed to target the interconnectivity and functional capacity of the CAN may hold promise in improving PMS symptoms.

However, further studies with expanded paradigms are needed to determine whether this effect is mediated by a reduction in stress throughout the menstrual cycle or by an increase in the capacity of the CAN, which may buffer modulatory fluctuations throughout the cycle. It also remains unclear whether there is a critical phase in the menstrual cycle when HRVB has a more significant impact on subsequent premenstrual symptoms. It is possible that practicing HRVB throughout the preceding follicular phase reduces chronic stress (Goessl et al., 2017) and, consequently, chronic ALLO exposure. This prolonged exposure has been suggested to contribute to atypical GABA receptor reactivity to ALLO fluctuations later in the cycle, which is assumed to cause PMS (Hantsoo & Epperson, 2020). Another possibility is that during the premenstrual phase, the acute stress-relieving effects (see e.g. Meier & Welch, 2016; Prinsloo et al., 2013) of HRVB directly alleviate the symptom burden.

Independently of mechanisms of action, HRVB is an easily learned intervention with minimal to no side effects, offering PMS sufferers an opportunity to enhance their symptom management self-efficacy. Furthermore, it can lower the threshold for receiving treatment. When delivered through a smartphone application, it becomes even more accessible and, if its effectiveness is established, can be seamlessly integrated into widely used menstrual cycle-related health apps.

Our results also demonstrated improvements in depressive symptoms, as well as anxiety and stress symptoms, through the smartphone-based HRVB intervention. This aligns with prior research using other HRVB intervention methods (Goessl et al., 2017; Pizzoli et al., 2021), although the effects we observed are somewhat smaller than the meta-analytic effects on depression and anxiety/stress. This discrepancy may be due to ceiling effects. The majority of studies investigating HRVB effects typically focus on clinical populations with very high values in the respective outcome measures. Our inclusion criteria, on the other hand, involved individuals with above-average PMS symptoms or slightly elevated depressive symptoms. 30% of the participants were included in our study due to only PMS symptoms. While clinically significant affective premenstrual symptoms (premenstrual dysphoric disorder) are often comorbid with anxiety and depression (Yonkers & McCunn, 2007), our subclinical sample likely had lower baseline scores in both BDI-II and DASS values compared to the samples in most studies included in the meta-analysis. This could account for the slightly smaller effect sizes observed in our study.

We did not observe improvements in vmHRV (RMSSD) following the HRVB intervention. Contrary to our findings, Laborde, Allen, Borges, Dosseville, et al. (2022) reported consistent elevations in vmHRV parameters after HRVB and slow-paced breathing interventions in their meta-analysis. The effect size for this improvement was approximately *Hedges' g* = 0.3. Notably, this effect size is smaller than the meta-analytic effect sizes for depressive symptoms ($g = 0.4$; Pizzoli et al., 2021) or anxiety/stress ($g = 0.8$; Goessl et al., 2017). These findings suggest that improvements in vmHRV alone do not fully account for the observed affective and cognitive effects. This is consistent with other findings that demonstrate physiological and clinical outcomes do not always change simultaneously in HRVB (Wheat & Larkin, 2010). Critically, our study may not have detected this effect due to its relatively small sample size. A G*Power analysis indicates that a sample size of more than 70 would be

required to replicate the effect of 0.3 with a power of .8. Our sample size was significantly below this threshold. The reason why effects were found in other outcome measures lies in the advantage of mixed model analysis, which allows us to include each item/trial individually without the need to condense the information into a composite score. This significantly increases the number of data points included, by 20 to 144 times, depending on the measurement. However, in the case of vmHRV, it is necessary compute a single value per measurement, which drastically reduces statistical power. This suggests the possibility that HRVB may have had a beneficial impact on vmHRV, but our study may have been underpowered to detect this effect.

The influence of the HRVB on the attentional control domains yielded mixed results. We chose to employ the Executive and Orienting Scores of the ANT-R as outcome measures, given their documented correlations with vmHRV (Blaser et al., 2023a; Quintana et al., 2017; Ramírez et al., 2015; Sørensen et al., 2019). Interestingly, despite previous studies (Quintana et al., 2017; Sørensen et al., 2019) indicating a stronger association between the Orienting Score and vmHRV (compared to the Executive Score vmHRV association), we did not observe any improvements in this measure. However, we did find enhancements in the Executive Score following the intervention period. These varying outcomes align with the findings of a meta-analysis conducted by Tinello et al. (2022), who reported positive effects of HRVB on Executive Functions in approximately half of the studies they reviewed, with a slightly higher likelihood of effects in the attention domain. This highlights the need for further research to elucidate the specific impact of HRVB on cognitive outcomes.

Although we found significant beneficial effects of smartphone-based HRVB on several mental health and some cognitive outcomes, our study has several limitations that need to be considered. Firstly, the most notable limitation is our small sample size. Although linear mixed model analyses help to overcome the limited statistical power due to small samples by

including individual items/trials in the analysis, it is important that the interpretation of the results and their applicability to larger populations must be considered with caution. Another limitation is related to the passive control group, which has methodological weaknesses. In future studies, it would be beneficial to implement active control groups to better distinguish the intervention's effects from any potential placebo effects. Additionally, we did not conduct clinical assessments of PMS or depression. However, it is essential to note that our study was not aimed at identifying treatments for a clinically relevant premenstrual dysphoric disorder. Instead, our primary focus was on investigating a user-friendly intervention to help individuals self-manage premenstrual symptoms, regardless of their severity levels. Furthermore, our study included participants regardless of their use of hormonal contraceptives and their current menstrual cycle phase. For future studies, it is advisable to standardize these criteria to ensure a more consistent assessment.

Conclusion

In summary, smartphone-based HRVB has proven to be effective in enhancing both emotional and cognitive well-being, without the need for external devices. This intervention holds promise as a novel approach for self-managing premenstrual symptoms and provides a more accessible solution for harnessing the known benefits of HRVB for depressive, stress, and anxiety symptoms, as well as certain aspects of attention.

Acknowledgements

The project was partly funded by the Funding of Knowledge and Technology Transfer (FöWiTec) of the University of Potsdam. The first author was partly supported by a PhD scholarship from the University of Potsdam (Potsdam Graduate School) with fundings from the Graduate Fund of the State of Brandenburg (Germany).

During the preparation of this work, the first author utilized ChatGPT 3.5 to enhance the text's readability. Prompts used were aimed at tasks such as “check grammar and spelling in this paragraph.” After employing this tool/service, the author reviewed and edited the content as necessary and assumes full responsibility for the publication's content.

We would like to thank Dr. Michael Vesker and Kenkou GmbH for providing the biofeedback App as well as Kenkou GmbH for partly providing the participant compensation.

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A.6 Manuscript 6

The effect of a single-session heart rate variability biofeedback on attentional control: Does stress matter?

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Frontiers in Psychology

2023

The effect of a single-session heart rate variability biofeedback on attentional control: Does stress matter?

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Running head: Heart rate variability biofeedback and attention

Keywords: attention, self-regulation, heart rate variability, biofeedback, cognitive control, stress, vagal tone, slow-paced breathing

Abstract

Vagally mediated heart rate variability is an index of autonomic nervous system activity that is associated with a large variety of outcome variables including psychopathology and self-regulation. While practicing heart rate variability biofeedback over several weeks has been reliably associated with a number of positive outcomes, its acute effects are not well known. As the strongest association with vagally mediated heart rate variability has been found particularly within the attention-related subdomain of self-regulation, we investigated the acute effect of heart rate variability biofeedback on attentional control using the revised Attention Network Test.

Fifty-six participants were tested in two sessions. In one session each participant received a heart rate variability biofeedback intervention, and in the other session a control intervention of paced breathing at a normal ventilation rate. After the biofeedback or control intervention, participants completed the Attention Network Test using the Orienting Score as a measure of attentional control.

Mixed models revealed that higher resting baseline vagally mediated heart rate variability was associated with better performance in attentional control, which suggests more efficient direction of attention to target stimuli. There was no significant main effect of the intervention on attentional control. However, an interaction effect indicated better performance in attentional control after biofeedback in individuals who reported higher current stress levels. The results point to acute beneficial effects of heart rate variability biofeedback on cognitive performance in highly stressed individuals. Although promising, the results need to be replicated in larger or more targeted samples in order to reach stronger conclusions about the effects.

Introduction

"Take a deep breath" is an idiom commonly used in everyday life. Most people seem to understand that breath control has some kind of connection to one's mental state. Indeed, the goal of these breathing exercises is usually to refocus attention away from salient stimuli toward more relevant targets, such as interrupting anxious thought loops before an exam or bringing the attention back from unfocused distraction. Research shows consistent associations between this skill of top-down regulation and the physiological correlate of vagally mediated heart rate variability (vmHRV), an index of parasympathetic activity (1). Critically, vmHRV parameters are strongly influenced by breath (2). This influence is driven by respiratory sinus arrhythmia (RSA), the phenomenon where heart rate increases with inhalation and decreases with exhalation (3, 4). These sinus wave-like fluctuations of heart rate are produced by phasic vagal input to the sinoatrial node during exhalation (2). RSA is largely vagally mediated (5), and the quantifications of the contribution of RSA to heart rate (although not the magnitude of the RSA itself, see 6, 7) are interpreted as the extent of cardiac parasympathetic activation. In heart rate variability biofeedback (HRV BFB) interventions, RSA can be maximized through slow-paced breathing, which increases HRV both during and after the intervention (8). Practicing this slow-paced breathing over a longer period of time (e.g., 4 weeks) has been shown to have a wide range of positive emotional and cognitive effects (9–11). Click or tap here to enter text.

Two recent meta-analyses by Holzman and Bridgett (12) and Zahn et al. (13) found consistent, albeit small associations between vmHRV measures at rest and performance on different laboratory self-regulation tasks. A theoretical framework for this association has been proposed by Thayer and Lane (1) in their model of neurovisceral integration. The authors suggest vmHRV as a peripheral marker for the capacity as well as a reciprocal functional part of the central autonomic network (CAN). Thayer and Lane (14) suggest that the reciprocal inhibitory connectivity of the ventromedial prefrontal cortex (vmPFC) and the amygdala is the

core mechanism of this complex system, which coordinates behavioral, cognitive and physiological self-regulation. Thayer and Lane (1) argue that vmHRV can be viewed as an indicator of the extent of the influence the higher processing structures such as the vmPFC have on brainstem and autonomic activity. This reflects the organism's capacity to inhibit automatic responses and instead react flexibly to environmental demands. In their vagal tank theory, Laborde et al. (15) expand on the neurovisceral integration framework. The authors propose that cardiac vagal control (vmHRV) reflects self-regulatory resources, which can be depleted or replenished like a tank. While resting vmHRV is positively associated with self-regulation, vmHRV reactivity's association with self-regulation depends on the level of activity and stress. In high activity/stress situations, a larger reduction in vmHRV is seen as adaptive, while in low activity/stress situations, a lower drop is better for self-regulatory performance. Self-regulation manifests itself in multiple domains. Although not statistically significant, both meta-analyses on resting vmHRV and self-regulation (12, 13) have observed that these associations are larger in the attentional control domain. One way of assessing attentional control is via the revised attention network test (ANT-R, 16). The ANT-R differentiates between the three networks of attentional processes proposed in the attentional network theory by Posner and Petersen (17). The Alerting Network is the network that sets the system into a general, vigilant arousal state enabling faster reaction times once action is needed. The Orienting Network is a system of structures that enables the efficient and rapid selection of the correct modality and location from which sensory input should be primarily processed. In doing so, salient information that is not relevant for goal attainment is suppressed. Petersen and Posner (18) describe the Executive Network as a system to provide focal attention, the limited awareness of relevant information which inhibits the processing of other input and enables the complex neuro-structural activation system that comprises consciousness. In comparison to the Alerting and Executive Networks, the Orienting Network, which is assessed through a cueing paradigm and specifically requires active employment of goal-directed self-regulation, has been closely

linked to vmHRV measures at rest (medium to large associations (Pearson's R between -.3 and -.55); 19–21). Additionally, active engagement of the Orienting Network is associated with activation in the ventral PFC (18), which plays a central role in the CAN proposed by Thayer and Lane (1).

All parts within Thayer and Lane's (14) CAN are assumed to be bidirectional, which implies that the manipulation of vmHRV can have modulational effects on self-regulatory capacity. One way to improve vmHRV is through HRV BFB training, in which the individual receives visual feedback on momentary vmHRV and learns to influence it via breathing rhythm. A slow-paced breathing frequency is set at 0.1 Hz or at an individual resonance frequency between 0.07-0.12 Hz (22), which has been shown to maximize (individual resonance frequency) or at least strongly increase (0.1 Hz) RSA (2). And indeed, research suggests that the effects of HRV BFB are almost exclusively driven by slow-paced breathing rather than the visual feedback of momentary HRV (23).

It has been suggested that, among other interventions, particularly abdominal slow-paced breathing at around 0.1 Hz increases vmHRV through the approach of resonance of the respiration-heart beat phasic relationship and the baroreflex (24). A recent literature review elaborates on this by explaining how the temporal coherence between respiratory, blood pressure, and cardiac phases offers the ideal timing for a complete release of acetylcholine, which orchestrates the reactive drop in heart rate during exhalation, and its subsequent hydrolysis (25). This, in turn, leads to an enhanced baroreflex. HRV BFB has been found not only to enhance baroreflex gain during training but also to produces long-term increases in baroreflex gain at rest (26). The altered autonomous activity can then affect higher cognitive processing levels through afferent pathways. Lehrer and Gevirtz (24) describe one of the most important among these pathways to be the baroreflex afferent input during exhalation to the amygdala via the nucleus of the solitary tract, where sensory signals from the baroreceptors are integrated and processed and projections branch extensively into structures of the CAN (27).

More recent research has found additional effects of a complementary afferent input to the nucleus of the solitary tract via afferents from slowly adapting pulmonary stretch receptors, which increases sympathetic activity during prolonged inhalation while their activity is terminated during prolonged exhalation (28).

In addition, HRV BFB may stimulate the afferent vagal pathway (24), which also projects into all structures of the CAN and can therefore influence higher cognitive processing levels as proposed in the theory of neurovisceral integration (14). Through these afferent pathways projecting into the CAN, the non-adaptive default threat response as proposed by Thayer and Lane (1) can be altered to ensure more adaptive regulatory processes.29 Gerritsen et al. (29) propose that this respiratory vagus nerve stimulation is the driving factor behind the many benefits of contemplative practices.

Furthermore, the interplay between the afferent input from the pulmonary stretch receptors and baroreceptors do not only impact CAN activity but also produces synchronized cortical rhythms in the same frequency as the slow-paced breathing (28). These slow global potentials could potentially interact with other networks involved in stress and memory, including the default mode network. Mental effects of the concentrative practice in HRV BFB as well as direct cortical pathways via activation of the olfactory bulb might be additional elements (24).

Based on the proposed mechanisms of HRV BFB (24), it is not clear which of the effects of HRV BFB are immediate and which develop over the course of long-term training. Several meta-analyses (9–11) demonstrate the beneficial long-term effects of HRV BFB on cognitive and emotional states, possibly by way of increased general activity as well as functional connectivity of and within the CAN (30). Tinello et al. (31) found mixed results in a systematic review of HRV BFB effects on executive functions with about half of the included studies reporting beneficial effects. The authors reported effects especially in the domain of attention and inhibition and in vulnerable populations such as samples experiencing high stress or

clinical samples. However, it remains unclear whether the acute increase in CAN activity due to afferent vagal activation is sufficient to observably affect cognitive and emotional measures.

A small number of studies, however, already point to immediate beneficial effects in terms of stress relief. One study found acute anxiety-reducing and calming effects of HRV BFB in a sample of students with high perceived stress levels (32). Similarly, another study found that HRV BFB acutely reduces the excitability of motoneurons in the medulla (33). Prinsloo et al. (34) studied a small group of men (N = 18) in managerial positions who rated high in perceived life stress as well as current work stress, and found acute increases in self-reported relaxation, energized positive feelings and mindfulness and decreases in anxiety (35). Additionally, they showed changes in electroencephalography (EEG) signals both during and after the intervention, which reflected increased relaxation and attention (36). Furthermore, lower levels of salivary alpha-amylase were found in participants who completed an HRV BFB session after a stress-inducing laboratory task compared to a control group, but no difference in cortisol levels or self-reported stress, indicating differential effects on different measures of stress (37). A last study employing a one session slow-paced breathing intervention additionally showed changes in EEG frequency activity, i.e. increases in alpha-band activity and decreases in beta-band activity in areas critical to stress regulation as revealed by source localization (38).

Additionally, a handful of studies suggest an acute improvement effect of single-session HRV BFB on cognitive outcomes. In the study elaborated on in the previous paragraph, better performance on a modified Stroop task was also observed after the BFB intervention compared to a control condition (34, 39). Similarly, better performance in Stroop tasks was found after a one-session slow-paced breathing intervention in a population of adults who reported high stress levels (38), and in a population of athletes who underwent a physical exhaustion protocol (40). Another study also reported similar findings as well as improved performance in an operation span task after a slow-paced breathing intervention compared to a control condition

(41). Hoffmann et al. (42) investigated the effects of slow-paced breathing on the performance in a flanker task. The results showed no significant effect on task performance, but there was an increase in the amplitude of the error-related negativity component of the event-related potential, which has been interpreted as indicating increased attention to performance accuracy.

Taken together, these results point to acute effects of alleviating stress and improving cognitive outcomes. Most of the above-mentioned studies, however, focused on samples that rated high in baseline stress levels or underwent a stress-inducing protocol. While high self-reported stress might make individuals more susceptible to the BFB intervention, this question has not explicitly been examined yet.

To investigate the acute effects of HRV BFB on attentional control and whether or not stress is a moderating factor, we conducted a laboratory study that tests the effects of a single-session HRV BFB on the ANT-R. As a manipulation check in this study, we hypothesize that vmHRV indexed by the root mean square of successive differences (RMSSD) is higher during an HRV BFB intervention compared to paced normoventilation during a control condition (Hypothesis 1). Secondly, we aim to replicate the positive association between resting vmHRV and attentional control (Hypothesis 2). We furthermore hypothesize acute improvements in the Orienting Network score after an HRV BFB session compared to a control condition (Hypothesis 3). Lastly, we postulate that the effect of HRV BFB on the Orienting score of the ANT-R is moderated by the individual stress level, as indicated by a self-report questionnaire on current stress (Hypothesis 4).

Materials and methods

Participants

Sixty participants were recruited from the population of students at the University of Potsdam through flyers on campus as well as the online recruiting platform for study participants of the cognitive sciences (Sona Systems, https://www.sona-systems.com). One person dropped out after the first session and three had to be excluded due to incomplete data, leaving a sample size of 56 (age = 23.1±3.4 years, 75% women, 23% men, 2% diverse), see Table 1. Informed consent was given by all participants after being given both verbal and written information about the study. The study protocol was approved by the ethics committee of the University of Potsdam (proposal No 15/2021).

Following recommendations by Laborde et al. (43), individuals were excluded who took medication that alters autonomic functioning, had a chronic or acute disease associated with altered autonomic functioning or were pregnant. Competitive athletes were also excluded, as athletes show systematically altered HRV (44). Since vmHRV varies across the lifespan (45), in order to achieve a homogenous sample participants younger than 18 years and older than 30 years were excluded.

The sample size was calculated based on the effect size of HRV BFB on the RMSSD, which is around d = 1.6 (23). The Orienting component of the ANT-R shows a correlation between .3 and .55 with vmHRV at rest (19–21). Assuming conservatively that about half of the shared variance of the lowest value (covariance = $r^2 = .3^2/2$) might respond to the intervention leads to an estimated effect size of d = 1.6 * sqrt($.3^2/2$) = .34. To observe this main effect in a within-subject design, a G*Power analysis (46) revealed a necessary sample size of N = 55. To account for dropouts and data trimming, 60 participants were tested.

Table 1

Sample characteristics (N=56)

Variable	Mean	SD	Min	Max
Age in years	23.1	3.41	19	30
BMI	21.4	2.4	18.4	29
Gender	75% female; 23% male, 2% diverse			
RMSSD baseline in ms	44.4	31.5	12.2	207.3
RMSSD gain from BFB in ms	20.3	17.1	-42.3	56
ANT-R Alerting network score	37.5	32.3	-48.7	127.8
ANT-R Orienting network score	95	37.6	10.1	190.8
ANT-R Executive network score	122	32.1	49	221.4
ANT-R Orienting-Executive interaction score	18.8	37.7	-89.1	127
ANT-R Alerting-Executive interaction score	-1	52.2	-148.8	143.2
Perceived stress scale score	27.9	6.1	14	41

Note. SD - standard deviation; Min - minimum; Max - maximum; BMI - body-mass-index; RMSSD - root mean square of successive differences, BFB - biofeedback; ANT-R - revised attention network test.

Testing procedure

Participants were tested in two different sessions exactly one week apart, at the same time of day between 9 am and 7 pm. Before signing up for the testing sessions, participants filled out an online questionnaire. The online questionnaire screened for exclusion criteria and assessed current perceived stress levels (German version of the Perceived Stress Scale - PSS; 47) as well as information known to be associated with vmHRV, namely age, gender (48), body-mass-index (BMI, 49), and habitual use of caffeine (50), nicotine and alcohol (51).

Following the recommendations of Laborde et al. (43), participants were asked not to drink alcohol or do intense physical training, and to follow their normal sleep routine and take note of the time they fell asleep and woke up 24 hours before the sessions. Furthermore, they were instructed not to drink caffeinated drinks or have a meal two hours before each session.

At the beginning and end of each session, the RMSSD at rest was measured to obtain a baseline RMSSD. Participants had been sitting down for at least 15 minutes before the measurement. The measurement was taken in a sitting position. Participants were instructed to sit comfortably, place their feet side by side on the floor, close their eyes and were told that they don't have to pay attention to anything in particular. Following the recommendations by Laborde et al. (43), the measurement had a duration of 5 minutes.

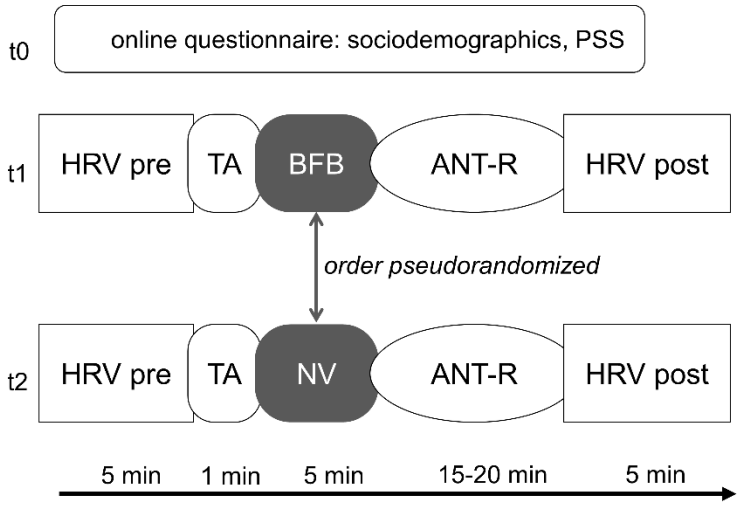
After the initial RMSSD assessment, a one-minute threshold assessment followed in each session. Secondly, participants completed a 5-minute HRV biofeedback training in one session and a comparative control condition in which normoventilation (NV) was applied in the other session.

Each participant was tested in both NV and BFB conditions. The order in which the participants received BFB and NV was pseudo-randomized. Since gender effects may be expected due to prior research showing differential RMSSD between those groups (52), the order of BFB and NV conditions was balanced among biological men and women. Additionally, an approximation of an age median split was applied before the testing, based on

prior samples in studies of our group (</≥ 23 years of age) (e.g. 53, 54). Within each of the four subgroups (women < 23 y/o, women ≥ 23 y/o, men < 23 y/o, men ≥ 23 y/o), condition order was balanced. After the breathing intervention, the ANT-R was completed followed by a second RMSSD assessment at rest (see Figure 1).

Figure 1

Testing procedure



Note. The order of BFB and control condition is randomized within sociodemographic groups. PSS – perceived stress scale; HRV – heart rate variability; TA – threshold assessment; BFB – biofeedback; NV – normoventilation; ANT-R – attention network test-revised. Online questionnaire was filled out before sign up, t1 and t2 were exactly one week apart at the same time of day.

Heart rate variability assessment, biofeedback and normoventilation

Resting RMSSD and biofeedback threshold assessments as well as HRV biofeedback (and the control condition) were conducted using the BioSign soft- and hardware ("HRV-Scanner"; Biosign®, D-85570, Ottenhofen, Germany). Heart rate was measured by a one-lead electrocardiogram (ECG) through two surface sensors attached to the right and left wrists of the participant. The device works with a sampling rate of 500 Hz and a 16-bit resolution.

Artifacts and abnormal beats were filtered in a two-step process following the protocol outlined in the HRV-Scanner software documentation (55). First, the HRV-Scanner software automatically marked areas of the heart rate curve that included implausible changes in heart rate through the division of the heart rate curve into small segments and a subsequent scan of each segment. This process is based on an algorithm patented by the BioSign® company that identifies outliers in a Poincaré plot, in which each RR interval is plotted against the previous RR interval.

Working with these recognized areas of possible disturbances, in the second step the R-spike recognition was manually assessed and corrected, and artifacts, alterations of the electric signal not related to the electrical activity of the heart due to movement or the like, were removed. After the two-step process the data quality was excellent, with less than 0.1% artifacts per measurement on average. Only 7% of the heart rate assessments had a measurement quality of less than 100%, of which the lowest was 96.6%.

HRV baseline assessment

We focused on the RMSSD as a measure of vmHRV (56). The high frequency (HF) component of power spectral analyses, which has also been shown to assess cardiac parasympathetic activity (56), is not used in this study for the following reasons. The HF is defined as the power of the frequency band between 0.15 and 0.40 Hz. This frequency band is based on normoventilation at a rate of 9-24 breathing cycles per minute. Heart rate oscillations in this frequency reflect RSA, which is largely driven by vagal activity. However, during the BFB intervention applied in this study, the paced breathing frequency was set at 0.1 Hz. A maximal peak at this frequency in power spectral analysis indicates maximal RSA. The RSA peak is therefore not inside the HF band and can consequently not be quantified by this parameter. In fact, during slow-paced breathing, the vagal contribution to heart rate oscillations falls into the low-frequency band (for pharmacological blockage study see 57). Furthermore, tonic sympathetic activity levels can additionally indirectly influence the HF component

measure (58). That means that the HF component can be interpreted as reflecting cardiac parasympathetic activation only under specific circumstances. The low frequency (LF) component has previously been observed to increase in power through HRV BFB (8). This is due to the RSA frequency falling into the LF component during SPB, as described above. Since RSA operates within a different frequency band during spontaneous breathing, this component, like the HF component, does not assess vmHRV in a comparable manner. The RMSSD was therefore used as an indicator of vmHRV for each assessment. For each session, the RMSSD assessment at rest from the beginning of the session was used as baseline vagal activity (43). The RMSSD was calculated in the BioSign® Software "HRV-Scanner" following the formula:

$$RMSSD = \sqrt{\frac{1}{N} \times \sum_{i=1}^{N} (RR_{i+1} - RR_i)^2}.$$

Biofeedback threshold assessment

An individual threshold was assessed for the BFB training. For the assessment, participants were asked to breathe as deeply as possible in a paced breathing rhythm at 0.1 Hz for one minute, as the ECG continued to record their heart rate following the protocol outlined in the documentation of the HVR-Scanner software (55). At this rate, the breathing pace approaches the resonance frequency of most individuals and RSA is therefore strongly increased.

With this data, spectral analysis was performed through a Fast Fourier transform based on linearly interpolated R-R intervals in the HRV-Scanner software. In a patented algorithm by BioSign® (59), two components are identified from the integral of this spectral analysis. The first one contains the integral around the peak of the variance distribution and the other one the leftover frequencies. The two components are then normed and adjusted. The ratio of the adjusted integral components indicates the relative contribution of RSA to the total variance of oscillations and is calculated to assess individual thresholds for the feedback in the

biofeedback intervention. The precise algorithm for the calculation can be found in the registered patent by Beise (59).

BFB and NV

The biofeedback was presented as visual feedback in the form of a hot air balloon flying through a landscape. Participants saw the balloon rising when the current HRV component ratio, calculated as described in the segment above, rose toward and above their individual threshold based on the biofeedback threshold assessment (and fell when it dropped below the individual threshold). A detailed description of the task can be found in the software documentation (55). Participants were provided with explanations on how the biofeedback system works, and that the rising balloon indicated synchronization of breath and heart rate. They were instructed to breathe in the induced frequency through their nose in a relaxed, natural way. Participants practiced the biofeedback for about a minute before the start of the exercise. If participants reported any tension or hyperventilation symptoms after the initial practice, the experimenter instructed them to practice shallower breathing and/or provided advice to comfortably slow down the breathing rate. If necessary, another one-minute practice session was conducted before the start of the exercise to ensure successful completion.

The ratio described above, which is used to quantify breath-to-heart-rate synchronization, was constantly recalculated, and updated to ensure swift visual feedback of the current RSA levels within the BioSign® software. This algorithm was developed specifically to ensure a higher dynamic of online feedback.

A bar moving up and down indicated the slow-paced breathing rhythm at 0.1 Hz, which has been shown to maximize resonance between the breathing cycle and heart rate (2). For the control condition, participants saw only a breathing bar on a black background, which dictated a breathing rhythm to imitate normoventilation at 0.25 Hz. For the HRV biofeedback, the biofeedback threshold assessment suggested a threshold of the ratio described above individually for each participant in order to achieve a comparable task difficulty.

The RMSSD was calculated for the ECG recordings during the intervention. The RMSSD baseline values were then subtracted from the RMSSD during the intervention for each session. This score indicates the gain (or decrease if the value is negative) in RMSSD during the intervention in comparison to the baseline, subsequently referred to as $RMSSD_{gain}$.

Revised attention network test (ANT-R)

We used the ANT-R (16), based on the original attention network test (60), which is a reaction time paradigm combining the Eriksen flanker task (61) and the Posner cueing task (62).

In this task, participants respond to a target stimulus of a black horizontal arrow on a grey background. By pressing the correct button with either their left or right index finger, they are asked to decide in which direction the target arrow points.

The original ANT-R consists of 288 trials, in which the first and second runs (of the 144 trials each) are identical. The whole test lasts a total duration of 30 minutes. Prior studies showed high split-half reliability (63) in the Executive ($r = .74$) and Orienting network scores ($r = .70$). In order to achieve maximum effects and reduce strain on participants, only one of the two identical runs was completed by the participants per session.

The task was programmed and applied using the software Presentation® (Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) following the detailed description of Fan et al. (16). The task was presented on a 24-inch screen, placed 80 cm away from the participants. Participants completed 6 practice trials with feedback and 32 practice trials without feedback after receiving written and visual instructions. A description of the results can be seen in Table 1.

Perceived stress scale

The perceived stress scale (PSS-10) is a short (10 items) scale assessing self-reported current stress experienced during the last seven days (64) on a 5-point Likert scale (0-4). The German version of the scale showed good internal consistency and construct validity in a large, representative sample (N>2400) (47).

Statistical analysis

All statistical analyses were carried out in R Version 4.1.2. All linear mixed models were calculated using the lm4 package (v1.1-31) (65). Degrees of freedom and p-values were calculated using the Satterthwaite's degrees of freedom method in the lmerTest package (v3.1-31). RMSSD values as well as the reaction times were BoxCox transformed (66) to account for skewness.

To test whether the BFB intervention successfully increased RMSSD compared to the control condition (Hypothesis 1), a linear mixed model was calculated for the intervention gain score ($RMSSD_{gain}$). Participant intercepts were modeled as random effects. Four different models were fitted which included only the condition (BFB or NV) and then the successive addition of the RMSSD baseline, the interaction term of the condition and RMSSD baseline and the control variables (age, BMI, gender). The goodness of fit was then assessed through an ANOVA, checking for additional explained variance through a Likelihood Ratio Test from each model to the next complex one, yielding a p-value from the χ^2-test (see proposition by 67). The Bayesian and Akaike Information Criteria (BIC and AIC) were also assessed but played a secondary role in the model selection. The best-fitting model was then used to test the hypothesis.

To test Hypotheses 2-4, a linear mixed model of reaction time (RT) was calculated. The mixed model has several advantages compared to traditional analyses of the composite scores (16). First and foremost, the power of the statistic is increased, as a mixed model allows the inclusion of each trial into the analysis instead of just one data point per session (resulting in

up to a 96-fold increase in data points). Secondly, there is a loss of information and distortion of the effects when analyzing the composite scores. The composite scores are calculated by subtracting the average reaction times of correctly answered trials of different conditions from each other (e.g., mean RT of trials with invalid cues – mean RT of trials with valid cues). In the ANT-R, each trial consists of a cue and flanker condition. If the participant answers 100% of the trials correctly, the mean $RT_{valid\ cue}$ and $RT_{invalid\ cue}$ then include 50% of trials with congruent and incongruent flankers. However, accuracy is not the same for all conditions. Each participant has an individual loss in accuracy depending on the condition. Typically, there will be more wrong answers in the invalid cue, incongruent flanker condition than in the valid cue, incongruent flanker condition. This leads the mean $RT_{invalid\ cue}$ to include more congruent flanker trials than the $RT_{valid\ cue}$, which are responded to faster and mask part of the orienting effect. In the composite scores, it is therefore not possible to differentiate between the individual contributions of the conditions. A mixed model includes each trial, which enables accurate identification of the contribution of the cue and flanker to the reaction time.

To maintain parsimonious models and reduce convergence issues, the random effect structure was kept simple and included only intercepts in participants to account for individual differences in average reaction time and allow for subject-wise clustering of the data points. In an iterative process similar to the one described above, predictors were consecutively added to the fixed effects, with each step of complexity being tested for improvement of fit through Likelihood Ratio Testing to the next simpler model. Predictors were maintained for the next step if they improved the model. Predictors included in the model were flanker, cue, RMSSD baseline, condition, PSS, age, gender, BMI, RMSSD * cue interaction, cue * condition interaction and cue * condition * PSS interaction.

The simplest model included only the factors of flanker (2 levels: congruent/incongruent) and cue (2 levels: valid/invalid), which equal the Executive and Orienting network contributions to the reaction times. The relevant factors were dummy coded

so that positive slopes would indicate the expected effects (i.e., slower responses in incongruent and invalid trials) to facilitate interpretation. Trials with double or no cues were not included in the analysis because they are used to assess the Alerting Network, which was not the focus of our hypotheses in this study. Trials assessing the Orienting Network (congruent/incongruent cues) and the Alerting Network (no/double cues) are mutually exclusive and, as such, cannot be simultaneously modelled. This results in up to 108 trials (comprising 72 valid cues and 36 invalid cues) per participant per condition, dependent on individual accuracy levels. The hypotheses were accepted when the final model included the RMSSD * cue interaction (Hypothesis 2), the cue * condition interaction (Hypothesis 3) and the cue * condition * PSS interaction (Hypothesis 4), with each interaction being a significant predictor of reaction time and the interaction effect pointing in the expected direction.

Results

The BoxCox transform showed λ-values between 0 and -.5 for RMSSD baseline data and RMSSD intervention data. This indicates that either a log(RMSSD) (for 0) or a -1/sqrt(RMSSD) (for -0.5) transform is appropriate to correct for skewness of the data. To maintain consistency between the data and enable comparability with other HRV research (21), a logarithmic transform was applied. Visual inspection of the distribution of the log-transformed RMSSD data revealed approximately normal distributions.

Similarly, BoxCox analysis showed a positive skew of the raw reaction time data. Approximate normal distribution was achieved through log transform.

All participants completed the ANT-R with at least 80% accuracy in the main block and 96% accuracy on average. T-tests for dependent samples showed no significant difference in accuracy between conditions ($t = .40$, $p = .69$) and a slight improvement over sessions ($mean_{accuracy\ t1} = .944$, $mean_{accuracy\ t2} = .955$, $t = 2.67$, $p < .05$).

Hypothesis 1

The first hypothesis was that the HRV BFB intervention yields a higher RMSSD than the normoventilation condition. The first model predicting $RMSSD_{gain}$ (from baseline) during the intervention included only the condition as a fixed effect. Adding the HRV baseline as a predictor improved the model. This is reflected in both the highly significant Chi-squared value for the additional explained variance and the lower AIC and BIC values. The interaction term between RMSSD baseline and the condition did not significantly improve the fit, as seen in all three indicators. Including sociodemographic parameters also did not improve the model fit.

The fit that predicts $RMSSD_{gain}$ (from the intervention) through the condition and RMSSD baseline was therefore chosen as the model with the best fit and used to test H1 (see Table 2 for results). The condition was a significant predictor of $RMSSD_{gain}$ ((RMSSD during intervention) - (RMSSD baseline)) in this model ($p < .001$).

Figure 2 indicates that the direction of the effect was in the expected direction. $RMSSD_{gain}$ through the BFB condition was higher than through the control condition of paced breathing at a normoventilation rate. The standardized regression coefficient of the condition in the linear mixed model was $\beta = 1.5$, which implies that during the BFB, RMSSD had increased 1.5 standard deviations more than during the NV from the baseline on average. T-tests for dependent samples verified that in the BFB condition the RMSSD during the intervention was significantly higher than the RMSSD baseline ($t = 4.57$, $p < .001$), whereas during the control condition the RMSSD was slightly lowered ($t = -2.07$, $p < .05$).

A negative β of the RMSSD baseline as a predictor indicates that individuals with a higher RMSSD baseline respond to the BFB intervention to a lower degree.

Table 2

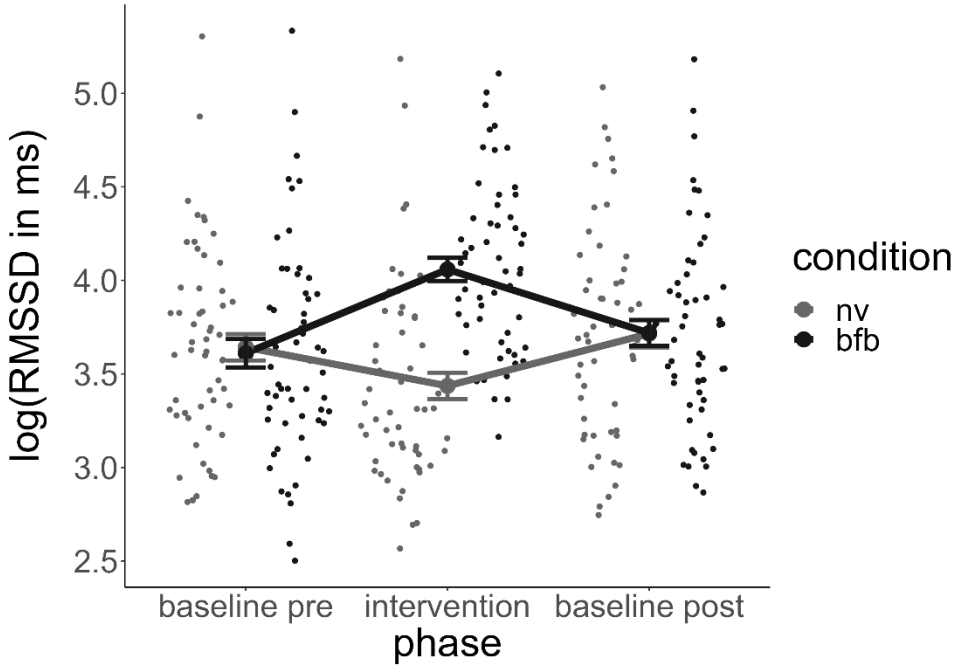
Results of the hierarchical linear mixed models for $RMSSD_{gain}$ during intervention

	Standardized $RMSSD_{gain}$					
Predictors	*β*	*std. Error*	*CI*	*t value*	*p*	*df*
(Intercept)	-0.75	0.08	-0.91 – -0.60	-9.77	<0.001	111
RMSSD	-0.28	0.06	-0.39 – -0.17	-4.94	<0.001	69
condition	1.51	0.11	1.30 – 1.72	14.34	<0.001	56
Random Effects						
σ^2	0.31					
$\tau_{00\ vpn}$	0.02					
ICC	0.07					
$N_{\ vpn}$	56					
Observations	112					
Marginal R^2 / Conditional R^2	0.666 / 0.689					

Note. $RMSSD_{gain}$ is calculated through log(RMSSD during the intervention)-log(RMSSD baseline). In each fit, participant intercepts are modeled as random factors. Values reported are standardized regression weights (β). RMSSD – root mean square of successive differences.

Figure 2

Course of RMSSD across experimental phases by condition



Note. Error bars indicate standard errors. RMSSD – root mean square of successive differences; BFB – biofeedback; NV – normoventilation.

Hypotheses 2-4

The model with the best fit to the present reaction time data is the following:

RT ~ condition:cue:PSS + condition + PSS + cue * $RMSSD_{baseline}$ + flanker + (1 | participant)

Each fixed effect slope and interaction included in this model is a significant predictor. For standardized regression weights and individual R^2 contributions of the model, see Table 3.

Hypothesis 2

H2 stated that a higher RMSSD baseline, measured at rest, would predict better performance (lower scores) in the Orienting Network score of the ANT-R over both HRV biofeedback and control conditions. The cue * RMSSD baseline interaction confirmed the hypothesized association between the Orienting Network and RMSSD. Visual inspection of the interaction effect showed that the effect is in line with the hypothesized direction (see Figure 3). This was confirmed in post-hoc testing. This was confirmed in post-hoc testing. We compared the estimated marginal means of the linear trends that compared the slope of RMSSD predicting RT in valid and invalid cue trials using the emmeans package (v1.8.8). The marginal slope of the invalid trials was significantly steeper (-0.14) than the slope of the valid trials (-0.07), $d = 0.07$, $z_{ratio} = 4.22$, $p < .001$, leading to less difference between the slopes the higher the RMSSD.

Participants responded faster in trials with invalid cues the higher their RMSSD baseline was. This effect was also visible in a bivariate Pearson correlation of -.22 ($p < .05$) between RMSSD baseline and the Orienting Score (calculated $RT_{invalid\ cue}$ - $RT_{valid\ cue}$) when including only control condition data points in the calculation. As expected, higher RMSSD at rest was associated with better Orienting Network performance.

Table 3

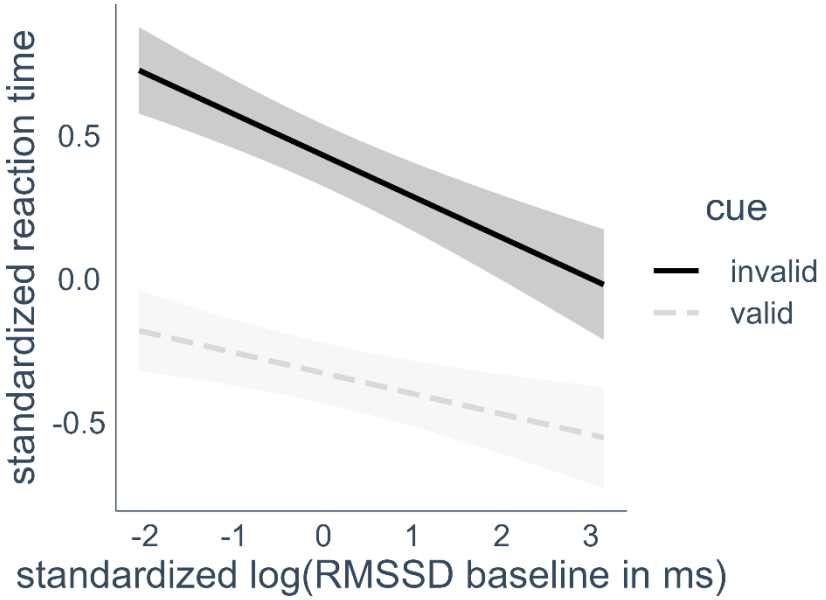
Results of the model with the best fit for reaction times

	Standardized reaction time					
Predictors	*β*	*std. Error*	*CI*	*t value*	*p*	*df*
(Intercept)	-0.76	0.05	-0.86 – -0.65	-13.87	<0.001	60
PSS	0.09	0.05	-0.02 – 0.19	1.60	0.109	56
condition	-0.04	0.01	-0.06 – -0.01	-2.39	0.017	10010
cue	0.76	0.02	0.73 – 0.79	44.52	<0.001	9991
RMSSD	-0.07	0.02	-0.12 – -0.03	-3.13	0.002	1979
flanker	0.95	0.01	0.92 – 0.98	64.74	<0.001	9991
cue × RMSSD	-0.07	0.02	-0.11 – -0.04	-4.22	<0.001	9991
(condition × cue) × PSS	-0.07	0.02	-0.12 – -0.03	-3.19	0.001	10020
Random Effects						
σ^2	0.53					
$\tau_{00\ vpn}$	0.16					
ICC	0.23					
N_{vpn}	56					
Observations	10047					
Marginal R^2 / Conditional R^2	0.329 / 0.482					

Note. Participant intercepts are modeled as random factors. β – standardized regression weight; RMSSD – root mean square of successive differences; PSS – perceived stress scale.

Figure 3

Interaction effect of heart rate variability and cue condition on reaction time



Note. RMSSD – root mean square of successive differences; valid cues – spatial cues in the same location that target appears in later; invalid cues – spatial cues in a different location than the target. Highlighted areas indicate 95% confidence intervals.

Hypothesis 3

We hypothesized that the Orienting Network scores of the ANT-R performance would be better after an HRV biofeedback intervention compared to the control condition. The cue * condition interaction neither appeared in the final model nor proved to be a significant predictor in any iteration. Contrary to Hypothesis 3, HRV BFB did not significantly improve the Orienting Network performance.

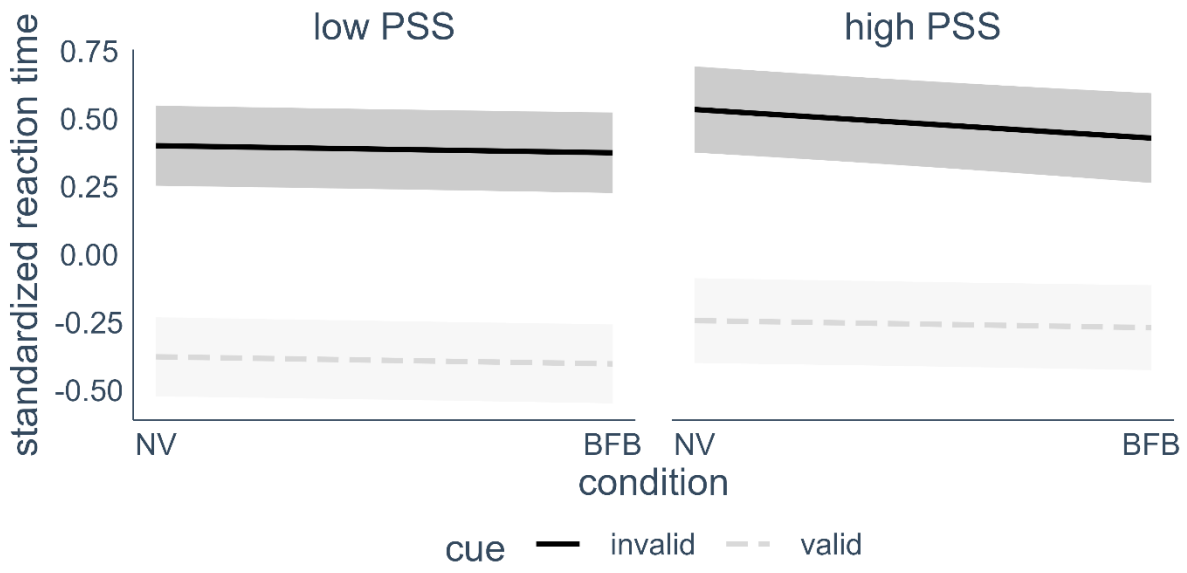
Hypothesis 4

We also postulated that the current stress level moderates the effect of HRV BFB on the Orienting Network performance of the ANT-R.

The 3-way interaction of self-reported stress, condition (normoventilation or biofeedback) and cue (valid or invalid spatial cue) appeared as a significant predictor of reaction time in the final model ($p < .05$). A visualization of the effect (see Figure 4) revealed that the biofeedback had a differential effect on the Orienting Network reaction times depending on the stress level of the individuals. In line with Hypothesis 4, there was a beneficial effect of the BFB for participants who reported high levels of stress, compared to less stressed individuals. Although there was no overall effect of HRV BFB on Orienting Network performance, in individuals with higher stress levels reaction times were lower in invalid spatial cue trials after the BFB condition compared to the normoventilation condition. The effect was quite small, however, with about 0.5% unique additional variance explained when adding this effect.To confirm the hypothesis, we conducted post-hoc Tukey testing. In order to facilitate the interpretation of the post-hoc testing, we conducted a median split with the PSS values and then performed a Tukey test on the three-way interaction, including PSS as a factor. The Tukey test confirmed that the interaction was driven by a significant difference between the NV and the BFB condition only in invalid cue trials in the high PSS group, $d = 0.11$, $z_{ratio} = 2.81$, $p < .01$. None of the other NV vs. BFB comparisons were significant.

Figure 4

Interaction effect of current perceived stress (median split), cue condition and intervention on reaction time



Note. For visualization purposes, a median split was conducted that separated the participants into a low stress (n=30) and a high stress (n=26) group. In the analyses however, the PSS score was treated as a continuous variable. Highlighted areas indicate 95% confidence intervals. PSS – perceived stress scale; NV – normoventilation; BFB – biofeedback; valid cues – spatial cues in the same location that target appears in later; invalid cues – spatial cues in a different location than the target.

Discussion

In the present study, we explored the acute effects of HRV BFB on attentional control. The HRV BFB had the expected effect of increasing the vmHRV during the intervention compared to the paced normal ventilation condition and the baseline. The data also revealed the expected association of a higher vmHRV baseline with better (lower) scores in the ANT-R Orienting Score. The Orienting Score was not significantly improved by the biofeedback intervention over all participants. However, an interaction effect of current self-reported stress levels and the condition showed that individuals with high stress performed slightly better in the Orienting Score after the biofeedback condition compared to the control condition.

Mechanisms of HRV biofeedback

The improved vmHRV during the HRV BFB condition implies that the BFB fulfilled its intended function of increasing the vmHRV at least temporarily during the intervention. As can be observed in Figure 2, the post-HRV baseline, assessed approximately 15-25 minutes after the intervention, did not differ between the biofeedback and control conditions. The effects of vmHRV improvement through the BFB therefore seem to have been rather short-lived.

This might be due either to the actual transience of the effects or to the circumstance that during this time participants engaged in a cognitive task. Active engagement usually leads to a reactive drop in vmHRV (43), and therefore might have counteracted a possible vmHRV improvement over a longer time frame. However, previous research suggests that the increased vmHRV during slow-paced breathing returns to baseline shortly after the intervention, even without a reactive drop due to task engagement (68). Taken together, these findings suggest relatively short-term effects on improving vmHRV through a single session of HRV BFB.

The proposed mechanisms of feedback loops and temporal coherence between heart rate and breathing cycle (24, 25) are supported by the present data. In line with the authors' claim that the heart rate, breathing and blood pressure oscillations resonate at a local maximum frequency of 0.1 Hz, our data showed a strong increase in vmHRV when participants were asked to breathe at a rate of 0.1 Hz but not when breathing at a rate of 0.25 Hz.

Not all participants were able to profit from the BFB. Some did not show an improvement in vmHRV. This is likely due to the very short intervention with only minimal coaching. Learning to adjust physiological processes in the body is no easy task and can therefore not necessarily be expected to be learned in 5 minutes but may require more intensive training. Excluding non- or low responders from the analysis, however, did not change the results. The association of HRV baseline and the HRV gain through biofeedback must also be

noted. Participants who had a higher resting vmHRV were profiting less from the biofeedback, indicating potential ceiling effects.

The fact that the control condition, which also induced paced breathing, did not lead to an increase in vmHRV speaks against the contribution of simple concentrative effects of HRV BFB on cardiac parasympathetic activation. As a matter of fact, the control condition even had a slightly detrimental effect on the vmHRV. This finding is in line with previous research which has extensively shown that increases in vmHRV during paced breathing are only found in low frequencies between 4 and 7 cycles per minute (e.g. 69). The literature has also showed the superiority of HRV BFB over concentrative/meditative practices, such as progressive muscle relaxation, in improving vmHRV (70, 71).

Resting vmHRV and attentional control

The associations between the Orienting Score of the ANT-R and the vmHRV baseline at rest (RMSSD) (19–21) were replicated in this study. Consistent with prior attentional control research (12, 13), a higher vmHRV at rest was associated with better top-down goal-directed attentional control as indicated by lower Orienting Scores.

Within the ANT-R Orienting paradigm, valid spatial cues outweigh invalid ones (3:1). This leads to a positive expectation of the appearance of the stimuli in the indicated location and the conditions' orientation toward the cued location, leading to consistently faster reaction times in trials with valid vs. invalid cueing. The activity of the amygdala, among others, is related to the conditioned allocation of spatial attention (72). The theory of neurovisceral integration (14) proposes that non-ideal conditioned behavior patterns such as this conditioned attention allocation can be attuned through functional inhibitory connectivity from vmPFC to the amygdala, which can therefore enable efficient reorientation after an invalid cue. According to the model of neurovisceral integration (73), this functional connectivity is reflected in vmHRV measures. The data found in this study – an association between the physiological

marker of CAN capacity (HRV) and the efficiency in spatial attention reallocation – offers further evidence for this theoretical framework.

Overall, the BFB intervention did not improve attentional control. After the HRV BFB intervention, participants did not achieve significantly better values in the Orienting Score, which contradicts our expectations based on prior findings of associations between the constructs. The present findings speak against cognitive effects from simply "activating" the CAN by means of afferent vagal activation through the BFB. It is possible that effects can only be observed after the strengthening of the connectivity and activity of the CAN through long-term BFB training. The results also do not support the findings of Prinsloo et al. (34), who found acute improvement on a cognitive task after BFB, although their study was severely underpowered with a sample of only seven individuals in the biofeedback and nine individuals in the control condition. A major difference between the two studies as well as from the other studies finding positive effects (38–40) is that the current study was conducted with a healthy sample, whereas the previous studies investigated highly stressed individuals or individuals who had just been exposed to a stressor.

HRV biofeedback, attentional control and stress

We also included current stress, measured as self-reports using the Perceived Stress Scale, in the analysis. The interaction term of condition and stress was a significant predictor of attentional control. This revealed that the BFB had different effects in different subgroups. The more stressed the participants were, the more they could profit from the biofeedback intervention regarding their attentional control capacity. Similarly, a previous study found that a single-session HRV BFB reduced anxiety only in individuals with high baseline anxiety in a sample of musicians (74).

The most probable mechanistic pathway, which explains differential effects dependent on stress levels, is implied by attentional control theory (75). This theory states that deficits in attentional control are elicited by stress and anxiety. Stress is related to enhanced worrying,

which in turn withdraws attentional resources from current tasks. Additionally, a state of anxiety induces preferential stimulus-driven, bottom-up attention direction. HRV BFB has been shown to momentarily decrease anxiety and increase calmness in stressed students (32), which might directly reduce these detrimental effects only in participants who were affected in the first place.

The current acute effects of HRV BFB on attentional control in stressed participants would also speak for the feasibility of immediate activation of the central autonomic network in individuals whose CAN either shows a lower functional capacity or less frequent activation. Mechanisms through which this direct enhancement of cognitive functioning through HRV BFB can occur include the afferent pathway (24).

Another possible mechanism for the acute cognitive effects is the direct mechanical pathway from the olfactory bulb to cortical areas. The sensory registration of airflow through the nose produces slow cortical potentials (SCPs) in the same frequency as the rhythmic air flow (76). These SCPs have enhancing effects on self-regulation and voluntary attention allocation, which is why SCP biofeedback is an effective treatment for attention deficit disorders (77).

It must be noted, however, that the differential effect of HRV BFB on attentional control depending on stress levels is quite small (only 0.15% of the variance was explained across all reaction time trials). In fact, the effect is only visible when variance due to flanker condition has been removed from the raw reaction time data. The raw average composite scores do not show the interaction effect. Whether or not the effect size amounts to a noticeable practical effect in high acute or chronic stress would have to be further investigated with specific target populations.

Limitations and prospects for future research

A limitation comes from conducting this study during the onset and course of the Covid-19 pandemic. The conditions under which the study was conducted were especially strict (face

mask, interpersonal distance, regular disinfection, etc.), which might have decreased the potential for the relaxing effects of the HRV BFB.

Another limitation is the length of the biofeedback intervention. Participants only practiced the biofeedback for a total of about 6 minutes. Whether or not this is enough to induce effects that last for at least 15 minutes (the duration of the ANT-R) is not clear. The previously conducted studies investigating acute effects on cognitive functions each employed slow-paced breathing or HRV BFB interventions with time durations between 10 and 17 minutes (38–42). This may shed light on why there was no main effect found in this study.

Additionally, the control condition of induced paced breathing to simulate normoventilation had a slightly detrimental effect on vmHRV, which might have subsequently altered the reaction time performance. While it was useful to specify the mechanisms through which HRV BFB is able to unfold its effect, it might have altered the ANT-R scores in an unexpected way, which thus might have covered up the effects.A clear implication for future research would be to focus on a sample of individuals with a compromised vmHRV, such as persons under acute stress (38–42), who are likely able to profit more from the BFB intervention (78) and therefore have a higher chance of also profiting from acute effects on attentional control. HRV BFB did not increase resting vmHRV in all individuals, also among those with a below average vmHRV. Future studies should investigate what differentiates individuals who can profit from the BFB from those who cannot. Instructions and coaching might also have to be adjusted in order to ensure benefits for all participants. An interesting prospect would also be to test the effects of long-term HRV BFB training on the same cognitive parameters to compare the effects of functional training and strengthening of the CAN capacity to the acute activation. Future research might also look more closely at the duration of the acute effects of HRV BFB. The results of this study showed that 15-20 minutes after a 5-minute intervention, vmHRV was already back at baseline. This might be due to a rebound reaction from the reaction time task (79) or the actual transience of the effects.

To further investigate the specificity and the mechanisms by which HRV BFB affects stressed individuals, conducting a comparative study between HRV BFB and another relaxation technique, such as progressive muscle relaxation, would be essential. Additionally, a study design that assesses attentional control before and after the intervention, rather than on two separate days as seen in other studies examining the acute effects of HRV BFB (e.g. 39), could help minimize confounding variables and might be better suited to detect effects.

Conclusion

In conclusion, we found differential acute effects of a single-session 5-minute HRV BFB intervention on attentional control. Highly stressed individuals profited from the intervention, whereas less stressed individuals did not and might even show adverse effects. The effect was quite small, however, which warrants further research into the nature of this effect.

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Appendix B: List of publications and conference contributions

Publications

Blaser, B.L., Weymar, M., Wendt, J. (2023). Ökonomische Erhebung prämenstrueller Symptomatik – Deutsche Übersetzung der Kurzversion der Premenstrual Assessment Form und deren psychometrische Überprüfung. Psychotherapie – Psychosomatik – Medizinische Psychologie. DOI: 10.1055/a-2136-6941

Blaser, B.L., Weymar, M., Wendt, J. (2023). The effect of a single-session heart rate variability biofeedback on attentional control: Does stress matter? Frontiers in Psychology. DOI: 10.3389/fpsyg.2023.1292983

Blaser, B.L., Hufenbach, M.C., Ventura Bort, C., Weymar, M., Wendt, J. (2023). Fear acquisition across the menstrual cycle: The moderating role of vagally mediated heart rate variability. Manuscript submitted for publication. DOI: 10.22541/au.169516750.01875818/v1

Blaser, B.L., Weymar, M., Wendt, J. (2023). Smartphone-based heart rate variability biofeedback training improves premenstrual and depressive symptoms as well as anxiety/stress symptoms and attentional executive control: a pilot study. Manuscript submitted for publication. DOI: 10.22541/au.170000973.36600989/v1

Blaser, B.L., Weymar, M., Wendt, J. (2023). Associations between fluctuations in premenstrual symptoms and vagally mediated heart rate variability in daily assessments throughout the menstrual cycle: a feasibility study. Unpublished manuscript preprint available. DOI: 10.22541/au.170000985.55376250/v1

Blaser, B.L., Weymar, M., Wendt, J. (2023). Premenstrual syndrome is associated with differences in heart rate variability and attentional control throughout the menstrual cycle. Manuscript submitted for publication.

Conference contributions

Blaser, B.L., Weymar, M., Wendt, J.: Acute effects of heart rate variability biofeedback on self-control [Society for Psychophysiological Research (SPR) – Annual Meeting 2021; poster]

Blaser, B.L., Weymar, M., Wendt, J.: Heart rate variability and attentional control in premenstrual syndrome [Psychologie und Gehirn (PuG) 2022; poster]

Blaser, B.L., Weymar, M., Wendt, J.: Effect of smartphone based heart rate variability biofeedback on mental health, attentional control and heart rate variability [Psychologie und Gehirn (PuG) 2023; poster]

Blaser, B.L., Hufenbach, M.C., Ventura Bort, C., Weymar, M., Hamm, A.O., Wendt, J.: Heart rate variability biofeedback, anxiety, and fear extinction [Deutscher Psychotherapiekongress (DPK) 2023; symposium talk]

Appendix C: Declaration of authorship

I hereby certify that the thesis I am submitting is entirely my own original work except where otherwise indicated. I am aware of the University's regulations concerning plagiarism, including those regulations concerning disciplinary actions that may result from plagiarism. Any use of the works by any other author, in any form, is properly acknowledged at their point of use.

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Eigenständigkeitserklärung

Hiermit bestätige ich, dass ich die vorliegende Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe. Die Stellen der Arbeit, die dem Wortlaut oder dem Sinn nach anderen Werken (dazu zählen auch Internetquellen) entnommen sind, wurden unter Angabe der Quelle kenntlich gemacht.

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Datum Unterschrift

Danksagung

[Die Danksagung ist nicht Teil der Veröffentlichung.]