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LETTER TO THE EDITOR

The Process of Heart Rate Variability, Resonance at 0.1 hz, and the Three Baroreflex Loops: A Tribute to Evgeny Vaschillo

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Our origin story

As a research psychologist trained in the areas of cognition and neuropsychology, I (MEB) was writing a grant application to study how acute alcohol intoxication affects emotional memory processes in persons at high versus low risk for alcohol use disorder. Over time, my plan to capture these phenomena on a strictly psychological level began to feel incomplete because it ignored that visceral physiological experience (i.e., bodily states and reactions) is so intricately intertwined with cognition, memory, and the 'feeling' of emotion. It seemed psychophysiological theory and methods might help to provide a more holistic picture of these phenomena through the measurement of mind-body relationships, especially at the intersection of cognition and emotion. But where to start? I arranged what turned out to be a fortuitous meeting with an eminent psychophysiologist at my institution to brainstorm an integrative research strategy. That researcher made a compelling case for value of including heart rate variability (HRV) based on his own research and growing bodies of literature documenting the broad relation of HRV to physical and mental health.

That was nearly 20 years ago and the psychophysiologist I met with is the current Editor of *Applied Psychophysiology and Biofeedback*, Paul Lehrer. That grant application was successful, and Dr. Lehrer was kind enough to introduce me to Drs. Evgeny Vaschillo and Bronya Vaschillo who then joined our research team as engineering and clinical physiologists. Evgeny, trained in Russia as an electrical engineer and a physiologist, is internationally renowned as a leading researcher in the area of HRV, and was an originator of HRV biofeedback. The Vaschillos provided guidance on designing and implementing the first of our psychophysiologically-informed studies. Over the intervening years, they went on to inspire what has emerged as a major thrust of our research program in alcohol and drug use, health behaviors, and mechanisms of behavior change. Thus, the Cardiac Neuroscience Laboratory (CNL) at Rutgers University – New Brunswick emerged and continues today in diverse and expanding areas of psychophysiological inquiry. The CNL has grown to encompass multiple principal investigators, and to provide training to a large number of undergraduate students, graduate students, postdoctoral fellows, and early career investigators.

Evgeny's untimely death robbed the psychophysiology field of one of its most forward-thinking, innovative, and inspiring scientists. His impact lives on, however, through the contributions of the trainees and researchers he has inspired world-wide. We especially value this opportunity to convey the innovations that Evgeny brought to the way in which the established and rising researchers in our lab not only think about and study HRV, but also our work to develop more holistic conceptions and applications of the baroreflex mechanism in relation to substance use and other health behaviors. Here we highlight just a few of the theoretical and applied contributions that Evgeny made to our understanding of HRV, HRV biofeedback, and the baroreflex loops in an effort to continue to promote innovation and momentum in the field of psychophysiology.

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Seminal insights of Evgeny Vaschillo

HRV is a *biomarker* of future physical and psychological health (Young & Benton, 2018), an *indicator* of stress (Kim et al., 2018), an *index* of resilience (An et al., 2020), and emotional regulation (Appelhans & Luecken, 2006), a *correlate* of cognitive load (Solhjoo et al., 2019), and an *associate* of memory consolidation (van Schalkwijk et al., 2020). The list could go on and on; the point is that HRV has ubiquitous relations to wide-ranging components of physical and mental health. Yet, at the same time, the potential impact of HRV research often has been limited by conceptualizing autonomic nervous system activity as a "response" or an "objective measure" of a psychophysiological process, rather than the process itself. The past work of Evgeny and the many ongoing and future-planned projects inspired by Evgeny in our laboratory push past this limitation. Herein, we describe what we see as Evgeny's legacy. We then highlight our laboratory studies that utilized these insights to advance understanding of alcohol use behaviors.

1. HRV is a dynamic, integrative process

Evgeny impressed upon us, first and foremost, that HRV is a physiological *process* that unfolds continually over time. Real life is complex and ever-changing, and the cardiovascular system is elegantly adapted to this context. HRV is the result of the ongoing integration of "inputs" not only from the brain to the body, but from the body to the brain. This means that information flow is bidirectional; that not only do neural inputs influence the heart, but also cardiovascular inputs influence the brain via ascending pathways that deliver sensory feedback for integration in subsequent behavioral responding (Bates & Buckman, 2013; Buckman et al., 2018; Critchley, 2009; Eddie et al., 2020; Reyes Del Paso et al., 2009). This further implies that the baroreflex mechanistically contributes to the systemic changes that come about from integrated sensory inputs, cognitive interpretations of sensory data, and subsequent motor responses, such as can be observed during experimental challenge conditions, and modeled together with brain response and subjective reports of internal states and experiences. These considerations of HRV as an active process organically led us to a focus on experiments that included psychological, behavioral, and pharmacological challenges in order understand adaptive capacity and behavioral flexibility in terms of how well an individual can modulate arousal in real time under the influence of alcohol use and in contexts reflective of daily life.

2. The cardiovascular system has resonance properties

The baroreflex, like other reflexes, can be considered as a closed-loop control system (Halámek et al., 2003; Hammer & Saul, 2005). Such feedback systems reveal resonance properties if a delay in the loop is present (Grodins, 1963). The length of the delay determines the specific resonance frequency; the shorter the delay, the higher the resonance frequency. Arterial baroreceptors react to blood pressure (BP) changes and trigger increases or decreases in heart rate (HR) to compensate for BP shifts. The delays between HR and BP changes (10 s period) result in a resonance frequency at about 0.1 Hz and is specific to the HR branch of the baroreflex. Knowledge of such resonance properties of the cardiovascular system were used to advance our research in two important ways. First, we developed a method to enhance the sensitivity of detecting the impact of experimental manipulations of arousal, as laboratory challenges are less potent than personally salient stressors in everyday life. Internal or external stimulation paced at the resonance frequency of the HR closed-loop (i.e., at 0.1 Hz) maximizes the amplitude of HR oscillation at this frequency (e.g., (Song & Lehrer, 2003; Task Force, 1996; Vaschillo et al., 2004; Vaschillo et al., 2011), providing us a method to enhance detection of within-person changes and between-person differences in laboratory settings. Second, we derived a novel 0.1 Hz HRV index, which measures the amplitude of the power spectrum density function at 0.1 Hz and has been shown to be associated with baroreflex activity (deBoer et al., 1987; Vaschillo et al., 1983, 2002, 2006).

3. The three branches of the baroreflex

Based on the flexibility and precision of BP control in relation to the internal and environmental challenges of daily living, it is reasonable to assume that cardiovascular changes arise from more than changes in the timing of heart contractions. While HR and HRV have been the focus of clinical research over many decades due to the ubiquity of electrocardiograph (ECG) devices and the ease of non-invasively measuring heart contractions, it is well-established that the cardiovascular system also adjusts the volume of the blood ejected by the heart per beat (i.e., stroke volume; SV) and the balance of vasodilatory and vasoconstrictive forces (i.e., vascular tone, VT) to control BP and sensitively convey bodily status updates to the brain. Evgeny made significant strides in conceptualizing and measuring the baroreflex as a *three -branch* closed-loop system: the HR baroreflex, whereby HR is adjusted to stabilize BP, the stroke volume baroreflex, whereby the strength of the heart contraction is adjusted to stabilize BP, and the vascular tone baroreflex, whereby vessel diameter is adjusted to stabilize BP. Each baroreflex branch plays its own specific role in blood flow distribution and may react differently to challenges, yet, all three branches are coordinated by the baroreceptors. This implies that the cardiovascular system has built-in redundancies and that, like HR, stroke volume and vascular tone are components of the baroreflex.

4. Cardiovascular reactivity is integrated into the human experience

In most research, HRV is examined in isolation – separate from other components of the cardiovascular system, separate from neural activation, separate from other organ systems, especially those associated with stress reactivity. Evgeny contributed to our lab's dynamic systems approach as a framework within which to conceptualize, model, and assess cardiovascular processes as phasic reactivity and modulatory processes that express in relation to other system processes (e.g., central executive network, hypothalamic–pituitary–adrenal (HPA) axis). His frequent teachings and deep knowledge base allowed us to explore new ways to frame questions that moved beyond static conceptions of individual differences in psychosocial and behavioral research. Our laboratory has built, and continues to build, a strong evidence base demonstrating the importance of cardiovascular functioning on the modulation of cognition, emotion, and behavior, especially as it relates to alcohol use behaviors.

The Cardiac Neuroscience Laboratory today

External stimulation at 0.1 hz using contextual cues: arousal, emotion, and alcohol salience

These novel psychophysiology methods were used by our laboratory to study alcohol effects on dynamic changes in arousal as they occurred within the person while they were responding to environmental contexts that evoked varying emotional states. Using a methodology that combined a 0.1 Hz frequency of stimulus presentation with measurement of the 0.1 Hz HRV index, we examined HRV response to 5 min blocks of standardized emotional picture cues (Bradley & Lang, 2007) following an acute alcohol, placebo, or control beverage (Vaschillo et al., 2008). This allowed us to examine alcohol effects on arousal regulation in varying emotional contexts when cognitive control was intact, degraded by alcohol challenge, and cognitively manipulated via placebo challenge. We observed that 0.1 Hz paced visual stimulation with picture cues induced notable resonance frequency oscillation in HR and yielded overall increases in the HRV spectra with spectral peaks at 0.1 Hz. Stronger effects were observed in response to positive and negative emotional stimuli, compared to neutral stimuli. Thus, even in the laboratory setting using static picture cues, we showed that HRV was a sensitive indicator of how an individual modulates arousal in emotionally valenced contexts. This is significant in that the effect of paced visual stimulation on HRV was independent of the influence of respiratory sinus arrhythmia (RSA) in this study (i.e., respiration spectra did not vary across neutral and emotional cue conditions), adding support for the premise that baroreflex modulation was the underlying mechanism. We further compared measurement characteristics of the 0.1 Hz HRV index to standard time and frequency domain HRV indices (Task Force, 1996). Evidence of convergent validity of the 0.1 Hz HRV index was observed in that it was suppressed following an acute dose of alcohol, as were traditional HRV measures (SDNN, PNN50, HF HRV) in this study and in other labs (Ralevski et al., 2019). Evidence for discriminant validity was found in that the 0.1 Hz HRV index was significantly elevated in response to emotional picture cues, compared to the other HRV indices which decreased. Finally, the 0.1 Hz HRV index was especially sensitive to negative emotional stimuli and cognitive expectancy effects of alcohol (placebo condition), compared to the other HRV indices, indicating higher predictive validity (Vaschillo et al., 2008).

Through the use of model-based cluster analysis, we further found that high risk drinkers in this sample who had behavioral disinhibition and emotional suppression motivations for drinking showed significant, large effect size changes in 0.1 Hz HRV in response to visual alcohol and drug cues, as well as to emotional cues, in contrast to the low risk drinkers (Mun et al., 2008). In an independent sample of college students, who were mandated to a brief intervention program for violating university policies about on-campus substance use, differences in the severity of the infraction were related to significant differences in arousal modulation in response to both neutral and emotionally valences stimulus cues, potentially indicating less effective modulation of arousal in the students who went on to escalate their drinking behaviors over the next two years (Buckman et al., 2010). These studies demonstrated the value of psychophysiological data, and specifically the 0.1 Hz HRV index, in identifying heterogeneity in arousal modulation, especially in response to emotional and appetitive contexts, which may reflect individual differences in susceptibility to stress and substance use vulnerability. Overall, these initial study results supported the validity of the 0.1 Hz HRV index, suggested that tonic emotional contexts, created within the laboratory using 5 min blocks of similarly emotionally valenced or appetitive picture cues presented at 0.1 Hz, were effective in eliciting notable within-person changes in arousal modulation, and demonstrated that differences between persons in arousal modulation within the context of alcohol and drug cues align with high versus low risk motivations for alcohol use involving emotional and behavioral regulation.

A large follow-up study of emerging adult drinkers who were stratified by a biobehavioral risk marker of familial history of alcohol use disorder (FH+) found that FH + drinkers showed less suppression of 0.1 Hz HRV index of cardiovascular reactivity and modulation by alcohol, especially in response to negatively valenced emotional cues and alcohol-related cues, compared to those without this familial history (Bates et al., 2020). Yet, resting state HRV and reactivity to neutral cues did not vary between groups. This suggests that HRV response to challenge in specific environmental contexts provided additional information about the phenomenon of low sensitivity to alcohol, which is a risk factor for the development of alcohol use disorders. It is especially noteworthy that even within the same person, physiological sensitivity to acute alcohol can vary within a drinking occasion dependent on characteristics of the environment (i.e., negative emotion and salient alcohol cues). We further found that following alcohol consumption, the magnitude of 0.1 Hz HRV response to alcohol cues correlated with extent of memory bias towards those same cues only in FH + participants (Leganes-Fonteneau et al., 2020a, b). These studies extended understanding of risk related to low response to alcohol by uncovering diminished cardiovascular sensitivity to alcohol in FH + individuals, the importance of environmental context to its expression, and the interrelation of cognitive, emotional, and physiological components of risk for alcohol use disorder.

Internal stimulation at 0.1 hz: HRV biofeedback and episodic resonance paced breathing (eRPB)

Evgeny and his colleague Paul Lehrer were early pioneers in the study of resonance paced breathing and the development of HRV biofeedback (Lehrer et al., 2000; Vaschillo et al., 2002, 2006). Their work has inspired the application of HRV biofeedback in a variety of clinical populations such as those affected by asthma, hyper- and hypotension, fibromyalgia and depression, and other disorders (Hassett et al., 2007; Karavidas et al., 2007; Lagos et al., 2008; Lehrer et al., 2006, 2020). As well, both HRV biofeedback and slow-paced breathing show substantial efficacy in reducing subjective stress and anxiety (Goessl et al., 2017).

Difficulties in adaptively modulating arousal, stress, and negative affective states are cardinal features of substance use disorders, suggesting that adjunctive interventions to normalize baroreflex modulation of arousal states should be especially useful for bolstering recovery from substance use disorders. That is, while there are effective behavioral interventions for substance use disorders, a primary challenge is the ability to sustain recovery after treatment, when relapse rates increase sharply over time (Bates et al., 2022). Everyday experiences of stress, negative affect, and alcohol and drug cues in the environment can interrupt recovery by serving as potent triggers for substance use. Further, these internal and external challenges appear to affect behavior ‘automatically’ in that the experience of visceral arousal during urges and craving usually is not subject to cognitive control via strategies learned in treatment. Theoretically, internal stimulation of the baroreflex mechanism via HRV biofeedback or resonance paced breathing could provide a tool to bolster cognitive control efforts by interrupting or dampening automatic-visceral reactions that unintentionally undermine treatment gains (Bates et al., 2022).

Given that HRV and baroreflex sensitivity are often impaired in this population (Bär et al., 2006), the baroreflex is a promising mechanistic target to enhance arousal modulation. In fact, we observed that baroreflex sensitivity and HRV spontaneously improved in women receiving outpatient cognitive behavioral therapy for alcohol use disorders (Buckman et al., 2019). In that study, the baroreflex mechanism was not manipulated, yet inherent system plasticity was evident from pre- to post-treatment, even in women who continued to engage in some level of drinking. The results were consistent with our experimental demonstrations that the baroreflex provides a malleable treatment target in high-risk drinkers and clinical samples and supported the hypothesis that the baroreflex mechanism participates in the natural biobehavioral processes of recovery from substance use disorders (Bates et al., 2022).

As a next step to determine whether active manipulation of the baroreflex could enhance normalization of arousal modulation, we conducted a pilot study of a brief HRV biofeedback intervention in young men receiving intensive inpatient treatment for substance use disorders. A larger effect size reduction in substance craving in participants who received 3 sessions of biofeedback, compared those who received treatment as usual was found (Eddie et al., 2014). In addition, for patients in the treatment-as-usual group, low levels of HRV at treatment entry were associated with less positive changes in craving over time, while low basal HRV was not a risk factor for less craving improvement in those who received the HRV biofeedback. These findings are consistent with the idea that HRV biofeedback enhanced neurocardiac signaling thereby promoting physiological modulation of the craving response and diminishing the risk associated with low resting HRV levels.

We further evaluated a longer course of HRV biofeedback as an adjunct to the supportive interventions being provided to college students in substance use recovery housing (Eddie et al., 2018). The effect of twelve weeks of HRV biofeedback on changes in craving, as well as anxiety and depression symptoms and perceived stress, was compared to wait-list control. Significant reductions in craving were observed during HRV biofeedback compared to wait-list. Individual-level spaghetti graph plots suggested that craving reductions were greatest in students who began biofeedback with the highest levels of craving. A follow-up, multi-level model of these data (Alayan et al., 2019) identified a quadratic pattern of craving reduction wherein reductions accelerated over time in students who were relatively older and who practiced HRV biofeedback on their own for greater than 12 min per day. In addition, within-person increases in depression assessed weekly during treatment attenuated HRV biofeedback effects on craving. Together, these three factors explained over 20% of the variance in craving changes over time, highlighting the combined influence of age, affect, and behavior on biofeedback effectiveness for craving reduction.

These promising results were obtained within the contexts of inpatient treatment and residential recovery programs. Yet, the majority of persons with substance use disorders do not receive inpatient treatment, or indeed any formal treatment at all. This raises important questions about acceptability, accessibility, feasibility, and compliance with a traditional course of HRV biofeedback as an adjunctive intervention for persons receiving outpatient treatment for substance use disorders, persons attending self-help groups, and those in natural recovery. We strategized with Evgeny about whether it would be possible to employ a brief episode of the 'active ingredient' of HRV biofeedback, i.e., episodic resonance paced breathing (eRPB[1]), as a just-in-time intervention that persons could self-administer, at will and in their natural environment, to dampen visceral arousal when they anticipated or experienced emotions and situations that may trigger substance use.

This 'in-the-moment' approach to manipulating the baroreflex mechanism outside of the laboratory or clinic environment and at the moments of highest relapse vulnerability was facilitated by the advent of smart phone applications (app) and biosensors. We used one such electronic health (e-health) approach to examine a clinical application of eRPB in a highly vulnerable population of parenting women who were attending a 12-wk community-based, outpatient addiction treatment program. Women were randomly assigned to an active eRPB intervention (6 breaths per min.) or sham breathing control intervention (14 breaths per min). An existing iPhone HRV biofeedback/paced breathing app was used to pace breathing for the two conditions. The women were randomly assigned to the eRPB or sham condition and asked to use the app in their daily lives whenever they anticipated or encountered risky emotions and situations that might trigger alcohol or drug use for them. Beyond the effects of formal treatment, it was hypothesized that the eRPB, compared to the sham intervention, would mitigate craving and improve affect. While positive and negative affect did not vary between groups, a significant group X app use interaction effect on craving was found (Price et al., 2022). Frequent app use during the intervention phase was associated with lower craving levels in the eRPB group relative to the sham breathing group. While the sham group experienced increasing levels of craving over time, as is typical of persons in outpatient treatment, the eRPB group maintained relatively stable, low levels of craving over time. The use of a sham breathing control provided evidence that eRPB did not function primarily as a distractor from risky internal or external cues, as craving was not mitigated in frequent users of the sham breathing intervention. Thus, in addition to the clinical benefits that appear to accrue cumulatively following multi-week sessions of HRV biofeedback and practice, eRPB may provide a useful just-in-time intervention that persons can self-initiate in their daily lives to dampen substance use urges and craving.

To help understand the mechanisms through which eRPB may impart clinical benefit, we developed a nonlinear computational model of the baroreflex that represented the baroreflex mechanism as the output of a complex brain-body system that includes dynamics of heart and vascular musculature, ascending and descending neural tracts, and an array of chemo- and mechanoreceptors (Fonoberova et al., 2014). This approach provided a noninvasive paradigm to capture many otherwise unobservable physiological processes and determine which were most affected by resonance breathing and the extent to which these varied between persons. Respiration rate was the input and HR and BP data collected at rest and during a 5-minute eRBP episode were used to validate the model. Several notable responses in cardiac muscle, vasculature, and afferent neural traffic were found that occurred specifically in response to resonance breathing, and these positive changes were observed in the majority, but not all participants (Fonoberova et al., 2014). We are currently studying factors that may account for individual differences in response to eRPB and factors that influence the likelihood of its use by persons recovering from substance use disorders.

Evgeny had a long-term interest in understanding HRV biofeedback and resonance paced breathing as a behavioral manipulation to affect neuroplasticity (i.e.,

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[1] It is important to note that our applications of eRPB to date have involved pacing breaths at 0.1 Hz, i.e., 6 breaths per minute. In practice, however, there are individual differences in resonance frequency that vary from 4.5 to 6.5 breaths per minute. Future research is needed to gauge the trade-off between the time and effort needed to determine precise resonance at the individual level versus ease and feasibility of broad scale application in hard-to-reach populations with respect to effectiveness of eRPB interventions.

neuromodulation) in brain regions involved in integrated cardiovascular and addiction circuitry (Bates & Buckman, 2012; Buckman et al., 2018). Inspired by the early work of Lacey (Lacey & Lacey, 1978) he often spoke of the role of intrinsic cardiovascular feedback loops in brain inhibition processes. We subsequently developed a proof-of-concept functional magnetic resonance imaging (fMRI) study to assess changes in brain reactivity to unique sets of alcohol cues presented before and after a 5-min eRPB intervention, compared to a low cognitive demand task, in young men and women with varying light to heavy drinking behaviors (Bates et al., 2019). We showed that resonance breathing altered neural responses to alcohol cues by decreasing visual cortex activation (e.g., left inferior and superior lateral occipital cortices, right inferior lateral occipital cortex), suggesting that afferent modulation of the baroreflex loop reduces attentional bias to alcohol cues in drinkers. eRPB further increased activation in brain areas implicated in behavioral control, internally-directed cognition, and brain-body integration (e.g., medial prefrontal, anterior and posterior cingulate, and precuneus cortices). The control group showed no significant changes in brain response from the first to the second set of alcohol cues. These findings provided initial evidence that modulation of the afferent stream of the HR baroreflex loop through eRPB alters neural activation in a manner theoretically consistent with a dampening of automatic sensory input and strengthening of higher-level cognitive processing. A follow up study is in progress to directly test these hypotheses using electrophysiology to assess event-related brain potentials (ERPs) using experimental tasks that tap attention and inhibition processes.

Internal stimulation at 0.03 hz: the use of paced sighing as a sympathetic challenge

Evgeny developed a cross-spectral technique that used changes in pulse transit time (PTT, in ms) caused by one mmHg change in BP, with consideration of coherence and spectral frequency ranges (Vaschillo et al., 2011), as a measure of vascular tone branch of the baroreflex. PTT is measurable on a beat-to-beat basis and provides insight into peripheral vascular resistance (Schwartz, 2005) and arterial wall elasticity (Naka et al., 2006; Smith et al., 1999; Vaschillo & Vaschillo, 2021). While not a perfect proxy for vascular tone, it offers a direction forward for elucidating vessel dynamics as a key source of cardiovascular variability and potential contributors to cognition and emotion.

In conjunction with this method for measuring VT baroreflex activity, Evgeny was also investigating the potential for a second resonance frequency that could be harnessed for research and clinical purposes akin to the 0.1 Hz resonance frequency of the HR branch of the baroreflex. As noted above, breathing paced at 0.1 Hz aligns cardiac oscillations driven by RSA with cardiac oscillations driven by the HR baroreflex to instantaneously enhance parasympathetic activity. Because vascular control is mediated only via input from the sympathetic nervous system (Goldstein, 2001), identification of a resonance frequency in the vascular tone branch of the baroreflex could potentially provide a means for manipulating sympathetic activity. Evgeny proposed a second resonance at ~ 0.03 Hz, which would correspond to a hypothetical 15 s delay (or 30 s period) in the VT response to BP (Vaschillo et al., 1983, 2002). However, empirically supporting this proposed second resonance proved challenging at first because most individuals cannot maintain a breathing rate sufficiently slow to align RSA with the proposed VT branch of the baroreflex. As an alternative, Evgeny developed a paced sighing task wherein participants breathed normally except when cued to perform a voluntary sigh at certain frequencies. As he hypothesized, rhythmical sighing elicited strong and immediate responses that rippled across the cardiovascular system with no signs of habituation; this effect included increases in skin conductance, a purely sympathetic physiological system (Vaschillo & Vaschillo, 2020; Vaschillo et al., 2015, 2018). Rhythmical sighing provoked these responses when it was paced at 0.02 Hz (1 sigh every 50 s), 0.03 Hz (1 sigh every 30 s) and 0.06 Hz (1 sigh every 15 s), but evidence of resonance was not readily observable. It remains unknown whether there is a second resonance frequency in the very low frequency range, but work in this field continues.

In typical Evgeny form, he was undeterred by the lack of resonance. He had, in fact, observed two other promising outcomes that he was actively investigating at the time of his death. First, he was working on HRV reactivity to 0.066 Hz sighing, which he proposed as a putative clinical marker of early changes in arterial elasticity (Vaschillo & Vaschillo, 2020). Second, he was developing a theory that "anti-resonance", or a stabilizing frequency, exists in the low/very low frequency range of the RRI spectrum, at which variability in the cardiovascular system appeared suppressed. That was the thing about Evgeny: he had so many more theories and ideas than he could ever test, even had he lived to 100 years. Our lab endeavors to keep his efforts going, and we encourage others to read his papers and continue to reimagine the cardiovascular system as an ideal system to understand and improve the human condition.

The future of the Cardiac Neuroscience Laboratory:

Integrating Evgeny's legacy across disciplines

Evgeny's legacy lives on in the CNL. Our research team continues to advance understanding of how HRV is linked to arousal, attention allocation, and contextual factors that influence an individual's substance use behaviors. In addition, we are actively building on Evgeny's interest in using paced sighing as a sympathetic challenge and exploring how substance use and other behaviors affect vascular dynamics. Further, through Evgeny's direct and indirect influences, we continue to train the next generation of scientists, who join our laboratory in pursuit of fusing psychophysiological principles, methods, and theories into their own independent lines of research interests. While the prior section of this article demonstrated the depth of Evgeny's influence on our laboratory and the field of addiction, below we asked our current trainees (presented in order of the time they have spent in the lab) to demonstrate the breadth of his influence.

Neel Muzumdar, Doctoral Student

I (NM) joined the laboratory in my first undergraduate year; that was 7 years ago. Within first five minutes of meeting Drs. Evgeny and Bronya Vaschillo, Evgeny had turned my interview into a lesson on baroreflex and neurocardiac relationships. I am fortunate to be among the last CNL trainees to be mentored by both Bronya and Evgeny. Under Bronya's supervision, I learned how to consistently collect high-quality psychophysiological data and how to rapidly screen for signal abnormalities due to methodological issues and cardiovascular dysfunction in real time. Her mentorship exponentially expanded my clinical knowledge, which was highly salient to me at the time as I intended to go to medical school. Evgeny brought depth to my ability to *understand* signals – both normal and abnormal and, more generally, to understand what ECG, pulse, and respiratory signals tell us about physiological (and neural) systems. His lessons and his confidence in my abilities were important factors that led me to seek a PhD in Kinesiology and Applied Physiology rather than an MD.

Evgeny was always offering new perspectives on cardiovascular physiology; he saw potential in measuring variability in HR, pulse transit time, stroke volume, and BP to see the body's ability to adapt in real-time, which pushed past the idea that HRV was valuable as an objective physiological biomarker of health and performance, Evgeny sought new tools to measure and manipulate the vascular tone and stroke volume baroreflex branches in addition to the HR baroreflex branch; this included developing non-taxing physical loads to generate strong responses in the baroreflex. Load is often looked at as a challenge, but it is also a tool to drive noticeable physiological response and thus can enable observation of otherwise hidden systemic activity. Rhythmic breathing and sighing have shown to amplify baroreflex activity and their effects can be evaluated from a straightforward peak amplitude measurement. His work, at the time of his death, also challenged the idea that HRV is an excellent tool to measure parasympathetic, but not sympathetic nervous activity. He was exploring paced breathing and sighing as a means to parse physiologically relevant signals in the low frequency band of the RRI spectrum.

Beyond his strong influence on my technical training, Evgeny's work on the cardiovascular implications of alcohol use set a strong foundation for my dissertation research. I am working to expand on this foundation and characterize the cardiovascular effects of cannabis use. With the recent wave of state-level cannabis decriminalizations and legalizations, the public health implications of understanding the physiological effects of recreational and medical cannabis use the substance have increased dramatically. Cannabis use research is still in its infancy – there are few studies on its cardiovascular effects (mostly from medical settings). More critically, there is little research into the physiological implications of alcohol and cannabis co-use, which is increasingly common in the US, especially in young adults. My future research goal is to understand how physical, pharmacological, and cognitive loads can "pile up" to diminish health. Using Evgeny's breathing tasks, coupled with cognitive load tasks, I plan to observe the difference in physiological reactivity between cannabis users, alcohol users, and co-users.

Mateo Leganes-Fonteneau, Research Associate

I (MLF) joined the CNL when Evgeny and the team had already built a solid foundation for the role of HRV and baroreflex functioning as processes that can enhance vulnerability to, or help protect against, unhealthy behaviors such as drinking. They had already developed the breathing techniques used to modulate the cardiovascular system and the methods to quantify cardiovascular response. My decision to join the lab grew from my graduate research that examined cardiac interoceptive awareness, that is, the ability to feel internal bodily sensations and heartbeats (Garfinkel et al., 2015). Despite a large and growing literature on cardiac interoception, there was a lack of research examining the cardiovascular mechanisms that support conscious perception of heartbeats. I saw opportunities to use existing literature on HRV and baroreflex sensitivity to explain the processes that researchers in the emerging field of interoception were trying to disentangle.

Since joining the CNL, I have made considerable strides to merge knowledge from cardiovascular psychophysiology with the theories of interoception; Evgeny's pioneering work with the 0.1 Hz signal, in particular, has importantly shaped the work I have done and continue to do in my career. In a registered report (Leganes-Fonteneau et al., 2021a, b), we examined how 0.1 Hz HRV and HR BRS contribute to performance in the heartbeat discrimination task (Katkin et al., 1983; Whitehead et al., 1977). We hypothesized that if perception of heartbeats depends on the strength of baroreceptor signaling, then resonance breathing could be used to improve interoceptive awareness. Contrary to our hypotheses, we found that HF HRV, 0.1 Hz HRV and HR BRS negatively correlated with baseline performance in the heartbeat discrimination task. Further, changes in 0.1 Hz HRV and HR BRS during resonance breathing positively correlated with increases in heartbeat perception. From this, we put forth a predictive coding perspective on HRV (Corcoran et al., 2021; Ottaviani, 2018; Rae et al., 2018), wherein a downregulation of cardiac variability facilitates the integration of interoceptive and exteroceptive information. Within that perspective, resonance breathing re-organizes HRV within a tight oscillatory pattern to increase the predictability of heartbeats, reducing interoceptive prediction errors to facilitate conscious heart-beat detection (Hohwy, 2014; Seth & Friston, 2016).

Using Evgeny's 0.1 Hz HRV peak measure, we also have expanded understanding of the role that interoceptive signals play in reward processing and addiction. We conceptualize 0.1 Hz HRV as a novel measure of afferent heart-brain connectivity that importantly adds a "lower order interoceptive signal" to current conceptualizations of interoceptive processing (Suksasilp & Garfinkel, 2022). In an aforementioned study (Leganes-Fonteneau et al., 2020a, b), we examined 0.1 Hz HRV as an interoceptive marker for risk of alcohol use disorder. We found that in FH + persons, alcohol administration triggered changes in 0.1 Hz HRV in the presence of alcohol cues that correlated with memory for those same stimuli. In other words, the interoceptive signature associated with alcohol-related stimuli can then shape responses towards them. In a separate, placebo-controlled study (Leganes-Fonteneau et al., 2021a, b), we found that the extent to which acute alcohol modulates 0.1 Hz HRV positively correlated with alcohol attentional biases. That is, individual differences in how alcohol modulated heart-brain connectivity were associated with the value of alcohol related stimuli after alcohol priming. We are currently examining how alcohol affects the cardiovascular system to impact the cardiac amplification of emotion, and whether these effects are mediated by changes in 0.1 Hz HRV and baroreflex sensitivity (Leganes et al., 2021). These studies build support for 0.1 Hz HRV as a basic interoceptive signal that is integrated to construct subjective perceptions of satiety and intoxication, and thus reward.

My future research goals remain focused on addiction and mental health, particularly to understand the interoceptive basis of cognitive and emotional processes, and how resonance breathing might be used to improve emotion regulation (Leganes-Fonteneau et al., 2020a, b), decision making (Herman et al., 2021), and response inhibition (Rae et al., 2018) through the modulation of interoceptive cardiac signals. Using the tools and concepts developed by Evgeny, I believe that the basic cardiovascular underpinnings of interoceptive processes can be understood and used to benefit clinical populations.

Julianne Price, Postdoctoral Fellow

I (JP) was drawn to the CNL because it addressed the science of alcohol and substance use with a whole-body perspective. Of particular interest to me was the lab's conception of the baroreflex as and adaptable and malleable system with resonance properties. This paralleled my own work in the hypothalamic-pituitary-adrenal (HPA) axis. In my graduate training, I had noticed that research on the HPA axis often viewed it as if it were a static biomarker and its indices (e.g., momentary cortisol levels) as stable endpoints. Yet, research had clearly shown that HPA axis activity involves continuous streams of afferent and efferent information that fluctuate to regulate the body and respond to changes in their homeostatic resting points. Its body-brain pathway incorporates feedback as well as feed-forward processes that integrate bodily information with central processing of emotion and cognition. Thus, as initially proposed in the seminal allostatic load paper (McEwen & Stellar, 1993), the HPA axis is an allostatic system - adaptive and flexible, capable of a wide range of function in a healthy individual, and sensitive to frequent reactivation and overactivation that creates disease vulnerability through a loss of system elasticity. Evgeny's perspective on HRV and the baroreflex clearly aligned with the cardiovascular system as another allostatic stress response system. Over the last 30 years, addiction science researchers have leveraged the allostatic model to study the HPA axis, but the cardiovascular system as an allostatic process often has been overlooked.

My initial projects in the CNL centered on the recently completed randomized clinical trial described above. Beyond showing that more frequent use of an app delivered eRPB was associated with lower craving levels across the 8-week intervention(Price et al., 2022), we showed that both time-varying and state-level factors predicted the utility of eRPB: app use frequency varied positively with the 0.1 Hz peak achieved and perceived usefulness positively varied with blunted resting state high frequency HRV (Price, submitted). In other words, those with greater cardiovascular capacity and flexibility used the app more, and those with lower parasympathetic control found that the app was more useful. Throughout the intervention, exposure to negative triggers (e.g. feeling stressed, overwhelmed, anxious) was associated with higher ratings of usefulness. Together, the results of this clinical trial suggest that the use of eRPB to dampen arousal in the face of drug and alcohol triggers (particularly stress-inducing triggers) effectively and cost-efficiently blocked elevations in craving during outpatient recovery—a highly vulnerable period in recovery.

My future research goals seek to integrate my knowledge of the HPA axis with Evgeny's many insights about dynamic neurocardiac baroreflex system response to acute and chronic alcohol use. My research builds on observational studies in humans and experimental paradigms in animals that show interactions of the HPA axis with peripheral and central arms of the cardiovascular control system. I am developing a series of studies that examine the baroreflex and HPA axes in tandem, assessing their parallel afferent pathways and their bidirectional interactions that occur both centrally and peripherally. Thus, although I joined the CNL at the beginning of the COVID-19 pandemic and missed the opportunity to work with him in-person, my current work and future goals are highly influenced by Evgeny.

Kelsey Piersol, Doctoral Student

I (KP) was drawn to the CNL during my second year of doctoral studies at Rutgers. During my first year, before I even knew the work the CNL and Evgeny were doing, Bronya gave me a brief training in resonance breathing and explained the concepts of resonance frequencies to assist with an ongoing study I was running at the time. I was awed by the immediate, robust oscillations in HR simply from slowing respiration to 6 breaths per minute and more generally by the idea of using the mechanical properties of the human body and its regulatory systems to not only assess, but also manipulate and train cardiovascular functioning. Unfortunately, it would be another year before I officially joined the team of scientists in CNL. By then, the pandemic had hit and the opportunity for more direct training from Evgeny was gone. Nonetheless, I dove quickly into learning the robust psychophysiological assessments, software, and analyses used that they had established in CNL. Today, I manage the lab's ongoing psychophysiological data processing, a job performed by Evgeny and Bronya not so long ago. It is a daunting task to follow in their footsteps, but they laid a solid foundation for me, and I hope to carry Evgeny's legacy forward throughout my career.

My current work is focused on replicating and expanding an earlier study from Evgeny that explored several novel strategies from measuring cardiovascular dysregulation in a sample of young binge drinkers (Vaschillo et al., 2018). One of these strategies evaluates the interdependence, or intercorrelations, of cardiac and vascular parameters. In the original paper, binge drinkers, compared to social and non-drinkers, showed greater correlations among average HR, stroke volume, pulse transit time, and systolic BP. Evgeny proposed that this coupling of cardiovascular parameters reflected reduced flexibility in homeostatic regulation of the cardiovascular system, which was not evident from evaluating parameters independently. I am currently working to expand these findings using data from CNL's recently completed clinical trial of parenting women in treatment for a substance use disorder. Using a principal component analysis, we have identified changes in factor structures from pre- to post-treatment that support Evgeny's early theories: as women enter treatment, there is greater intercorrelation among cardiovascular parameters and factors that dissipates over the 8-week treatment. We have more data and more samples still to play with and hope to create strong support for using this statistical approach to detect cardiovascular rigidity.

More broadly, my independent research line will apply many of Evgeny's ideas to improving women's health across the lifespan. I am studying the role of somatic cues, both within and outside of conscious awareness, in women's behavior choices and overall physical health. Women who consume alcohol are at greater risk for cardiovascular disease than men. Women experience multiple reproductive changes (e.g., menarche, pregnancy, and menopause) and hormonal fluctuations that differentially impact cardiovascular health (e.g., altered HF HRV across menstrual cycle, increased blood volume/circulation during pregnancy, higher BP in menopause). Further, women with cardiovascular disease or those who experience cardiovascular events, such as heart attack, present differently than men and are often misdiagnosed (Keteepe-Arachi & Sharma, 2017). Understanding and identifying changes in cardiac and vascular system dynamics during these life phases may reveal vulnerable time points for disease progression and/or reveal protective factors that enhance cardiovascular system resilience. By leveraging the framework of Evgeny's work to assess the cardiovascular system from multiple dynamic perspectives, I hope to expand our understanding of female-specific factors that contribute to increased risk of cardiovascular symptom presentation and disease development in women.

Ian Frazier, Postdoctoral Fellow

I (IF) joined CNL in 2021 to add a cardiovascular perspective to my interests on how brain and behavioral correlates of socioemotional cognition are affected by alcohol misuse. Although I never had the opportunity to meet Evgeny, his body of research is clearly a major influence on my current work. First, Evgeny's view of the cardiovascular system as more than a passive autonomic "response" system shapes my perspective on what the body can tell us about neural processing. Second, Evgeny's identification of resonance frequencies in the cardiovascular system, especially the 0.1 Hz resonance frequency, are fundamental elements in my ongoing studies. And third, I seek to build Evgeny's conceptualization of cardiovascular dynamics as an integrated component in human experience by merging his ideas and methodologies with my background in neuroimaging and socioemotional cognitive theory.

The CNL previously reported that a 5-minute epoch of resonance breathing reduced BOLD activation in occipital regions and increased activation in cognitive and emotional control regions (i.e. prefrontal and cingulate cortices) during alcohol cue exposure in college-age drinkers (Bates et al., 2019). Building from this fMRI finding, we are currently extending our testing of the impact of resonance breathing as an intervention that effects cognitive control, alcohol cue salience, and performance monitoring in binge drinkers by utilizing electroencephalography (EEG) paradigms. Binge drinking is associated with impairment in awareness-related functions (Almeida-Antunes et al., 2021) that manifest in part as worse task performance and impaired error-related negativity (ERN) during various cognitive tasks (Kim & Kim, 2019; Lannoy et al., 2017; Smith et al., 2016). Such impairments may represent early deficits that can eventually hinder complex socioemotional cognition (e.g., alexithymia, affective theory of mind, empathy) (Bora & Zorlu, 2017; Cruise & Becerra, 2018; Le Berre, 2019). Our new study looks at the effects of eRPB on an alcohol cued Go/NoGo task in binge drinkers, measured from task performance and event related potentials (N2 and ERN). The theory is that the neural correlates of performance monitoring are negatively affected by binge drinking, which may in turn contribute to the development of substance use disorders. If eRPB improves the brain and behavioral correlates of performance monitoring in the presence of salient alcohol cues in binge drinkers, it would provide support the utility of resonance breathing as a tool to influence decision making. This study is an extension of Evgeny's view of cardiovascular processes as embedded components of affect and cognition that, in turn, motivate human behavior.

Moving forward, I draw from an extensive literature showing that HRV is linked to a variety of socioemotional cognitive functions, such as emotion recognition (Quintana et al., 2013) and regulation (Mather & Thayer, 2018), self-control (Zahn et al., 2016), decision making under chance and risk (Forte et al., 2021), and social cooperation (Beffara et al., 2016). In addition, lower HRV is associated with a range of developmental and mental health disorders that are characterized by impaired socioemotional functioning, including autism spectrum disorder (Van Hecke et al., 2009), anxiety (Kemp et al., 2012), depression Karavidas et al., 2007; Kemp et al., 2010, p. 2010), and alcohol use disorder (Buckman et al., 2019; Ingjaldsson et al., 2003; Quintana et al., 2013). Given the mounting evidence for HRV's relevance to socioemotional cognition, both in healthy and clinical samples, I see research potential in examining the mechanistic role of cardiovascular processes in basic (e.g. emotional awareness) and higher order (e.g. social trait learning and decision making) social cognition processes.

Jennifer Buckman, Associate Professor

I (JFB) joined Marsha Bates and the CNL just one year before Bronya and Evgeny. In the 12 years that we worked together, Evgeny and I built an incredible system for collaboration, one that overcame his limited fluency in English and my limited fluency of cardiovascular physiology (thank you, Bronya!). Those early days with the Vaschillos helped me recognize that the heart was not just some muscle that the brain controlled, as neuroscience education can lead students to think, but the ever-important, life-sustaining supply chain, which, when compromised, can easily starve even the hardiest of neurons and glia. These days, I am still aware that my mastery of cardiovascular psychophysiology pales in comparison to his but feel honored to have worked so long and so often with Evgeny and to have written two successful NIH grants with him, both that explored alcohol and the vasculature.

First, we leveraged data from that very first study that Marsha performed with Evgeny, a study that measured cardiovascular reactivity during the ascending limb of the blood alcohol curve in college drinkers (Buckman et al., 2015). We found that those who drank alcohol (peak BAC ~ 0.08% to mimic a binge episode) versus juice showed significant elevations in average HR and reductions in average stroke volume. This multi-process response suggests adaptive cardiovascular adjustment during intoxication in healthy young people, which differs from the more common, single-process maladaptive change (elevated HR) that has been reported for decades. We also noted that alcohol intoxication reduced variability across the cardiovascular system, observable in both low and high frequency HRV, stroke volume, pulse transit time, and BP. Less variability in the system implies more rigidity; it also likely reflects allostatic processes at play. Finally, we observed that blood vessels reacted more strongly to a 1-unit change in BP after, compared to before, alcohol was consumed (i.e., greater vascular tone baroreflex sensitivity). Thus, during the ascending limb of the blood alcohol curve, the vasculature was hypersensitive, pressure and flow were more tightly linked, and/or the sympathetic nervous system was more activated. Taken together, we posited that binge drinking reduces parasympathetic activity and increases sympathetic activity, creating two parallel pathways of system loading. We also proposed that blood vessels were particularly quick to detect the presence of alcohol and preemptively activated to offset alcohol's suppressive effects on the cardiovascular system following oral consumption.

In a second, independent study funded through Evgeny's first NIH grant, cardiovascular function was compared in non-drinkers, social drinkers, and binge drinkers at rest and during a sympathetic (paced sighing) and parasympathetic (paced breathing) challenge (Vaschillo et al., 2018); no alcohol was administered. Binge and social drinking groups demonstrated only modest, non-significant differences in average cardiovascular functions (e.g., average HR, systolic BP). Likewise, while there was a consistent pattern of subtle reductions in variability indices in the binge versus social drinking group, none were statistically significant. Thus, it appeared that cardiovascular reactions to intoxication did not persist in young healthy individuals without an AUD. Yet, the sensitivity of the vascular tone baroreflex in the unchallenged rest state, and during a sympathetic challenge (0.03 Hz paced sighing) and a parasympathetic challenge (0.1 Hz paced breathing) revealed subtle differences. At rest, local vascular control systems are tonically active and no group differences were evident [43]. However, as loading increased and the system was taxed, central control systems (i.e., baroreflex) came online to supplement these tonic systems in the social drinkers to a greater extent than binge drinkers. These studies drove the development of a larger longitudinal study (ongoing at the time of writing) that tests whether it is possible to see pre-clinical changes in the vasculature of ostensibly healthy young adults as the result of "normative" college drinking.

In addition to the fortune of having a decade of working together, I am fortunate to have had the opportunity to say goodbye to Evgeny before his death. I wanted him to know how much he had contributed to my career direction and trajectory. I wanted to reiterate that we were a good team and that it was such a pleasure and honor to work with him.

Conclusions

One focus of the CNL today builds from Evgeny's two NIH funded studies on the vasculature. Numerous student-driven and NIH-funded studies have expanded his ideas to consider the cardiovascular system as a primary allostatic system and the often-small challenges, triggers, and obstacles of daily life as the central components of 'stress' and behavioral inflexibility. These studies utilize Evgeny's paced sighing tasks and the eRPB task as a graded physiological challenge that allows characterizing of real-time cardiovascular adaptation. The goal of these studies, just as Evgeny envisioned, is to see whether the physiological effects of life's hassles – like a bad night of sleep or an evening of heavy drinking, or a combination of both –accumulate to begin the insidious march towards disease, and whether that march can be detected earlier, and perhaps redirected, long before disease sets in.

Another focus is to push forward Evgeny's quest to uncover ways in which the cardiovascular system and brain work together to adapt to life's daily challenges, and the physiological mechanisms that underlie interventions that enhance body-brain communication. He began work to provide proof-of-concept for the use of body oscillations to stimulate oscillations in the brain by using transfer function analysis to explore dynamic associations between the RRI and blood-oxygen-dependent (BOLD) signals during eRPB compared to a control task that did not alter typical breathing rate (Vaschillo et al., 2016). We are continuing to study the impact of eRPB on brain responses to better understand the centrally-mediated clinical benefits of HRV biofeedback and eRPB.

Evgeny's absence at our frequent (and often long) team science meetings is still acutely felt, but his name is still often part of the discussion. We sit on Zoom and ponder … hmmm, let's think that through … hmmm, what does that mean – WWES (*what would Evgeny say*)?

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