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Getting to the Heart: Autonomic Nervous System Function in the Context of Evidence-Based Music Therapy

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Abstract

As evidence-based music therapy turns its attention to physiological responses, it will need outcome measures that are grounded in an understanding of mechanisms which drive physiological activity. Despite strong indications for the involvement of the autonomic nervous system (ANS) in health and disease and its response to music, few studies have systematically explored the therapeutic or interventional effects of music on ANS dysfunction. After reviewing the experimental and interventional literatures on music and ANS response, a "neurovisceral integration" perspective on the interplay between the central nervous system and ANS is introduced, and the associated implications for physiological, emotional, and cognitive health are explored. The construct of heart rate variability is discussed both as an example of this complex interplay and as a useful metric for exploring the sometimes subtle effect of music on autonomic response. Suggestions for future investigations using musical interventions are offered based on this integrative account.

Keywords

autonomic nervous system, heart rate variability, music, neurovisceral intergration

The present review concerns the role of the analysis of physiological change as a component of evidence-based music therapy.[1–3] Physiological change is the broad label given to the actions of the central nervous system (CNS; brain and spinal cord) on the major peripheral organs and organ systems via the autonomic nervous system (ANS). The "wiring" of the ANS is extensive, extending through the circulatory (heart, blood vessels), digestive (gastrointestinal tract glands and sphincters, kidney, liver, salivary glands), endocrine (adrenal glands), integumentary (sweat glands), reproductive (uterus, genitals), respiratory (bronchiole smooth muscles), urinary (sphincters), and visual (pupil dilator and ciliary muscles) systems. The wiring itself is usually discussed as having 2 major branches—the sympathetic nervous system (SNS) branch, associated with energy mobilization, and the parasympathetic nervous system (PNS) branch, associated with vegetative and restorative functions.

The density and complexity of this network explains why ANS dysfunction (or "dysautonomia") is associated with a host of complex and heterogeneous disorders and diseases with distinct etiologies,[4–6] such as diabetic autonomic neuropathy, hyperhidrosis, orthostatic intolerance/postural tachycardia syndrome, pure autonomic failure, and vasovagal syncope. More generally, autonomic dysfunction is present in conjunction with neurodegenerative diseases such as Alzheimer disease, multiple system atrophy, and Parkinson disease; neuro-developmental disorders such as autism spectrum disorders; autoimmune diseases such as multiple sclerosis; mental disorders such as generalized anxiety, major depression, and schizophrenia; and following ischemic stroke or myocardial infarction.

Music and the ANS: Experimental and Interventional Investigations

Remarkably, nearly every one of the ANS organ targets mentioned previously has been investigated in conjunction with musical stimuli. Table 1 summarizes 2 comprehensive reviews on ANS response to music[7,8] as well as a recent search of PubMed, highlighting the many and varied electrical, chemical, or volumetric signatures that have been probed.

The literature on the effect of music on ANS activity in healthy participants is quite large; the literature on how music affects individuals with ANS dysfunction (especially within the

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Table 1. A tally of investigations of physiological responses to music,[a] as summarized from Bartlett[7] and Hodges[8]

	Hodges (2009)		
Measure	Sig.	Nonsig.	Bartlett (1996)
HR/IBI	42	25	69
Blood pressure	12	9	23
Respiration	19	4	17
EDA/SCR	24	6	22
EMG	12	2	14
Skin temperature	12	5	10
Gastric motility	3	0	3
Chills–SCR	5	1	—
Blood volume	2	2	6
Blood-oxygen saturation	2	0	—
Biochemical responses	—	—	11
SigA	10	2	—
Cortisol	11	2	—
ACTH	2	1	—

Abbreviations: ACTH, adrenocorticotropic hormone; EDA, electrodermal activity; EMG, electromyographic activity; HR, heart rate; IBI, inter-beat interval; SCR, skin conductance response; Sig., statistically significant; Nonsig., not statistically significant; SigA, secretory immunoglobulin A.

[a] Cell counts are not mutually exclusive, as some studies included multiple dependent measures.

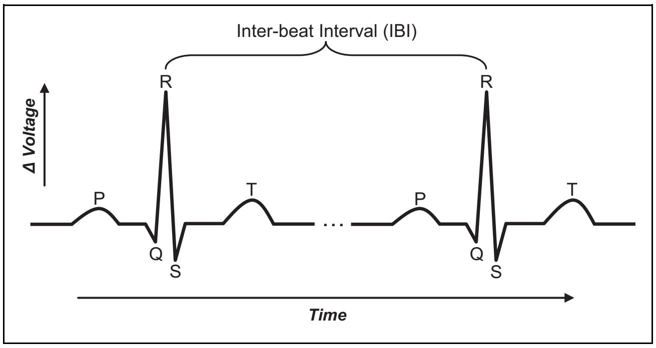

Figure 1. A prototypical electrocardiographic waveform, with characteristic voltage changes (labeled P through T) associated with the pumping and filling of the heart. The "R spike" is the quantitative analog of the heartbeat.

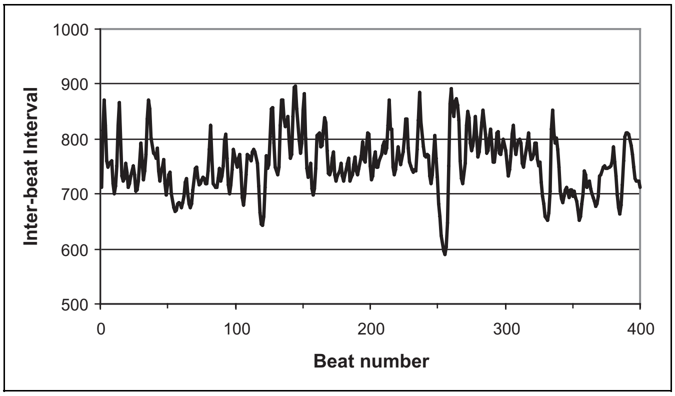

Figure 2. A sample time series of 400 inter-beat intervals (IBIs). Successive IBIs (x-axis) are plotted against the duration of each IBI (y-axis).

context of musical interventions) is less developed. In both literatures, however, changes in physiological activity (eg, heart rate [HR], blood pressure, electrodermal activity) are often investigated and discussed from 1 of 2 distinct (and tacit) perspectives: as either (1) the by-products of arousal, mood, anxiety, and other psychological states which are the primary target of study or (2) definitive barometers of those psychological states. The second perspective assumes that statistically significant changes in ANS activity reflect meaningful changes in the state of the organism (when in fact they may not). Conversely, the first perspective assumes that, since physiological changes are the downstream consequences of changes in "central" states, they have only limited diagnostic utility. Neither perspective addresses a fundamental issue: that the ANS (and activity in its targets) is exquisitely linked, bidirectionally, with the CNS, endocrine system, and immune system[4,9,10] (cf Figure 3). For these reasons, the ANS may serve as a sensitive, dynamic mechanism by which music exerts a beneficial effect on health and a therapeutic effect on disease. This hypothesis has only begun to be explored; the present article may thus serve as a conceptual springboard for future study.

The present review was based on a series of parallel searches with CINAHL, Google Scholar, ISI Web of Science, MEDLINE, and RILM during October 2009[11] and again in October 2011. Table 2 summarizes the search parameters queried (which will be referred to throughout the text in {braces}) and tallies the corresponding number of hits in PubMed. Three summary points may be made: (1) less research exists on ANS responses to music versus CNS responses to music, be it general discussions {A3–A5 vs A1}, specific disorders {B5–B11 vs B2–B4}, or measures of physiological activity {E3–E11 vs E1–E2}; (2) specific conditions associated with ANS dysfunction {D1–D9} have received very little investigation in conjunction with music; and (3) when ANS activity is recorded during a musical intervention, it is most often in the context of reducing anxiety {C1} or pain {C3} in patients {F21} during the perioperative period {F22}.

In the following summary, distinctions are made based on the study population (experimental studies on healthy participants vs interventional studies on patients) and method of interaction with music (listening to vs entraining to vs making).

Listening to Music

Listening to music for the purpose of a therapeutic benefit in a single or group setting is the most long-held tradition in music therapy. The origins of this practice date to the writings of the ancient Greeks; most notably, Pythagoras, Aristotle, and Plato; lengthier discussions of the healing power of music listening emerged in the Middle Ages, beginning with Boethius.[12] In modern times popular methods (eg, "Guided Imagery and Music"[13]) and therapeutic schools (eg, traditional oriental music therapy[14]) employ a wide repertoire of the so-called receptive methods[15] (eg, relaxation to music, reminiscence of lifetime

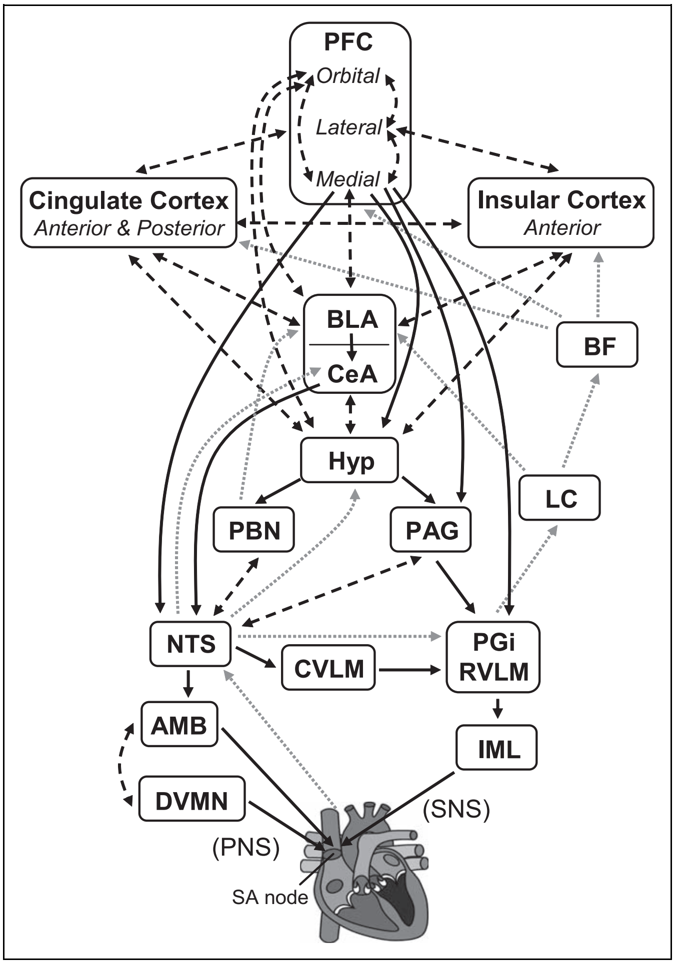

Figure 3. Neural structures involved in the control of heart rate.[55-59] Solid black arrows indicate descending pathways to the heart, including right vagus nerve (PNS) and stellate ganglion (SNS) inputs to the SA node. Dotted gray arrows indicate ascending pathways to medullary structures via aortic baroreceptor signals carried through the vagus. Dashed black arrows indicate bidirectional connections; AMB, nucleus ambiguus; BF, basal forebrain; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; CVLM, caudal ventrolateral medullary neurons; DVMN, dorsal vagal motor nuclei; IML, intermediolateral cell column of the cord; LC, locus coeruleus; LHA, lateral hypothalamic area; mPFC, medial prefrontal cortex; NTS, nucleus of the solitary tract; PAG, periaqueductal gray; PBN, parabrachial nucluei; PGi, nucleus paragigantocellularis; PN, pontine nuclei; PVN, paraventricular nucleus of the hypothalamus; RVLM, rostral ventrolateral medullary neurons; SA, sinoatrial; PNS, parasympathetic nervous system; SNS, sympathetic nervous system. Heart graphic (http://en.wikipedia.org/wiki/File: Heartgraphic.svg) used under the GNU Free Documentation License. Figure adapted from "Music and autonomic nervous system (dys)function" by R. J. Ellis and J. F. Thayer. Copyright 2010 by the University of California Press.[11]

events), wherein the client simply listens to music. In addition to numerous psychotherapeutic applications, music finds great acceptance in physical medicine, especially in perioperative[16,17] (eg, for its anxiolytic and analgesic effects) and routine care[18] environments and also as a component of nursing interventions to support well-being in the hospital environment.[19]

Experimental

Physiological investigations of listening to music date back over 125 years; in his review, Diserens[20] cites some 24 investigations between 1880 and 1918 alone. Nearly every organ in the body with an electrical, chemical, or volumetric signature has at some point been investigated in conjunction with musical stimuli (for comprehensive reviews, see Bartlett[7] and Hodges[8,21]). Heart rate, electrodermal activity, blood pressure, and respiration rate are the most commonly measured peripheral ANS responses; a PubMed search retrieved nearly 500 articles in English which recorded at least one of these measures while the participants interacted to music.

A number of studies have reported that listening to sedative music (ie, slow tempo, legato phrasing, minimal dynamic contrasts) can lead to decreased HR, respiration rate, and blood pressure. Notably, however, these effects are inconsistent. For example, of the 67 investigations reviewed by Hodges[8] measuring HR changes to music, 32 reported significant effects, 15 reported nonsignificant effects, and 10 reported a mixture of significant and nonsignificant effects. Thus, despite the relative ease at recording the electrical signature of a beating heart, the utility of *mean* HR is not without question. This issue is elaborated on later.

Interventional

A number of randomized controlled trials have reported that music possesses anxiolytic and analgesic properties and is associated with decreased HR, respiration rate, and blood pressure in perioperative patients (for reviews, see, eg, Dunn[22] and Evans[18]). Two caveats must be noted, however. First, the type of anxiety experienced would be considered "state" rather than "trait," given the short-lived nature of the anxiogenic stimulus (the operative procedure). Second, and more relevant for the current topic, the primary target in these studies is usually a reduction of *anxiety*; physiological changes are considered secondary.

Entraining to Music

Entrainment is the process by which 2 oscillating systems assume the same period (or period ratio) when they interact. In experimental paradigms, entrainment usually refers to the synchronization of endogenous rhythm in the participant with an exogenous rhythm in the environment. Endogenous rhythms exist at many orders of magnitude in a number of physiological processes, such as reproduction and menstruation (~30 days), sleep–wake (~24 hours), rapid eye movement sleep (~3 hours), blood pressure (~0.1–0.15 Hz), breathing (~0.15–0.4 Hz), cardiac pulse (~1–2 Hz), and electroencephalographic activity (~1–100 Hz).

In discussing the entrainment literature {F6}, it is useful to distinguish spontaneous entrainment (ie, unconscious or passive) from volitional entrainment (ie, conscious or active). Spontaneous entrainment has been reported in a

Table 2. Search Terms Queried[a]

Item	Category/search term	PubMed tally
	General search	
A1	(Brain) or (Central Nervous System)	1,532
A2	Cardiovascular System	75
A3	Autonomic Nervous System	62
A4	(Parasympathetic Nervous System) or (parasympathetic)	14
A5	(Sympathetic Nervous System) or (sympathetic)	45
	Disorder classes	
B1	(Anxiety Disorders) or (Panic Disorder)	110
B2	Central Nervous System Diseases	720
B3	Multiple System Atrophy	0
B4	Neurodegenerative Diseases	56
B5	(autonomic) and (disorder)	6
B6	(autonomic) and (dysfunction)	26
B7	Autonomic Nervous System Diseases	7
B8	Cardiovascular Diseases	291
B9	dysautonomia* or (Primary Dysautonomias)	0
B10	Dysautonomia, Familial	0
B11	Peripheral Nervous System Diseases	35
B12	(Cerebrovascular Disorders) or (Stroke)	157
B13	(Basal Ganglia Diseases) or (Parkinson Disease) or (parkinson's disease)	63
	General states	
C1	Anxiety	512
C2	Arousal	576
C3	Pain	464
	Specific symptoms/conditions	
D1	Arrhythmias, Cardiac	18
D2	Bradycardia	1
D3	Hyperhidrosis	3
D4	(Hypertension) or (hypertensive)	38
D5	(Hypotension) or (hypotensive)	5
D6	Hypotension, Orthostatic	0
D7	Syncope	3
D8	Tachycardia	7
D9	Postural Orthostatic Tachycardia Syndrome	0
	Physiological Measures/Tools	
E1	(Magnetic Resonance Imaging) or (Positron-Emission Tomography) or (Magnetoencephalography)	513
E2	Electroencephalography	395
E3	Blood Pressure	191
E4	Chills	7
E5	(Galvanic Skin Response) or (skin conductance) or (electrodermal activity)	56
E6	gastric	15
E7	Heart Rate	317
E8	(heart rate variability) or (hrv)	46
E9	(Respiration) or (Respiratory Rate) or (breathing)	196
E10	Skin Temperature	27
E11	(Vasodilation) or (Vasoconstriction)	6
	Interventions/Therapies	
F1	(autonomic) or (parasympathetic) or (sympathetic)	66
F2	(Biofeedback (Psychology)) or (biofeedback)	57
F3	(Breathing Exercises)	24
F4	(dance) or (dancing)	78
F5	(drum) or (drumming) or (percussion)	26
F6	entrain* or entrainment	11
F7	feedback	79
F8	(Gait) or (Walking) or (movement*)	244
F9	(heart rate) or (respiration) or (breathing) or (blood pressure)	286
F10	(heart rate variability)	21
F11	listen*	637
F12	Mind-Body Therapies	318
F13	Music Therapy	1,960
F14	(paced breath*) or (deep breath*)	5
F15	(performing or producing or making)	200
F16	(performance anxiety)	40
F17	(rhythmic auditory stimulation)	43
F18	(sing) or (singing)	123
F19	(Visceral Afferents) or (visceral afferent) or (interocept*)	1
F20	(Randomized Controlled Trial) or (Clinical Trial)	854
F21	Patients	1,313
F22	(Surgical Procedures, Operative) or (surgery)	450

[a] Tallies were obtained by searching PubMed (articles in English) using the format "music*[Title/Abstract] and (*search term*)" for terms in groups A-E, or "music*[Title/Abstract] and (intervention or therapy) and (*search term*)" for terms in group F. Capitalized terms are MeSH terms.

number of experimental studies, while volitional entrainment is more often explored in an interventional context.

Experimental

A few studies have reported spontaneous entrainment of blood pressure[23] and respiration rate[24–26] to musical tempo. While all explicitly refer to entrainment, "correlated with" tempo rather than "entrained to" tempo seems a more accurate (and tenable) conclusion given (1) the wide range of tempos precludes direct entrainment (eg, 42–124 or 55–150 beats/min [bpm]); (2) the lack of specificity of the period of entrainment (ie, at the level of the beat vs the measure vs the phrase); and in some cases, (3) the lack of generalizability of stimuli (eg, stimuli designed to match natural respiration frequencies.[23] Thus, although *passive* entrainment of ANS activity thus does not appear to happen per se, *volitional* entrainment of at least some processes (most obviously, breathing) is certainly possible, as discussed next.

Interventional

As an intervention, volitional entrainment has featured prominently in the recovery of speech function and gait. While some studies have recorded electromyographic activity in limb muscles (eg,[27]), none has measured ANS activity.

Breathing is one of the few physiological processes that can come under voluntary control (eg,[28]), making it a prime candidate for interventions. Several randomized controlled trials have reported significant decreases in both systolic and diastolic blood pressure in patients with chronic heart failure[29] or hypertension[30,31] using a "device-guided breathing" paradigm. Participants were instructed to synchronize their inhalations and exhalations to a high and a low tone, respectively. Tone duration was controlled by a device which monitored respiration via a chest strap and gradually lengthened the duration of the exhalation tone until the desired slow breathing rate was reached (10 breaths/min). While such a paradigm has been termed "breathe with interactive music,"[30,31] music itself has not been used as a component of the experimental procedure. Future studies should also consider how device-guided or entrained breathing to music differ from breathing exercises that do not utilize voluntary entrainment to an auditory signal but that report similar changes in physiological activity (eg,[32]).

Making Music

Active (or interactive) music therapy involves both the client's and the therapist's participation.[33] The music itself might either be improvisational (ie, spontaneous creation of sounds and music) or reproductive (ie, playing sheet music or singing familiar songs). The therapy itself may incorporate a variety of instruments (including the voice), specific methods (eg, musical role-play, symptom improvisation), and techniques (eg, imitating, accompanying).[34,35] Clinical goals (eg, nonverbal communication, self-expression) vary according to the client's needs and symptoms.

Experimental

While singing can reduce tension, increase energy, and improve mood in healthy participants (eg,[36]), its impact on physiological activity seems dependent on how the task is perceived by the participants. For example, Grape et al[37] found that professional singers showed greater HR variability ([HRV] an index of parasympathetic activity; see below) after a singing lesson, whereas amateur singers showed less HRV after the lesson. Valentine and Evans[38] reported a slight (2.5 bpm) increase in HR after solo singing, but a comparable decrease after choral singing. Fechir et al[39] reported a more substantial (7 bpm) increase in HR after solo singing—a task which the authors considered to be stressful. Thus, how a task is perceived by the participants should be considered when examining how that task affects physiological activity.

Interventional

Singing {F18} and drumming {F5} have been used in a variety of behavioral treatments, such as the recovery or improvement of language abilities and motor skills. Very few studies, however, have measured ANS changes associated with these activities. Wade[40] found that singing improved expiratory flow rates more than relaxation therapy in children with asthma. Takahashi and Matsushita[41] reported that elderly patients with dementia who participated in 2 years of weekly sessions of group singing and drumming activities did not experience a typical age-related increase in systolic blood pressure that was evident in a control group of participants. In interpreting these results, and others like them, it is important to consider whether singing offers benefits over the nonmusical breathing exercises discussed above.

Autonomic nervous system changes associated with dancing {F4} as part of an intervention have been reported in patients with chronic heart failure,[42] with diabetes,[43] who are overweight,[44] or who are elderly.[45] Although dancing can be considered a musical behavior, it is also clearly a form of exercise. From an empirical perspective, therefore, it is important to consider (1) whether dancing offers additional physiological benefits that other forms of exercise to music (eg,[46]) do not and (2) whether exercise to music results in different outcomes than exercise without music (eg,[47]).

Neurovisceral Integration: Linking the CNS and ANS

Much of the literature cited previously examines changes in ANS activity de facto rather than de jure; that is, measured and analyzed from a point of convenience rather than from an understanding of their physiological basis. In the remainder of this article, we use the beating of the heart as an example of the "front end" of a complex machinery driven by the intimate interplay between the CNS and ANS, and the importance of choosing outcome measures that are grounded in an understanding of the mechanism and dynamics of these interactive systems.

The Telltale Heart

By any count, the most frequently recorded measure has been the large voltage change associated with the contraction of the heart's ventricles (illustrated in Figure 1) and indexed either as *mean inter-beat interval* (IBI; the time in milliseconds [ms] between successive "R spikes" in the electrocardiogram [ECG]) or as *mean HR* (defined as 60 000/IBI, and reported in bpm).

The EKG has a long history within the field of psychophysiology; indeed, the waveform shown in Figure 1 was transcribed and labeled in exactly this manner over 110 years ago by the Dutch physiologist Willem Einthoven,[48] measured using his string galvanometer and buckets of saline as electrodes (for an early "photograph" of a string galvanometer in use, see[49]).

As noted earlier, however, in addition to its ubiquity, another notable feature of mean HR/IBI is its inconsistency: of the 67 studies tallied by Hodges,[8] 37% showed nonsignificant effects of music. Thus, even now, these findings seem to echo the concern of Rigg[50] made some 45 years ago, regarding music and affective response: "The verbal report, in spite of its subjectivity, has been more satisfactory than the physiological measurements."(p427) We suggest that a primary reason for the inconsistency of mean HR/IBI is the analysis of the measure itself: a focus on *mean* activity rather than on *variability of* activity.

Heart Rate Variability

Most studies which measure HR report it as an average value in bpm. In reality, however, there is no such thing as an "average" HR. It has been known since the mid-1700s that a healthy heart does not beat in a "metronomic" fashion but instead exhibits rhythmic, beat-to-beat fluctuations in time.[5] Figure 2 illustrates 400 consecutive IBIs recorded from a young healthy participant while resting comfortably. A clear rhythmicity is present in the rising and falling of IBIs along the y-axis. Early psychophysiologists, however, attributed this variability to measurement error, and (per that inference) considered average HR to be a more "stable" estimate of the physiological process.[51] Over the past 40 years, however, the link between the HRV and organism health, adaptability, and performance has been explored and clarified.[4,9,51,52] Because HR is a product of the complex interplay of the 2 divisions of the ANS (SNS and PNS), changes in mean HR (eg, prestimulus, poststimulus) are illuminated only to a degree.[9,51] Heart rate variability attempts to tease out the *relative* contributions of sympathetic and parasympathetic activity.

Sympathetic and Parasympathetic Control of HR

Chronotropic (ie, the timing of heart beats) control of the heart is achieved via the complex interplay of the SNS and PNS branches of the ANS. Medical physiology texts (eg,[53]) often discuss ANS control over the heart as a push–pull system: the SNS increases the force and rate of contractions, and the PNS decreases the force and rate of contractions. This, however, is an oversimplification.

Under resting conditions, the PNS dominates cardiovascular physiology.[54] The PNS governance of the heart is accomplished through direct enervation of the heart via the vagus nerve (cranial nerve X) at the sinoatrial node (a ganglion of cardiac pacemaker cells responsible for generating the heart beat). While the intrinsic firing rate of pacemaker cells is around 105 bpm, healthy adult resting HRs are only 60 to 80 bpm. That is, the PNS exerts a *tonic inhibition* over the heart via the vagus, and the removal of that inhibition (without any change in SNS activity) can lead to an increase in HR. Furthermore, pacemaker cells respond rapidly (150 ms latency) to changes in PNS input but more slowly to changes in SNS input (30-60 seconds until maximum effect), due to neurotransmitter differences (acetylcholine for PNS and norepinephrine for SNS). Furthermore, an "accentuated antagonism" has been reported in the interaction between SNS and PNS inputs: the deceleratory chronotropic effects of PNS activation are increased as the level of background SNS activity increases.[55]

The complexity of this dual innervation is redoubled, however, by its connection to an intricate neuroarchitecture with descending, ascending, and bidirectional links between cortical, midbrain, and brain stem structures,[56–60] as illustrated in Figure 3. Thayer and Lane[9] have noted that subsets of these structures have been given various labels: *central autonomic network*,[56] *anterior executive region*,[61] and *emotion circuits*.[62] This suggests a shared "neural wetware" driving cognitive, affective, and physiological regulation, formalized by Thayer and Lane[4,9] as the *neurovisceral integration* model.

Empirical findings support this hypothesis. Decreased HRV at rest is found in individuals with (1) depression, generalized anxiety disorder, and posttraumatic stress disorder[63]; (2) poorer emotion regulation abilities[64]; and (3) poorer performance on tasks of executive function.[65]

Implications for Psychophysiological Research

Based on the above discussion, it becomes clear that the concept of mean HR, although easy to obtain, is only partially grounded physiologically. Rather, it is the beat-to-beat change in HR rather than the average change in HR that more accurately reflects the underlying dynamics and complex interplay of the SNS and PNS branches of the ANS.

Heart rate variability is a physiologically grounded,[54] theoretically explicated,[9] and empirically supported,[4,66] and computationally tractable[5] measure of autonomic function. Recording HRV has come a long way since the days of Einthoven's galvanometer. A number of vendors have released suites of "plug-and-play" recording equipment capabilities, typically connecting to a laptop or desktop computer via Ethernet or USB cable and frequently with ambulatory capabilities (for a review, see[67]). Even more portable technology takes the form of fitness watches, which log the timing of heartbeats (detected via a sensor located within an elastic band that is fitted around the participant's chest, just below the sternum) in the watch and connect via infrared to the analysis computer. At least 1 model (the Polar RS800 series; Polar Electro, Finland; www.polar.fi/en/) has a sampling rate (1000 Hz) required for high-fidelity recording of an IBI time series[66] and yields comparable results to those obtained from standard 3-or 12-electrode ECG setups.[68,69] In a similar vein, graphics-based, user-friendly HRV analysis tools are freely available, such as *Kubios*[70] (http://kubios.uku.fi) and *PhysioToolkit*[71] (www.physionet.org/tutorials/hrv-toolkit). Thus, HRV is well suited to serve as a translational research component from "bench to bedside."

Heart Rate Variability and Music

Despite its theoretical basis, empirical support, computational tractability, simplicity of recording, and ease of analysis, however, the literature on HRV and music {E8} relative to mean HR and music {E7} is relatively small in both the experimental and the interventional literatures. Heart rate variability is not mentioned in either of the major experimental literature reviews of music and physiological response.[7,8] Isolated empirical investigations of HRV during music *listening* have reported significant differences as a function of music mood,[24,72,73] genre,[74] familiarity,[75] or tempo[76] while listening to music during exercise[77–79] or during music listening versus music performance.[80] With respect to HRV during music *performance*, investigations are even more scarce. Recently, however, Nakahara et al[80,81] reported greater parasympathetic withdrawal (leading to increased HR) when expert pianists performed an emotional piece of music (while limiting bodily movements) versus when they "listened emotionally" to that same piece of music.

Heart rate variablility receives little more than a few passing references in the comprehensive series of Cochrane Collection Reviews dedicated to musical interventions: in patients with coronary heart disease,[82] with dementia,[83,84] with depression,[85] with schizophrenia,[86] under mechanical ventilation,[87] or during end-of-life care[88]; for pain relief[89]; or for individuals with autism spectrum disorders.[90,91] Indeed, our own searches uncovered only a handful of studies that utilized music as an intervention and HRV as a dependent measure, across a wide range of patient populations: pediatric oncology,[92] myocardial infarction,[93] dementia,[94,95] cancer,[96] or geriatric[94]; or patients undergoing various surgical procedures.[97–99] In all of these HRV studies, the primary use of music was for its anxiolytic or analgesic properties.

Conclusion

Humans interact with music, both consciously and unconsciously, at behavioral, emotional, and physiological levels. William James, a pioneer in modern experimental psychology, mused[100] that the ANS "forms a sort of sounding-board, which every change of our consciousness, however slight, may make reverberate."(p191) While that sounding board certainly reverberates to music, it is hoped that the present review begins to illustrate just how complex that interaction may be and the associated implications for future research. In particular, we have highlighted HRV not only as an example of this underlying complexity, but also how this complexity can be measured, analyzed, and interpreted within the context of experimental paradigms and evidence-based music therapy. A number of previous music-based intervention studies have examined HRV as it indexes listeners' emotional state; future interventions might seek to explore HRV in interventions targeting cognition or attention.

"Every disease is a musical problem," claimed the 18th-century philosopher Novalis; "every cure is a musical solution."[101] In other words, every intervention should be uniquely customized to the particular condition—indeed, the particular patient—being treated. However, we hope that this review offers a broadly applicable message that might inform a variety of future investigations. With respect to experimental studies, it is important to explore how specific features of music (eg, its beat, tempo, or mean pitch level) trigger neurophysiological, psychophysiological, emotional, and behavioral responses. With respect to interventions with physiological targets (eg, hypertension, tachycardia), it is important to consider that ANS dysfunction is mediated by the CNS and that treatment of the former should be sensitive to the state of the latter. With respect to interventions with psychological targets (eg, depression, anxiety), it is important to understand that ANS processes are not merely the downstream flotsam of activity in the CNS, but also function as part of a sensitive feedback and feed-forward mechanism. Continued work within these different paradigms may reveal a common finding: that the ANS serves as a sensitive, dynamic mechanism by which music exerts a beneficial effect on health and a therapeutic effect on disease.

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