RESEARCH PAPER

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A relationship between brainstem auditory evoked potential and vagal control of heart rate in adult women

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Numerous studies have investigated the connection between autonomic control of heart rate (HR) and auditory stimulus. Yet, the literature lacks evidence of a close association between auditory brainstem processing and HR autonomic control. We aimed to evaluate and verify the relationship between auditory brainstem response (ABR) and HR variability (HRV) in healthy women. Forty-six healthy female subjects, between the ages of 18 and 30 years old participated in the study. They were subjected to an audiometry examination, followed by rest for 10 minutes for HR recording. Next, ABR evaluation was completed discretely in both ears, with I, III and V wave components. Linear regression revealed that the root-mean square of differences between adjacent normal RR intervals (RMSSD) and the triangular interpolation of RR interval (TINN) exhibited a significant association with Wave I in the right ear. These variables contributed to 28.2% (R^2) of Wave I. In conclusion, there was a significant interaction between the autonomic control of HR and auditory processing in the right ear, suggesting that vagal tone interacts with the cochlear nerve.

Key words: autonomic nervous system, cardiovascular system, hearing, neurophysiology, speech, language and hearing sciences

INTRODUCTION

The central nervous system (CNS) has several regions that modulate the autonomic nervous system (ANS), in addition to the solitary nucleus (Hermann and Rogers 2009), paraventricular nucleus of the hypothalamus (Zucker et al. 2014) and amygdala (Schulz et al. 2016). The involvement of subcortical regions in autonomic control of heart rate (HR) has been, up until now, investigated via heart rate variability (HRV) (Beissner et al. 2013). Thayer et al. (2012) completed a meta-analysis and revealed the key areas involved in HRV control, including the amygdala and the prefrontal cortex. The relevance of the brain areas in emotional regulation have been described. Thayer et al. (2012) endorsed HRV as a reliable method for brain integration with peripheral mechanisms during stress and wellbeing.

More recently, the correlation between cerebral cortical thickness, evaluated by functional neuroimaging techniques, and autonomic function, assessed through HRV, muscle sympathetic nerve activity and cardiovagal baroreflex, was studied (Wood et al. 2017). Their study observed that the medial prefrontal cortex and the insular cortex were associated with HRV in healthy subjects.

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In this way, the brainstem was further demonstrated to be another area involved in HR autonomic control. Functional magnetic resonance imaging has been utilized to detect changes in the brainstem during stimulation of the vagus nerve. The solitary tract nucleus and the locus coeruleus were activated during electrical stimulation of the auricular branch of the vagus nerve at the Cymba conchae (Yakunina et al. 2017).

Likewise, Pyatigorskaya et al. (2016) applied diffusion tensor imaging in patients experiencing Parkinson's disease to verify whether damage in the medulla oblongata is connected to the sympathetic-vagal balance. Moreover, the study demonstrated that dysfunction of the medulla oblongata is associated with impairment in HRV and respiratory patterns.

The CNS is correspondingly involved with auditory processing (Paulraj et al. 2015). Vibrations from sound cause mechanical stimulation of the tympanic membrane that transmits mechanical energy to minuscule bones, inducing electrical stimulation of the inner ear, and directs electrical signals transmitted to the brainstem through primary auditory glutamatergic neurons. The afferent neurons reach the cochlear nucleus, trapezoid nucleus, superior olivary complex, lateral lemniscus, inferior colliculi, medial geniculate nucleus and auditory cortical areas (Meas et al. 2018).

Auditory processing and the ANS were concurrently investigated in a previous study (Nakamura et al. 2009) that examined the effects of auditory stimulation with music on the gastric vagal nerve activity in urethane-anesthetized rats (Nakamura et al. 2009). A key outcome from the study was the determination that this specific stimulation was able to elevate parasympathetic activity. The same group reported that an identical auditory stimulation decreased sympathetic activity through renal sympathetic nerve activity analysis and that this physiological response was partly due to histaminergic neurons located in the hypothalamic suprachiasmatic nucleus (Nakamura et al. 2007).

A technique necessary for evaluating auditory processing is the auditory brainstem response (ABR) examination, in which waves with positive and negative peaks are generated at several anatomical sites in the brainstem through an external auditory stimulus. Each wave corresponds to a structure, with Wave I corresponding to the distal portion of the auditory nerve, Wave III representing the cochlear nucleus and Wave V indicating the lateral lemniscus (Fernandes et al. 2013).

Attempts have been made to define the interaction between central auditory processing and the ANS. Sushil et al. (2016) investigated ABR in controlled and uncontrolled diabetic subjects and proposed delayed brainstem and midbrain pathway transmission occurred, indicating involvement of central diabetic neuropathy in auditory processing. In this way, the relationship between ABR and HRV may be affected by attention. It is for this reason that another previous study investigated 200 students in order to confirm the influence of executive attentional control during situations involving neutral stimuli on HRV (Ramírez et al. 2015). The study demonstrated that HRV has a substantial association with attentional control and decision-making. Moreover, social attention was discovered to be a variable involved in ABR deviations (Geva et al. 2017).

Taken together, we raised the premise that parasympathetic regulation of HR analyzed through HRV is significantly associated with brainstem areas related to auditory processing evaluated by ABR.

Discerning the relationship between the ANS and brainstem auditory processing is essential in order to achieve a better understanding of communication mechanisms and develop new treatments for social function disorders, specifically, since non-invasive therapies activating the ANS have been used to treat social function disorders such as autism (Jin and Kong 2017). Moreover, activation of the parasympathetic nervous system via the vagus nerve was demonstrated to have beneficial effects on clinical depression (Howland 2014) and regulation of recognition of other emotions (Colzato et al. 2017). Therefore, we propose that an improved understanding of the role of the ABR-HRV relationship will support the development of new interventions focused on the ANS, that may have an impact on social dysfunction treatments.

Although the above-mentioned studies focused on areas in the CNS involved in the interaction between the ANS and auditory processing, it is unclear if the brainstem and the cochlear nerve are related to autonomic control of HR. Consequently, we endeavored to investigate the association between HR autonomic regulation and brainstem auditory processing.

METHODS

Study description

We studied 46 female subjects (21.67±1.87 years old). We excluded subjects that had cardiopulmonary, psychological or neurological disorders or any other impairments that prevented the subject from performing procedures. Subjects undergoing treatment with medications that influence cardiac autonomic regulation were also excluded. We omitted women between the 11–15th and 21–25th days of the menstrual cycle so as to circumvent the influence of the luteal and follicular phases.

All subjects were informed about the procedures and objectives of the study and signed a confidential in-

formed written consent. The entire study's procedures were approved by the Ethics Committee in Research of UNESP, Marilia (No. CEP-0419/2012) and followed the 466/2012 National Health resolution.

Protocols details

The data was logged at the same time of day (14: 00 to 16: 00) to avoid circadian effects. The subjects were instructed to avoid ingestion of coffee, tea and other ANS stimulants for 24 hours before the data collection. All subjects performed the tests in the same order, which are described in details below:

Audiological evaluation

To exclude subjects with auditory disorders, we carried out the following tests in an identical soundproofed room:

1. An auditory examination was performed to obtain information on acoustic health history of the subjects' anamnesis;
2. Pure tone audiometry to assess hearing thresholds (air and bone conduction) of subjects. The examination was conducted with a two-channel audiometer, GSI 61 Grason-Stadler, with TDH-39.

We omitted subjects with a hearing impairment (tonal thresholds below 25 decibels) (Lloyd and Kaplan 1978) in both ears and constructed a Type A tympanometric curve, which represents normality of the tympanic bone system (Jerger 1970).

ABR examination

Electrophysiological assessment was attained using middle-latency auditory evoked potential recording. Bio-logic Systems Corporation equipment was required for the ABR recording. The active electrodes were placed on the forehead (Fpz=ground electrode), the cranial vertex (Cz=active electrode), and the earlobes (reference electrode: A1=LE and A2=RE), according to the International 10–20 System, with the headphones suitably attached (TDH-39).

The chief purpose of this electrophysiological examination was to assess the integrity of the auditory pathway in the brainstem. Examination of ABR was finalized in a soundless room with the subject seated and instructed to remain alert whilst both ears were examined.

For the procurement of ABR the following parameters were necessary: filter between 1000 and 1500 Hz, click stimulus, stimulus rate of 29.9 ms/sec interval between stimuli of 1.1 ms, with intensity of 80 dB nHL, with a sample of 2000 stimuli, and it was excluded in cases of artifacts exceeding 10% (200 stimuli).

We followed the guidelines described by Durrant and Ferraro (1991). The investigation consisted of three components: Waves I, III and V. The I wave corresponds to the distal area of the cochlear nerve, the III wave represents the cochlear nucleus and finally, the V wave corresponds to the inferior colliculus and lateral lemniscus. We selected these waves because they are the most visible and demonstrate the highest clinical value.

Peaks were revealed as milliseconds of absolute latency, denoted by the time elapsed between the start of the stimulus and the wave response. Wave I should reach values of approximately 1.5 ms, Wave III should have a peak at around 3.57 ms and Wave V should present the peak at about 5.53 ms (Soares et al. 2010).

Linking values related to the time elapsed between two waves should be almost 2.0 ms. The interaural difference should not exceed 0.3 ms.

HRV analysis

The interbeat intervals (RR) intervals were recorded by the portable RS800CX HR (HR) monitor at a sampling rate of 1 kHz and were downloaded to the Polar Precision Performance program (v. 3.0, Polar Electro, Finland). Particulars regarding HRV analysis have been previously described (Roque et al. 2013, da Silva et al. 2014). After digital filtering, supplemented with manual filtering for the elimination of artifacts, 256 stable RR intervals were required for each volunteer for the data analysis. Only series with greater than 95% sinus rhythm were included in the study (Camm et al. 1996). For computation of the time (SDNN – standard deviation of normal-to-normal RR intervals, pNN50 – percentage of adjacent RR intervals with a difference of duration greater than 50 ms and RMSSD – root-mean square of differences between adjacent normal RR intervals in a time interval) and frequency domain (LF – low frequency, HF – high frequency in both normalized and absolute units and LF/HF ratio) indices we used the HRV Analysis software (Kubios® HRV v.1.1 for Windows, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) (Tarvainen et al. 2014).

Throughout the HRV recordings subjects remained seated and at rest under normal breathing. We monitored respiratory rate, which varied between 9 to 13 cycles per minute.

Statistical analysis

The sample size calculation was accomplished using the online software contained on the website www.lee.dante.br

utilizing the rest RMSSD index for correlation analysis. The level of statistically significant differences assumed was 30 ms, with a standard deviation of 10 ms, with risk of 5% alpha and beta of 80%. The sample size as calculated resulted in 35 subjects.

We applied Shapiro-Wilk normality test to evaluate the distribution. To evaluate the correlation between at rest HRV indices and ABR components, we calculated the Pearson correlation coefficient for parametric distributions and for non-parametric distributions we used the Spearman correlation coefficient. Strong correlation was accepted for $r>0.5$, moderate correlation was recognized for r between 0.5 and 0.3 and weak correlation was acknowledged for $r<0.3$.

To investigate the effect of independent variables on dependent variables a simple linear regression model was constructed by the "forced entry" test. The choice of the independent variables was achieved by the correlation analysis, by considering only the variables with significant correlation ($p\leq0.05$). In the model, we inserted all combinations of predictor variables (independent variable). The R^2 was evaluated to support the coefficient of determination of the percentage of variation described by the model and the adjusted R^2 to evaluate the stability of the model.

We considered a value statistically significant when the probability of a Type I error was less than 5% ($p<0.05$).

RESULTS

We observed normal physiological values of mass, height, body mass index (BMI) and cardiovascular parameters including HRV (Table I).

One sample of an ABR recording was demonstrated (Fig. 1).

Correlation between ABR and HRV indices are presented in Table II. There was a significant positive correlation of Wave I in the right ear with RMSSD, pNN50 and HF indices, while Wave I negatively correlated with TINN. Wave V in the right ear demonstrated a significant negative correlation with TINN and SDNN. For the left ear a significant positive correlation was observed between LF/HF and Wave III.

To evaluate the effect of HRV on ABR, we completed linear regression analysis considering HRV as an independent variable. We observed a significant association between RMSSD and TINN and Wave I in the right ear (24.8%) and that the LF/HF ratio was significantly associated with Wave V in the right ear (7.1%) (Table III, Fig. 2).

Similarly, we evaluated the relationship between ABR and HRV. Wave I in the right ear displayed a significant association with RMSSD (10.8%), pNN50 (6.7%) and TINN (7.4%) while Wave III in the left ear showed a significant association with the LF/HF ratio (7.1%) (Table IV, Fig. 3).

Table I. Descriptive statistics of age, mass, height, BMI, cardiovascular variables and HRV.

Variables	Mean	SD	Q25	Q50	Q75
Age (years)	21.67	1.87	20.00	22.00	23.00
Mass (Kg)	61.63	11.77	52.50	60.00	68.00
Height (m)	1.63	0.06	1.60	1.63	1.66
BMI (Kg/m²)	23.19	3.55	20.70	22.59	25.64
SAP (mmHg)	109.33	8.37	105.00	110.00	115.00
DAP (mmHg)	69.78	9.41	60.00	70.00	80.00
RMSSD (ms)	46.03	21.81	31.40	41.30	58.70
pNN50 (%)	26.96	17.71	13.50	20.50	37.75
RR_tri (ms)	13.19	4.17	10.27	12.54	15.29
TINN (ms)	237.51	59.65	195.00	220.00	267.50
SDNN (ms)	64.89	32.38	46.65	57.50	69.60
LF (ms²)	1,040.38	605.12	465.00	1,006.00	1,415.00
HF (ms²)	865.78	797.71	271.00	504.00	1,157.00
LF/HF	25.32	152.75	0.82	1.60	3.46

SD: Standard deviation; m: meters; kg: kilograms; mmHg: millimeters of mercury; RMSSD: square root of the mean of the squares of the successive differences between adjacent RR; SDNN: standard deviation of all normal-to-normal RR intervals; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50 ms; LF: low frequency; HF: high frequency; RR tri: Triangular index; TINN: Triangular interpolation of RR intervals.

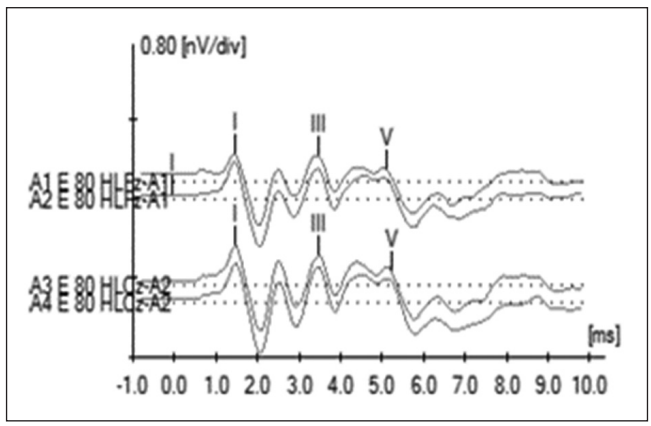

Fig. 1. An example of one sample of an ABR recording.

DISCUSSION

In order to further understand physiological mechanisms related to hearing, this investigation aimed to validate if there is an association between auditory processing in the brainstem and autonomic regulation of HR. Based on our results, we have highlighted three important interpretations: the interaction between ABR and HRV was detected predominantly in the right ear; parasympathetic modulation of HR dynamics was significantly associated with Wave I of the ABR and; vagal control of HR had an association with the distal portion of the cochlear nerve.

The relationship between autonomic regulation of HR and auditory processing has been reviewed and studied in rats (Nakamura et al. 2009) and the association between parasympathetic nerve activity and auditory stimulus was previously highlighted (Valenti et al. 2012). An elegant investigation recorded gastric vagal nerve activity in rats while they were exposed to white noise and relaxant music (Traumerei by Schumann) (Nakamura et al. 2009). The study revealed an increased number of c-Fos-immunoreactive cells in the auditory cortex and increased parasympathetic activity during auditory stimulation with Traumerei music, therefore demonstrating that musical auditory stimulus increases vagal activity through the auditory pathway. This study supports our linear regression analysis which demonstrated a significant association between the cochlear nerve (distal portion) on the vagal component of HRV (RMSSD - 10.8% and pNN50 - 6.7%).

Nakamura et al. (2007) similarly evaluated the effects of musical auditory stimulus with music and white noise (50dB) on renal sympathetic activity in anesthetized rats. Their investigation revealed that exposure to relaxant music decreased renal sympathetic activity in rats, and that the effect was mediated by histaminergic receptors in the hypothalamic suprachiasmatic nucleus and was dependent on the auditory cortex. In light of our results that uncovered a significant association between Wave III and the LF/HF ratio, we propose that the cochlear nucleus is involved in the sympathetic-vagal balance of HR. Consequently, our results support a relationship between brainstem auditory processing and autonomic regulation of HR.

We were unable to detect an association between the inferior colliculus (Wave V) (Fernandes et al. 2013) and autonomic modulation of HR. Chemical or electrical stimulation of the inferior colliculus induces escape, freezing or alertness followed by autonomic responses categorized as defense reactions (Brandão et al. 1993). This led us to hypothesize that Wave V and HR autonomic control would be strongly associated. Yet, we perceived only a weak negative correlation coefficient (TINN: r=-0.253; SDNN: r=-0.265; p<0.05).

Table II. Correlation coefficient analysis between ABR waves and HRV indices.

HRV indices	ABR					
	RE I	RE III	REV	LE I	LE III	LE V
RMSSD	0.357*	0.004	-0.184	0.205	0.048	-0.093
pNN50	0.296*	-0.111	-0.216	0.227	-0.070	-0.146
RR_tri	0.050	0.061	-0.101	0.160	0.117	-0.163
TINN	-0.308*	-0.019	-0.253*	0.087	-0.016	-0.138
SDNN	0.071	-0.145	-0.265*	0.169	-0.112	-0.230
LF ms	0.147	-0.058	-0.119	0.063	-0.017	-0.168
HF ms	0.253*	-0.026	-0.126	0.240	-0.012	-0.044
LF/HF	-0.002	0.187	0.135	-0.162	0.302*	0.002

*p<0.05; RE: Right ear; LE: Left ear; I: Wave I; III: Wave III; V: Wave V; RMSSD: square root of the mean of the squares of the successive differences between adjacent RR; SDNN: standard deviation of all normal-to-normal RR intervals; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50 ms; LF: low frequency; HF: high frequency; RR tri: Triangular index; TINN: Triangular interpolation of RR interval.

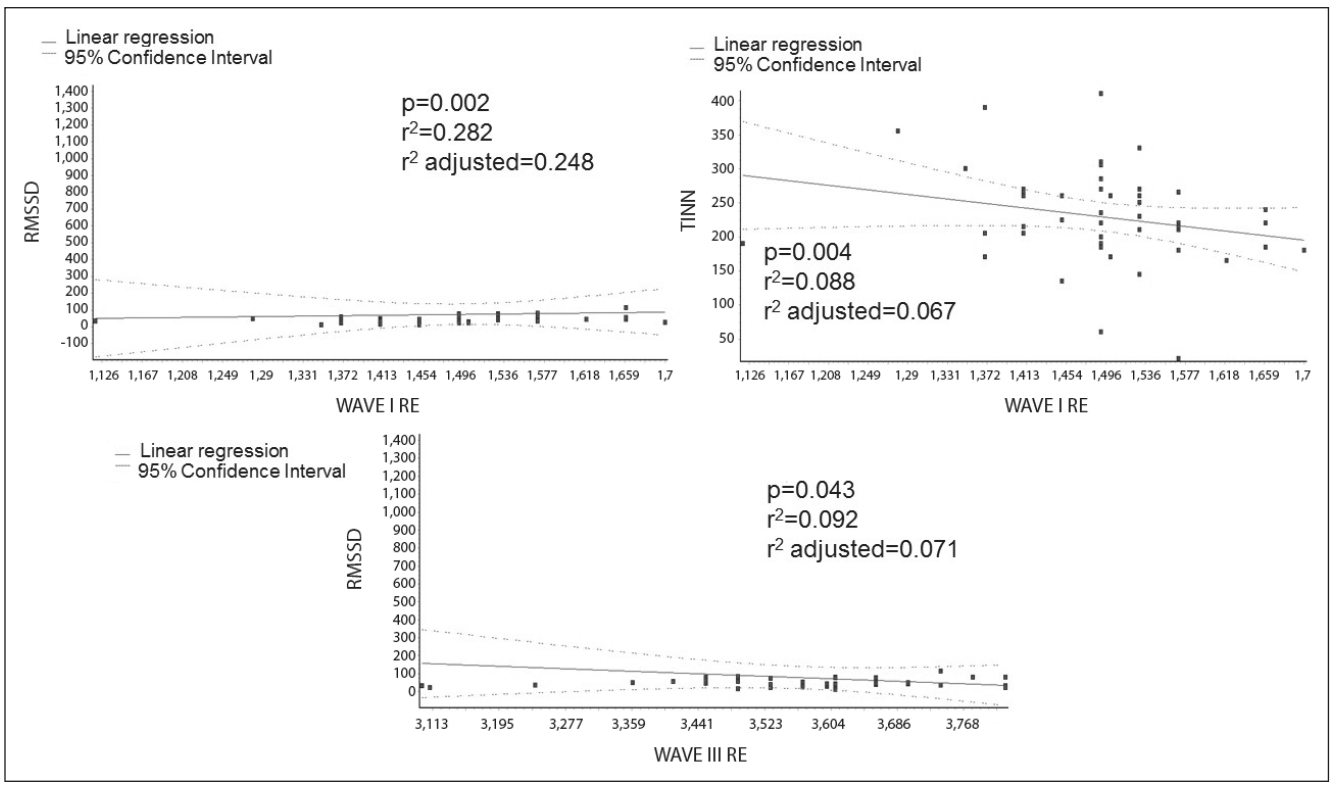

Fig. 2. Regression analysis to verify the interaction between HRV and ABR waves. RE: Right ear; LE: Left ear; I: Wave I; III: Wave III; V: Wave V; RMSSD: square root of the mean of the squares of the successive differences between adjacent normal RR intervals; TINN: Triangular interpolation of RR intervals; LF: low frequency; HF: high frequency.

The substantial relationship between the RMSSD (vagal control of HR) (Camm et al. 1996) and Wave I (distal portion of the cochlear nerve) (24.8%) (Fernandes et al. 2013) reported in our study is thought to be relevant to social function. This outcome suggests that parasympathetic control of HR interacts with auditory processing and supports a relationship between communication and the ANS, which is thoroughly explored by the Polyvagal theory (Porges 1995).

The Polyvagal theory describes two branches of the vagus nerve, the dorsal motor nucleus and the nucleus ambiguous (Porges 1995). Those areas surround the fourth cerebral ventricle and were revealed to be involved in HR regulation in rats (Valenti et al. 2010). Vagal activation

Table III. Regression analysis to verify the interaction between HRV and ABR waves.

			CI95%				
Variables		β	Inferior	Superior	R^2	R^2 adjusted	p
RE I	Constant	1.563	1.488	1.639	0.282	0.248	0.000
	RMSSD	0.001	0.001	0.002	—	—	0.002*
	TINN	0.000	-0.001	0.000	0.088	0.067	0.004*
RE V	Constant	5.546	5.425	5.667	0.093	0.050	0.000
	TINN	0.000	-0.001	0.000	—	—	0.313
	SDNN	-0.001	-0.002	0.000	—	—	0.256
LE III	Constant	3.587	3.553	3.620	0.092	0.071	0.000
	LF/HF	0.0002	0.00001	0.00044	—	—	0.043*

β regression coefficient; CI confidence interval; * p≤0.05 significant interaction; RE: Right ear; LE: Left ear; I: Wave I; III: Wave III; V: Wave V; RMSSD: square root of the mean of the squares of the successive differences between adjacent; SDNN: standard deviation of all normal-to-normal RR intervals; TINN: Triangular interpolation of RR intervals; LF: low frequency; HF: high frequency.

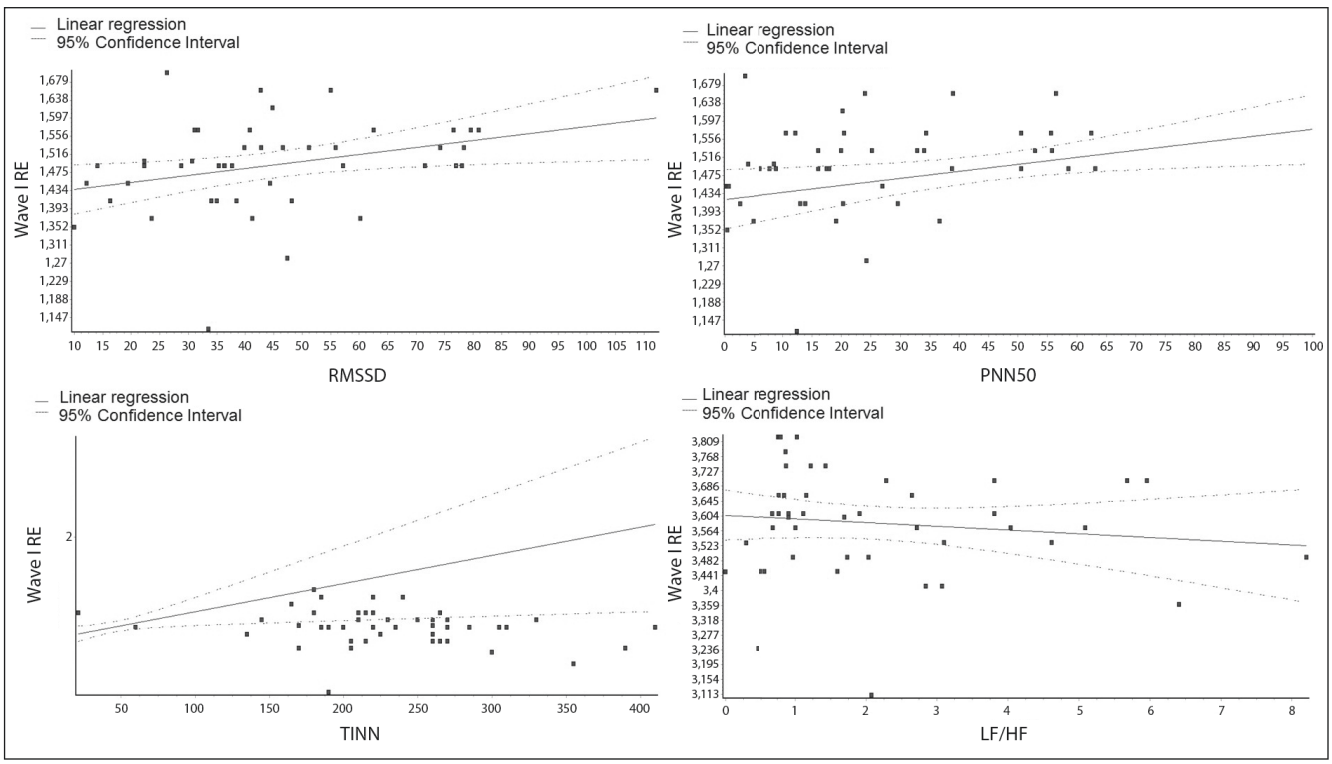

Fig. 3. Regression analysis to verify the interaction between ABR and HRV. RE: Right ear; LE: Left ear; I: Wave I; III: Wave III; RMSSD: square root of the mean of the squares of the successive differences between adjacent normal RR intervals; TINN: Triangular interpolation of RR intervals; LF: low frequency; HF: high frequency; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50 ms.

inhibits sympathetic input to the heart when sustained attention is adaptive, decreasing heart rate and preparing the subject for social engagement (Porges 1995). According to Porges (2011), the phylogenetic development of the ANS was vital to the progression of affective mechanisms and emotion related to social behavior, essential to communication. Taken together, our results support a relationship between the parasympathetic nervous system and social function as proposed in the Polyvagal theory.

In this context, the association between Wave I and HRV found in our investigation is supported by animal studies, since neurotransmitters related to parasympathetic activity (acetylcholine) were observed in cochlear nerve activity (Merchan et al. 1993). Such evidence allowed for the recognition that T stellate cells form an ascending pathway to the inferior colliculus, contributing to cholinergic feedback inhibition of the cochlear nucleus (Merchan et al. 1993). Fujino and Oertel (2001) demonstrated that stellate cells are regulated by cholinergic inputs through the ventral nucleus of the trapezoid body. Similarly, they described that cholinergic olivocochlear efferent fibers suppress responsiveness to sound in the cochlear.

Additionally, He et al. (2014) revealed that acetylcholine is a neuro-modulatory transmitter responsible for monitoring synaptic plasticity in the peripheral auditory pathway. The study emphasized that cholinergic modulation has a neuroprotective function, in that it defends the cochlea from exposure to high intensity noises. Altogether, our data and the abovementioned reports reinforce the connection between neural auditory processing and the ANS.

According to our study, the association between ABR and HRV was observed predominantly in the right ear. The ascending fibers from the upper olivary complex (IV wave) cross to the contralateral cerebral hemisphere (Guinan et al. 1983). Primarily, we suggest that auditory information approaching from the right ear crosses to the left hemisphere (Ferreira et al. 2008), indicating involvement of the contralateral hemisphere.

Several studies can help in elucidating our statistical outcomes. A study by Penhune et al. (1996) demonstrated the asymmetry between the right and left Heschl gyri, determining that, due to a greater amount of white and gray matter, the left Heschl gyri is larger than the right side, indicating that the left primary auditory cortex is also larger than the right one. Similarly, the study utilized imaging and suggested that the primary auditory cortex has a superior role regarding aspects of auditory stimuli.

Cortical lateralization and its relationship with the ANS are an important point for consideration. It is unclear which cortical hemisphere primarily impacts the ANS.

Previous studies found evidence of an effect of cortical lateralization on ANS dysfunction in patients who have experienced a stroke (Oppenheimer et al. 1992). Left-sided forebrain structures were demonstrated to have a chief role in regulating parasympathetic tone (Craig 2005) and the left was anticipated to be the main cortical hemisphere related to vagal activity (Yoon et al. 1997, Wittling et al. 1997). However, this aspect of lateralization has yet to reach consensus in the literature. There are human studies, including neuroimaging results employing cognitive and affective tasks, which have indicated the right hemisphere as being responsible for parasympathetic activity (Thayer and Brosschot 2005, Thayer and Lane 2009).

Strength and Limitations

Several points from our study warrant highlighting. Data achieved from the current study followed the prerequisites for performing a regression analysis, presented a normal distribution and did not violate homoscedasticity (no residuals increase or decrease with adjusted values, variables that generate around zero and that are not arranged randomly, and points in the graph are very distant from the others).

We examined only women to avoid differences due to sexual hormones in the group. This is because HRV is sensitive to androgens (Poliwczak et al. 2013) and estrogens (Campos et al. 2014). It was previously documented that testosterone supplementation in men with metabolic syndrome is able to influences resting HRV (Poliwczak et al. 2013). Furthermore, another investigation in female Wistar rats demonstrated that 17-β estradiol administered subcutaneously caused significant changes in HRV. In this sense, our data should not be extrapolated to males.

It is also necessary to address an important limitation of our study. Our investigation lacks inclusion of an experimental model such as attention and short-term memory. The abovementioned protocols might certainly affect the relationship between HRV and ABRs. On the other hand, very recently, our laboratory demonstrated a significant association between auditory attention analyzed through cortical auditory evoked potentials and HRV (Marcomini et al. 2018, Regaçone et al. 2018).

Table IV. Regression analysis to verify the interaction between ABR and HRV.

			CI95%				
Variables		β	Inferior	Superior	R^2	R^2 adjusted	p
RMSSD	Constant	-132.372	-275.683	10.938	0.128	0.108	0.069
	RE I	117.441	23.191	211.691	—	—	0.016*
pNN50	Constant	-93.012	-212.020	25.995	0.088	0.067	0.122
	RE I	78.978	0.711	157.245	—	—	0.048*
1 TINN	Constant	1,392.165	399.067	2,385.263	0.149	0.108	0.007
	RE I	-261.599	-520.192	-3.006	—	—	0.048*
	RE V	-139.145	-312.163	33.874	—	—	0.112
2 TINN	Constant	658.388	259.170	1,057.606	0.095	0.074	0.002
	RE I	-277.055	-539.606	-14.503	—	—	0.039*
3 TINN	Constant	1,065.557	93.095	2,038.020	0.064	0.042	0.032
	RE V	-152.152	-330.812	26.507	—	—	0.093
SDNN	Constant	535.369	9.328	1,061.410	0.070	0.049	0.046
	RE V	-86.449	-183.093	10.194	—	—	0.078
HF ms	Constant	-3,762.195	-9190.957	1,666.568	0.064	0.043	0.169
	RE I	3,046.499	-523.806	6616.803	—	—	0.092
LF/HF	Constant	-1,435.607	-2,849.522	-21.693	0.092	0.071	0.047
	LE III	406.666	13.279	800.053	—	—	0.043*

β regression coefficient; CI confidence interval; * p≤0.05 significant interaction; RE: Right ear; LE: Left ear; I: Wave I; III: Wave III; V: Wave V; RMSSD: square root of the mean of the squares of the successive differences between adjacent; SDNN: standard deviation of all normal-to-normal RR intervals; TINN: Triangular interpolation of RR intervals; LF: low frequency; HF: high frequency; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50 ms.

Another limitation of our study is the size of the group (n=46). Although this is a restricted number if compared to large clinical trials, we calculated sample size based on resting RMSSD for correlation analysis, which provided that a sample of 35 subjects was sufficient.

A strong point of the study is highlighted by evidence revealing an interaction between the ANS and auditory pathways in humans. Based on ABR examination and HRV analysis our data supports previous research done in animals. This study provides new additional evidence for the involvement of vagal tone in social function, which has been emphasized in the Polyvagal theory (Porges 2009). The present datasets may benefit and advance research for developing clinical protocols including techniques such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation.

CONCLUSION

An association was identified between autonomic control of HR and brainstem auditory processing. We propose that parasympathetic control of HR significantly engages the distal area of the cochlear nerve.

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