Association between heart rhythm and cortical sound processing

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Abstract
Processing of sound signals is an important factor for conscious human communication and such sound signals may be assessed through cortical auditory evoked potentials. Heart rate variability provides information about heart rate autonomic regulation. The association between resting heart rate variability and cortical auditory evoked potentials was investigated. Resting heart rate variability in the time and frequency domain and the cortical auditory evoked potential components were investigated. Subjects remained at rest for 10 minutes for recording of heart rate variability. Cortical auditory evoked potential examinations were then undertaken through frequency and duration protocols in both ears. Linear regression indicated that the amplitude of the N2 wave of the cortical auditory evoked potentials in the left ear (not right ear) was significantly influenced by the standard deviation of normal-to-normal heart beats (17.7%) and percentage of adjacent heart beat intervals with a difference of duration greater than 50 milliseconds (25.3%) for the time domain heart rate variability indices in the frequency protocol. In the duration protocol and in the left ear the latency of the P2 wave was significantly influenced by low (20.8%) and high frequency bands in normalized units (21%) and low frequency/high frequency ratio (22.4%) indices of heart rate variability spectral analysis. The latency of the N2 wave was significantly influenced by low frequency (25.8%), high frequency (25.9%) and low frequency/high frequency ratio (28.8%). In conclusion, it is proposed that resting heart rhythm is associated with thalamo-cortical, cortical-cortical and auditory cortex pathways involved with auditory processing in the right hemisphere.

Keywords
Autonomic nervous system; cardiovascular physiology; heart rate variability; neurophysiology; sound; speech

1. Introduction

Conscious understanding of sound is necessary for communication and development of cognitive abilities [1] and our cognitive system provides the most important distinguishing characteristic for humans and other mammals [2].

Sound processing in the brain may be analyzed through cortical auditory evoked potentials (CAEP). This is a well-recognized technique for evaluation of central auditory mechanisms related to auditory processing [3]. It affords information regarding automatic perception, discrimination, passive, and sound recognition and is associated with the alert response during the early allocation of attention [4, 5].

CAEP includes the P100 (P1), N100 (N1), P200 (P2), N200 (N2), and P300 (P3) waves. The P1 wave reflects synaptic transmission in the thalamus-primary cortical level [6]. The N1 and P2 waves correspond to secondary auditory cortex pathways from the thalamus and different cortical areas [7]. The N2 component is associated with passive and sound recognition [4]. Finally, P3 is linked to the alert response during early allocation of attention. It is elicited by a distractor stimulus [5] and has an association with prefrontal cortex activity [8, 9].

Interaction between the autonomic nervous system (ANS) and auditory processing in the central nervous system has previously been reported for rats [8, 10]. Both the parasympathetic [9] and sympathetic [10] divisions of the ANS in rats have been found to be involved in autonomic and heart rate (HR) responses induced by auditory stimulation. It has been demonstrated that the auditory cortex has a pivotal role in autonomic responses elicited by sound.

Under these circumstances, heart rate variability (HRV) is a simple, inexpensive, reliable, and noninvasive method for analysis of autonomic HR regulation [11, 12] previously validated in pharmacological studies [13, 14]. HRV describes the fluctuations of the intervals between two consecutive heart beats (RR-interval of the electrocardiographic signature) and indicates the capacity of the heart to respond to external and physiological stimuli. HRV is analyzed by mathematical procedures based on the RR-interval. Here, these include standard deviation of normal-to-normal RR-intervals (SDNN),
percentage of adjacent RR-intervals with a difference of duration greater than 50 milliseconds (pNN50) and root-mean square of differences between adjacent normal RR-intervals in a time interval (RMSSD) – Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [15]. Time and frequency domains are the most commonly applied indices for linear HRV investigation [16].

Significant correlation of N2, P2 and P3 waves with resting HR in the left ear (right cortical hemisphere) has been reported [17]. This study suggested the hypothesis that HRV may be associated with sound discrimination and facilitation of attention and memory mechanisms during stimulus processing.

Although, as previously noted, there is an interaction between auditory mechanisms and the ANS [18], it is unclear whether auditory processes related to attentional mechanisms are associated with the ANS. Furthermore, mechanisms regarding auditory attention processing and parasympathetic modulation could provide additional evidence for the role of ANS in social interactions and engagement. Thus, here it was aimed to evaluate the association between cortical auditory processes and resting autonomic HR regulation.

2. Method

2.1. Study population

Twenty-three healthy male non-athletic subjects, all non-smokers and aged between 18 and 30 years old were assessed. All subjects were informed about the procedures and objectives of the study and after approving, informed confidential written consent was obtained. All study procedures were approved by the Ethics Committee in Research of the Faculty of Sciences of the Universidade Estadual Paulista, Campus of Marilia (No. CEP-0419/2012) and obeyed resolution National Health Resolution 466/2012.

2.2. Non-inclusion criteria

Subjects were excluded for the following conditions: systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mm, body mass index (BMI) > 35 kg/m², cardiopulmonary, psychological, and neurological related disorders, impairments that prevented the subject from performing the protocols, and treatment with medications that influence cardiac autonomic regulation. Arterial blood pressure was measured with a manual cuff and stethoscope by a well-trained professional.

2.3. HRV analysis

HRV analysis followed the procedures of the Task Force of the European Society of Cardiology [15]. The RR-intervals were recorded by a portable RS800CX HR monitor (sampling rate 1 kHz). These data were downloaded to a Polar Precision Performance program (version 3.0, Polar Electro, Finland). This software permitted HR visualization and extraction of a text format RR-interval data file. Digital filtering was subsequently complemented with manual filtering to eliminate premature ectopic beats and artifacts. 256 stable consecutive RR-intervals were then analyzed. Only RR-intervals with more than 95% normal rhythm (95% sinus rhythm, without artifacts) were included in the study [15, 19]. Resting HRV was recorded for minutes prior to the CAEP examination.

2.4. Linear indices of HRV

Analysis in the time domain obtained the SDNN, pNN50, and the RMSSD (root-mean square of differences between adjacent normal RR-intervals in a time interval) [16].

For HRV analysis in the frequency domain, the spectral components of high frequency (HF: 0.15 to 0.40 Hz) in absolute (ms²) units were employed to correspond to vagal modulation. The spectral analysis was computed by Fast Fourier Transform [20].

Kubios HRV (version 2.0) software was employed to study these indices [21].

2.5. Audiological evaluation

A soundproofed room was employed to exclude auditory anomalies during the following assessments:

- Pure tone audiometry to assess hearing thresholds (air and bone conduction). Examination conducted with a two-channel audiometer, GSI 61 Grason-Stadler, with TDH-39 earphone;
- Auditory examination to obtain information about the medical history of the subject’s anamnesis.

Audiological acceptance criteria included: subjects without hearing impairment, tonal thresholds above 25 dBNA [22] in both ears, and a Type A tympanometric curve, indicating normality of the tympanic bone system [23].

2.6. Examination of cortical auditory evoked potential (CAEP)

All procedures were in agreement with the International 10-20 System. Electrophysiological examination was conducted using the P300-P3 long-latency auditory evoked potential. Bio-logic Systems Corp. equipment was used for the P3 recording. Active electrodes were placed on the earlobes (reference electrode: A1 = LE and A2 = RE), the forehead (Fpz = ground electrode) and on the cranial vertex (Cz = active electrode) and headphones were suitably positioned (TDH-39 earphone).

The principal function of this electrophysiological examination was to estimate the integrity of the auditory pathway in the brain. Examination of CAEP was completed in a silent room with the subject seated and instructed to remain alert. The aim was to evaluate the ability of the subject to discriminate sound frequency and duration.

The oddball paradigm was undertaken for electrophysiological recordings. This paradigm is based on distinguishing randomly and infrequently repeated target stimuli from frequently repeated non-target stimuli. Monaural auditory stimuli were presented by earphones, delivered to each ear independently, and for two different five minute protocols (duration and frequency). Right and left ears were randomly selected.

The frequent protocol (non-target) comprised a 1 kHz stimulation, whereas, the rare 1.5 kHz (target) stimulus occurred with 20% probability. The duration protocol was comprised of a 100 ms frequent (non-target) stimulation and a 50 ms rare (target)stimulus, the latter also occurred with a 20% probability.

To facilitate detection of auditory stimuli by a subject, the stimulation intensity for elicitation of P3 extended from 20 to 25 dBSL (decibel sensation level, specifically, 20–25 dBSL above the auditory threshold for the frequency applied) for the frequencies used for the frequent and rare stimuli. If this level of stimulation was uncomfor-
able, the highest level of comfort reported by the subject at which they could detect the sound was employed.

The following parameters were used: frequent (probability 80%) low frequency binaural acoustic stimulation (tone bursts with 50 millisecond duration, plateau 30 milliseconds, and rise/fall time of 10 milliseconds) and a higher rare (probability 20%) stimulus. The frequency and intensity of both the frequent and rare stimuli were selected by the pure tone audiometry, explicitly, frequencies with detectable thresholds. The stimulation intensity was also varied according to the frequency applied but always remained supra-threshold.

Three-hundred artifact-free stimuli (approximately 60 rare and 240 frequent stimuli) were applied to evoke potentials. The firing frequency or rate of presentation was one stimulus per second.

Wave identification followed criteria given in the literature, including visualization of sequential peaks of negative-positive-negative waves between 60 ms and 300 ms, that is, the N1, P2, N2 complex, respectively, observed in two traces [24]. The component P3 latency was marked before 350 ms.

To compute amplitude and latency their peaks were recorded from baseline and amplitude and latency units were μV and milliseconds, respectively.

3. Protocol

Data collection for all subjects was undertaken in the same soundproofed room. Temperature was between 21 °C and 25 °C, and the relative humidity was 50% to 60%. Subjects were instructed not to consume alcohol, caffeine or other ANS stimulants for 24 hours prior to the evaluation. Data were individually collected, always between 13:00 and 17:00 to standardize circadian influences [25]. All procedures required for data collection were separately explained to each subject, and the subjects were instructed to remain rested and avoid conversation during data collection. Before auditory examination subjects remained seated for 10 minutes to record their HRV under spontaneous breathing with no auditory or visual stimulation. The auditory studies were then conducted.

The sample size calculation began with a pilot test. Online software from www.lee.dante.br was used to view the RMSSD index. The magnitude of statistically significant difference was assumed to be 7 ms, standard deviation 10 ms, with a 1% alpha and 80% beta risk, sample size 22 subjects. The Shapiro-Wilk normality test was used to evaluate distributions.

To evaluate the correlation between HRV indices at rest and CAEP components during the examination, the Pearson correlation coefficient for parametric distributions and the Spearman correlation coefficient for nonparametric distributions were employed to evaluate any correlation between either HRV indices or CAEP components, respectively. Strong correlation was defined as a $r > 0.75$; moderate correlation for $r$ between 0.75 and 0.5, and weak correlation when $r < 0.25$ [26]. Statistical significance was accepted when the probability of a Type I error was less than 5% ($p < 0.05$).

Following determination of significant correlations ($p < 0.05$) in the selection of independent variables, simple linear regression models were applied to model HRV indices as outcome variables. Predictors included continuous variables representing the CAEP components. Due to the non-normality of pNN50 and LF/HF indices, prior to analysis these data were transformed by taking the square root and logarithm, respectively, so as to fit the regression model.

To compare the obtained CAEP waves (frequency protocol in right ear vs. duration protocol in right ear vs. frequency protocol in left ear vs. duration protocol in left ear), a one-way analysis of variance was applied to parametric distributions, followed by a Bonferroni post-test. Effect size was calculated using “Cohen’s d” to quantify the magnitude of difference between protocols. Values > 0.9 were considered to indicate large effect size, values between 0.25 and 0.5 were considered medium, and values < 0.25 were assumed to be small [27].

Raw data are available in the Supplementary Materials.

4. Results

Baseline diastolic (DAP) and systolic arterial pressure (SAP), weight, height, and body mass index (BMI) of subjects are presented in Table 1.

Correlation of HRV time domain indices with N1, P2, N2 and P3 latency are illustrated in Table 2. No significant correlations were present.

Table 1. Diastolic blood pressure (DBP) and systolic (SBP), heart rate (HR), mean RR intervals, mass weight, height, and BMI of subjects. Mean ± standard-deviation. m: meters; kg: kilograms; mmHg: millimeters of mercury.

| Variable       | Value       |
|----------------|-------------|
| Age (years)    | 26.3 ± 5    |
| Height (m)     | 1.79 ± 0.06 |
| Mass (kg)      | 79.3 ± 15   |
| BMI (kg/m2)    | 24.9 ± 4.2  |
| SAP (mmHg)     | 116.4 ± 10  |
| DAP (mmHg)     | 74.1 ± 9.1  |

With regard to N1, P2, N2 and P3 latency, significant positive correlation was found between N1 and pNN50 for the duration protocol, between N2 and pNN50 in the frequency protocol, and between N2 and SDNN for the left protocol in the left ear (see Table 3).

Table 2 shows data regarding latency of CAEP waves and spectral analysis of HRV. There was significant correlation in the left ear – a positive correlation of LF (n.u.) with P2 and N2 waves in the duration protocol, negative correlation of HF (n.u.) with P2 and N2 waves in the duration protocol, and positive correlation of LF/HF with P2 and N2 waves in the duration protocol. In the frequency protocol, there was a positive correlation of LF (n.u.) with the N2 wave, negative correlation of HF (n.u.) with the N2 wave, and positive correlation of LF/HF with the N2 wave.

Correlation between amplitude of CAEP waves and spectral analysis of HRV is indicated in Table 5. There was significant correlation for only the left ear – positive correlation of HF (ms2) with the N1 wave for the duration protocol and positive correlation of HF (ms2) for the N2 wave.

Simple linear regression analysis provided additional details of the association between resting HRV and CAEP. Amplitude of the N2 wave in the left ear was significantly influenced by SDNN (17.7%) and pNN50 (25.3%) indices for the frequency protocol (see Table 6).

Furthermore, for the duration protocol in the left ear, the latency of the P2 wave was significantly influenced by LF (n.u.) (20.8%).
A small effect size for all comparisons ($\phi = 0.94$, $F = 0.97$) did not yield any significant differences with regard to N1 latency and LF/HF (28.8%) (see Table 6).

HF (n.u.) (21%), and LF/HF (22.4%). Latency of the N2 wave was significantly influenced by LF (n.u.) (25.8%), HF (n.u.) (25.9%), and LF/HF (28.8%) (see Table 6).

So as to control the false discovery rate when enforcing multiple statistical tests, CAEP waves were compared during each protocol. No significant differences were found with regard to N1 latency ($p = 0.35$, $F = 1.096$), P2 latency ($p = 0.63$, $F = 0.574$), N2 latency ($p = 0.97$, $F = 0.063$), P3 latency ($p = 0.98$, $F = 0.04$), N1 amplitude ($p = 0.94$, $F = 0.12$), P2 amplitude ($p = 0.76$, $F = 0.38$), N2 amplitude ($p = 0.95$, $F = 0.108$), P3 amplitude ($p = 0.37$, $F = 1.03$) or N2-P3 amplitude ($p = 0.95$, $F = 0.11$). Cohen’s d calculation only indicated a small effect size for all comparisons ($< 0.25$).

### 5. Discussion

To provide details regarding the relationship between central auditory processing and the ANS, this study investigated the association between CAEP components and resting time and frequency domain indices of HRV. The following outcomes are highlighted: (1) There was significant association of the vagal component of HR control and sympathovagal balance at rest with the N2 and P2 waves; (2) This association only occurred in the left ear, indicating involvement of the right cortical hemisphere; and (3) The hypothesis is proposed that the autonomic component of heart rhythm interacts with cortical sound processing.

According to the results reported here, the SDNN was signifi-
The N2 component is involved in pre-attention mechanisms related to communication [29]. The N2 component is also related to obligatory (exogenous) cortical processes. Amplitude and latency of obligatory CAEP are contingent on the acoustic parameters of stimuli [30]. This wave is associated with the superior temporal cortex [31] and attentional orientation toward a visual target stimulus surrounded by several distracters [32]. The N2 wave represents the quality of sound perception, classification, and recognition [33].

Another related result is the association of P2 with HRV. Similarly with N2, P2 latency was significantly influenced by LF (20.8%) and LF/HF (22.4%). Linear regression indicated that if LF increases one unit the P2 latency increases 0.519 ms and if the LF/HF ratio similarly increases, the P2 latency increases 0.026 ms. Vagal HR control was likewise observed to significantly influence the P2 wave if HF increased one unit the P2 latency was reduced by 0.519 ms.

The P2 wave is required for the ability to process sounds based on its phonetic and acoustically-related properties since it provides information regarding the arrival of an auditory stimulus at the cortex and onset of cortical processing, thus indicating whether a sound signal is properly acknowledged in the cortex [30, 34].

Taken together, it is proposed that the parasympathetic control of HR is associated with sound reception in the cortex and sound processing control, while sympathetic tone degrades this. The superior temporal cortex is involved in this mechanism, reinforcing evidence that supports the relationship between the ANS and social functioning [35, 36]. This observation is supported by Nakamura...
et al. [9, 10], who reported the role of the auditory cortex in the sympathetic responses induced by auditory stimulation in rats.

The influence of the ANS on cortical auditory processing may be explained by previous animal studies. Acetylcholine, the main parasympathetic neurotransmitter, was found to play an important role in the auditory cortex [37]. It has been reported that acetylcholinergic synaptic mechanisms may mediate the effects of acetylcholine on receptive fields in auditory cortex. Also, sound processing may favor sensory information relayed through the thalamus to cortical activity in response to increased acetylcholine release [38]. This leads to a theory that parasympathetic activation inducing increased acetylcholine release may positively influence sound reception in the auditory cortex.

Consequently, an adrenergic mechanism has also been recognized to be involved in central auditory processing [39]. However, the exact role of adrenergic neurotransmission in auditory evoked responses remains unclear [40].

According to these data, only the left ear showed association with HRV, indicating that the right cortical hemisphere related to auditory processing is associated with HR autonomic regulation. Conversely, it does not explain which hemisphere plays the main role in the ANS. The left-sided forebrain areas were observed to have a primary function in modulating vagal activity and it has been suggested as the major cortical hemisphere related to parasympathetic nervous system activity [41–43]. Yet, there are studies in humans using neuroimaging with affective and cognitive tasks that indicate the right hemisphere as responsible for vagal activity [44, 45].

Here only males were investigated to avoid gender-dependent effects on HRV. This was reinforced by a recent study that evaluated the role of gender regarding short-term HRV analysis [46]. Those authors detected significant gender effects that involved association between HRV and stress and indicated that gender also presented an important influence on short-term HRV analysis.

The findings reported here provide important information for comprehension of cognition, as evidence is presented for a role for the ANS in cortical auditory processing, which is relevant for communication and social behavior [1, 2]. In this study, mechanisms of cortical auditory processing were revealed to be associated with the parasympathetic control of HR and sympathovagal balance. This signifies that the ANS may have a significant impact on specific cognitive processes. Support for this assumption requires further research, including pharmacological techniques of parasympathetic and sympathetic blockade.

6. Conclusion

There is significant association between resting HR autonomic control and right cortical auditory processing. Here, it is proposed

| Variables | Right Ear Duration Protocol | Left Ear Duration Protocol | Right Ear Frequency Protocol | Left Ear Frequency Protocol |
|-----------|-----------------------------|----------------------------|----------------------------|-----------------------------|
|           | Amplitude N1                | 0.3228                     | 0.1330                     | 0.2971                      |
|           | Amplitude N2                | 0.3247                     | 0.1306                     | 0.0840                      |
|           | Amplitude N3                | 0.1607                     | 0.4639                     | −0.1621                     |
|           | Amplitude N2-P3             | 0.1616                     | 0.4612                     | 0.0361                      |
|           | Amplitude N3-P3             | 0.3597                     | 0.4612                     | 0.0894                      |
|           | Amplitude N2-P3             | 0.3142                     | 0.4599                     | 0.0988                      |
|           | Amplitude N2-P3             | 0.1409                     | 0.4599                     | 0.0988                      |
|           | LF (ms²)                    | 0.3520                     | 0.1225                     | 0.3232                      |
|           | HF (ms²)                    | 0.1520                     | 0.1225                     | −0.3232                     |
|           | Amplitude N1                | 0.0304                     | 0.1225                     | 0.2401                      |
|           | Amplitude N2                | 0.3276                     | 0.1225                     | −0.0074                     |
|           | Amplitude N3                | 0.3766                     | 0.1225                     | 0.3018                      |
|           | Amplitude N3-P3             | 0.3597                     | 0.1225                     | 0.3018                      |
|           | Amplitude N2-P3             | 0.3142                     | 0.1225                     | 0.3018                      |
|           | LF (nu)                     | 0.3276                     | 0.1225                     | 0.3018                      |
|           | HF (nu)                     | 0.3520                     | 0.1225                     | 0.3018                      |
|           | Amplitude N1                | 0.3081                     | 0.1527                     | 0.3271                      |
|           | Amplitude N2                | 0.0437                     | 0.1527                     | 0.3271                      |
|           | Amplitude N3                | 0.0350                     | 0.1527                     | 0.3271                      |
|           | Amplitude N3-P3             | 0.1049                     | 0.1527                     | 0.3271                      |
|           | LF/HF                       | 0.3766                     | 0.1527                     | 0.3271                      |

*p < 0.05 (Pearson correlation); **p < 0.05 (Spearman correlation); LF: low frequency; HF: high frequency; n.u.: normalized units; m: meters; s: seconds.
that the parasympathetic regulation of HR and the sympathovagal balance at rest are associated with thalamo-cortical pathways and cortical-cortical circuits involved in auditory processing.

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Conflict of Interest
All authors declare no conflicts of interest.

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Table 6. Linear regression models of relationship between CAEP and HRV.

| Models | Left Ear Frequency Protocol | β    | 95% C.I.            | p    | r-adjusted |
|--------|----------------------------|------|---------------------|------|------------|
| N2 Amplitude | 1 – SDNN                  | 8.732 | 1.149; 16.315        | 0.026* | 0.177      |
| N2 Amplitude | 2 – pNN50                 | 1.136 | 0.325; 1.947        | 0.008* | 0.253      |
| P2 Latency 4 – LF (n.u.) | 3 – LF (n.u.)               | 0.081 | −0.157; 0.320         | 0.488 | −0.023     |
| P2 Latency 5 – LF/HF | 0.081 | −0.319; 0.157        | 0.486 | −0.023     |
| P2 Latency 6 – HF (ms2) | 0.004 | −0.006; 0.016         | 0.400 | −0.012     |
| N1 Amplitude | 27.127                  | 0.006 | −0.103; 0.157        | 0.671 | −0.038     |

| Left Ear Duration Protocol | β    | 95% C.I.            | p    | r-adjusted |
|-----------------------------|------|---------------------|------|------------|
| N1 Amplitude 8 – LF (n.u.)  | 25.042 | −0.010; 1.095        | 0.054 | 0.125      |
| P2 Latency 5 – HF (n.u.)    | 1.059 | 0.105; 0.932        | 0.016* | 0.208      |
| N2 Latency 10 – HF (n.u.)   | 0.322 | 0.095; 0.550         | 0.008* | 0.258      |
| P2 Latency 11 – HF (n.u.)   | −0.519 | −0.932; −0.107       | 0.016* | 0.210      |
| N2 Latency 12 – HF/HF       | −0.322 | −0.549; −0.095       | 0.008* | 0.259      |
| P2 Latency 13 – LF/HF       | 0.026 | 0.006; 0.046         | 0.013* | 0.224      |
| N2 Latency 14 – HF (ms2)    | 0.016 | 0.005; 0.027         | 0.005* | 0.288      |
| N1 Amplitude 16 – pNN50     | 69.838 | −51.94; 191.61       | 0.246 | 0.018      |

*p < 0.05; SDNN: Standard deviation of all NN intervals; RMSSD: Square root of the sum of the squares of differences between adjacent NN intervals; pNN50: percentage of adjacent RR-intervals with a difference of duration greater than 50 milliseconds; LF: low frequency; HF: high frequency; n.u.: normalized units; m: meters; s: seconds.
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