Coupling of sympathetic nerve traffic and BP at very low frequencies is mediated by large-amplitude events

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BURGESS, DON E., DAVID C. RANDALL, RICHARD O. SPEAKMAN, AND DAVID R. BROWN. Coupling of sympathetic nerve traffic and BP at very low frequencies is mediated by large-amplitude events. Am J Physiol Regul Integr Comp Physiol 284: R802–R810, 2003.—This study explores the functional association between renal sympathetic nerve traffic (NT) and arterial blood pressure (BP) in the very-low-frequency range (i.e., <0.1 Hz). NT and BP (n = 6) or BP alone (n = 17) was recorded in unanesthetized rats. Data were collected for 2–5 h, and wavelet transforms were calculated from data epochs of up to 1 h. From these transforms, we obtained probability distributions for fluctuation amplitudes over a range of time scales. We also computed the cross-wavelet power spectrum between NT and BP to detect the occurrence in time of large-amplitude transient events that may be important in the autonomic regulation of BP. Finally, we computed a time sequence of cross correlations between NT and BP to follow the relationship between NT and BP in time. We found that NT and BP follow comparable self-similar scaling relationships (i.e., NT and BP fluctuations exhibit a certain type of power law behavior). Scaling of this nature 1) points to underlying dynamics over a wide range of scales and 2) is related to large-amplitude events that contribute to the very-low-frequency variability of NT and BP. There is a strong correlation between NT and BP during many of these transient events. These strong correlations and the uniformity in scaling imply a functional connection between these two signals at frequencies where we previously found no connection using spectral coherence.

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wavelet analysis; sympathetic nervous activity; cross correlation; blood pressure fluctuations; transient events; self-similar invariance

arterial blood pressure (BP) and sympathetic nerve traffic (NT) are well known to be functionally coupled, or highly coherent, to maintain normal homeostatic function. In the unanesthetized rat, for example, oscillations in sympathetic NT that repeat in ~2.5 s are clearly very tightly coupled with fluctuations in BP that have a similar period (3). This high coherence can be explained on the basis of the baroreflex (4). This 0.4-Hz rhythm appears to be a natural instability within this reflex, similar to a resonance in an electrical circuit or mechanical system produced by the time constants and delays in the constituent physical and neuronal phenomena. A similar phenomenon in the rabbit occurs at 0.3 Hz (13) and in the human at 0.1 Hz (7, 17). Conversely, the coherence between sympathetic activity and BP in the rat falls to very low values below a frequency of 0.1 Hz (3). In other words, the mathematical processes used to compute the coherence do not detect a close functional relationship between rhythmic changes in BP and corollary changes in sympathetic NT, or vice versa, that require more than ~10 s to repeat. A weak coupling between sympathetic activity and BP within the very low frequencies (i.e., <0.1 Hz) is unexpected, because the baroreflex is widely credited with minimizing BP fluctuations during, for example, postural changes that certainly fall at least within the upper limits of the low-frequency range.

Stationarity of a signal, or “time series,” is required in spectral analysis, which is the basis of the coherence computation. A process is stationary if its statistical characteristics are the same when examined at any given moment during the time sequence. However, we recently described nonstationarity in rat BP recordings in the form of erratic, large-amplitude events (5). In addition, Roach et al. (21) described temporally localized contributions to human heart rate variability at ultralow frequencies (<0.0033 Hz). It appears that, rather than being stationary, very-low-frequency variability in cardiovascular variables is dominated by temporally localized, large-amplitude events (5, 15, 21, 22). Consequently, conclusions based on standard spectral analysis of cardiovascular variables within the low-frequency range, including that of a weak functional relationship between sympathetic nerve activity and BP, can be misleading (5).

Another very interesting property of cardiovascular signals is that, when examined in the frequency domain, the power is generally perceived to increase as a function of $1/f_\beta$ for very low frequencies, where $\beta$ is the slope of the power spectrum curve on a log-log plot (14, 15, 21).
Such a power law relationship between two variables (i.e., power and frequency) is a defining characteristic of a self-similar scaling relationship. Examples of self-similar scaling that are familiar to everyone include the branching patterns in tree limbs or the variations in a coast line: the patterns are similar irrespective of the scale one examines (e.g., a section of coast a few hundred yards long or a few hundred miles long). Lack of stationarity in cardiovascular signals could limit the effectiveness of power spectral processes in the analysis of these signals. Wavelet analysis, which does not demand that a signal be stationary (12), is an alternate means to detect the presence of a scaling relationship. A wavelet is effectively a digital band-pass filter that can be tuned to any given frequency of interest. Restated, the wavelet scale can be chosen that specifically selects those components (i.e., frequencies) in the signal that are of particular interest. In addition, the wavelet can analyze the frequency content of the signal over time: one “slides” the wavelet through the signal across time to determine how power at that frequency fluctuates from moment to moment. The entire data set can then be scrutinized to determine how often a fluctuation of a given amplitude occurred in the signal in the frequency range determined by the scaling function. This analysis can be performed for any given frequency range of interest by changing the time scale of the wavelet.

The result of the analysis described above is a probability distribution for amplitudes of fluctuations over a range of frequencies determined by the time scale chosen to tune the wavelet. One defining characteristic of any self-similar signal is that it conforms to a “generalized homogeneous function.” A function \( P(x,\lambda) \) is a generalized homogeneous function if it satisfies the following equation

\[
P(L^x x, L^\lambda \lambda) = LP(x,\lambda)
\]

(1)

for all positive values of the parameter \( L \), where \( x \) is time and the parameter \( L \) has the effect of changing the time scale. The “message” of Eq. 1 is that the function \( P(x,\lambda) \) has the same shape (the “equal” sign) over a wide range of time scales (i.e., regardless of the value of \( L \)). We found, for example, that the probability density curves for BP and NT for different frequency ranges (i.e., scales) have different widths and different peak locations, but, except for one unique frequency, all have the same shape or form. In a more specific sense, Ivanov et al. (12) showed that a self-similar cardiovascular signal (i.e., heart rate) fits a specific homogenous function called the gamma distribution. Finally, power law behavior is a natural consequence of the properties of generalized homogeneous functions. For example, the gamma distribution is proportional to the parameter \( \lambda \) when plotted as a function of the dimensionless variable \( \lambda x \) (Eq. 4).

In the present experiment, we sought to quantify the relationship between sympathetic NT and BP in the very-low-frequency range. We had several specific objectives: 1) We were intrigued by the isolated, large-amplitude fluctuations that contribute to the very-low-frequency variability. A wavelet analysis was a natural choice to study these temporally localized events, because it does not require that the signal be stationary and it is the best compromise for localizing an event in time and in frequency (6). 2) We computed the cross-wavelet power spectrum (24) between NT and BP to detect the occurrence in time of these large-amplitude, transient events and to determine the frequency range of these events. 3) In addition to these wavelet analyses, we computed a time sequence of cross correlations between NT and BP from overlapping data sets to follow the correlation between NT and BP in time. The combination of a wavelet analysis and a more traditional cross-correlation analysis gave us a consistent picture of the relationship between the sympathetic nervous system and BP in intact animals in the very-low-frequency range and helps explain why standard spectral processes do not detect a strong coherence between these two signals below \(-0.1 \text{ Hz}.\)

**METHODS**

Experiments were performed on 23 Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) weighing 330–450 g. The standards for care and use of animals of the American Physiological Society were observed at all stages of the experiment.

**Surgery.** The rats were anesthetized with pentobarbital sodium (65 mg/kg ip) and prepared for sterile surgery. A Teflon catheter (0.012 ID; catalog no. 30 LW, Small Parts, Miami Lakes, FL) was inserted into the aorta by way of the femoral artery in all 23 animals. In six rats a sympathetic nerve coursing over the aorta toward the kidney was also identified through a flank incision. A small section of this nerve, usually from the cephalad angle formed by the renal artery and aorta, was dissected free of connective tissue and placed on fine, closely spaced (0.4–0.8 mm), bipolar gold electrodes (A-M Systems, Seattle, WA). The exposed nerve and electrode were encased in silicone gel (Wacker Chemie, Munich, Germany). The distal ends of the catheter and wires soldered to the end of the electrodes were tunneled under the skin, exited at the nape of the neck, and led through a flexible tether.

**Data acquisition.** Data were collected 24 h after surgery in the conscious state while the rat rested quietly in a cage. The arterial pressure signal from a Cobe transducer attached to the femoral artery catheter was amplified and displayed by a Grass model 7 polygraph. The electrical signal from the renal sympathetic nerve was amplified (50,000) and band-pass filtered between 30 Hz and 3 kHz by a Grass P511 differential amplifier.

To obtain accurate measurements from the sympathetic nerve recordings, data were digitized at 10,000 samples/s using a Cache 486 microprocessor and Data Translation DT2821-F analog-to-digital converter. Data were collected for 2–5 h. The initial highly detailed NT signal was full-wave rectified and averaged over every 10 points to produce a 1,000 samples/s signal. This process retains cumulative information from the initial 10,000 samples/s signal. The pressure signals were compressed “on-line” to a 1,000 samples/s signal by saving every 10th point. Because we were interested in the low-frequency range, the data were further compressed to 50 samples/s by averaging every 20 data points. We carefully removed artifacts from the raw time series, using soft-
were developed in our laboratory in Visual C++ and saved the edited time series with a sample rate of 500 Hz.

Wavelet analysis. We performed two different types of wavelet analysis. The first, cumulative variation amplitude analysis, detects the presence of scaling (12). Cumulative variation amplitude analysis consists of three steps. In step 1, we calculated the wavelet transform of the time series. The wavelet transform \( \tilde{x}(s,t) \) allows the study of the signal on any chosen scale \( s \). The continuous wavelet transform of a time series \( x(t) \) is defined as

\[
\tilde{x}(s,t) = \frac{1}{\sqrt{s}} \int_{-\infty}^{\infty} x(t') \psi \left( \frac{t' - t}{s} \right) dt'
\]  

(2)

where the analyzing wavelet \( \psi \) has a width on the order of the scale \( s \) and is centered at time \( t \). The Mexican hat wavelet, which is the second derivative of a Gaussian function, is orthogonal (i.e., insensitive) to linear trends (12). Because we were not interested in detecting linear trends in the data, we used the Mexican hat wavelet in our analysis. For this wavelet, there is a conversion factor of \( \sqrt{2} \) between the scale \( s \) and the corresponding Fourier period (24); i.e., applying a wavelet with a scale \( s = 0.5 \) to a time series selects for rhythms that have a period of \( \sim 2.0 \) s. Using a standard Fourier transform routine, one can efficiently calculate the convolution integral in the frequency domain and then take the inverse Fourier transform to find the wavelet transform in the time domain.

In step 2, we extracted the amplitudes of the variations in our time series at the frequency range specified by the scale \( s \) by using an analytic signal approach (12). Let \( c(t) \) represent an arbitrary signal. The analytic signal, a complex function of time, is defined by \( a(t) = c(t) + s(t) \), where \( s(t) \) is the conjugate time series. For example, the sine curve is conjugate to a cosine curve. Then, the amplitude \( A(t) \) of the time series is the magnitude of the complex number \( a(t) \); i.e., \( A(t) = \sqrt{c^2(t) + s^2(t)} \). To obtain the conjugate time series, one calculates the Hilbert transform of \( c(t) \). This operation is easily performed in the frequency domain. In the frequency domain, the Hilbert transform simply multiplies the positive-frequency Fourier modes by \( i \) and the negative-frequency modes by \( -i \). In summary, to compute \( A(t) \), we calculated the wavelet transform \( \tilde{x}(s,t) \) and its conjugate time series by taking the Hilbert transform of \( \tilde{x}(s,t) \).

In step 3, we calculated the probability distribution of the amplitudes \( A(t) \) at the specified frequency range for our time series. After sorting the amplitudes from smallest to largest, we partitioned the amplitudes into \( n = 200 \) bins with equal numbers of entries to obtain a probability distribution \( P(A) \). To aid in obtaining the peak value \( P_{\text{max}} \) of \( P(A) \), we smoothed the variations in the experimentally measured curve for \( P(A) \) by applying a second-order Savitsky-Golay filter (18) with a window of 17.

The experimentally measured probability distributions were well fit by the gamma probability density, namely

\[
P(x;\alpha,\lambda) = \frac{(\lambda x)^{\alpha-1}}{\alpha - 1} \exp(-\lambda x)
\]  

(3)

In the context of Poisson processes (random events with no memory), \( P(x;\alpha,\lambda)dx \) represents the probability for \( \alpha \) events to occur in time interval \( x \), where \( \lambda \) is the mean rate at which events occur. In our case, \( x \) represents the amplitude of a fluctuation, instead of a time interval. Possibly, the amplitude of a fluctuation is proportional to an integration time that is determined by \( \alpha \) events. We found that the probability distributions for fluctuation amplitudes from different frequency ranges had different \( \lambda \) values but the same \( \alpha \). By scaling the probability distribution by \( 1/\lambda \), one obtains a one-parameter distribution

\[
P(\lambda x;\alpha) = \frac{(\lambda x)^{\alpha-1}}{\alpha - 1} \exp(-\lambda x)
\]  

(4)

Consequently, when a family of probability curves are plotted as a function of the dimensionless argument \( \lambda x \), they all fall onto the same curve. In other words, the probability densities for NT and BP fluctuations are described by a generalized homogeneous function, which depends on one variable but, after rescaling, depends on only two. Because \( P_{\text{max}} \) is proportional to \( \lambda \), we can achieve the same effect by scaling by \( P_{\text{max}} \). Following Ivanov et al. (12), we rescaled the probability distribution according to

\[
P(A) \rightarrow P(A)/P_{\text{max}}
\]

\[
A \rightarrow AP_{\text{max}}
\]

The normalized probability density function can be written as

\[
P(x) = \left( \frac{x}{x_0} \exp\left[\frac{-(x-x_0)}{6}\right]\right)^{\alpha-1}, \quad x > 0
\]  

(5)

where \( x_0 \) is the location of the peak. We used the “Isqnonlin” function in MATLAB 5.3 (Math-Works, Natick, MA) to find the parameter \( \alpha \) that minimizes the least-squares residual error between the fit to the gamma distribution and the scaled \( P(A) \). Because the location of the peak \( x_0 \) after scaling is a complicated function of \( \alpha \), it was convenient to simultaneously fit \( \alpha \) and \( x_0 \).

In a very different application of wavelet analysis, we also calculated the cross-wavelet power spectrum (24) between NT and BP. This is an effective way to detect large-amplitude time-localized events. Given two time series \( x(t) \) and \( y(t) \), with wavelet transforms \( \tilde{x}(s,t) \) and \( \tilde{y}(s,t) \), the cross-wavelet spectrum \( W_{xy}(s,t) \) is defined as

\[
W_{xy}(s,t) = \tilde{x}(s,t)\tilde{y}^*(s,t)
\]

where \( \tilde{y}^*(s,t) \) is the complex conjugate of \( \tilde{y}(s,t) \). The cross-wavelet spectrum is complex; therefore, one can define the cross-wavelet power as \( |W_{xy}(s,t)| \). [Because the Mexican hat wavelet is real, we used the Hilbert transform of \( \tilde{x}(s,t) \) as the complex part of the wavelet transform.]

If it is assumed that both wavelet spectra are \( \chi^2 \) distributed with two degrees of freedom (for the real and imaginary parts of the transform), then significance levels for the cross-wavelet power can be computed from the probability distribution for the square root of the product of two \( \chi^2 \) distributions (24), namely

\[
f(z) = zk_0(z)
\]  

(6)

where \( z \) is the random variable and \( k_0(z) \) is the modified Bessel function of order zero. The probability distribution for the cross-wavelet power is given by

\[
P\left(|W_{xy}(s,t)| < \frac{z}{2}\right) = \int_0^z f(z)dz
\]  

(7)

where the factor of \( \sqrt{2} \) takes care of the number of degrees of freedom and \( \rho_{xy}(s) \) is the average local wavelet power spectrum given by

\[
\rho_{xy}(s) = \langle \tilde{x}(s,t)\tilde{y}^*(s,t) \rangle
\]  

(8)
The angular brackets denote an ensemble average. To calculate the average of the local wavelet power spectrum, we constructed 50 phase-randomized surrogate data sets. For each surrogate data set, we calculated its wavelet transform and averaged over the values for each scale at the midpoint of the time series to avoid edge effects.

To detect large-amplitude, transient events in a time series of length \( N \), we made contour plots of the cross-wavelet power spectrum scaled by \( \sqrt{P_x(s)P_y(s)} \) for a set of \( J \) scales \( s \). For a given significance level \( p \), we divided \( p \) by the number of values in the contour plot to obtain \( p' = p/N \times J \). Then we inverted the integral of \( f(z) \) for the probability \( P = 1 - p' \) to obtain a threshold \( Z/2 \). In other words, if it is assumed that the time series is a stationary random process, the probability is less than \( p \) that any one of the values for the scaled cross-wavelet power will exceed \( Z/2 \).

**Correlations.** In addition to the wavelet analysis, we studied the correlation between NT and BP in the time domain. To study the correlations between NT and BP at low frequencies, the data were passed through an eighth-order Butterworth low-pass filter with a cutoff frequency of 0.2 Hz and compressed to a sampling rate of 5 Hz. Each time series was then divided into \( \sim 700 \) segments containing 256 points (or a period of 51.2 s) with 50% overlap. The correlation between NT and BP was calculated using the fast Fourier transform algorithm on zero-padded data segments. The correlation in the time domain between lags from \(-10\) to \(+10\) s was computed using the inverse fast Fourier transform. We displayed the results on a contour plot where the time for each data segment is defined as the time of the center of the segment.

**RESULTS**

The physiological NT and BP time series display rhythmic fluctuations and transient, intermittent fluctuations. Raw time series for NT and BP from *rat sds* are shown in Fig. 1. The sampling rate for these time series is 500 Hz. In Fig. 1A, a 5-s interval is displayed. Pulse synchronous nervous activity is readily apparent during the occasional dips in BP. Figure 1B shows a 20-s interval from the same recording. Note the prominent 2.5-s rhythm in BP and the corresponding bursts in NT. The bursts are roughly 180° out of phase with the BP fluctuations. Each "burst" of NT in Fig. 1B corresponds to the increase in NT during the dip in BP in Fig. 1A. Figure 1C shows a 20-min interval from the same data recording. Note the transient, large-amplitude events in BP at \( \sim 142, 146, 150, 153, \) and \( 158 \) min and the changes in NT corresponding to these events. The duration of these events is \( \sim 40 \) s. In the three events at 142, 150, and 158 min, changes in sympathetic nervous activity lead changes in BP. The other two events have a different character from these three events (see below).

**Wavelet analysis.** Figure 2A shows the probability \( (P) \) of occurrence of BP fluctuations of a given amplitude \( (A) \) in *rat sdm*. Blue represents a scale \( s = 1 \), which corresponds to BP fluctuations with a period of \( \sim 4 \) s; red \((s = 0.5)\) corresponds to \( \sim 2 \) s. For example, the blue distribution shows that the probability of observing a fluctuation of amplitude 0.8 mmHg within the \( \sim 0.25\)-Hz range was relatively high, whereas larger and smaller fluctuations in this frequency range were less likely. In comparison, the red distribution \((\sim 0.4 \) Hz) was considerably broader, with a peak that was thereby smaller and less focused. To test for the presence of scaling, we rescale these probability curves to see if they fall onto a universal curve (12). We normalize the ordinate against the peak value for each respective curve \( [P(A)/P_{\text{max}}] \) and the abscissa by the
reciprocal of the same peak value [AP$_{max}$]. After this rescaling, the curves for the larger scales (i.e., blue, green, and yellow) are superimposed, whereas the curve for $s = 0.5$ (red) is clearly offset. This collapse of the blue, green, and yellow curves to a common distribution indicates the presence of a universal scaling in the dynamics underlying the production of the low-frequency variability in NT and BP. The scale $s = 0.5$ corresponds approximately to the frequency of the 0.4-Hz rhythm (3, 4). The presence of the 0.4-Hz rhythm disrupts the self-similar scaling behavior apparent for the larger scales (i.e., $s \geq 1.0$).

To test this result further, we examined the BP time series from a group of 17 rats that were instrumented for BP alone. From these rats, we determined the $x_0$ and $\alpha$ parameters of the gamma function to which the data for $s = 0.5, 1, 2, 4, 8, 16,$ and 32 were fit (Eq. 5).

The results are shown in Table 1. We ran a one-way, repeated-measures ANOVA ($P < 0.0001$ for $x_0$ and $P = 0.003$ for $\alpha$) followed by Bonferroni’s post hoc tests. The post hoc test for $x_0$ (i.e., the location of the peak for the probability distribution curves; see Eq. 5) showed a significant difference ($P < 0.05$) between $s = 0.5$ and all other scales. However, there were no other significant differences between scales, indicating self-similarity between scales ranging from $s = 1$ to $s = 32$. This quantitatively confirms the visual impression in Fig. 2 that the red trace is offset from all the others. The $\alpha$ post hoc tests (i.e., the general shape of the probability distribution curve) showed significant differences only between $s = 0.5$ and $s = 1$ and 2.

In the six rats in which BP and NT were recorded, we found a universal probability distribution in both variables that appeared to be robust over scales from $s = 1$ to $s = 64$. Scaled probability distributions for NT and BP fluctuations for the larger scales (i.e., not including the unique distribution for $s = 0.5$) for rat sds are shown in Fig. 2C. After rescaling, the probability distribution curves for different scales $s$ and for NT and BP fluctuations collapse onto essentially one curve. A summary of the parameters we obtained for each rat from fitting the gamma distribution to our histograms is shown in Table 2. The paired t-test shows no significant difference between BP and NT for $x_0$ ($P = 0.569$) and for $\alpha$ ($P = 0.773$). In contrast to the construction of Table 1, the values in Table 2 are calculated by fitting data from all scales, except $s = 0.5$, rather than a particular scale.

Contour plots of the wavelet power spectrum of NT and BP for rat sds are shown in Fig. 3. Fig. 3C is the contour plot of the cross-wavelet power spectrum between NT and BP. These contour plots are analogous to a contour map where the peaks represent regions in time and frequency where there were unusually large fluctuations in NT, BP, or both simultaneously. (There are fewer contours in Fig. 3A because of the low signal-to-noise ratio for NT relative to BP.) The time window of these plots is the same as the time window in Fig. 1C. The contours near 142, 146, 150, 153, and 158 min in Fig. 3 correspond to the large-amplitude transient fluctuations in Fig. 1C. The events at 146 and 153 min are localized in time and frequency space differently from the other three events (see below). A summary of the results for cross-wavelet analysis is shown in Table 3. Statistically significant, transient, large-amplitude events were detected in all six rats at an average rate of two to three per hour. Moreover, the long tails in the probability distribution curves shown in Fig. 2 indicate the small, but significant, probability of occurrence of these large-amplitude fluctuations. Although the event at 146 min does not reach statistical significance (and is not recorded in our statistical summary), strong activity is apparent, especially in BP. Possibly, this event in BP is amplified by other physiological systems outside the baroreflex.

**Time domain analysis.** A contour plot of the correlation in the time domain between NT and BP for rat sds is shown in Fig. 4. There are strong positive and negative correlations between NT and BP at certain discrete times. The positive and negative correlations between 140 and 160 min correspond to the large-amplitude events detected with the cross-wavelet power spectrum in Fig. 3. During the strong positive correlations, NT leads BP (negative lag in Fig. 4). In addition to strong positive correlations, we find strong negative correlations (e.g., at 146 and 153 min in Fig. 4) where fluctuations in BP lead fluctuations in NT. Such dynamics are indicative of a biofeedback control system with a functional competency on the order of tens of seconds (e.g., the baroreflex). The event near 146 min that did not reach statistical significance in the cross-wavelet analysis shows up here as a relatively weak negative correlation of about $-0.55$ between NT and BP. A summary of the results of our correlation analyses is shown in Table 4. At certain discrete times, we found strong positive and negative correlations between NT and BP in all six rats indicative of large-amplitude transient events on time scales approaching 1 min.

**DISCUSSION**

Signal analysis of physiological recordings often yields insights as to how the biological system functions or how its function is controlled, which would

<table>
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<th>Scale</th>
<th>$x_0$</th>
<th>$\alpha$</th>
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<tbody>
<tr>
<td>0.5</td>
<td>0.52 ± 0.02</td>
<td>2.82 ± 0.12</td>
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<tr>
<td>1.0</td>
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<td>2.41 ± 0.03</td>
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<tr>
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<td>0.40 ± 0.01</td>
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<td>2.51 ± 0.07</td>
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<td>2.53 ± 0.10</td>
</tr>
<tr>
<td>16.0</td>
<td>0.43 ± 0.02</td>
<td>2.69 ± 0.13</td>
</tr>
<tr>
<td>32.0</td>
<td>0.43 ± 0.02</td>
<td>2.71 ± 0.13</td>
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Values are means ± SE; $n = 17$. 

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otherwise go unnoticed. In particular, we (5) and others (15, 21, 22) previously described large-amplitude changes in BP and NT that are transient and occur at irregular intervals. These events were clearly seen to contribute to the very-low-frequency variability in the NT and BP signals, but their physiological significance was not at all clear. Resolving this issue was a particular challenge, because the irregular occurrence (i.e., nonstationarity) of the events precluded the use of “workhorse,” spectral analysis tools that are otherwise very powerful. Our analysis circumvented these restrictions and quantified the functional relationship between NT and BP as it changed over time. During many of these transient events, we found a strong correlation between NT and BP that provides, we believe, new insight into how BP is regulated within this very-low-frequency range. Moreover, we found a sharp distinction between the self-similarity that characterized the majority of the lower-frequency signals and fluctuations with periods of ~2 s.

Our time domain analysis (Fig. 4), similar to the cross-wavelet analysis (Fig. 3), revealed that BP and NT were strongly positively correlated during many of the transient events. Because NT leads BP in certain cases, some of these events appear to be produced by nonbiofeedback mechanisms (e.g., central commands), such as we have shown are evoked by an acute behavioral stress (19), or perhaps result from the integration of subtle shifts in blood volume or BP by low-pressure receptors (e.g., atrial receptors). We have reported that these strong positive correlations are absent after transection of the spinal cord between T1 and T2 and, therefore, appear to depend on intact sympathetic outflow to the heart and vasculature (2). In other events, BP leads NT after an inversion, indicative of a feedback control reflex with a time scale of seconds. The baroreflex is the obvious candidate for exerting this latter control. Between these large-amplitude events, the time domain analysis used to construct Fig. 4 suggests that NT and BP are weakly correlated within the frequency range we examined (i.e., at a time scale that far exceeds the usual 2- to 3-beat sequences on which attention typically focuses). It is this apparent poor coupling between these two signals and the mutual “washing out” of the positively and negatively correlated transient events that lead to the lack of coherence between NT and BP that has been reported within the low-frequency range (3).

### Table 2. Parameters $x_0$ and $\alpha$ for probability distributions of variations in amplitudes of fluctuations in NT and BP

<table>
<thead>
<tr>
<th>Rat</th>
<th>NT $x_0$</th>
<th>NT $\alpha$</th>
<th>BP $x_0$</th>
<th>BP $\alpha$</th>
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<tr>
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<td>2.454</td>
<td>0.494</td>
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<td>2.633</td>
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</table>

Mean ± SE

- $0.46 ± 0.01$ for NT
- $0.44 ± 0.02$ for BP

Parameters are from fits to combined histograms from scales $s = 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0$.
The wavelet analysis allows a different perspective on the relationship between NT and BP within this low-frequency range. First, the probability distributions for BP with periods that equal or exceed \( \frac{1}{H} \) s (Fig. 2A) “collapse” to virtually a single distribution when rescaled, or normalized, against \( P_{\text{max}} \) (Fig. 2B). [The clear exception to this generalization was the rhythm with a period of \( \frac{1}{H} \) s (see below).] Perhaps even more impressive, however, was the virtual identity between the probability distributions for NT and BP fluctuations within the low-frequency range (Fig. 2C). The describing parameters of gamma distributions to which the BP data were fit were statistically indistinguishable from those to which the NT data were fit (Table 2). This analysis reveals, we believe, a strong functional association between the two signals that is not detected by standard coherence computations (3, 5). The most parsimonious interpretation is that the NT and BP signals are being driven by a common control mechanism. Again, the baroreflex is an obvious candidate, but irrespective of the mechanism, it seems irrefutable that NT and BP are, indeed, functionally coupled at frequencies that are much lower than the 0.1-Hz “cutoff” previously described (5).

These large-amplitude fluctuations are related to the self-similar scaling property that we observed in NT and BP. Surrogate data sets (see METHODS) were constructed by randomly “scrambling” the actual data set (i.e., to produce a “phase-randomized time series”) so that the overall content (i.e., the “average of the local wavelet power spectrum”) is unchanged but the distinguishing features of the actual data disappear. Most especially, the isolated large-amplitude fluctuations no longer appear in the phase-randomized time series. The resultant probability density curve computed from this surrogate data set is no longer described by a gamma function (data not shown) (12). That is, data sets from which the large-amplitude, transient events are eliminated but have the same average spectrum no longer show the type of self-similar scaling that we observed for NT and BP fluctuations.

The fact that the data conformed to a generalized homogeneous function, i.e., the gamma function, is associated with power law behavior, which, in turn, is characteristic of scaling (see the introduction). Physically, scaling relations arise when the underlying dynamics “look” the same, irrespective of the time scale of the analysis (10). In sharp contrast, the characteristics of signals with strong rhythmicity absolutely depend on the time scale chosen for their analysis. It follows,
therefore, that because we observed self-similar scaling, the dynamics underlying the production of these large-amplitude events occur over a range of time scales; i.e., there is no one characteristic time scale, as is the case for rhythmic fluctuations. Although isolated large-amplitude events dominate very-low-frequency variability (0.001–0.1 Hz), feedback oscillations dominate the low-frequency range (0.1–1.0 Hz) (4, 20). The probability distribution centered around a period of 2 s (i.e., 0.4 Hz; red trace in Fig. 2, A and B) was clearly offset from all the curves describing the lower frequencies. We believe that this change from self-similar to rhythmic fluctuations explains the fundamentally different statistical characteristics of the fluctuations with a 2-s period. In reference to Table 2, our values for $\alpha$ from NT and BP fluctuations compare very well with the findings of Ivanov et al. (12), who reported $\alpha = 2.8$ and 2.4 for daytime and nighttime heart rate variability, respectively, in humans. (Their parameter $\nu$ is equal to our $\alpha - 1$.) We found a significant deviation between the tail of the gamma distribution and the universal probability distribution from the data; i.e., large-amplitude events are more probable in the data than would be expected from a true gamma distribution. Again, this discrepancy for the probability distributions of NT and BP fluctuations is in agreement with the observations of Ivanov et al. for the nighttime heart rate variability.

**Perspectives**

Perhaps, sympathetic regulation of the cardiovascular system may be in part through large-amplitude, transient events (Fig. 1C). The presence of large-amplitude, transient events in NT indicates the cooperative behavior of a large number of neurons. Moreover, the presence of a universal scaling law in our data indicates that the cooperative dynamics may be governed by a single physical process with no special time scale. The emergent behavior of large populations of neurons may occur on a range of scales that is described by the renormalized dynamics (10) of interaction between single neurons. Possibly, the large-amplitude events resulting from the dynamics of large populations of neurons are due to the integration of information from the cardiovascular system over a range of time scales. These events may be coordinated in parasympathetic and sympathetic activity to the heart and to the vasculature to control BP.

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**Table 4. Correlation in the time domain between sympathetic NT and ABP**

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REFERENCES


