

## Functional Stochastic Resonance in the Human Brain: Noise Induced Sensitization of Baroreflex System

Ichiro Hidaka,<sup>1</sup> Daichi Nozaki,<sup>2</sup> and Yoshiharu Yamamoto<sup>1,\*</sup>

<sup>1</sup>*Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo,  
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

<sup>2</sup>*Department of Motor Dysfunction, Research Institute of National Rehabilitation Center for the Disabled,  
4-1 Namiki, Tokorozawa, Saitama 359-8555, Japan*

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We demonstrate experimentally that noise can enhance the homeostatic function in the human blood pressure regulatory system. The results show that the compensatory heart rate response to the weak periodic signal introduced at the venous blood pressure receptor is optimized by adding noise to the arterial blood pressure receptor. We conclude that this *functional* stochastic resonance most likely results from the interaction of noise with signal in the brain stem, where the neuronal inputs from these two different receptors first join together.

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It is now well known that noise can enhance the response of the nonlinear system to weak signals, via a mechanism known as stochastic resonance (SR) [1]. This concept has proposed a general mechanism for weak signal transmission in a variety of neuronal systems, possibly including the brain. In fact, previous experimental results have reported that the sensitivity of sensory neuron to weak signals can be optimized by adding noise [2]. Furthermore, several recent studies have shown that the higher central nervous system can actually utilize the noise enhanced sensory information; it enhances the human tactile sensation [3], the human visual perception [4], or the animal feeding behavior [5]. Whether these functional improvements would be caused by the enhanced sensory afferents at the receptor level or by the effects of noise in the central nervous system is, however, still unknown.

In this Letter, we demonstrate experimentally that the SR mechanism can enhance a functional end-organ response in the human autonomic nervous system. Different from the above studies [3–5], this functional SR most likely results from the neuronal interaction of noise with signal in the human brain stem nucleus, not in the receptor organs.

The experiments were conducted on the blood pressure regulatory system in humans. Short-term blood pressure homeostasis is primarily maintained by a negative feedback system known as “baroreflex,” where an increase (or a decrease) in blood pressure is automatically compensated by decreases (or increases) in heart rate and vascular resistance [6,7]. The baroreflex system has two types of receptors, the arterial and the cardiopulmonary baroreceptors, which, respectively, monitor arterial and central venous blood pressures. The afferent inputs from these receptors are independently transmitted to a reflex center in the brain stem [Fig. 1(a)]; from here the integrated outputs to peripheral organs such as the heart and the vascular system are sent via common efferent pathways [8]. We hypothesize that the injection of noise into one receptor enhances the

response of the baroreflex system to a small signal added to the other receptor, and thus SR occurs in the baroreflex system via the interaction between signal and noise in the brain stem.

To test this hypothesis, we periodically unloaded the cardiopulmonary baroreceptor by sinusoidally oscillating a computer controlled, motor driven tilt table [Fig. 1(a)]. The frequency of oscillation was fixed at 0.026 Hz, which is sufficiently slower than the neurally mediated baroreflex responses. Previous physiological studies showed that when the tilt angle [9] and hence a decrease in central venous pressure [10] were small, the end-organ responses such as changes in heart rate and arterial blood pressure were minimal, while greater tilt angle or lower central venous pressure resulted in marked hemodynamic responses [9,10]. Thus, in the small amplitude regime, the response of heart rate or cardiac interbeat intervals (RR intervals of an electrocardiogram; RRI) is considered to be minimal, as schematized in Fig. 1(c). Because of the small hydrostatic pressure gradient at shallow tilt angles, the arterial baroreflex is also considered to be silent, as indicated by the lack of hemodynamic responses [9,10]. We used this small periodic stimulus to the cardiopulmonary baroreceptor as a possibly subthreshold driving signal added to the baroreflex system.

Noise was added to the arterial baroreceptors located in the carotid sinus by compressing or depressing a pneumatic neck chamber [11] [Fig. 1(a)]. The intrachamber pressure was regulated by a computer on the beat-by-beat basis to generate Gaussian white noise with zero mean gauge pressure. The changes in the carotid sinus pressure introduced by the neck chamber device are readily transmitted to the central nervous system because the arterial baroreflex response of RRI to the changes in the carotid sinus pressure in normal humans has been shown to be highly linear near the operating point [6], as schematized in Fig. 1(b). We employed this mode of stimulation as a noise source to the baroreflex system with different intensities. Subjects

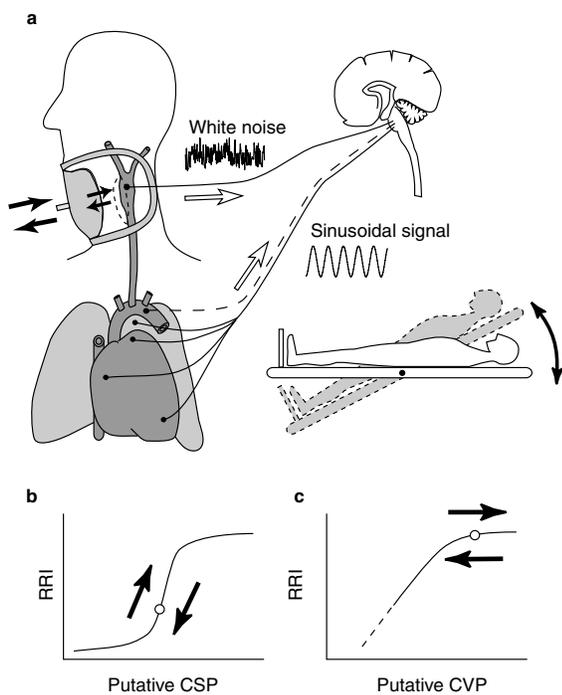


FIG. 1. Experimental setup and schematic representations of the human baroreflex system. (a) The human baroreflex system has two stretch receptors: the arterial and the cardiopulmonary baroreceptors. The afferent signals from these receptors are independently transmitted to the nucleus tractus solitarius in the brain stem, through which the integrated outputs to peripheral organs are sent via common efferent pathways [8]. In this study, the cardiopulmonary baroreceptor was periodically stimulated by an oscillating tilt angle. This weak periodic signal merged in the brain with noise added to the carotid arterial baroreceptors by randomly changing a pneumatic neck chamber pressure. (b) A typical response curve of RRI to steady-state changes in the carotid sinus pressure (CSP) sensed by the carotid arterial baroreceptors [6]; (c) a typical response curve of RRI to steady-state changes in the central venous pressure (CVP) sensed by the cardiopulmonary baroreceptor [7]. Note that the latter response curve has thresholdlike nonlinearity wherein a small change in CVP does not result in appreciable changes in RRI.

were requested to synchronize their breathing with a metronome's sound (0.25 Hz) so that RRI modulation by respiration did not contaminate the frequency component of the RRI time series at the signal frequency [12].

We first measured RRI values from eight healthy young subjects ( $27.5 \pm 3.7$  yr; mean  $\pm$  SD) with five different levels of noise intensity [13]; the standard deviation (SD) of the intrachamber pressure was set to 0, 5, 10, 20, and 30 mm Hg. The oscillating tilt angle in this experiment was fixed to  $0^\circ$ – $20^\circ$ , where  $0^\circ$  corresponds to the supine position. Each subject performed five 12 min sessions in a random order while the data for the last 9 min were analyzed.

Unequal RRI were aligned sequentially and regarded as the data sampled regularly at their mean interval. The resting human heart rate often shows a very slow trend [14], which would prevent the accurate estimation of spectral power of RRI near the signal frequency. Hence, before analyses, the slow trend was filtered out by using a

technique of robust locally weighted regression (a window length of 70 beats) [15]. In addition, a 31st-order finite impulse response low-pass filter (cutoff frequency; 0.075 Hz) was used to eliminate frequency components higher than the signal frequency.

Figure 2(a) shows a typical example of the filtered RRI time series with varying levels of noise SD. Compared with the case where no noise was added, the oscillatory component in the RRI time series at the signal frequency was more discernible as the noise level was increased. At the greatest noise level (SD = 30 mm Hg), however,

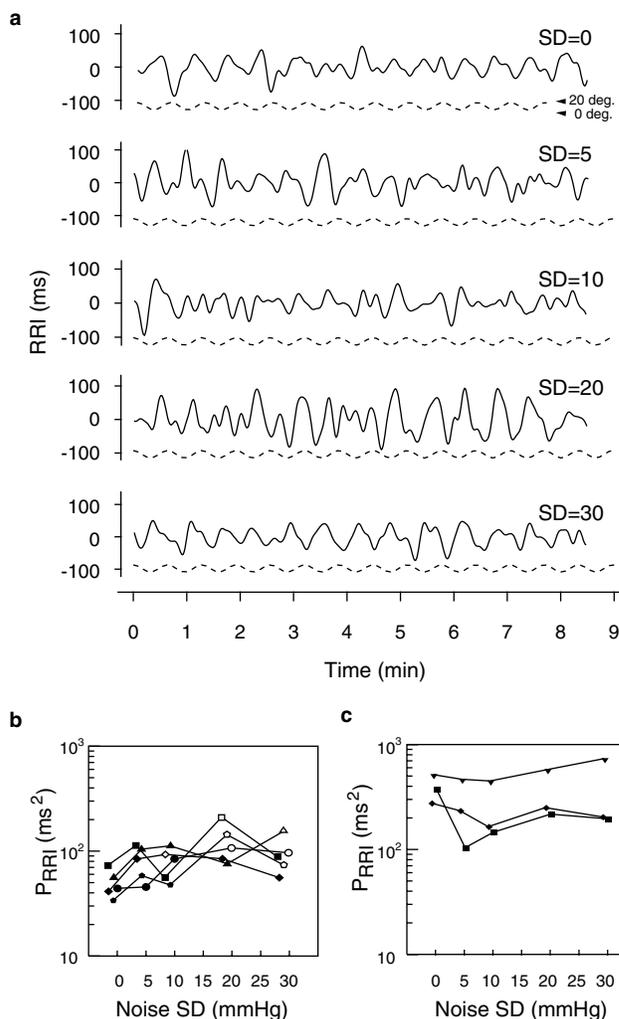


FIG. 2. Responses of RRI to noise added to the baroreflex system in the first experiment. (a) Representative recordings of band-pass filtered RRI time series from one subject. Dashed lines indicate the oscillating tilt angle. Note that the oscillatory component in RRI at the signal frequency was more discernible when the noise intensity was intermediate (SD = 20 mm Hg). (b) Relationships between noise SD and the spectral power of RRI ( $P_{RRI}$ ) around the signal frequency for five subjects whose  $P_{RRI}$  with additive noise was significantly greater than that without noise and therefore exhibited SR. Open symbols denote the corresponding values with the statistical significance; squares correspond to the subject shown in panel (a). (c) Relationships between noise SD and  $P_{RRI}$  for the other three subjects without noise induced increases in  $P_{RRI}$ . Note that, in these subjects, the greater  $P_{RRI}$  was observed even without additional noise.

the RRI oscillation decreased. For five of eight subjects shown in Fig. 2(b), the spectral power of RRI at the signal frequency ( $P_{\text{RRI}}$ ) [16] with some levels of additional noise was significantly ( $P < 0.05$ ) greater than that without noise [17]. The greatest spectral power was observed at the intermediate noise levels for all these subjects except one, suggesting the existence of the SR. This result was not due to the increase in  $P_{\text{RRI}}$  by the noise injection *per se*, because consistent monotonic increases in  $P_{\text{RRI}}$  were not always observed.

For the remaining three subjects, the RRI oscillatory component at the signal frequency did not change significantly over the entire range of noise levels [Fig. 2(c)], indicating that the noise added to the arterial baroreceptors at least did not degrade the response of the baroreflex system to a cardiopulmonary baroreceptor input. However, SR was not clearly observed. We believe this stems from larger RRI oscillations without noise [Fig. 2(c)]. In other words, for these subjects the signal amplitude of  $0^\circ$ – $20^\circ$  likely lies above the threshold, precluding a SR curve. We therefore conducted an additional experiment for six subjects including the three subjects where the signal amplitude was tuned individually before adding noise.

For this purpose, the local maxima of the oscillatory tilt angle was gradually increased from  $0^\circ$  to  $30^\circ$  ( $1^\circ/\text{min}$ ) with the frequency of oscillation fixed at 0.026 Hz. From the frequency content at 0.026 Hz calculated by a time-frequency analysis [18], the response curves of the magnitude of both RRI and systolic blood pressure (SBP) oscillations at the signal frequency were obtained. Typically, they initially increased slowly, followed by abrupt increases [Fig. 3(a)]. We adopted the maxima of the oscillatory tilt angle at this transition point as a fixed signal amplitude. The maxima of the tilt angle determined in this way was  $15.0^\circ \pm 7.6^\circ$  (mean  $\pm$  SD). Thereafter, a

single 40 min session where the noise level was gradually increased as  $\sigma = 0.01875t^2$ , where  $\sigma$  and  $t$  are, respectively, noise SD in mmHg and time in minutes, was conducted to observe transient responses in RRI oscillations at the signal frequency [19].

The results of this additional experiment were very convincing in that the magnitude of RRI oscillations by the subthreshold oscillatory tilt increased initially, reached a maximum, and then gradually decreased as the noise level increased [Fig. 3(d)]. The transient changes in the RRI oscillation magnitudes, as measured by the Wigner-Ville distribution [18] at the signal frequency ( $\text{WVD}_{\text{RRI}}$ ), exhibited bell-shaped curves, typically observed in SR phenomenon [1], for all of the six subjects [Fig. 3(e)].

The response of RRI to central venous pressure is known to be nonlinear [10], and, in our experimental setup where SR behavior was observed, the operating point is considered to be located at the flat region of this response curve [Fig. 1(c)]. Thus, without adding noise, weak changes in the central venous blood pressure induced by the oscillatory tilt do not result in appreciable heart rate and blood pressure responses [Fig. 3(a)], which might in turn activate the arterial baroreflex. We therefore hypothesize that the enhancement of the baroreflex response in the brain derives from this thresholdlike nonlinearity in the cardiopulmonary baroreflex. Such threshold behavior is often associated with SR [1,20].

One might suspect the possibility that the interaction of noise with signal could occur not in the brain stem but at the peripheral arterial receptors. However, we consider this unlikely for two reasons. First, the arterial baroreflex response of RRI to a blood pressure input is known to be linear [6] around the operating point. In other words, the arterial baroreflex system does not have the nonlinearity indispensable for SR. Second, we have recently conducted

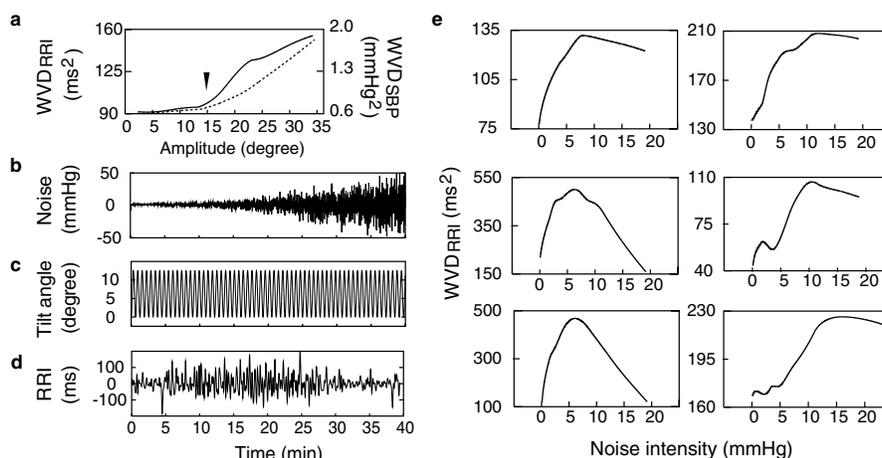


FIG. 3. Effects of time-varying noise intensity on the magnitude of RRI oscillations in the second experiment. (a) Responses of Wigner-Ville distribution of RRI ( $\text{WVD}_{\text{RRI}}$ ; a solid line) and SBP ( $\text{WVD}_{\text{SBP}}$ ; a dotted line) at the signal frequency during a graded increase in the local maxima of the oscillatory tilt angle (0.026 Hz). The test signal amplitude was set as the transition point indicated by an arrow. (b) Noise; (c) signal; (d) a band-pass filtered RRI time series from one subject. Note that the RRI responses were markedly enhanced with an intermediate level of noise. (e) Relationships between noise SD and  $\text{WVD}_{\text{RRI}}$  at the signal frequency for each subject. The bottom left panel is for the subjects shown in panels (b)–(d). Note that typical bell-shaped SR curves were observed for all of the six subjects.

a different set of experiments where we used a sinusoidal lower body negative pressure to inject a signal into the central venous pressure with physically negligible effects on the arterial system [21]. In six of eight subjects examined, the SR in RRI was also observed in the experimental setting.

We believe these results to be important for three reasons. First, different from previous sensory SR studies that showed only receptor organ effects [2–5], our work strongly suggests that there can be functional benefits of added noise in the brain. While the noise enhanced information processing in the brain has been proposed by observing SR in a mammalian brain preparation [22] and the dynamical model [23], the current findings provide the first experimental support for a functional role for noise in the brain. Second, from a standpoint of baroreflex physiology, a simple evaluation of the linear transfer characteristics from the input (blood pressure) to the output (efferent neural activities and/or the target organ responses) [24] may not be sufficient, as the noise intrinsic to the human cardiovascular system [14] would be able to alter the baroreflex sensitivity even if the input stimuli were kept constant. This also suggests that the causality of the brain might be influenced by the existence of background “noise.” Finally, as the current observation on the enhancement of the brain stem responsiveness is obtained at a functional level in humans, it may provide an experimental basis for a biomedical engineering application [25] whereby externally added noise is used to compensate for brain dysfunction such as orthostatic disorders.

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\*Corresponding author.

Email address: yamamoto@p.u-tokyo.ac.jp

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- [12] Instantaneous lung volume was measured by a respiratory inductance plethysmograph (RESPITRAK, Non-Invasive Monitoring Systems) to confirm that the respiratory frequency was successfully controlled.
- [13] The beat-to-beat RRI was measured continuously from a surface electrocardiogram (ECG) by use of standard bipolar leads with an ECG device (LifeScope6, Nihon-Koden). The sequence of R waves in ECG was processed on a real time basis with a personal computer (GP6-266, Gateway) at a sampling frequency of 1000 Hz. Blood pressure was obtained by the noninvasive finger cuff method (Finapres 2300, OHMEDA) to provide beat-to-beat estimates of SBP at the carotid sinus level.
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- [16] Each RRI data set was split into five segments containing 128 points of data, and the averaged power spectral density was calculated using a fast Fourier transform with Bingham’s cosine-tapered data window. A weighted sum of power spectral density values near the signal frequency ( $P_{RRI}$ ) was used to quantify the RRI oscillations induced by the cardiopulmonary baroreflex.
- [17] The  $F$  test was used to test statistical differences among noise levels. Holm’s correction [S. Holm, *Scand. J. Stat.* **6**, 65 (1979)] was applied to keep the total error of the tests below 5%.
- [18] The RRI time series obtained in the second experiment, after applying the same filtering techniques as for the first experiment, was converted into analytic signals by Hilbert transformation before calculating the time-frequency distribution (Wigner-Ville distribution) [see L. Cohen, *Proc. IEEE* **77**, 941 (1989); P. Novak and V. Novak, *Med. Biol. Eng. Comput.* **31**, 103 (1993)] using a 128-point data window. A sum of distribution values near the signal frequency (WVD<sub>RRI</sub>) was used to quantify the smoothed [15] time-varying magnitude of RRI oscillations induced by the cardiopulmonary baroreflex.
- [19] The length of data collection (40 min) was determined based on the balance between the length of data and the restrictive stress of the subjects.
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