$1/f$ Noise Outperforms White Noise in Sensitizing Baroreflex Function in the Human Brain

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We show that externally added $1/f$ noise more effectively sensitizes the baroreflex centers in the human brain than white noise. We examined the compensatory heart rate response to a weak periodic signal introduced via venous blood pressure receptors while adding $1/f$ or white noise with the same variance to the brain stem through bilateral cutaneous stimulation of the vestibular afferents. In both cases, this noisy galvanic vestibular stimulation optimized covariance between the weak input signals and the heart rate responses. However, the optimal level with $1/f$ noise was significantly lower than with white noise, suggesting a functional benefit of $1/f$ noise for neuronal information transfer in the brain.

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Noise in the brain is often "colored" [1–4], i.e., it exhibits a $1/f$ type power spectrum indicative of long-range time correlation [5], as opposed to conventional white noise which has a flat power spectrum without any time correlation or with a short-time correlation. The examples are indeed abundant, including the dynamics of local neuronal activity [1,2] as well as activity in the cortical network [3], which can also be observed by monitoring the behavior of affected end organs [4]. The functional significance of these noisy fluctuations in the brain is, however, still unknown.

The ubiquitousness of $1/f$ noise in the brain, together with a growing recognition that noise can assist neural systems in detecting weak subthreshold signals [6] — a phenomenon known as stochastic resonance (SR) [7], recently led Nozaki and co-workers [8,9] to hypothesize that $1/f$ noise would be more effective than white noise for invoking SR in neural systems. Both numerical [8,9] and analytical [9] studies of mathematical models of neuronal activity whose dynamics mimicked those of real neurons showed that the optimal noise level for SR was much lower with $1/f$ noise than with white noise, if the noise contained frequency components that were sufficiently higher than the characteristic frequency of the system [9]. However, an attempt to test this hypothesis experimentally using rat cutaneous mechanoreceptors [10] failed to show a beneficial effect of $1/f$ noise perhaps due to a high frequency limitation of the mechanical noise.

Here, we provide the first experimental evidence for the superiority of externally added $1/f$ noise to the conventional white noise in sensitizing the human brain. We study the human baroreflex system, with which increases (or decreases) in blood pressure are automatically compensated for by decreases (or increases) in heart rate and vascular resistance via the autonomic nervous system, which was recently shown to exhibit SR-type behavior [11,12]. Different from Ref. [11], we use noisy galvanic vestibular stimulation (GVS), which is known to activate afferent signaling to the brain stem baroreflex centers [13], enabling higher frequency stimulation than the mechanical noise. We then test if the optimal noise level for the compensatory heart rate response to weak periodic signals introduced at the venous baroreceptors would be lower with $1/f$ noise than with white noise.

Nine subjects [14] underwent two or three 40-min experimental sessions during which their venous baroreceptors were periodically unloaded using a computer controlled, motor driven tilt table that was sinusoidally oscillated at a frequency of 0.025 Hz [Fig. 1(a)]. As in an earlier study [11], a fixed maximum change in tilt angle ($9.11 \pm 2.03°$ from the baseline supine position at 0°; mean ± SD) was predetermined to be below the response threshold in each subject, i.e., the maximum change in tilt angle was such that the change in heart rate elicited by the oscillatory input signal was negligible. In each session, either $1/f$ [Fig. 1(b)] or white [Fig. 1(c)] noise was added to the brain stem by bilateral cutaneous electrical stimulation of the vestibular afferents [15] using a double monaural configuration in which silver/silver-chloride electrodes were placed over the subject's bilateral mastoid processes [16] and forehead. With this configuration, zero mean noisy currents, if applied with greater intensity than was actually used, would produce a vestibular sensation equivalent to tilting up or down randomly, depending on the polarity, and would thus interact with the baroreflex system [17] under the influence of the oscillatory tilt. The noise intensity (local variance) was linearly increased during the session [Figs. 1(b) and 1(c)] by multiplying a linear modulating function by noise sources with zero means and unit variances [18]. The end point at the 40th minute was set to 90% of the subject's nociceptive threshold (0.48 ± 0.22 mA), which was determined beforehand. This means that the subjects were never

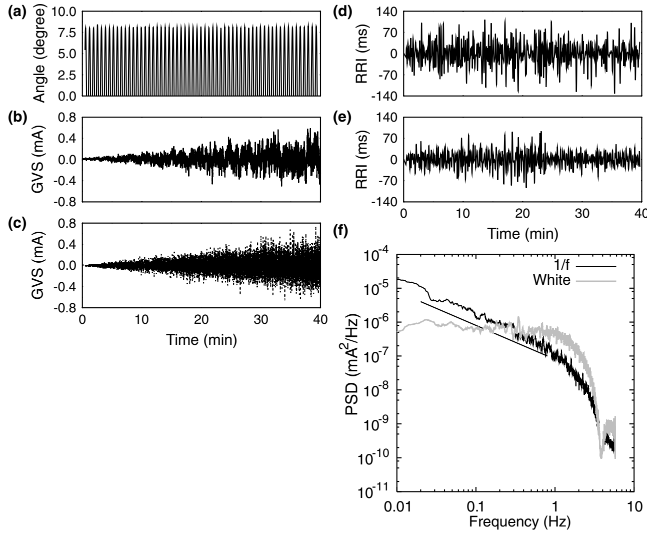

FIG. 1. Effects of time-varying noise intensity and noise color ($1/f$ or white) on the magnitude of RRI oscillations. (a) Tilt angle signal; (b),(c) GVS currents with $1/f$ (b) and white (c) noise; (d),(e) Band-pass filtered RRI records from one subject with $1/f$ (d) and white (e) noise. (f) The average power spectra of the injected GVS currents for $1/f$ (black) and white noise (gray lines).

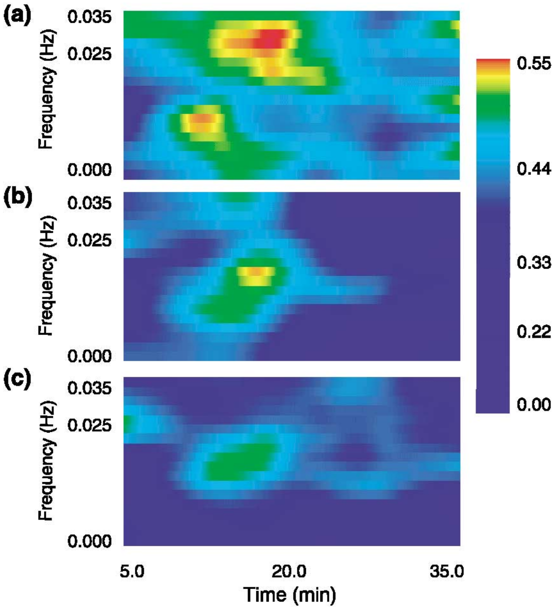

FIG. 2 (color). Smoothed cross Wigner-Ville distributions between band-pass filtered RRIs and tilt angle changes during sessions with $1/f$ (a) and white (b) noise, and during a control session without stochastic GVS (c). The Wigner-Ville distributions were normalized by the standard deviation of RRIs during 40-min test periods to cancel the effect of day-to-day RRI variability. The subject is the same as one in Fig. 1.

aware of the presence of GVS during the sessions. We also measured the actual currents to confirm that neither the mean nor the variance of the $1/f$ (mean; $0.000\,39 \pm 0.0030$ mA, variance; 0.0070 ± 0.0051 mA^2) and white (mean; 0.0048 ± 0.0092 mA, variance; 0.0068 ± 0.0053 mA^2) noise differed significantly ($p > 0.05$ by the paired t test). The group mean power spectra of the injected currents had desirable frequency characteristics within a range of 0.01–2.0 Hz [Fig. 1(f)]. In addition, five of the nine subjects also underwent a control session without GVS. The $1/f$, white and control sessions were conducted on separate days, with session order determined by random selection.

Changes in the filtered heart rate responses, measured from intervals of successive R waves in an electrocardiogram (RR intervals; RRIs) [19,20], elicited by the subthreshold oscillatory tilt were enhanced by intermediate levels of either $1/f$ [Fig. 1(d)] or white [Fig. 1(e)] noise. We examined this potentially beneficial effect of stochastic GVS more closely by using a time-frequency representation of the covariance between the filtered RRI and the tilt angle changes calculated with a cross Wigner-Ville (WV) distribution [22]. In this subject, WV distributions around the signal frequency (0.025 Hz) and the subharmonic band peaked for both $1/f$ [Fig. 2(a)] and white [Fig. 2(b)] noise during the first half of the sessions, when the noise levels were weak to intermediate, and the responses to $1/f$ noise were greater than to white noise. Note that during the control session with the same subject (as well as four other subjects who underwent control sessions) such sharp peaks were not observed [Fig. 2(c)], indicating that the increased local covariances were due to the stochastic GVS, not to factors such as a hysteresis effect of monotonically increased noise.

We next examined the group mean, absolute lag-zero covariance between the filtered RRIs and the tilt angle changes calculated every 5 min. We found that the input-output covariance was significantly ($p < 0.01$ by one-way ANOVA) increased by stochastic GVS both for $1/f$ and white noise, with a slight indication of leveling off at the highest $1/f$ noise level [Fig. 3(a)]. Assigning a value of 1.0 to the noise level ($V^{1/f}_{\mathrm{peak}}$; mA^2) at which an individual's covariance for $1/f$ noise was maximal caused the normalized (to $[0, 1]$) covariance curves to become bell shaped [Fig. 3(b)], which is typical of SR phenomena [7]. Moreover, the noise levels at the peak covariance were much smaller for $1/f$ noise than for white noise. Finally, the ratio of the noise intensity at the peak covariance to an individual's maximal noise level was significantly lower (0.56 ± 0.08 and 0.79 ± 0.07 for $1/f$ and white noise, respectively; $p < 0.05$ by the paired t test) when $1/f$ noise was added to the baroreflex system. Thus, $1/f$ noise with a frequency range of 0.01–2.0 Hz outperformed white noise in that it was able to fully optimize the baroreflex system at a lower noise level.

It is noteworthy that the frequency range of 0.01–2.0 Hz corresponds to the range at which spike trains in single medullary neurons exhibiting sympathetic nerve-related and spontaneous activity show long-range time correlations [2]. Interspike interval (ISI) histograms of these spontaneous activities are reported to be highly

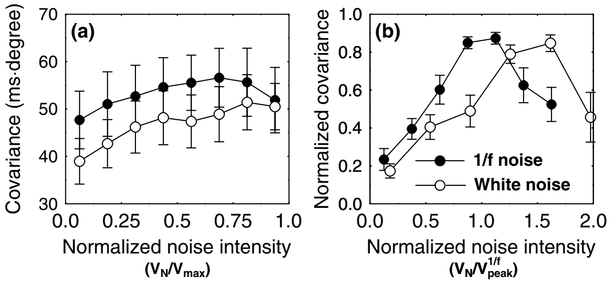

FIG. 3. Effects of $1/f$ and white noise on the baroreflex response estimated by covariances between filtered RRIs and tilt angle changes. (a) The relationship between noise intensity (V_N) normalized by maximal noise variance used ($V_{\max}$) and the input-output covariance. (b) The relationship between noise intensity V_N normalized by the noise variance at which the peak covariance was observed with $1/f$ noise ($V^{1/f}_{\text{peak}}$) and the normalized (to $[0, 1]$) covariance. Values are means ± SEM. Filled and closed symbols, respectively, represent the results with $1/f$ and white noise.

skewed by occasional longer ISIs, giving rise to the long-range correlation [2]; furthermore, the longer ISIs in some medullary neurons have a facilitatory effect on the sympathetic efferent activity and result in increases in heart rate. Because $1/f$ noise also has greater low-frequency components than white noise having the same variance [Fig. 1(f)], it would be expected that override of spontaneous medullary activity and sensitization of baroreflex within the brain stem would be mediated by effects of added noise equivalent to those causing the longer ISIs.

We demonstrated this effect using the same linearized version of the FitzHugh-Nagumo model used by Nozaki *et al.* [9] to show the superiority of $1/f$ noise over white noise for invoking SR:

$$\dot{v} = -\gamma_1 v - \gamma_2 w + \mu + S(t) + \xi(t), \qquad \dot{w} = \lambda_1 v - \lambda_2 w,$$

where $v(t)$ is an excitatory variable potentially leading to increases in heart rate (t, time), $w(t)$ is a "recovery" variable, μ is a constant (DC) input, $S(t)$ is a subthreshold sinusoidal signal (0.025 Hz) with zero mean, and $\xi(t)$ is either white [Fig. 4(a)] or $1/f$ [Fig. 4(b)] Gaussian noise with a frequency range of 0.01–0.2 Hz. Because the efferent sympathetic activity influencing heart rate is known to have a mean response time (i.e., the time constant plus delay) of 3.65 s [23], a value of $\gamma_1 = 1/3.65$ was used. In humans, heart rate dynamics exhibit intrinsic oscillations at ≈ 0.1 Hz [24]. We therefore adjusted other parameters so that the natural frequency $\sqrt{2\gamma_1\lambda_2 + 4\gamma_2\lambda_1 - \gamma_1^2 - \lambda_2^2}/(4\pi)$ is equal to 0.1 Hz. In addition, $\gamma_1 + \lambda_2$ must be positive for the stable system. By taking these factors into account, we used $\gamma_2 = 1.3$, $\lambda_1 = 0.3$, and $\lambda_2 = 0.2$ [25,26]. The added noise was considered to have a facilitative effect when the variable v crossed a predefined threshold.

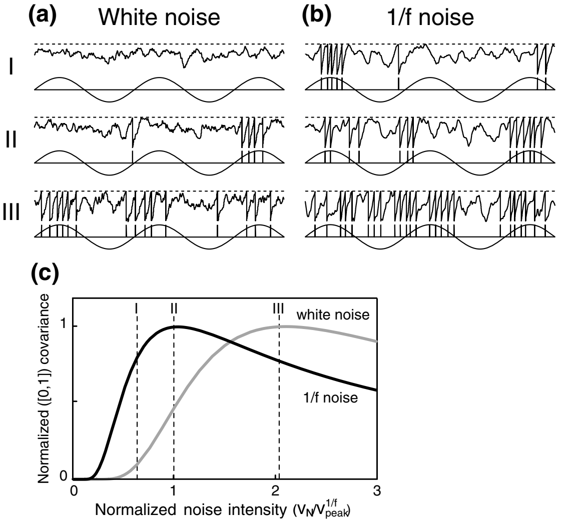

FIG. 4. Effects of $1/f$ and white noise on the response of a mathematical baroreflex model. (a),(b) Typical time courses of variable v (top trace; the broken line represents the threshold) and spike trains (bottom trace; the signal is superimposed) over a period of 100 s when either white (a) or $1/f$ (b) noise with three different intensities was added. The noise intensities were 0.8×10^{-3} (I), 1.28×10^{-3} (II), and 2.61×10^{-3} (III). (c) Theoretical prediction for normalized (to [0,1]) covariance between the subthreshold sinusoidal signal and the firing frequency of the output spike trains. Vertical broken lines (I),(II),(III) correspond to the noise intensities shown in panels (a) and (b).

The basic features of this system were: (i) the "firing" rates increased with incremental increases in noise intensity; (ii) at intermediate noise levels, the firing tended to occur at times when the sinusoidal signal was strongest; and (iii) $1/f$ noise invoked features (i) and (ii) at lower noise intensities than white noise [Figs. 4(a) and 4(b)]. Theoretical curves given in Ref. [9] in which the normalized (to $[0, 1]$) covariance between the instantaneous firing frequency and the input signal were plotted against normalized (to $V^{1/f}_{\text{peak}}$) noise intensity [Fig. 4(c)] nicely predicted the experimental results (i.e., the noise level at the peak covariance was much smaller for $1/f$ noise than for white noise [Fig. 3(b)]). This model can be thought of as a feedback system regulating the variable v to a fixed point (i.e., a "resting" level), which suggests that one advantage of $1/f$ noise in this system, and perhaps the actual baroreflex system as well, lies in its greater ability to kick systems out of insensitive fixed states. Furthermore, studies carried out with model neurons [8,9] indicate that Brownian motion has little or no ability to invoke SR, despite having even greater low-frequency components than $1/f$ noise. It thus seems likely that $1/f$ noise is optimal for sensitizing the brain's responsiveness.

The functional significance of $1/f$ noise in the human brain is not yet clear, despite its ubiquitous presence in the external physical environment [5], and in the central nervous system [1–4]. However, our finding that $1/f$ noise is suitable for invoking SR in the brain stem baroreflex centers suggests the novel hypothesis that external or internal $1/f$ noise might be used by the brain to optimize its responsiveness. Also, the practical significance of this finding is exemplified by our earlier report that external mechanical noise added to the arterial baroreceptors was able to compensate for the blunted autonomic efferent responses to a postural challenge in patients with primary autonomic failure [27]. That is, application of baroreceptor noise to these patients, who were otherwise unable to maintain adequate blood pressure after a passive standup to remain conscious, often ameliorated the orthostatic hypotension to a point where the patient was able to retain consciousness. Thus, SR invoked by externally added sensory noise could be used to "treat" patients with central nervous system dysfunction. Although the mechanical device used in our previous studies [11,12,27] is not practical for this purpose, given its large size and immobility, the present results suggest the possibility of using a portable GVS apparatus to treat patients with central nervous system dysfunction. If so, $1/f$ noise would be superior to white noise, as it would require less power to invoke SR and sensitization of brain stem responses.

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[19] The methods of data collection including that for RRIs in this experiment were the same as those in Ref. [11].

[20] Unequal RRIs were aligned sequentially and regarded as the data sampled regularly at their mean interval. To eliminate frequency components lower than the signal frequency, the slow trend was filtered out using the technique of robust locally weighted regression (a window length of 15 s) [21]. In addition, a 20th-order finite impulse response low-pass filter (cutoff frequency; 0.2 Hz) was used to eliminate frequency components higher than the signal frequency.

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[26] By setting $\mu = (\gamma_1 \lambda_2 + \gamma_2 \lambda_1)/\lambda_2$, we started the simulation from an equilibrium point at which $(v, w) = (1, \lambda_1/\lambda_2)$. The system was driven by a subthreshold signal $S(t) = A \sin(2\pi t/T)$ $(A = 0.025,\ T = 40\ \mathrm{s})$ and noise $\xi(t)$ with different intensities. Once v crossed a threshold value of $\theta = 1.05$, a narrow pulse was generated, and the values of v and w were reset to 0.9 and λ_1/λ_2, respectively. This resulted in a refractory period approximating $T_R = 2.3$ s. The simulations were obtained by numerical integration of the model every 12.2 ms.

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