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ORIGINAL COMMUNICATION

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Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders

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Abstract Through the cerebellar vermis, the vestibular nerves are known to influence the basal ganglia and the limbic system. By means of noisy galvanic vestibular stimulation (GVS), it may be possible to ameliorate movement disorders, particularly akinesic symptoms, in patients with central neurodegenerative disorders. We evaluated the effect of 24-hour noisy GVS on a power-law temporal autocorrelation exponent of daytime wrist activity, separately for higher (local maxima) and lower (local minima) levels of activity, in 14 hospitalized patients. The power-law exponent for the local maxima was significantly ($p < 0.002$) lower with the noisy GVS than with sham stimulation, suggestive of more frequent switching behavior from low to high levels of activity or less severe akinesia. The noisy GVS may thus potentially improve certain motor dysfunctions in patients with distinct central neurodegenerative diseases.

Key words Parkinson's disease · multiple system atrophy · physical activity · power-law exponent · stochastic resonance

Introduction

With galvanic vestibular stimulation (GVS), electrical current is delivered transcutaneously to the vestibular afferents through electrodes placed over the mastoid bones, modulating their continuous firing levels [6]. The vestibular nerves are known to influence the basal ganglia and the limbic system [1, 2] via the cerebellar vermis [3, 9]. As these projections have a strong effect on the turnover of dopamine and noradrenaline in these areas [1, 2], activation of these pathways may alleviate the lack of a monoamine-mediated limbic-to-motor link, such as that responsible for the akinesic symptom observed in Parkinson's disease (PD) patients [4], in addition to the direct vestibulo-cerebellar effects on motor functions. We thus hypothesized that the GVS may alleviate movement disorders, particularly akinesic symptoms, in patients with PD and other central neurodegenerative disorders, including multiple system atrophy (MSA).

Indeed, Yamamoto et al. [17] evaluated the effect of continuous GVS on day-long spontaneous trunk activity dynamics in patients with either levodopa responsive PD or levodopa unresponsive parkinsonism, and reported a quickening of bradykinesic rest-to-active transitions probed by a power-law temporal autocorrelation measure. Also, they used zero-mean, noisy stimulation applied with a portable device, which is more advantageous than constant GVS because it does not cause side effects in the form of unilateral oculomotor and postural responses [14]. The rationale behind using noisy stimulation is the beneficial role played by input noise in sensitizing neural systems [5, 8], possibly through a mechanism known as stochastic resonance, a basic physical mechanism underlying noise-enhanced responses of nonlinear systems to weak signals [16], and it is hypothesized that a central circuit signaling the onset of movement of which the threshold is relatively increased due to the diseases may benefit from noisy modulation of the afferent firing rates. However, symptom-

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atic correlates of the alteration in the autocorrelation measure by noisy GVS are still unknown.

Recently, Pan et al. [11] showed that the power-law exponent (α) for higher levels of wrist activity – measured by a standard actigraph device [15] – or at the so-called local maxima of coefficients of the wavelet transform significantly correlated with the symptom severity of PD patients; the less severe PD patients exhibited lower α values for the local maxima, suggestive of more frequent switching behavior from low to high levels of physical activity or less severe akinesia. Thus, by using this power-law exponent for local maxima in the present study, we aim to evaluate the possible ameliorating effect of noisy GVS on impaired motor functions of patients with central neurodegenerative disorders.

Patients and methods

Participants

Ten patients with akinesia and four with ataxia at the Department of Neurology of the University of Tokyo Hospital participated in this study (Table 1). All the patients were ambulant but exhibited gait disturbance due to akinesia or ataxia. Medication was kept the same throughout the experiment. Seven of the fourteen patients (Nos. 3–6, 11, 13, 14) were also tested in our previous study [17]. The study was approved by the Ethics Committee of the Graduate School of Medicine, The University of Tokyo, and performed under the principles outlined in the Declaration of Helsinki.

Procedures and data analyses

The GVS devices used and the experimental procedures were the same as those used previously [17]. In brief, a portable GVS device was used to deliver currents using a bilateral unipolar configuration [6], in which electrodes were placed over the patient's bilateral mastoid processes with the reference electrodes placed on the forehead. The waveform, a zero-mean, linearly detrended noisy current with a 1/f-type power spectrum within a range of 0.01–2.0 Hz or a constant zero current for control, with a duration of 300 s was continuously repeated during the tests. The device has a switch inside so that the experimenter could choose the waveform to use; this was, however, concealed from the patients and doctors in charge of them. The tests started at about noon during the patients' hospital stay. After determining the nociceptive threshold of each patient, the magnitude (standard deviation) of noisy GVS was set to 60 % of each subject's nociceptive threshold (SD of the current amplitude; 0.29 ± 0.20 mA), ensuring the absence of apparent oculomotor responses and that the patients were not aware of the presence of the GVS during the tests. Then, either the noisy GVS or the control zero current was continuously applied for the first 24 hours, and then switched to the counterpart and applied for another 24 hours, while the patients' wrist activity was monitored continuously for 48 hours. The order of conditions was determined for each patient by random selection.

The methods for data collection and analyses were the same as those in Pan et al. [11]. Briefly, all the patients wore a small watch-type activity monitor equipped with a computer (Ruputer Pro, Seiko Instruments, Chiba) [17] on the wrist of their non-dominant hand. Zero-crossing counts were recorded for every minute and were separated into the time awake and the time asleep, according to the patient's report. Only the data during the time awake were used for analyses. The wavelet coefficients ($W(S)$) at each point along the time series and at different time scales (S) were obtained by convolving the third derivative of the Gaussian function as the so-called "mother wavelet" with the time series. By this approach, the transient increases (low-high-low level activity patterns) yielded local maxima of the wavelet coefficients at their time points, while the decreases (high-low-high level activity patterns) yielded local minima of the wavelet coefficients. Then, the squared wavelet coefficients at the local maxima or minima were averaged for all the data points, and the power-law exponent (α) was obtained separately for local maxima and minima as the slope of a straight line fit in the double-logarithmic plot of S vs. $W(S)^2$ in the range of S corresponding to 8 to 35 min (Fig. 1 c, d). The differences in the α values for GVS and control condi-

Table 1 Demographic and clinical data of 14 patients

No. of patients	Age (yr)	Sex	Diagnoses	UMSARS PartI/PartII/PartIII	UPDRS (PartIII) /H&Y	Duration (yr)	Medication
1	72	M	PD	–	33/3	7	L 200 mg, A 150 mg, C 1 mg
2	78	M	PD	–	32/2	4	L 400 mg, A 150 mg, P 500 mg, D 300 mg
3	38	M	PD	–	35/3	8	L 400 mg, TL 0.4 mg, C 4 mg
4	74	M	PA	–	48/3	2	TZ 150 mg
5	77	F	MSA-p	22/30/3	–/3	3	L 300 mg
6	55	M	MSA-p	25/26/3	–/3	2	C 2 mg, L 300 mg, D 600 mg
7	63	M	MSA-p	34/37/4	–/4	3	L 300 mg, DB 10 mg
8	74	F	MSA-p	25/25/3	–/3	3.5	L 500 mg, S 100 mg, C 4 mg
9	56	F	MSA-p	26/28/3	–/3	4	L 450 mg
10	74	F	MSA-p	16/15/1	–/2	2	L 100 mg
11	54	M	MSA-c	20/19/2	–	1.5	PS 180 mg
12	59	M	MSA-c	23/20/2	–	5	none
13	52	M	CCA	15/6/1	–	4	none
14	61	M	CCA	11/13/2	–	6	TT 10 mg

H&Y Hoehn-Yahr staging; *UMSARS* unified MSA rating scale; *UPDRS* unified Parkinson's disease rating scale; *ARJP* autosomal recessive juvenile parkinsonism; *CCA* cortical cerebellar atrophy; *MSA* muitiple system atrophy with dominant cerebellar ataxia (c), or parkinsonism (p); *PA* pure akinesia; *PD* Parkinson's disease; *A* amantadine; *C* cabergoline; *D* droxidopa; *DB* distigmine; *L* L-dopa/DCl; *P* pergolide; *PS* pyridostigmine; *S* selegiline; *TL* talipexole; *TT* taltirelin; *TZ* trazodone

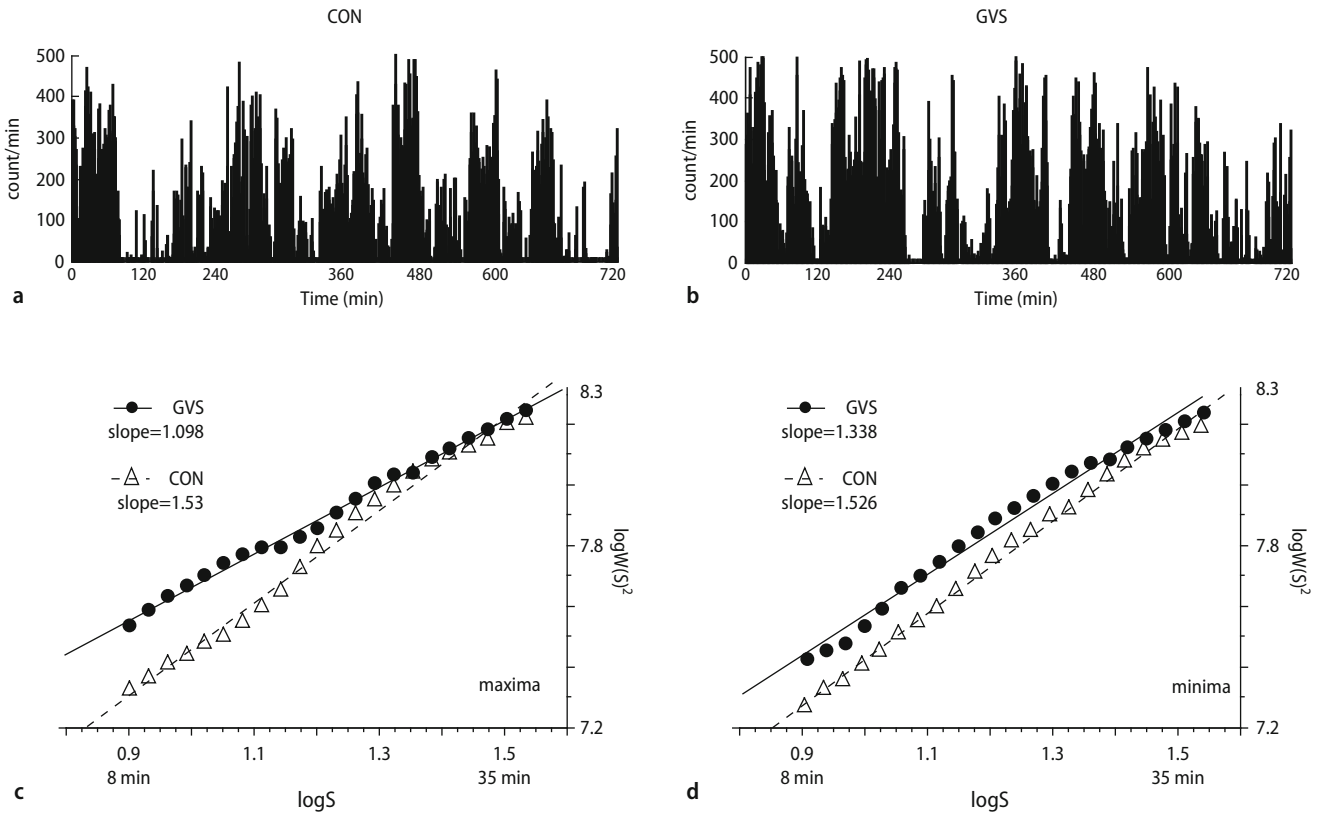

Fig. 1 Illustrative examples of wrist activity data of a PD patient during the control (CON) period (**a**) and during GVS application (**b**). The wavelet coefficients (*W(S)*) of these data, as a function of the wavelet scale (*S*), are shown for local maxima (**c**) and minima (**d**). The slopes are power-law exponents α

tions, and those for the first and the second days, were tested by a paired *t*-test.

Results

The representative wrist activity data of a PD patient during the control period (Fig. 1 a) and during the application of GVS (Fig. 1 b) are shown. Compared to control, GVS is associated with more frequent switching between higher and lower levels of activity. This results in a higher wavelet power ($W(S)^2$) with GVS (Fig. 1 c, d), particularly at smaller scales (*S*), or at higher frequencies, for local maxima (Fig. 1 c). The power-law exponent α, given by the slope of the log *S* vs. log $W(S)^2$ relationship and characterizing the nature of "switching" patterns between high and low values in a statistical sense, is smaller with GVS than with control stimulation, especially for the local maxima, suggestive of a quicker rest-to-active transition with GVS.

The group average wavelet coefficients exhibit linear relationships in the range of scales (*S*) from 8 min to 35 min both for local maxima (Fig. 2 a) and minima (Fig. 2 b) and for GVS and control conditions. The slope for local maxima with noisy GVS being substantially less than that with control stimulation (Fig. 2 a). For local maxima, the mean power-law exponent is significantly smaller ($p < 0.002$) for GVS than for the control, with the difference approaching 0.3 (Fig. 2 c). The mean α for local minima is also significantly smaller ($p < 0.02$) for GVS than for the control, but the difference is much less than that for the local maxima. When the mean α values for the first and the second days were compared, significant differences were not observed either for local maxima or minima ($p > 0.05$), suggesting that the above differences are due to the GVS application itself, not to an "order effect".

Discussion

The cranial nerves send direct inputs to the brain, and their stimulation may lead to alterations in various central functions. Such stimulation may potentially be used in the treatment of brain disorders [7]. In fact, stimulation of the vagus nerve by an implanted pulse generator has already been used to treat intractable epilepsy [13] and depression [12], its success presumably due to the vagus' connection to the nucleus tractus solitarius and subsequent noradrenergic innervation (via the locus ce-

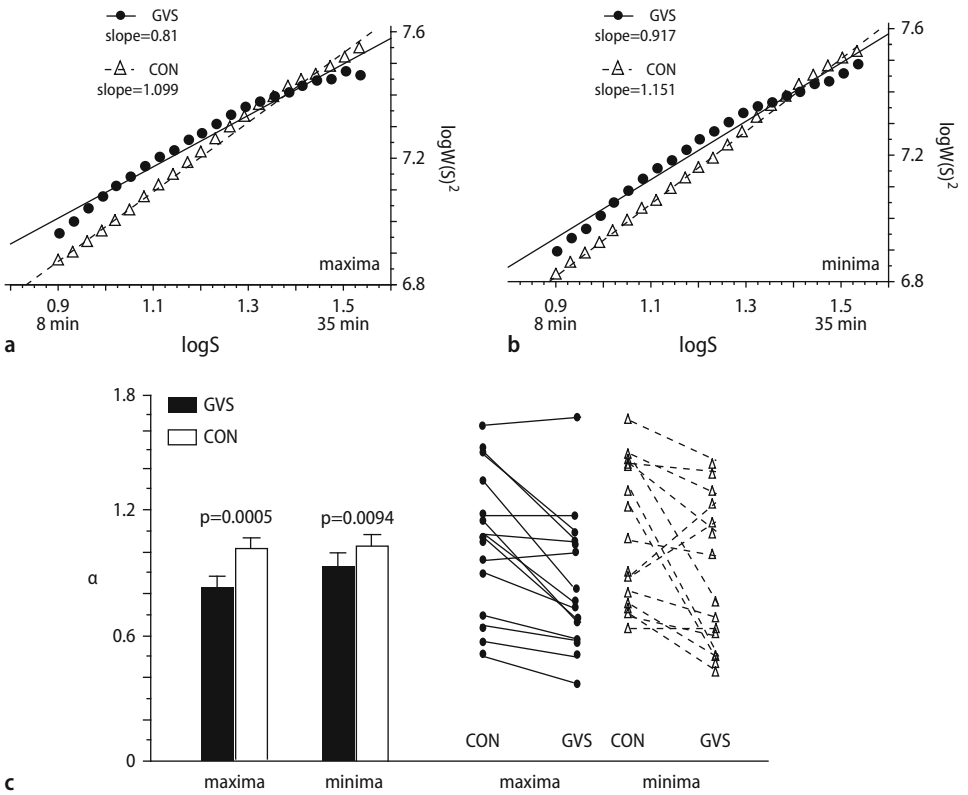

Fig. 2 The group average wavelet coefficients for local maxima (**a**) and minima (**b**) for GVS and control (CON) conditions. **c** Comparisons of the mean α for GVS and CON (left) and the within-individual differences (right). The error bars represent SEM

ruleus) of every level of the forebrain [7]. Considering its central connections [1–3, 9], the vestibular nerve can also influence limbic-to-motor functions, which is why we chose GVS in the current study. Moreover, by adding an equal number of new patients with dominant movement disorders, we confirmed the conclusion of our previous study [17], that a non-invasive and non-nociceptive application of noisy GVS, presumably through the mechanism of stochastic resonance [16], can be used to improve impaired motor functions of patients with degenerative neurological diseases.

Importantly, in this study we confirm the anti-akinesic effect of noisy GVS using a power-law temporal autocorrelation measure [10] of the patients' wrist activities, which were shown to be significantly correlated with symptom severities of PD patients [11]. Indeed, the observed decrease, approaching 0.3, in the mean power-law exponent α for local maxima by noisy GVS is comparable with, or even greater than, the decreases observed for PD patients between the severe and mild groups and of individual patients on "good condition" and "bad condition" days, as well as between days before and after anti-parkinsonism medication [11]. One non-negligible difference from the Pan et al. study [11] is the length of time for which data is available; here, we only analyzed data for a single day, while the previous study used data for >6 days. However, we confirmed that the observed decrease in α for local maxima is still greater than those obtained by reanalyzing Pan and coworkers' data [11] for a single day (1.085 ± 0.041 for severe and 0.847 ± 0.051 for mild parkinsonism; 1.034 ± 0.042 and 0.839 ± 0.037 for good and bad conditions, respectively; 0.903 ± 0.053 before and 0.719 ± 0.046 after medication; mean $\pm$ SEM), suggesting that the large decrease in the α values in this study is likely not affected by the limited time of data collection. Thus, we conclude that the presence of the anti-akinesic effect of noisy GVS with symptomatic correlates even in patients showing dopa-unresponsive parkinsonism, in addition to the anti-ataxic effect in patients with cerebellar ataxia, presumably through the demonstrated vestibulo-cerebellar connections [3, 9], calls for further research on the neurophysiological mechanisms and the effect of portable noisy GVS on the symptoms and quality of life in ambulatory patients with central neurodegenerative disorders.

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