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# Objective Evaluation of the Severity of Parkinsonism Using Power-Law Temporal Auto-Correlation of Activity

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## 1. Introduction

Parkinson disease (PD) is a neurodegenerative disorder not only with motor symptoms, including resting tremor, rigidity, bradykinesia and postural instability, but also with non-motor symptoms, including autonomic disturbance, sleep disturbance and depression. Due to the lack of objective biomarkers like the blood glucose level for diabetes mellitus, severity of parkinsonism has been evaluated by using the symptom-based Unified Parkinson Disease Rating Scale (UPDRS) (Martinez-Martin et al., 1994) that covers the various aspects of symptoms in patients with PD. Although the UPDRS is the standard method for the assessment of parkinsonism and the evaluation of drug effects, the scoring is not free from inter-rater variance or the fluctuation of the symptoms.

Wearable accelerometers enable long-term recording of patient's movement during activities of daily living, and hence might be a suitable device for quantitative assessment of the disease severity and progression. Alterations in locomotor-activity levels and disturbances in rest-activity rhythms have long been recognized as integral signs of major psychiatric and neurological disorders (Teicher, 1995; Witting et al., 1990). Improvement of ambulatory activity monitors (actigraph) has enabled precise calibration and storage of thousands of activity measurements acquired at predetermined times, hence enabled long-term recording of patient's movement during ordinary daily living (Katayama, 2001; Korte et al., 2004; Mormont et al., 2000; Okawa et al., 1995; Teicher, 1995; Tuisku et al., 2003; van Someren et al., 1996). It has been demonstrated that use of these devices is useful for the quantitative estimation of human behavior properties in normal subjects and patients with a variety of diseases, including depression, pain syndrome, and PD (Jean-Louis et al., 2000; Korszun et al., 2002; Nakamura et al., 2007; Ohashi et al., 2003; Pan et al., 2007; van Someren et al., 1993; 1998; 2006). However, because the pattern of daily activity greatly influences the recording with accelerometers, recorded activity levels may not adequately reflect the disease severity (Fig 1). Therefore, reliable analytical methods of the body acceleration signal free from the level of activity are required to describe the characteristics of body activity during daily living. Recently, fractal analysis was shown to be a robust tool to

disclose hidden auto-correlation patterns in biological data, such as heartbeat and limb movement (Ohashi et al., 2003; Pan et al., 2007; Peng et al., 1995; Sekine et al., 2004; Struzik et al., 2006). Power-law auto-correlation exponents for local maxima and minima of fluctuations of locomotor activity would be the most useful for our purpose, as they represent the level of persistency of movement patterns (Ohashi et al., 2003; Pan et al., 2007).
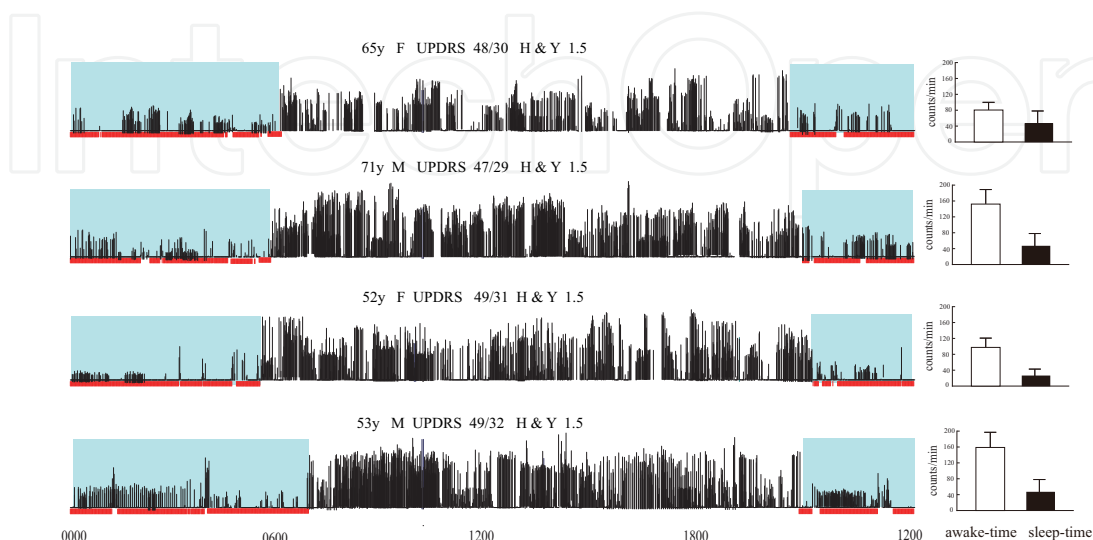


Fig. 1. Examples of 24 h actigraph recording. (left) Each vertical bar indicates activity counts per min. Sleep time is indicated in blue. Patients with approximately the same severity show different activity patterns and the activity counts (right: mean ± S.D.). UPDRS total/Part III.

In this review, we show how we can extract hidden autocorrelation patterns reflecting the severity of parkinsonism from the actigraph recording of patients' activity, and demonstrate that the analysis using power-law exponents is useful for the evaluation of effects of therapy on motor and non-motor symptoms of parkinsonism.

## 2. Analytical method of the motionlogger recordings for power-law auto-correlation exponents

We analyzed patients' physical activity records collected by an actigraph device using power-law exponents probing temporal auto-correlation of the activity counts. The power-law exponent for local maxima most sensitively and reliably reflects disability without being influenced by the presence of tremor or the patterns of daily living (Pan et al., 2007).

To examine temporal auto-correlation of the physical activity time series (i.e., *dynamic* aspects of physical activity), we used an extended, random-walk analysis, the detrended fluctuation analysis (DFA) (Peng et al., 1995), with a modification (Ohashi et al., 2003) for various "real-world" signals including activity time series. Briefly, a daytime physical activity time series was integrated, as in DFA, and wavelets with different time scales (*S*) were slid along the time series and correlated with the data to obtain the wavelet coefficients (*W*(*S*)) at each point. The third derivative of the Gaussian function was used as the so-called "mother wavelet":

$$\Psi(t) = t(3-t^2)e^{-0.5t^2, 2}$$

where $t$ is time. This is equivalent to using the Gaussian second derivative (so-called "Mexican hat") wavelet to examine the raw signals (Fig. 2), though the integration approach automatically removes the local mean and the local linear trend, as in DFA. By changing the scale of the wavelet, this "hat-shaped" template dilates or contracts in time, probing transient increases or decreases in activity records in different time scales. The transient increases (low-high-low activity patterns) yield local maxima of the wavelet coefficients at their time points, while the decreases (high-low-high activity patterns) yield local minima of the wavelet coefficients (see Fig. 2). Next, the squared wavelet coefficients at the local maxima or minima were averaged for all the available days. As the coefficient gives the magnitude of local fluctuations matching the shape of $\psi(t)$ with different time scales, the squared $W(S)$ was used, again as in DFA. Finally, the power-law exponent ($\alpha$) was obtained separately for local maxima and minima as the slope of a straight line fit in the double-logarithmic plot of $S$ vs. $W(S)^2$. This method yields the same $\alpha$–values as does DFA (Ohashi et al., 2003), but separately for periods with higher and lower activity levels. The power-law (scaling) exponent, $\alpha$, reflects the probability of a simultaneous increase or decrease in the variability at two distant points in time in the time series, applied to all distances up to *long-range* time scales, thereby probing the nature of "switching'" patterns between high and low values in a statistical sense. Larger power-law exponents indicate positive temporal auto-correlation or *persistency* in the increase or decrease, and lower values correspond to negative auto-correlation or *anti-persistency* (Ohashi et al., 2003).
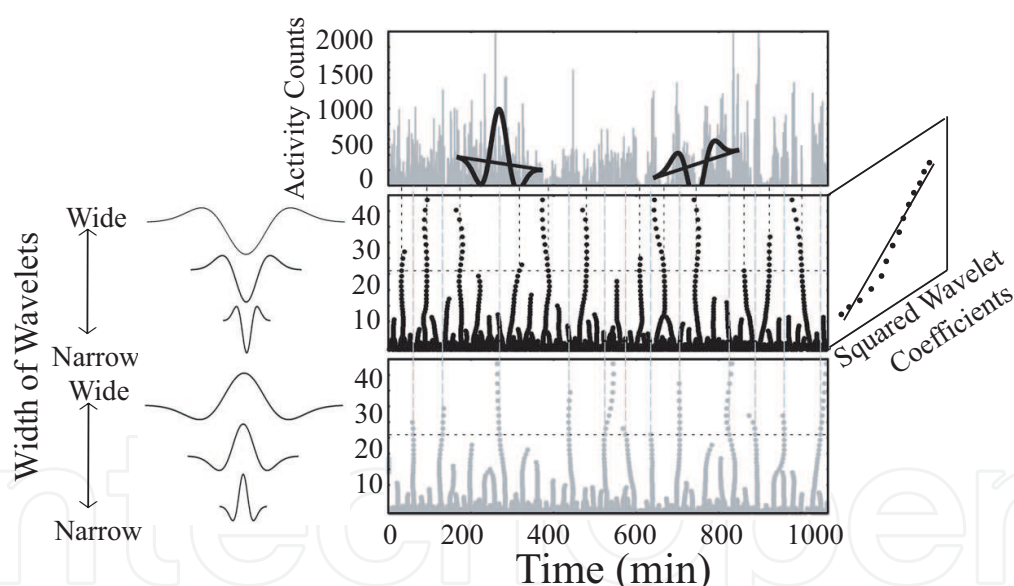


Fig. 2. Conceptual explanation of the method to obtain power-law exponents for local maxima and minima. (*top*) Various widths of hat-shaped wavelets are slid along the data to detect local minima (*middle*) and local maxima (*bottom*) of the wavelet coefficients. Note that the local minima and maxima appear at the transient decreases and increases of the activity, respectively. The power-law exponents are calculated from the slope of the log-log plot of squared wavelet coefficients vs. the scale for local minima and maxima. In the actual analysis, we used an integrated, rather than raw, time series and $\psi(t)$, i.e., the derivative of the "hat-shaped" wavelet. This yields the same power-law exponents as those obtained by the DFA method for the same local maxima and minima as obtained in this figure. Reprinted with permission from (Pan et al., 2007).

This method enables to evaluate relationships between time scales and magnitudes of fluctuation within each time scale, eliminating *non-stationarity* in the input data (i.e., changes in the baseline and trends within the data windows at different scales) that could affect calculation of the magnitudes of fluctuation. Therefore, this approach is suitable for the analysis of the long-term data collected in ambulatory settings (Pan et al., 2007).

## 3. Quantitative analysis of parkinsonism using power-law auto-correlation exponents

The data acquired during awake-time and sleep-time were separated with Action-W, Version 2 (Ambulatory Monitors Inc., Ardsley, NY) (Fig. 1) and the data during awake-time were used for analyses. Average wavelet coefficients for local maxima and minima of the severe and mild groups provided straight lines in the range of 8-35 min (Fig. 3A), indicative of very robust α-values. When the mean α-values for local maxima and minima were compared, they found a significantly lower α-value for local maxima in the mild group than in the severe group (Fig. 3B). All the patients (13 male and 9 female patients with Parkinson disease) in both the severe (Hoeh-Yahl score > 3.0; n=9)) and mild groups (H-Y score $\leqq$ 3.0; n=10)) showed significantly lower α-values for local maxima on good-condition (GC) days than on bad-condition (BC) days that were classified according to diary scores, whereas there was no significant difference in the mean α-values for local minima (Fig. 3C).
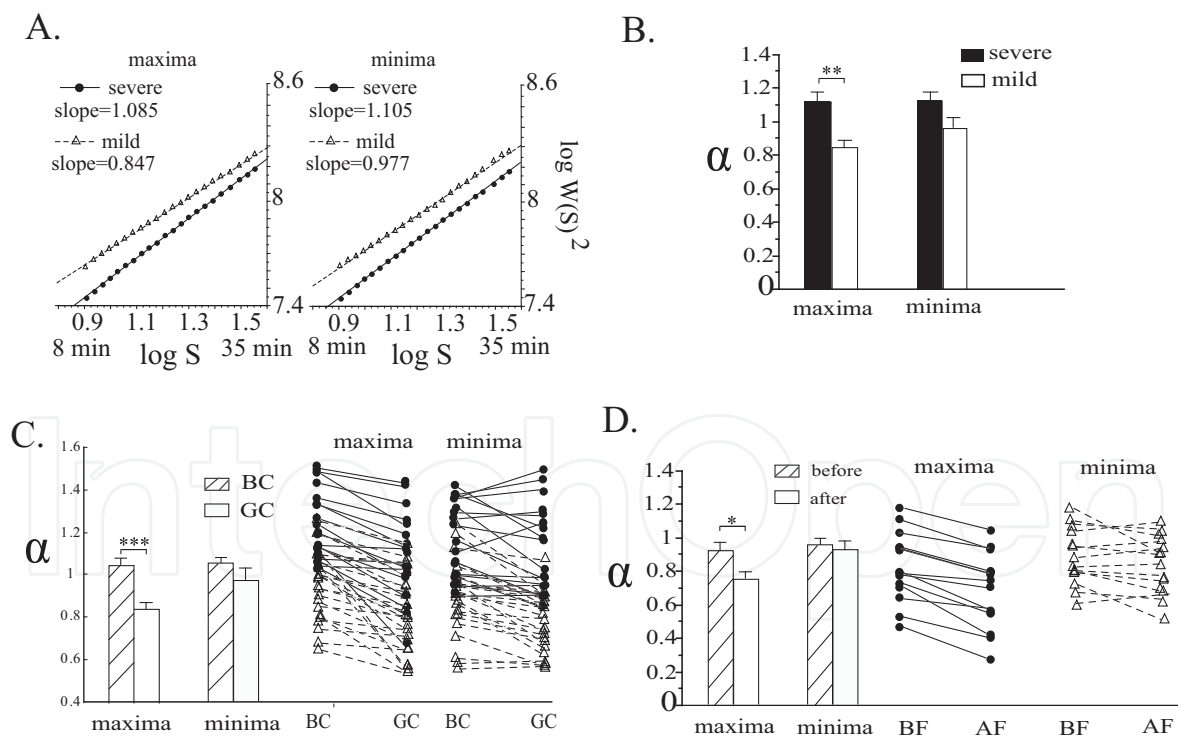


Fig. 3. Local maxima and minima of fluctuation of physical activity. (A) Average wavelet coefficients, as a function of the wavelet scale, for local maxima and minima. The slopes are power-law exponents, α. (B) Comparisons of the mean for the severe and the mild groups, (C) for BC and GC days and for individual patients, and (D) for days before and after antiparkinsonism medication and for each patient. *: $P < 0.05$, **: $P < 0.01$, and ***: $P < 0.001$. Reprinted with permission from (Pan et al., 2007).

When the effects of medication were examined, we found that all the patients who did not take any medication at the time of enrolement (n=6) showed lower α-values for local maxima on days more than three weeks after they received clinically effective anti-parkinsonism medication than on those before (Fig. 3D). Although presence of tremor significantly increased the activity counts in the arms with tremor as compared with those without tremor (Fig. 4A), power-law scaling of the records from arms with tremor showed a linear correlation between log $S$ and log $W(S)^2$ in the range of 8 to 35 min (Fig. 4B) and α-values for local maxima were the same between the arms with tremor and those without tremor (Fig. 4B) with significantly higher α-values in patient arms than in control arms (Fig. 4C)
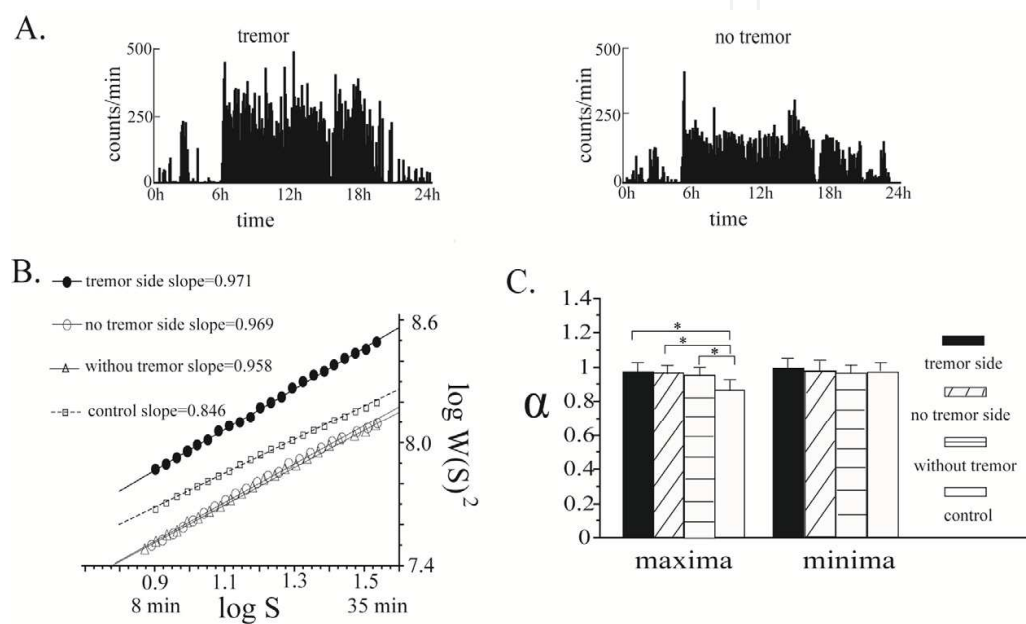


Fig. 4. Effects of tremor on actigraph counts and the power-law exponents. (A) Daily profiles of physical activity for the arm affected with tremor and that without tremor of a patient with unilaterally predominant parkinsonism with continuous tremor on one side. (B) Average wavelet coefficients for local maxima among arms with tremor (tremor) and without tremor (no tremor) of 6 patients with tremor, 26 arms of 13 patients without tremor (without tremor) and 20 arms of 10 control subjects (control). (C) The power-law exponents for local maxima and minima. *: $P < 0.05$. Reprinted with permission from (Pan et al., 2007).

Larger power-law exponents (α) indicate positive temporal auto-correlation, or *persistency*, in the increase or decrease in the variability of activity at two distant points in time in the time series, and lower values correspond to negative auto-correlation or *anti-persistency* (Ohashi et al., 2003). In other words, a lower α for local maxima or minima of activity records reflects more frequent switching behavior from low to high or high to low physical activity, respectively, and the switching behavior from lower to higher activity levels is considered to be related to akinesia in patients with parkinsonism. We found lower α-values for local maxima during GC days than during BC days, in the mild group than in the severe group, and before medication than after medication. Thus, these results demonstrate that the power-law analyses accurately describe the well known phenomenon that under these conditions patients switch their physical activity from lower to higher levels more easily, in

other words they exhibit milder akinesia, when the parkinsonism is mild than when it is severe. It is worthy to note that lower α-values for local maxima were obtained for all the patients after medication than before, and when in good condition than in bad condition (Fig. 3C, D), thereby providing a temporal profile of parkinsonism in each individual patient.

These results thus suggest that analysis of power-law temporal auto-correlation of physical activity time series using the bi-directional extension (Ohashi et al., 2003) is applicable to patients with parkinsonism for the evaluation of motor dysfunction irrespective of the presence of tremor and may provide useful objective data necessary for the control of drug dosage in the out-patient clinic and also for the evaluation of new drugs for parkinsonism (Pan et al., 2007).

## 4. Evaluation of effects of traditional Chinese medicine on parkinsonian symptoms

Conventional antiparkinsonism drugs effectively ameliorate the symptoms of patients with PD during the initial several years of onset, but become increasingly less effective and induce motor fluctuations including wearing-off, on-off, dopa-induced dyskinesia, and agonist-induced sleep attack (Arnulf et al., 2002; Comella, 2002; Hobson et al., 2002; Ondo et al., 2001; Pahwa et al., 2006). PD patients not infrequently suffer from non-motor symptoms, such as neuropsychiatric symptoms, autonomic symptoms, gastrointestinal symptoms, sensory symptoms, non-motor fluctuations (autonomic symptoms, cognitive or psychiatric symptoms, sensory symptoms including pain), fatigue, and sleep disturbance (Chaudhuri& Schapira, 2009; Miyasaki et al., 2006; Park& Stacy, 2009), and these non-motor symptoms may be intrinsic to the disease pathology or may be the result of treatment with dopaminergic agents. Several studies have established that the non-motor symptoms of PD are common, occur across all stages of PD, and are a key determinant of quality of life (Chaudhuri& Schapira, 2009).

Herbal remedies have a long history of use (particularly in East Asian countries) for alleviating various symptoms and have been increasingly used as alternative medicines worldwide, including the United States (De Smet, 2002). Traditional Chinese medicines (TCM) ameliorate various symptoms, particularly the ageing-related symptoms, and hence are likely to be beneficial for chronic diseases such as PD (Iwasaki et al., 2004; 2005a; 2005b). Good compliance for long-term use with few side effects may be another merit of TCM suitable for patients with PD (Lian& Luo, 2007; Zhao et al., 2007).

In order to evaluate the effects of TCM on symptoms of parkinsonism, we evaluated the effects of Zeng-xiao An-shen Zhi-chan 2 (ZAZ2) on patients with PD using this method together with conventional scales for parkinsonism (Pan et al., 2011a). ZAZ2 granule is made up of 14 kinds of herbs; *Uncaria rhynchophylla* 10 g, *Rehmanniae radix* 10 g, *Cornus officinalis* 8 g, *Asnaragus cochinchinensic* 10 g, *Paeonia lactiflora* 10 g, *Desertliving cistanche* 10 g, *Puerariae radix* 10 g, *Arisaema consanguineum Schott* 10 g, *Salviae Miltiorrhizae radix* 10 g, *Acorus tatarinowii* 10 g, *Curcuma longa Linn* 12 g, *Morindae officinalis radix* 10 g, *Rhizoma gastrodiae* 10 g, and *Rhizoma chuanxiong* 10 g. One hundred and fifteen patients with idiopathic PD took 8 g of either ZAZ2 granule or placebo granule that was not distinguished by appearance or taste for 13 weeks. Patients were randomly assigned to the ZAZ2 group (n=59) or placebo group (n=56). There was no difference in the mean age, gender ratio or disease duration between the ZAZ2 and placebo groups, and the post hoc test revealed no

significant baseline (week 0) differences in UPDRS scores, Hoehn & Yahr stages, mean counts, power-law temporal exponent α values, or in the dosage of antiparkinonian drugs between the two groups. All the patients were evaluated at week 0, week 1, and week 13 for the actigraph recording, UPDRS and Secondary Symptom Score, which is conventionally used in China to evaluate the effects of antiparkinsonism drugs and consists of 8 parts, including the assessments of non-fluent speech, vertigo, insomnia/nightmares, headache, sweating or night sweats, tiredness, sense of cold, and dysuria (Long, 1992). The awake-time and sleep-time actigraph data were used separately for the power-law temporal analyses.
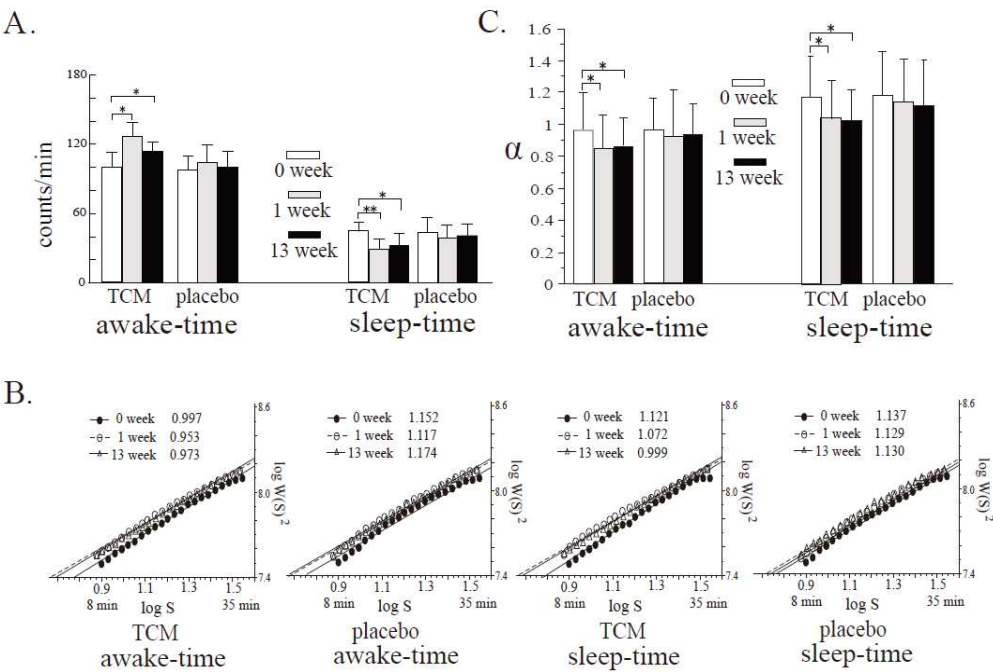


Fig. 5. Effects of TCM and placebo granules on actigraph recondings. (A) Counts of physical activity (mean ± S.D.). (B) Average wavelet coefficients, as a function of the wavelet scale for awake-time and sleep-time. The slopes are power-law exponents α. (C) Power-law exponents α (mean ± S.D.). *: $P < 0.05$, **: $P < 0.01$. (Pan et al., 2011a)

The local power-law exponent α values during both awake-time and sleep-time were significantly decreased after taking ZAZ2 granule, but not after taking placebo granule (Table 1, Fig 5). The average wavelet coefficients exhibited linear relationships in the range of scales from 8 min to 35 min both for the ZAZ2 and placebo groups (Fig. 5B). The local power-law exponent α values during both awake-time and sleep-time were significantly decreased both week 1 and 13 in the ZAZ2 group, but not in the placebo group (Table 1 and Fig 5C, $P<0.01$; Bonferroni test). The beneficial effects of ZAZ2 were shown with UPDRS scores, as well; significant and persistent improvements were found in the scores of Part II, Part II + Part III, and Part IV (Table 1). These scores at week 13 were significantly different between the ZAZ2 group and the placebo group. As the exploratory outcome of this study, most of the secondary symptoms were improved after taking ZAZ2 granule, whereas only a few symptoms were transiently improved in the placebo group (Table 2).

We evaluated the beneficial effects of TCM specifically on sleep disturbance of patients with parkinsonism. We used placebo-controlled, randomized study design, in which 48 patients

| | Placebo（n = 54） | | | TCM（n = 56） | | |
|---|---|---|---|---|---|---|
| | Week 0 | Week 1 | Week 13 | Week 0 | Week 1 | Week 13 |
| UPDRS total score | 46.6 ± 16.3 | 44.7 ± 15.3 | 45.9 ± 18.1 | 46.3 ± 17.1 | 37.1 ± 11.2*## | 40.7 ± 15.1*# |
| UPDRS I | 2.5 ± 0.7 | 2.3 ± 1.1 | 2.4 ± 1.2 | 2.6 ± 0.8 | 2.1 ± 0.7* | 2.3 ± 0.9 |
| UPDRS II | 15.7 ± 9.3 | 14.8 ± 11.2 | 15.3 ± 11.6 | 15.9 ± 11.3 | 12.5 ± 4.6*# | 13.4 ± 9.8*# |
| UPDRS III | 25.5 ± 12.9 | 23.8 ± 10.6* | 24.9 ± 12.7 | 25.4 ± 10.1 | 19.3 ± 9.8*# | 21.6 ± 10.4* |
| UPDRS IV | 3.1 ± 1.1 | 2.9 ± 1.6 | 3.0 ± 1.4 | 3.2 ± 1.4 | 2.6 ± 0.8*# | 2.7±1.3*# |
| Awake-time (counts/min) | 98.5 ± 14.1 | 102.6 ± 18.9 | 100.7 ± 16.9 | 99.8 ± 17.8 | 126.7 ± 13.4*## | 118.4 ± 11.8*## |
| Sleep-time (counts/min) | 42.9 ± 17.1 | 38.8 ± 15.6* | 40.1 ± 14.8 | 43.2 ± 11.6 | 35.6 ± 13.6*# | 32.8 ± 13.6*# |
| α(awake-time) | 0.97 ± 0.21 | 0.95 ± 0.28 | 0.96 ± 0.18 | 0.97 ± 0.24 | 0.88 ± 0.21*# | 0.86 ± 0.19*## |
| α(sleep-time) | 1.19 ± 0.28 | 1.16 ± 0.27 | 1.15 ± 0.29 | 1.18 ± 0.26 | 1.04 ± 0.22*# | 1.02 ± 0.18*## |

Data presented are mean ± SD.*:$P < 0.05$; **:$P < 0.01$ compared to week 0 (Repeated-measure ANOVAs).

#:$P < 0.05$; ##:$P < 0.01$ compared to placebo (Bonferroni test). UPDRS: Unified Parkinson's Disease Rating Scale.

α: power-law exponent.

Table 1. Measurements before and after taking test granules. (Pan et al., 2011a)

| Group | Time | Non-fluent speech | Vertigo | Insomnia/ nightmare | Headache | Sweating or night sweats | Tiredness | Sense of cold | Dysuria |
|---|---|---|---|---|---|---|---|---|---|
| TCM | week 0 | 1.08 ± 0.74 | 1.33 ± 0.83 | 2.77 ± 0.98 | 0.92 ± 0.56 | 2.11 ± 0.68 | 1.66 ± 0.57 | 1.90 ± 0.67 | 2.23 ± 0.69 |
| | week 1 | 0.56 ± 0.28* | 0.84 ± 0.26*# | 2.03 ± 0.78* | 0.64 ± 0.28*## | 1.38 ± 0.69* # | 1.21 ± 0.46* | 1.48 ± 0.57* | 1.43 ± 0.31*# |
| | week 13 | 0.65 ± 0.33*## | 0.95 ± 0.37* | 1.73 ± 0.38*# | 0.63 ±0.19*# | 1.48 ± 0.28*## | 1.27 ± 0.51*# | 1.58 ± 0.61 | 1.46 ± 0.36*## |
| Placebo | week 0 | 1.12 ± 0.59 | 1.31 ± 0.97 | 2.67 ± 0.87 | 1.03 ± 0.75 | 2.13 ± 1.32 | 1.70 ± 0.97 | 1.78 ± 0.39 | 2.29 ± 1.02 |
| | week 1 | 0.69 ± 0.32* | 1.12 ± 0.69 | 2.40 ± 0.69* | 0.96 ± 0.36* | 1.87 ± 0.58 | 1.35 ± 0.69* | 1.39 ± 0.81 | 1.69 ± 0.92* |
| | week 13 | 1.02 ± 0.36 | 1.28 ± 0.53 | 2.45 ± 0.38 | 0.99 ± 0.65 | 2.18 ± 0.56 | 1.58 ± 0.66 | 1.64 ± 0.58 | 2.18 ± 1.30 |

Data presented are mean ± SD.*: $P < 0.05$, **: $P < 0.01$ compared with 0 weeks (Repeated-measure ANOVAs).

#:$P < 0.05$, ##:$P < 0.01$ compared to placebo (Bonferroni test).

Table 2. Secondary symptom scores before and after taking test granules. (Pan et al., 2011a)

with idiopathic PD who had at least three awakenings per night occurring at least 3 nights per week participated. Patients wore the actigraph on the wrist of their non-dominant hand for seven consecutive days twice at week 0 (before) and week 6 of taking either one of the granule. For control, age-matched 25 patients with non-neurological diseases who had neither sleep disturbance nor parkinsonism wore the actigraph for seven consecutive days. Daily profiles of activity counts clearly demonstrated an improvement of the biological rhythm after the additional treatment in the TCM group but not in the placebo group (Fig. 6A). After treatment, sleep latency, median sleep efficiency and the median 5 least active hour, all of which were the parameters specifically reflected sleep disturbance (Pan et al., 2011b), shifted towards the values of the control group in the TCM group, but not in the placebo group (Fig 6B).

Scores in UPDRS Part II reflects the long-term outcome of the patients (Harrison et al., 2009). That both α-values for local maxima and the scores in UPDRS Part II, Part II + Part III and Part IV improved after TCM suggested that α-values for local maxima reflected patients' overall ADL, including motor symptoms and non-motor symptoms. Therefore, it is likely that analysis of the α-values is useful for the evaluation of drug effects on the long-term outcome of patient with PD (Pan et al., 2011a; 2011b).
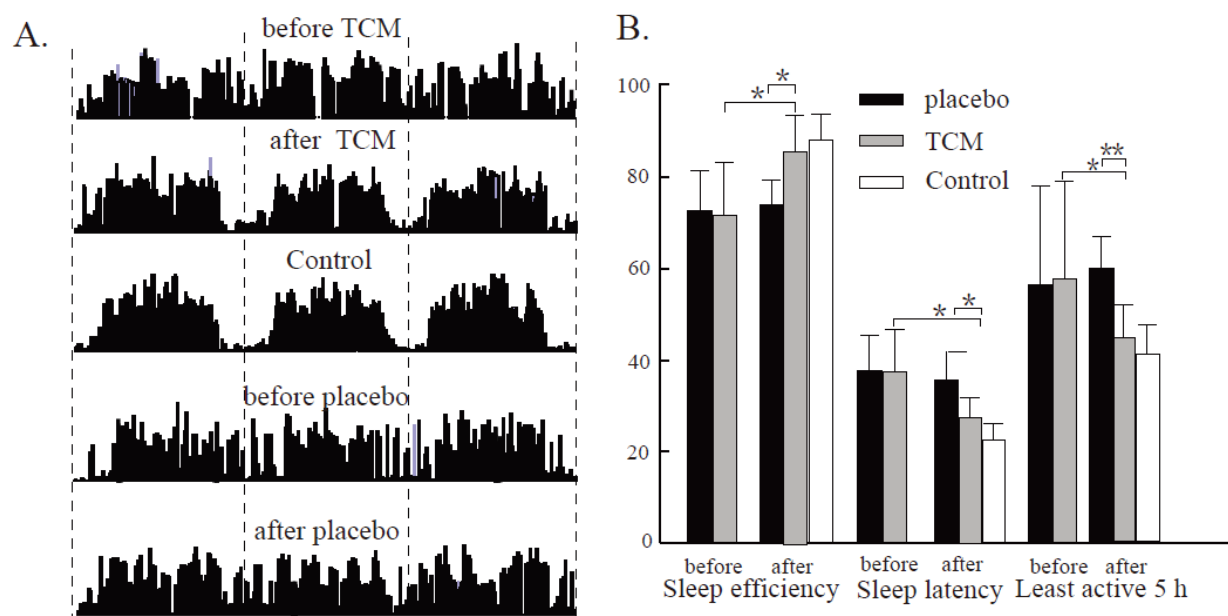
Fig. 6. Effects of cerebral granule (TCM). (A) Daily profiles of actigraph count for three consecutive days before and after taking TCM. Dashed line: midnight. (B) Changes from baseline in actigraph counts. Columns and bars (mean ± S.D.) indicate sleep efficiency (%), sleep latency (min) and the 5 least active hours (counts/min). *: $p < 0.05$; **: $p < 0.01$. Reprinted with permission from (Pan et al., 2011b).

## 5. Assessment for effects of GVS for ameliorating parkinsonism

Enhancing neuronal transmission is a possible non-pharmacological therapeutic strategy for neurological diseases. 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 a therapeutic strategy for brain disorders due to the low invasiveness as compared to deep brain stimulation. Considering its central connections, the vestibular nerve can influence limbic-to-motor functions, and we applied non-invasive and non-nociceptive noisy galvanic vestibular stimulation (GVS) to the patients with parkinsonism. We successfully improved parkinsonian symptoms by using noisy GVS at a low-frequency range targeting the vestibular nerves of patients with levodopa responsive PD and levodopa unresponsive parkinsonism (Yamamoto et al., 2005). This effect is presumably through the demonstrated vestibule-cerebellar connections, and input noise played the beneficial role in sensitizing neural systems, possibly through a mechanism known as stochastic resonance, a basic physical mechanism underlying noise-enhanced responses of nonlinear systems to weak signals. 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 emulation of the afferent firing rates. We analyzed whether the beneficial effects of GVS on parkinsonism was reflected in a decrease of the α-value for local maxima.

As previously described (Yamamoto et al., 2005), a portable GVS device was used to deliver currents using a bilateral unipolar configuration, 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 (Struzik et al., 2006) within a range of 0.01-2.0 Hz or a constant zero current for control, with a duration of 300 sec was continuously repeated during the tests. The magnitude of noisy GVS was set to 60% of each subject's nociceptive threshold (0.29 ± 0.20 mA). Then either the noisy GVS or the control zero current was continuously applied for the first 24 hours, and then switched to the counter-part and applied for another 24 hours, while the patients' wrist activity was monitored continuously for 48 hours. The order of noisy GVS and the control zero current was determined for each patient by random selection.



Fig. 7. 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. Reprinted with permission from (Pan et al., 2008).

The representative wrist activity data of a PD patient during the control period and during the application of GVS were shown in Fig. 7A, B. Compared to control, GVS was associated with more frequent switching between higher and lower levels of activity. This resulted in a higher wavelet power (*W(S)*$^2$) with GVS (Fig. 7C, D), particularly at smaller scales (*S*), or higher frequencies, for local maxima (Fig.7C). 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, was smaller with GVS than with control stimulation, especially for the local maxima (Fig. 7C,D).

The group average wavelet coefficients exhibited linear relationships in the range of scales (*S*) from 8 min to 35 min both for local maxima and minima and for GVS and control conditions (Fig. 8A, B). The slope for local maxima with noisy GVS was substantially less than that with control stimulation. For local maxima, the mean power-law exponent was significantly smaller for GVS than for the control (Fig. 8C). The difference in the mean α for local minima was much less than that for the local maxima. When the mean α-values for the
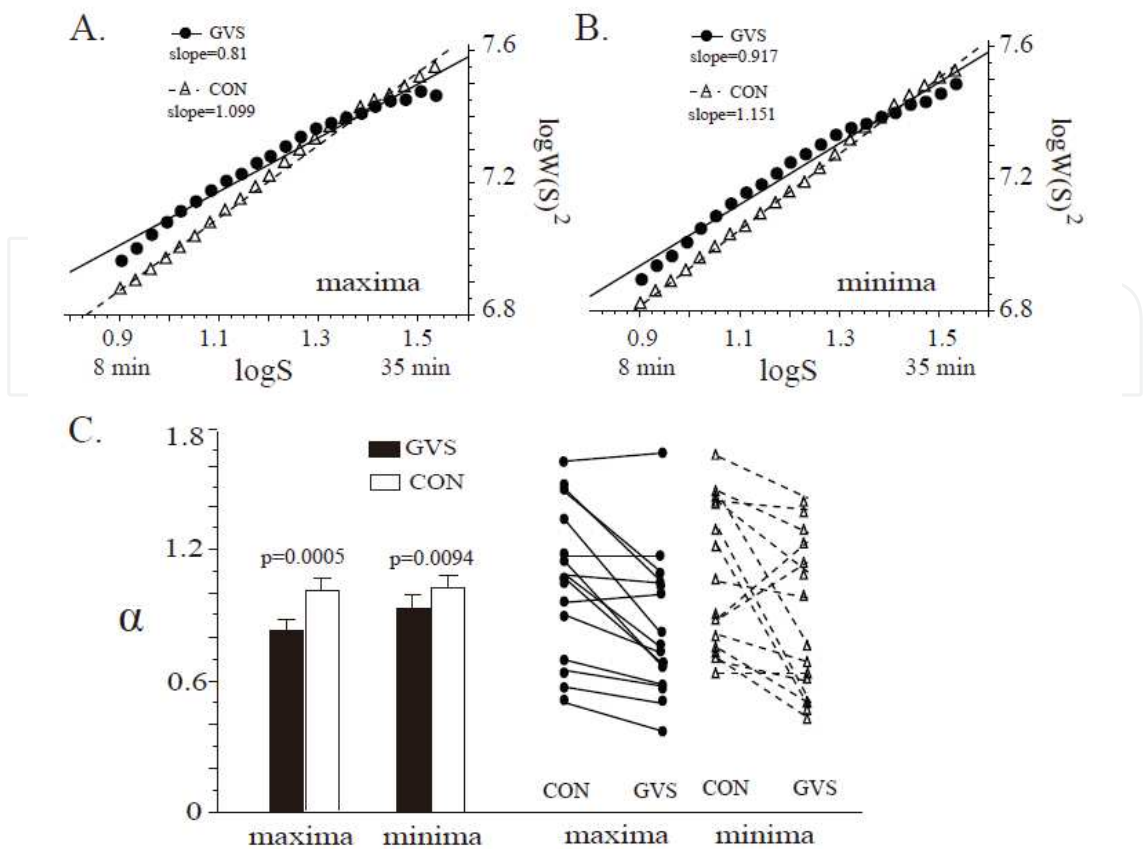
Fig. 8. The group average wavelet coefficients for local maxima (A) and minima (B) for GVS and control (CON) conditions. (C) Comparisons of the mean $\alpha$ for GVS and CON (left) and the within-individual differences (right). The error bars represent SEM. Reprinted with permission from (Pan et al., 2008).

first and the second days were compared, significant differences were not observed either for local maxima or minima, suggesting that the above differences were due to the GVS application itself, not to an order effect.

We confirmed that measurement of the mean $\alpha$ for local maxima detected the improvement of parkinsonism during GVS with sufficient sensitivity (Pan et al., 2008).

# 6. Conclusion

Analysis of patients' physical activity records collected by an actigraph device using power-law exponents probing temporal autocorrelation of the activity counts provides methods for the evaluation of disability resulting from motor and non-motor parkinsonism without being influenced by the presence of tremor or different patterns of daily living (Pan et al., 2007). Sufficient sensitivity and reliability of this method warrants the objectivity in the evaluation of symptom severity (Pan et al., 2008; Pan et al., 2011a) , hence this method may be useful for the evaluation of disease progression and efficacy of new drug.
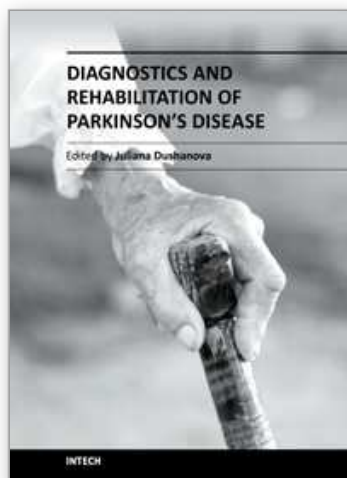
# 7. Acknowledgement

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**Diagnostics and Rehabilitation of Parkinson's Disease**

Edited by Dr. Juliana Dushanova

Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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