Aizawa H, Azuma N, Katayama T, Hasebe N, Inaba M, Sasajima T, Uchiyama S	Cerebrovascular Disease and Intracranial Artery Stenosis in Patients with Symptomatic Peripheral Artery Disease	***J Stroke Cerebrovasc Dis***	Jun 22. [Epub ahead of print]	1-7	2011
Tokuoka H, Muramatsu S, Ichinose C, Sakane H, Kojima M, Aso Y, Nomura T, Metzger D and Ichinose H	Compensatory regulation of dopamine after ablation of the tyrosine hydroxylase gene in the nigrostriatal projection.	***J Biol Chem***	286 (50)	43549-43558	2011
Asari S, Fujimoto K, Miyauchi A, Sato T, Nakano I and Muramatsu S	Subregional 6-[18F]fluoro-L-m-tyrosine uptake in the striatum in Parkinson's disease.	***BMC Neurol***		11-35	2011
Miyamoto M, Miyamoto T, Iwanami M, Muramatsu S, Asari S, Nakano I and Hirata K	Preclinical substantia nigra dysfunction in rapid eye movement sleep behaviour disorder.	***Sleep Med***	13 (1)	102-106	2011
相澤仁志、澤田潤、齋藤司、遠藤寿子、片山隆行、長谷部直幸、平沼初音、高橋康二、羽根田俊、守屋潔	Telestroke の有用性と課題.	*脳卒中*	33	133-137	2011
Aizawa H, Sawada J, Hideyama T, Yamashita T, Katayama T, Hasebe N, KimuraT, Yahara O, Kwak S	TDP-43 pathology in sporadic ALS occurs in motor neurons lacking RNA editing enzyme ADAR2.	***Acta Neuropathol***	120	75-84	2010
Hideyama T, Yamashita T, Nishimoto Y, Suzuki T, Kwak S	RNA editing enzyme abnormality in sporadic amyotrophic lateral sclerosis.	***J Pharmacol Sci.***	113	9-13	2010
Kwak S, Hideyama T, Yamashita T, Aizawa H	AMPA receptor-mediated neuronal death in sporadic ALS.	***Neuropathology***	30	182-188	2010
Hideyama T, Yamashita T, Suzuki T, Tsuji S, Higuchi M, Seeburg PH, Takahashi R, Misawa H, Kwak S	Induced loss of ADAR2 engenders slow death of motor neurons from Q/R site-unedited GluR2.	***J. Neurosci.***	30	11917-11925	2010

Hida A, Kowa H, Iwata A, Tanaka M, Kwak S, Tsuji S	Aceruloplasminemia in a Japanese woman with a novel mutation of *CP* gene: Clinical presentations and analysis of genetic and molecular pathogenesis.	***J Neurol. Sci.***	298	136-139	2010
Saito T, Aizawa H, Sawada J, Katayama T, Hasebe N.	Lesion of the nucleus intercalatus in primary position upbeat nystagmus.	***Arch Neurol.***	67	1403-1404	2010
Kumar MA, Jain A, Dechant VE, Saito T, Rafael T, Aizawa H, Dysart KC, Katayama T, Ito Y, Araki N, Abe T, Balice-Gordon R, Dalmau J.	Anti-N-methyl-D-aspartate Receptor Encephalitis During Pregnancy.	***Arch Neurol.***	67	884-887	2010
Krzyżosiak A, Szyszka-Niagolov M, Wietrzych M, Gobaille S, Muramatsu S, Krężel W.	Retinoid X receptor gamma control of motivated behaviours involves dopaminergic signalling in mice.	***Neuron***	66(6)	908 - 920	2010
Muramatsu S, Okuno T, Suzuki Y, Nakayama T, Kakiuchi T, Takino N, Iida A, Ono F, Terao K, Inoue N, Nakano I, Kondo Y and Tsukada H	A phase I study of aromatic L-amino acid decarboxylase gene therapy for Parkinson's disease.	***Mol Ther***	18(9)	1731 - 1735	2010
Muramatsu S, Asari S, Fujimoto K, Ozawa K, Nakano I	Gene therapy for Parkinson's disease. Strategies for the local production of dopamine.	***Gene Therapy & Regulation***	5(1)	57-65	2010
Muramatsu S	The current status of gene therapy for Parkinson's disease.	***Ann Neurosci.***	17(2)	92-95	2010

日出山拓人, 郭　伸	ALS における RNA editing 異常.	***Clinical Neuroscience***	28	246-247	2010
日出山拓人, 山下雄也, 郭　伸	グルタミン酸受容体と孤発性筋萎縮性側索硬化症.	*実験医学*	28	109-117	2010
日出山拓人, 郭　伸	孤発性 ALS 患者運動ニューロンに見出された分子病態 RNA editing 異常に基づいたモデルマウスの開発.	*医学のあゆみ*	235	246-250	2010
齋藤司、相澤仁志、澤田潤、油川陽子、片山隆行、長谷部直幸, 林恵充、安栄良悟、佐藤正夫、程塚明	小脳梗塞初期診断の問題点.	*脳卒中*	32	133-137	2010
Sawada J, Yamashita T (contributed equally with JS), Aizawa H, Aburakawa Y, Hasebe N, Kwak S	Effects of antidepressants on GluR2 Q/R site-RNA editing in a modified HeLa cell line.	***Neurosci Res.***	64(3)	251-258	2009
Fukushima F, Nakao K, Shinoe T, Fukaya M, Muramatsu S, Sakimura K, Kataoka H, Mori H, Watanabe M, Manabe M and Mishima M	Ablation of NMDA receptors enhances the excitability of hippocampal CA3 neurons.	***PLoS ONE***	4(1)	e3993	2009
Muramatsu S, Okuno T, Suzuki Y, Nakayama T, Kakiuchi T, Takino N, Iida A, Ono F, Terao K, Inoue N, Nakano I, Kondo Y and Tsukada H	Multi-tracer assessment of dopamine function after transplantation of embryonic stem cell-derived neural stem cells in a primate model of Parkinson's disease.	***Synapse***	63	541-548	2009
Okuno T, Nakayama T, Konishi N, Michibata H, Wakimoto K, Suzuki Y, Nito S, Inaba T, Nakano I, Muramatsu S, Takano M, Kondo Y, and Inoue N	Self-contained induction of neurons from human embryoniv stem cells.	***PLoS ONE***	4	e6318	2009

Ito T, Yamamoto S, Hayashi T, Kodera M, Mizukami H, Ozawa K and Muramatsu S	A convenient enzyme-linked immunosorbent assay for rapid screening of anti-adeno-associated virus neutralising antibodies.	***Ann Clin Biochem***	46 (Pt 6)	508-510	2009
Noguchi A, Matsumura S, Dezawa M, Tada M, Yanazawa M, Ito A, Akioka M, Kikuchi S, Sto M, Ideno S, Noda M, Fukunari A, Muramatsu S, Itokazu Y, Sato K, Takahashi H, Teplow DB, Nabeshima Y, Kakita A, Imahori K and Hoshi M	Isolation and characterization of patient-derived, toxic, high-mass amyloidβ-protein (Aβ) assembly from Alzheimer's disease brains.	***J Biol Chem***	284 (47)	32895-32905	2009
Kadkhodaei B, Ito T, Joodmardi E, Mattsson B, Rouillard C, Carta M, Muramatsu S, Ichinose C, Nomura T, Chambon P, Metzger D, Larsson N, Lindqvist E, Olson L, Bjorklund A and Ichinose H	Nurr1 is required for maintenance of maturing and adult midbrain dopamineneurons.	***J Neurosci.***	29 (50)	15923-15932	2009

WEB

著者氏名	論文タイトル名	監修	WEB タイトル	企画	掲載年	WEB
郭　伸	ALS，その早期診断と QOL の高い患者ケアのために			日経 BP	2010	http://medical.nikkeibp.co.jp/all/special/sa/als_rilutek/3-1.html
郭　伸	ALS の病態・機序	LTT プログラム委員会	LIVE TODAY FOR TOMORROW	ALS 疾患啓発委員会	2010	http://www.als.gr.jp/staff/sickstate/

3 筋萎縮性側索硬化症（ALS），運動ニューロン疾患

日出山拓人，郭　伸

筋萎縮性側索硬化症（amyotrophic lateral sclerosis：ALS）は，原因不明で，確立した治療法のない致死的神経変性疾患である．ALSは90％以上が孤発性に発症し，年間発症率は人口10万人あたり1～7人程度，有病率は2～8人程度（受給者証交付件数8,285，2009年3月末現在）で，やや男性に多い．日本での発症年齢は50～60歳代に多く，加齢とともに発症率が増加する傾向がある．多くは2～5年（平均3年）程度で呼吸筋麻痺による致死的換気不全に陥る．

全ALS患者の10％程度は家族性ALSで，10種前後の責任遺伝子が同定されている．superoxide dismutase 1（*SOD1*），fused in sarcoma（*FUS/TLS*），TAR DNA-binding protein（*TDP-43*）（*TARDBP*）の順に頻度が高く，この3遺伝子変異が家族性ALSの1/4～1/2を占める．一方，孤発性ALSの大多数には既知の責任遺伝子の変異は見出されていない．

病理学的には，脊髄前角の大型運動ニューロンの脱落が特徴で，残存ニューロン細胞質にはエオジン好性・cystatin C陽性封入体（Bunina小体）やユビキチン陽性・TDP-43陽性封入体（skein-like inclusion や Lewy body-like hyaline inclusion）が認められる．TDP-43陽性細胞質封入体はALSの残存運動ニューロンの約半数に観察され，これらの運動ニューロンでは，正常ニューロンにみられる核内局在を失っている．

A 診断と検査

ALSには特異的なバイオマーカーがないので，進行性の筋力低下をきたす疾患の除外診断による．一般的には，進行性の上位運動ニューロン障害と下位運動ニューロン障害による筋力低下であることを明らかにすることが重要であるが，初発部位はおよそあらゆる骨格筋に及び，上位運動ニューロン，下位運動ニューロンのいずれかまたは両者という組み合わせ，進行速度の遅速により臨床像は極めて多彩であり，診断に苦慮する症例もある．大きく，古典型，球麻痺型，上位運動ニューロン型（原発性側索硬化症PLSとされているものも含む），下位運動ニューロン型（PMAさらに上肢型，下肢型の特殊型がある），dementiaを伴うALSなどに分類可能であり，病型間で進

Topics

孤発性ALSモデルマウスの開発

a) Kawahara Y et al：Glutamate receptors：RNA editing and death of motor neurons. Nature 427：801, 2004

b) Hideyama T et al：Induced loss of ADAR2 engenders slow death of motor neurons from Q/R site-unedited GluR2. J Neurosci 30：11917-11925, 2010

c) Aizawa H et al：TDP-43 pathology in sporadic ALS occurs in motor neurons lacking the RNA editing enzyme ADAR2. Acta Neuropathol 120：75-84, 2010

孤発性ALSの変性運動ニューロンでは，グルタミン酸受容体（AMPA受容体）に本来生ずべきRNA編集が不十分であり[a]，それによるAMPA受容体からのCa^{2+}流入亢進が運動ニューロン死の原因であることを，モデルマウスの開発・解析から明らかにした．この分子変化は，RNA編集酵素adenosine deaminase acting on RNA 2（ADAR2）発現低下によるので，ADAR2を運動ニューロン選択的にノックアウトすると，外眼筋支配神経を除き，脊髄，顔面神経，三叉神経，舌下神経の運動ニューロン死が緩徐進行性の神経細胞死が起こり，ALS類似の表現型を示した[b]．興味深いことに，ALS患者運動ニューロンでは，ADAR2活性低下とTDP-43陽性封入体が共在し，封入体のない運動ニューロンは正常はADAR2免疫活性を保持している[c]．細胞死に関わる活性分子の特定により，特異治療への道が開けたと言え，このモデル動物は有用性が高いと言える．

行の速さに多少差があるものの，終末期には障害部位が全身に広がり，上位・下位運動ニューロン両者に病変が及ぶ．

上位運動ニューロン障害の症候は，痙性麻痺，腱反射亢進，Babinski徴候などの病的反射，頭頸部では，口蓋咽頭反射亢進，下顎反射亢進，強制泣き笑いなどとして表れる．下位運動ニューロン障害の症候は，筋力低下，筋萎縮，線維束性攣縮，腱反射低下，頭頸部では線維束性攣縮を伴う舌萎縮，顔面筋筋力低下，口蓋咽頭反射の低下，嚥下・構音障害として表れる．典型例では，同一部位で上位・下位運動ニューロン徴候が同時にみられるので，萎縮した筋で腱反射が亢進するという一見矛盾した徴候を呈する．この他，4大陰性徴候（外眼筋麻痺，感覚障害，自律神経障害，褥創のいずれをも欠く）が役立つ．大多数の症例では高次脳機能は保たれているが，前頭側頭型認知症にみられる性格・行動変化，進行性非流暢失語を呈する例がある．

鑑別診断

進行性の筋力低下を呈する様々な疾患の鑑別が問題になる．筋炎（封入体筋炎など）との鑑別は筋生検組織の検索が必要な場合がある．頸椎症性根脊髄症，肘部管狭窄症などは手術される場合さえある．

診断基準

初期臨床像が多彩であるため診断基準になじまない疾患であるものの，臨床試験における均一性を担保する目的でいくつかの診断基準が存在する．El Escorial改訂基準（1998年）が標準で，脳神経，頸部・上肢，体幹，腰部・下肢の4領域のうち，複数の領域に上位運動ニューロン症候，下位運動ニューロン症候をともに認めること，症状が進行性であること，他疾患が除外できること，がその中核となっている．これをもとに日本神経学会治療ガイドライン（2002年），厚労省神経変性疾患調査研究班の診断基準（2003年）（表1），米国神経学会（American Academy of Neurology：AAN）による新ガイドライン（practice parameter）（2009年）が作成されている．検査上，下位運動ニューロン障害は針筋電図検査により検出される．上位運動ニューロン障害の検査法には磁気刺激検査による運動誘発電位（MEP）による中枢運動神経伝導時間（CMCT）の延長，頭部MRIのT2強調画像での錐体路の信号変化などがあるが，感度は高くない．

B　治療の一般方針

治療薬

現時点では有効な特異的治療はない．riluzole（リルテック®）が唯一認可されている治療薬であり，AAN改訂版ではALS進行の遅延に有効で安全な薬剤として投与必須という位置づけにある．

処方例

▷リルテック®（50 mg）　2錠，分2

嚥下障害

低栄養や脱水，誤嚥性肺炎に注意し，進行度に応じて食餌形態の工夫やとろみづけを行う．経口摂取が不十分な場合には胃瘻からの経腸栄養を行う．経皮内視鏡的胃瘻造設術（PEG）は，呼吸機能が比較的保たれている時期（% FVC 50%以上）に行う．また，誤嚥性肺炎が反復する症例や，経口摂取の強い希望がある症例では，発声機能は失うが，喉頭気管分離術，声門閉鎖術も有効である．

呼吸管理

夜間の換気障害が呼吸筋の筋力低下の初期症状として表れることが多い．夜間覚醒，起床時頭痛・失熟眠感，昼間の睡魔，集中力低下などである．肺胞低換気の検出には，臥位での呼吸機能検査（% FVC）や夜間酸素飽和度モニター，最大吸気圧測定（MIP）が有用である．非侵襲的陽圧換気療法（NIPPV）の導入時期は，①$PaCO_2$ 45 mm Hg以上，②夜間酸素飽和度が88%以下を5分以上持続，③% FVCが50%以下，あるいは最大吸気圧が60 mmH_2O以下，のいずれかがみられた時点が推奨されている．NIPPV導入にあたっては，空気の漏れがない，よくフィットしたマスク（鼻・口）を選び，不安や苦手感をもたぬように，EPAPは最低値，IPAPは2 cmH_2O程度高くした設定で開始し，徐々にIPAP，装着時間

表1 ◆ ALS 診断基準（厚労省研究班）

1. 神経所見
   1）球麻痺所見：舌の麻痺，萎縮，線維束性収縮，構音障害，嚥下障害
   2）上位ニューロン徴候（錐体路徴候）：痙縮，腱反射亢進，病的反射
   3）下位ニューロン徴候（前角細胞徴候）：筋萎縮，筋力低下，線維束性収縮
2. 臨床検査所見
   1）針筋電図にて
      ①高振幅電位
      ②多相性電位
   2）神経伝導検査にて
      ①運動・感覚神経伝導速度は原則正常
      ②複合筋活動電位の低下
3. 鑑別診断
   1）下位運動ニューロン障害のみを示す変性疾患：脊髄性進行性筋萎縮症
   2）上位運動ニューロン障害のみを示す変性疾患：原発性側索硬化症
   3）脳幹病変によるもの：腫瘍，多発性硬化症など
   4）脊髄病変によるもの：頸椎症，後縦靱帯骨化症，椎間板ヘルニア，腫瘍，脊髄空洞症，脊髄炎など
   5）末梢神経病変によるもの：多巣性運動ニューロパチー（Lewis-Sumner症候群），ポリニューロパチー（遺伝性，非遺伝性）
   6）筋病変によるもの：筋ジストロフィー，多発筋炎など
   7）偽性球麻痺

[診断の判定]

次の1～5のすべてを満たすものを，筋萎縮性側索硬化症と診断する
   1）成人発症である
   2）経過は進行性である
   3）神経所見で，上記1～3のいずれか2つ以上がみられる
   4）筋電図で上記の所見がみられる
   5）鑑別診断で，上記のいずれでもない
4. 参考事項
   診断上，次の事項が参考となる
   遺伝性を示す例がある
   下肢から発症する場合は早期から下肢の腱反射が低下，消失することがある（下肢型）
   まれに初期から痴呆を伴うことがある
   感覚障害，眼球運動障害，膀胱直腸障害，小脳症状を欠く．ただし長期の経過では，これらの一部が認められることがある

を増やす．早期導入により，コンプライアンスを上げられるほか，QOL改善，FVC低下速度の遅延が期待できる．呼吸筋麻痺の進行により，NIPPVで呼吸障害が改善しなくなった場合には気管切開を実施したうえでの人工換気（tracheal positive pressure ventilation：TV）以外には救命の方法がない．しかし，TVには後述するような重大な問題が内在しているので，導入にあたっては患者本人，介護者の理解が欠かせない．

緩和ケア

呼吸苦，随意的な体動が極端に制限されるための疼痛（ベッドとの接触面，体表に触れるあらゆるもの，風，音，光など）のコントロールは必須である．AANや欧州のEFNS task forceでは，オピオイドがスタンダードな治療であり，癌の疼痛コントロールより少量で有効である．日本ではmorphineが保険適用外であることから，ガイドラインでも通常の治療としての位置づけには至っておらず，現場の臨床医を悩ませている．NSAIDs，抗不安薬，抗うつ薬，少量の酸素，抗痙縮薬などを用いる[1]．

3 臨床試験

riluzole以外に有効性が報告された薬剤はない．dextromethorphan（NMDA拮抗薬）とquinidine（dextromethorphanの血中濃度を上昇させる）の合剤であるNuedexta®がALSの偽性球麻痺，強制泣き笑いに有効であると報告され，安全性の確認後，FDAに認可された．米国で2010年10月に開始された脊髄損傷に対するES細胞の臨床試験のほか，ceftriaxone，神経栄養因子，抗酸化剤アナログ，edaravone（第Ⅲ相），ビタミンB_{12}大量療法（第Ⅲ相）試験の結果が待たれる（the ALS Association（http：//www.alsa.org/））．

C 生活指導

1 病状の説明

ALSは，有効な治療がない進行性の疾患であることから，病名の告知のうえ，将来出現する症状に対して，患者と介護者に具体的に説明する．運動障害，嚥下，呼吸，コミュニケーションなどの各項目について今後予想される障害を説明し，どのような医療的・社会的サポートが得られるのかを理解度を確認しながら，病期の進行度に応じて説明を繰り返し行う必要がある．なかでも，胃瘻増設術，補助呼吸を選択するかどうかは避けて通れない問題である．特にTVを装着した場合，長期生存が可能となるが，症状は進行するため，随意的に動かせる体の部分がますます少なくなり，コミュニケーションの方法がさらに制限される一方で，感覚は保たれ，むしろ研ぎ澄まされるため，体位交換が随意的に行えない状況では疼痛に悩まされることへの理解が必須である．さらに，日本では一度装着した人工呼吸器を意識が清明である患者からはずすことが違法であることも十分に理解している必要がある（欧州諸国では，患者の意思が尊重され，人工呼吸器をはずすことは患者の権利として認められている）．このような末期の病状は患者・家族にとってはなかなか理解しがたいものであり，病気の進行を実感する中で繰り返し説明することで徐々に受容されるものであるにもかかわらず，大多数の患者では病期の進行が速いため受容に必要な時間的余裕がないまま選択を迫られる状況に陥る場合が少なくない．ALS患者は換気障害が表れてからは急変することもあるため，緊急時にTVをするかどうかをあらかじめ決めておくことが望ましいものの，患者の決心もしばしば動揺する．

2 リハビリテーション

廃用と拘縮予防のための運動量を維持する．しかし，強すぎる負荷，筋の酷使は，症状を進行させる可能性があり，適度な運動負荷がどの程度なのかは残存筋力によっても異なる．意思表示を補助するものとして，文字盤，レッツ・チャット®やトーキングエイド®などのvoice output communication（VOCA），PCを利用した伝の心®やソフトウェアのオペレートナビ®，手，それ以外の可動部分を利用するセンサーの利用，脳血流，脳波を利用した脳インターフェースデバイスのマクトス®などがある．

文 献

1）雛波玲子：終末期の緩和ケア．ALSマニュアル決定版！，中島 孝（編），日本プランニングセンター，松戸，p333-336，2009

11

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

Weidong Pan[1,3], Yoshiharu Yamamoto[2] and Shin Kwak[1]
[1]*Department of Neurology, Graduate School of Medicine, The University of Tokyo,*
[2]*Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo,*
[3]*Department of Neurology, Shuguang Hospital Affiliated to Shanghai University of TCM,*
[1,2]*Japan,*
[3]*China*

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).

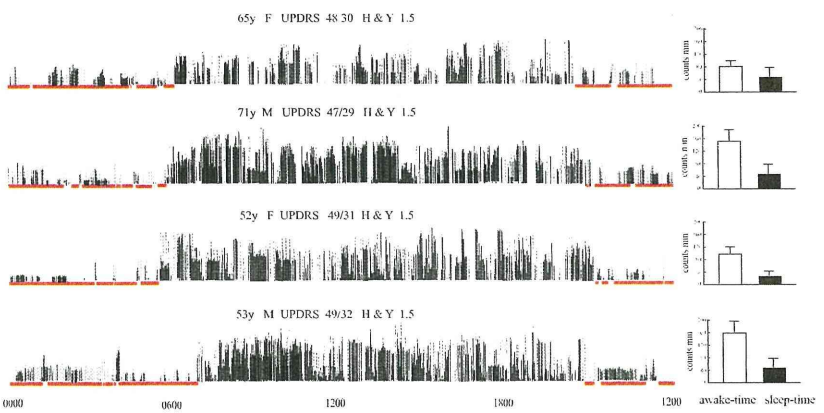

Fig. 1. Examples of 24 h actigraph recording. (left) Each vertical bar indicates activity counts per min. Sleep time is indicated in blue. Patients with approximately the same severity show different activity patterns and the activity counts (right: mean ± S.D.). UPDRS total/Part III.

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":

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

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 (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. $W(S)^2$. This method yields the same α-values as does DFA (Ohashi et al., 2003), but separately for periods with higher and lower activity levels. The power-law (scaling) exponent, α, 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).

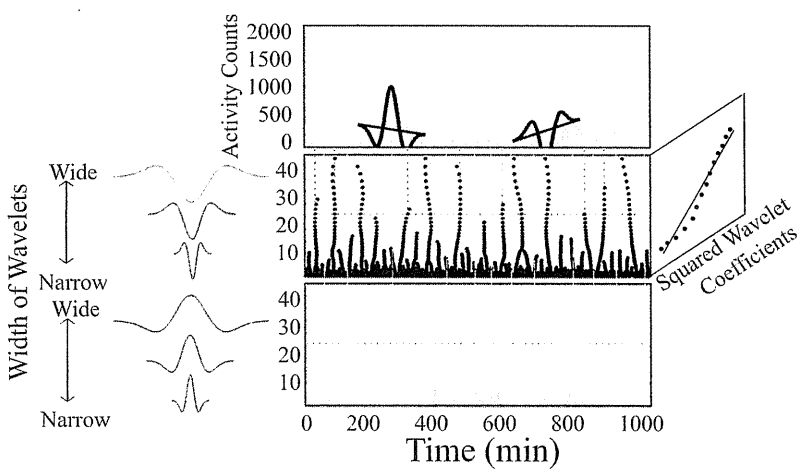

Fig. 2. Conceptual explanation of the method to obtain power-law exponents for local maxima and minima. (*top*) Various widths of hat-shaped wavelets are slid along the data to detect local minima (*middle*) and local maxima (*bottom*) of the wavelet coefficients. Note that the local minima and maxima 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 ≦ 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).

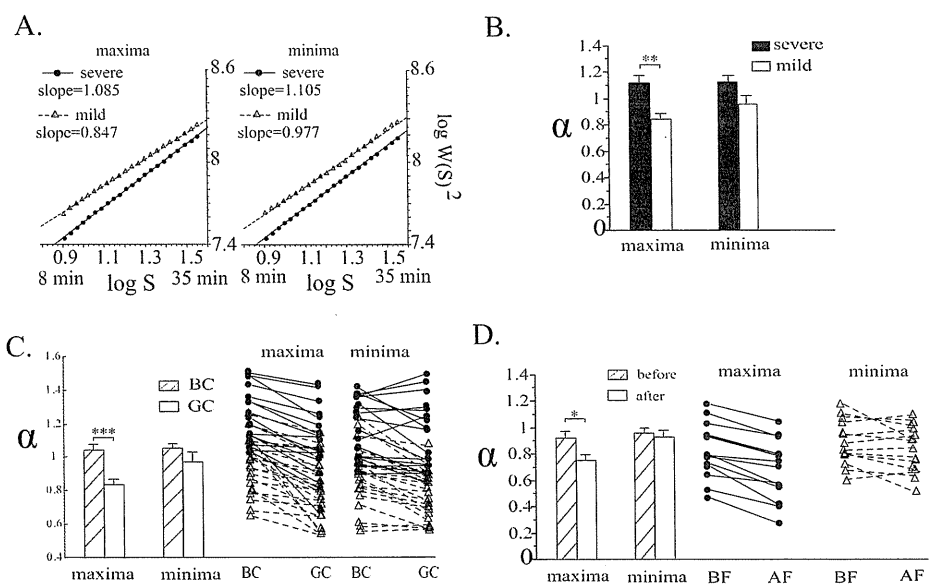

Fig. 3. Local maxima and minima of fluctuation of physical activity. (A) Average wavelet coefficients, as a function of the wavelet scale, for local maxima and minima. The slopes are power-law exponents, α. (B) Comparisons of the mean for the severe and the mild groups, (C) for BC and GC days and for 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)

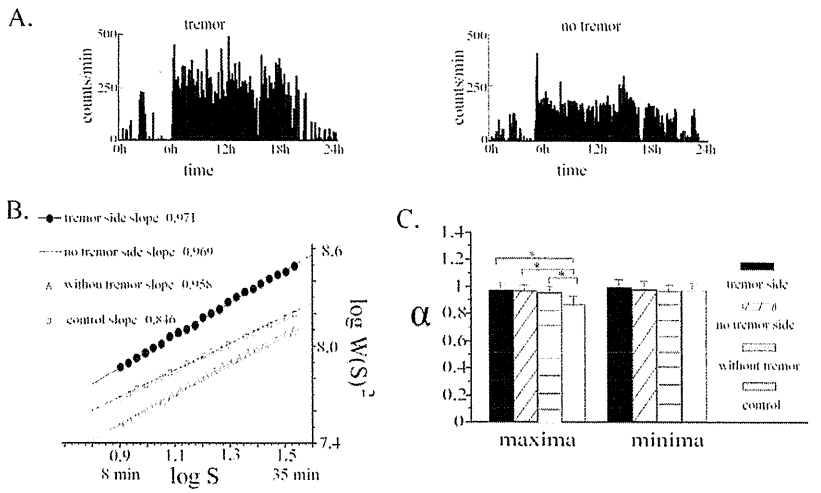

Fig. 4. Effects of tremor on actigraph counts and the power-law exponents. (A) Daily profiles of physical activity for the arm affected with tremor and that without tremor of a patient with unilaterally predominant parkinsonism with continuous tremor on one side. (B) Average wavelet coefficients for 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.

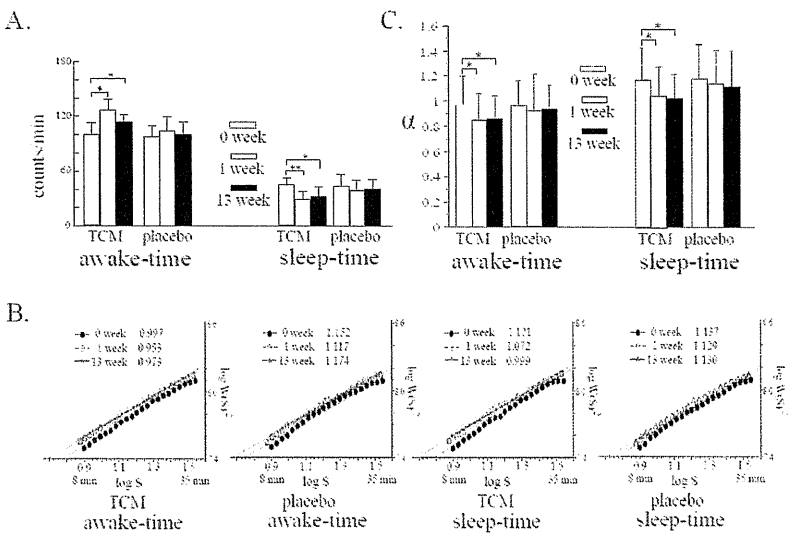

Fig. 5. Effects of TCM and placebo granules on actigraph recordings. (A) Counts of physical activity (mean ± S.D.). (B) Average wavelet coefficients, as a function of the wavelet scale for awake-time and sleep-time. The slopes are power-law exponents α. (C) Power-law exponents α (mean ± S.D.). *: $P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

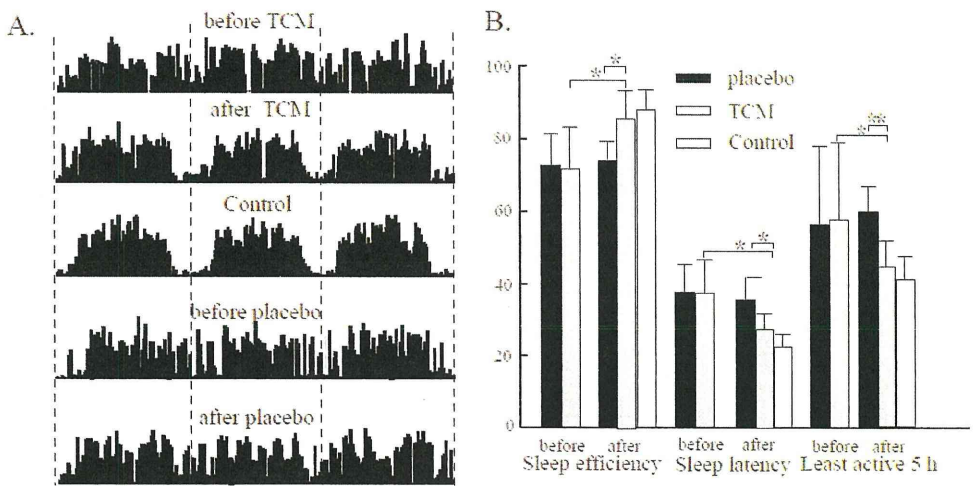

Fig. 6. Effects of cerebral granule (TCM). (A) Daily profiles of actigraph count for three consecutive days before and after taking TCM. Dashed line: midnight. (B) Changes from baseline in actigraph counts. Columns and bars (mean ± S.D.) indicate sleep efficiency (%), sleep latency (min) and the 5 least 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.

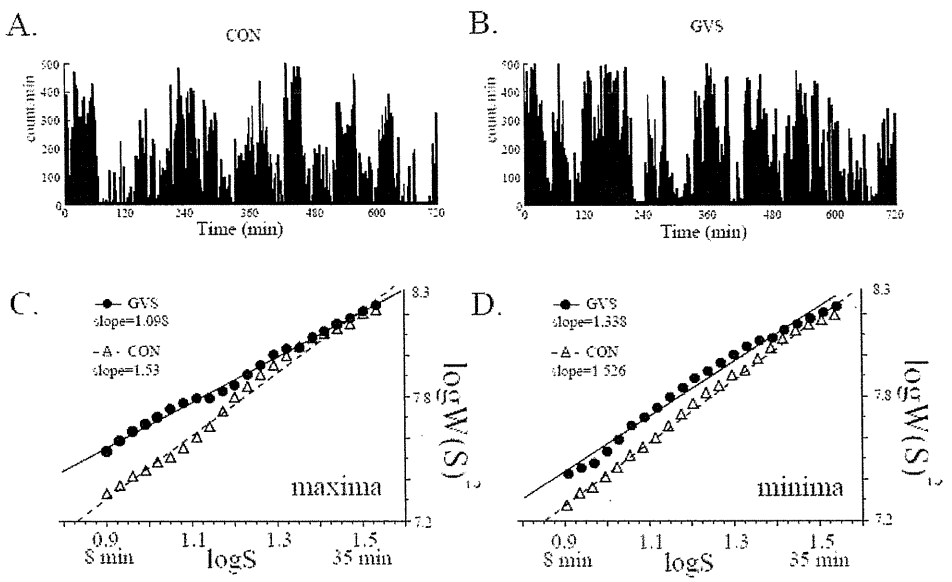

Fig. 7. Illustrative examples of wrist activity data of a PD patient during the control (CON) period (A) and during GVS application (B). The wavelet coefficients ($W(S)$) of these data, as a function of the wavelet scale (S) are shown for local maxima (C) and minima (D). The slopes are power-law exponents 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

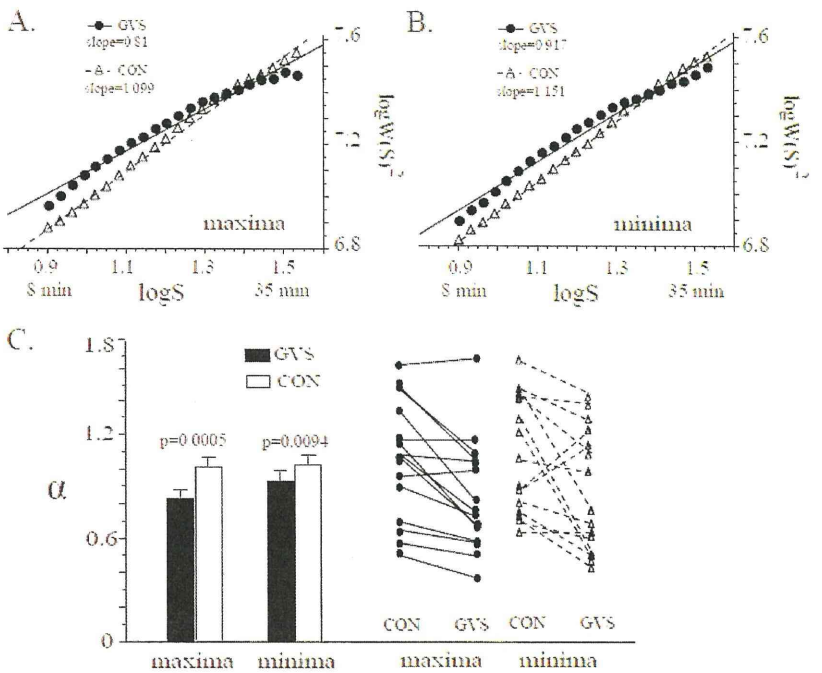

Fig. 8. The group average wavelet coefficients for local maxima (A) and minima (B) for GVS and control (CON) conditions. (C) Comparisons of the mean α for GVS and CON (left) and the within-individual differences (right). The error bars represent SEM. Reprinted with permission from (Pan et al., 2008).

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 α 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

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Health, Labor, and Welfare of Japan to S.K.

8. References

Arnulf, I., Konofal, E., Merino-Andreu, M., Houeto, J.L., Mesnage, V., Welter, M.L., Lacomblez, L., Golmard, J.L., Derenne, J.P. & Agid, Y. (2002). Parkinson's disease and sleepiness: an integral part of PD. *Neurology,* Vol. 58, No. 7, (Apr 2002), pp. 1019-1024, ISSN 0028-3878

Chaudhuri, K.R. & Schapira, A.H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol,* Vol. 8, No. 5, (May 2009), pp. 464-474, ISSN 1474-4422

Comella, C.L. (2002). Daytime sleepiness, agonist therapy, and driving in Parkinson disease. *JAMA,* Vol. 287, No. 4, (Jan 2002), pp. 509-511, ISSN 0098-7484

Comella, C.L., Morrissey, M. & Janko, K. (2005). Nocturnal activity with nighttime pergolide in Parkinson disease: a controlled study using actigraphy. *Neurology,* Vol. 64, No. 8, (Apr 2005), pp. 1450-1451, ISSN 1526-632X

De Smet, P.A. (2002). Herbal remedies. *N Engl J Med,* Vol. 347, No. 25, (Dec 2002), pp. 2046-2056, ISSN 1533-4406

Harrison, M.B., Wylie, S.A., Frysinger, R.C., Patrie, J.T., Huss, D.S., Currie, L.J. & Wooten, G.F. (2009). UPDRS activity of daily living score as a marker of Parkinson's disease progression. *Mov Disord,* Vol. 24, No. 2, (Jan 2009), pp. 224-230, ISSN 1531-8257

Hobson, D.E., Lang, A.E., Martin, W.R., Razmy, A., Rivest, J. & Fleming, J. (2002). Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA,* Vol. 287, No. 4, (Jan 2002), pp. 455-463, ISSN 0098-7484

Iwasaki, K., Kobayashi, S., Chimura, Y., Taguchi, M., Inoue, K., Cho, S., Akiba, T., Arai, H., Cyong, J.C. & Sasaki, H. (2004). A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. *J Am Geriatr Soc,* Vol. 52, No. 9, (Sep 2004), pp. 1518-1521, ISSN 0002-8614

Iwasaki, K., Maruyama, M., Tomita, N., Furukawa, K., Nemoto, M., Fujiwara, H., Seki, T., Fujii, M., Kodama, M. & Arai, H. (2005a). Effects of the traditional Chinese herbal medicine Yi-Gan San for cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia with Lewy bodies. *J Clin Psychiatry,* Vol. 66, No. 12, (Dec 2005), pp. 1612-1613, ISSN 0160-6689

Iwasaki, K., Satoh-Nakagawa, T., Maruyama, M., Monma, Y., Nemoto, M., Tomita, N., Tanji, H., Fujiwara, H., Seki, T., Fujii, M., Arai, H. & Sasaki, H. (2005b). A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry,* Vol. 66, No. 2, (Feb 2005), pp. 248-252, ISSN 0160-6689

Jean-Louis, G., Mendlowicz, M.V., Gillin, J.C., Rapaport, M.H., Kelsoe, J.R., Zizi, F., Landolt, H. & von Gizycki, H. (2000). Sleep estimation from wrist activity in patients with major depression. *Physiol Behav,* Vol. 70, No. 1-2, (Jul 2000), pp. 49-53, ISSN 0031-9384

Katayama, S. (2001). Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy. *Eur Neurol,* Vol. 46, No. Suppl 1, (2001), pp. 11-17, ISSN 0014-3022

Korszun, A., Young, E.A., Engleberg, N.C., Brucksch, C.B., Greden, J.F. & Crofford, L.A. (2002). Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. *J Psychosom Res,* Vol. 52, No. 6, (Jun 2002), pp. 439-443, ISSN 0022-3999

Korte, J., Hoehn, T. & Siegmund, R. (2004). Actigraphic recordings of activity-rest rhythms of neonates born by different delivery modes. *Chronobiol Int,* Vol. 21, No. 1, (Jan 2004), pp. 95-106, ISSN 0742-0528