

Emotional task-dependent low-frequency fluctuations and methylphenidate: Wavelet scaling analysis of 1/f-type fluctuations in fMRI of the cerebellar vermis

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Abstract

Ion channel currents, neural firing patterns, and brain BOLD signals display 1/f-type fluctuations or fractal properties in time. By design, fMRI methods attempt to minimize the contribution of variance from low-frequency physiological 1/f-noise. New fMRI methods are described to visualize and measure 1/f-type BOLD fluctuations in volunteers recalling affectively neutral or emotional memories or meditating (i.e., attending to breathing) then retrospectively rating emotional content. A wavelet scaling exponent (α) was used to characterize signals from 0.015625 to 0.5 Hz in cerebellar lobules VIII to X of the vermis (posterior inferior vermis; PIV), a region coordinating balance, eye tracking, locomotion, and vascular tone, and a possible site of pathology in attention deficit hyperactivity disorder (ADHD).

Results: Changes in α and emotional measures were correlated in PIV voxels ($r=0.622$, d.f. = 14, $P<0.0005$), but not other regions examined. In contrast, conventional means and standard deviations of PIV voxels were unchanged. Methylphenidate, shown to decrease slow oscillations in rodent basal ganglia [Ruskin DN, Bergstrom DA, Shenker A, Freeman LE, Baek D, Walters JR. Drugs used in the treatment of attention-deficit/hyperactivity disorder affect postsynaptic firing rate and oscillation without preferential dopamine autoreceptor action. *Biol Psychiatry* 2001;49:340–50.], abolished task-dependent α changes in the PIV of an adult with ADHD. Wavelet analysis of long BOLD time series appears well suited to fractal physiology and studies of pharmacologically modulated cerebellar–thalamic–cortical function in ADHD or other psychiatric disorders.

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1. Introduction

There is a growing interest in the role of low-frequency (0.01–0.1 Hz) fluctuations in brain hemodynamics (Obrig et al., 2000; Biswal et al., 1995, 1996, 1997; Biswal and Ulmer, 1999), EEG (Freeman et al., 2003; Linkenkaer-Hansen et al., 2001, 2004; Stam and de Bruin, 2004) and neural firing rates from the basal ganglia, cerebellum and frontal lobes (Allers et al., 2002; Ruskin et al., 1999; Walters et al., 2001) during perception (Billock, 2000; Billock et al., 2001; Mitina and Abraham, 2003; Rainer and Miller, 2000; Takehara et al., 2002; Zhou et al., 2004), sensorimotor integration (Miyazaki et al., 2004; Wing et al., 2004) and behavioral state change (Anderson et al., 1993, 1999; Anderson, 2000; Poupard et al., 2001). Dopamine (DA)

agonists and antagonists, particularly stimulants employed to treat psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), have been observed to modulate multisecond fluctuations in neural firing in the basal ganglia (Honey and Bullmore, 2004; Li et al., 2000; Ruskin et al., 1999, 2001, 2003) and possibly the cerebellum (Walters et al., 2001). Ruskin et al. (1999) observed that basal ganglia regions, including caudate (Cu), putamen (Pu), globus pallidus (GP) and substantia nigra pars reticulata (SNpr), show DA agonist-induced modulation of mean firing rate, oscillatory period, and internuclear phase relationships over periods of 2–60 s, mediated by the ipsilateral subthalamic nucleus (STN). DA agonists can increase regularity and correlations in cell firing in the basal ganglia and narrow the range of oscillatory fluctuations (Ruskin et al., 2000, 2001) or reduce low-frequency BOLD oscillations in cortex (Li et al., 2000). Ruskin et al. (2003) observed that unilateral lesions of the STN blocked DA agonist effects ipsilaterally, but did not eliminate slow firing rate fluctuations, suggesting a possible ori-

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gin for oscillations in basal ganglia cerebellar–thalamic–cortical efferents (Hilker et al., 2004; Houk et al., 1996; Kimura et al., 2004; Nagao, 2004; Stein and Aziz, 1999; Yamamoto et al., 2004). The method reported here, along with other recent work (Priori et al., 2004; Magill et al., 2004), reinforces the view that low-frequency oscillations in neuronal activity, metabolism, and hemodynamics are strongly influenced by the dynamics of brain stem monoamines (Mandell and Selz, 1993; Selz and Mandell, 1991).

Over the past decade, physiological fluctuations observed in BOLD fMRI experiments (Biswal et al., 1995) have gained new recognition as a possible source of brain state-dependent signals (Anderson, 1997, 2001; Anderson et al., 2002a,b; Maas et al., 1997a) rather than merely being unwanted physiological “colored” noise to be “whitened” (Bullmore et al., 1996, 2001, 2003; Fadili and Bullmore, 2002, 2004; Muller et al., 2003). Slow BOLD fluctuations at 0.1 Hz or lower frequencies can be described as “fractal in time” and are characterized by a 1/f-type spectrum (Bullmore et al., 2001, 2003). Fluctuations of neurobiological processes across many levels of brain function from ion channel current flows to global EEG display a 1/f-type spectrum (Anderson, 2000; Anderson and Mandell, 1996; Bieberich, 2002; Gisiger, 2001; Musha, 1981). Neurobiological 1/f-type fluctuations are characterized by long-range correlations, or persistent (Hurst parameter $> 1/2$) fluctuations; these are mathematically isomorphic descriptions (Bassingthwaite et al., 1994; Lowen and Teich, 2005; Thurner et al., 1997). Recently, 1/f fluctuations have also been observed in a wide array of human experimental paradigms (Gilden, 2001; but see Wagenmakers et al., 2004), and there are indications that these fluctuations are also influenced by the motor or perceptual task or by shifts in attention (Anderson and Mandell, 1996; Jeong et al., 1998; Wing et al., 2004). The growing literature reports of cognitive and brain 1/f-type fluctuations argues for the development of new methodological approaches to assess them in BOLD MRI experiments. We report here methods for the study of behavioral state-dependent and pharmacological manipulations of 1/f fluctuations in long-term BOLD MRI image sequences.

There are several reasons to explore new analytical methods, such as wavelet analysis, to study 1/f-type BOLD fluctuations. Traditional Fourier analysis of these 1/f-type noise processes often proves problematic (Mandelbrot, 1999; Ward, 2002), particularly in fMRI (Bullmore et al., 2003). Such signals typically exhibit baseline shifts or trends, which can confound classical Fourier techniques. Removal of these putative trends prior to Fourier analysis often results in the distortion of the primary signal of interest along with the trend. Wavelet analysis, in contrast, employs basis functions that are by construction insensitive to shifts and, with few exceptions, insensitive to trends. Furthermore, wavelet basis functions at different frequencies or scales share the same shape, making them ideal for the analysis of fractal signals, which contain statistically similar patterns on different time scales. In contrast, basis functions in Fourier analysis all have different shapes. Despite long-term correlation in the time domain of the signal under study, wavelet transforms yield coefficients that do not exhibit significant correlation (Lowen and Teich, 2005). This effectively eliminates the statis-

tical problems inherent in estimating hemodynamic responses to time-varying stimuli against slowly varying background fluctuations.

Wavelet analysis is indeed superb for separating experimental effect from physiological variation, as Bullmore et al. (2001) have pointed out. We take a complementary approach, proposing that multiscale physiological variation contains useful and valid information and is not merely noise. Rather than using wavelet analysis to remove the effects of physiological fluctuations in the fMRI data, we employ wavelet transforms to study the state- or drug-dependent characteristics of the fluctuations themselves.

2. Materials and methods

2.1. Subjects and procedures

Four volunteers, three males (one with ADHD) and one female, served as subjects in this study, which was approved by the McLean Hospital Institutional Review Board (see Table 1 for subject information). All images were collected on a 1.5-T magnetic resonance scanner (Echospeed, General Electric Medical Systems, Milwaukee, WI) equipped with a whole-body, resonant gradient set and a quadrature RF head coil (Ultracoil Head Coil, Pathway Medical Technologies, Redman, WA). Three or four sets of 640 T2* weighted images (gradient echo, TE = 40 ms, TR = 1000 ms, flip angle = 66°, thickness = 5 mm, skip = 0; in-plane resolution = 3.125 mm × 3.125 mm) were collected in three axial planes through the eyes, anterior temporal lobes, and cerebellum (Lobules VI–VIII) of each subject. Images for all three sets were corrected for in-plane frame-to-frame motion with the DART registration algorithm (Maas et al., 1997b). Before entering the scanner each volunteer was instructed to, in sequence, (1) recall an emotionally neutral memory, (2) recall an emotionally intense memory (i.e., argument with a loved one), and (3) relax and focus on their breathing (no memory). All subjects were instructed to keep their eyes open, and to minimize movements. One male subject with a clinical diagnosis of ADHD, off medication for 24 h prior to scanning, underwent a second set of scans (the same emotional states in the same order) 20 min following ingestion of a prescribed dose of MPH (10 mg) while supine. Subjects rated emotions experienced from none = 0 to extreme = 4 during each condition using an abbreviated profile of mood state (POMS; 1975 version, Educational and Industrial Testing Service, San Diego, CA 92107) for each condition shortly after leaving the scanner. Eight possible emotional responses were measured (anxiety, tension, anger, sadness, hopelessness, panic, nervousness, and guilt) and summed by subject and task (see Table 2).

Table 1
Subject characteristics

Subject	Sex	Age (years)	Weight (kg)
1	M	40	75
2	F	28	54
3	M	37	77
4	M	30	82

Table 2
Total profile of mood states (POMS) scores collected post-scan from all subjects

Subject	Neutral	Emotional	Meditation
1	2	8	0
2	4	10	7
3	0	4	0
4	0	4	0
1B	3	8	0
1P	1	4	0

2.2. Fractal exponents

For each of the ($64 \times 64 \times 3$ or 4 ; x, y, z slices) voxels, the corresponding voxel time series $s(n)$ was extracted from each fMRI data set (see Fig. 1A). From $s(n)$ the mean and variance were calculated. The results from subject 1 form columns A and B in Fig. 2, respectively. Next $s(n)$ was convolved with a Haar wavelet (see Fig. 1B) of scale 2, generating a wavelet transform at that scale. The variance of the transform (in contrast to the variance of the original voxel time series) was obtained. The process was performed for each voxel and for each fMRI data set at scales of 2, 4, 8, 16, 32, and 64. An image of the wavelet variance at a scale of 64 appears as column C in Fig. 2. Finally, the six wavelet transform variances for each voxel time series were fit to a straight line on a log–log plot, yielding a wavelet fractal exponent α for each voxel (see Fig. 1C). The exponent was mapped to a color, ranging from red for +2.00 to blue for

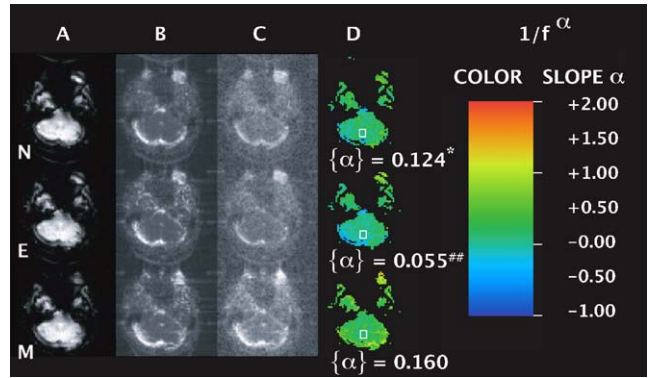


Fig. 2. For each voxel in the time series $s(n)$ the mean (A) and variance (B) were calculated for the neutral memory (N), emotional memory (E) and meditation (M) tasks for a single inferior slice. Column (C) is the variance of the convolution of $s(n)$ with a Haar wavelet of scale 64. Column (D) are exponent color maps of derived exponents α from the log–log linear fit of six wavelet-transformed variances for scales 2, 4, 8, 16, 32, and 64 at each voxel $s(n)$. Exponents were averaged $\{\alpha\}$ for each 4×4 ROI (indicated by the white box in column D) on the lower slice encompassing the posterior inferior vermis. Significant slope changes were observed for the neutral vs. emotional memory (two-tailed, * $P = 0.043$) and emotional memory vs. meditation (two-tailed, ## $P = 0.0028$) 11 min tasks.

–1.00. Voxels for which the variance did not exceed 46 were deemed to have insufficient signal to yield accurate results, and were set to black. Similarly, voxels for which the residual error exceed 1/36 of the average wavelet variance after the linear fit were also rejected and set to black. (The values 46 and 1/36

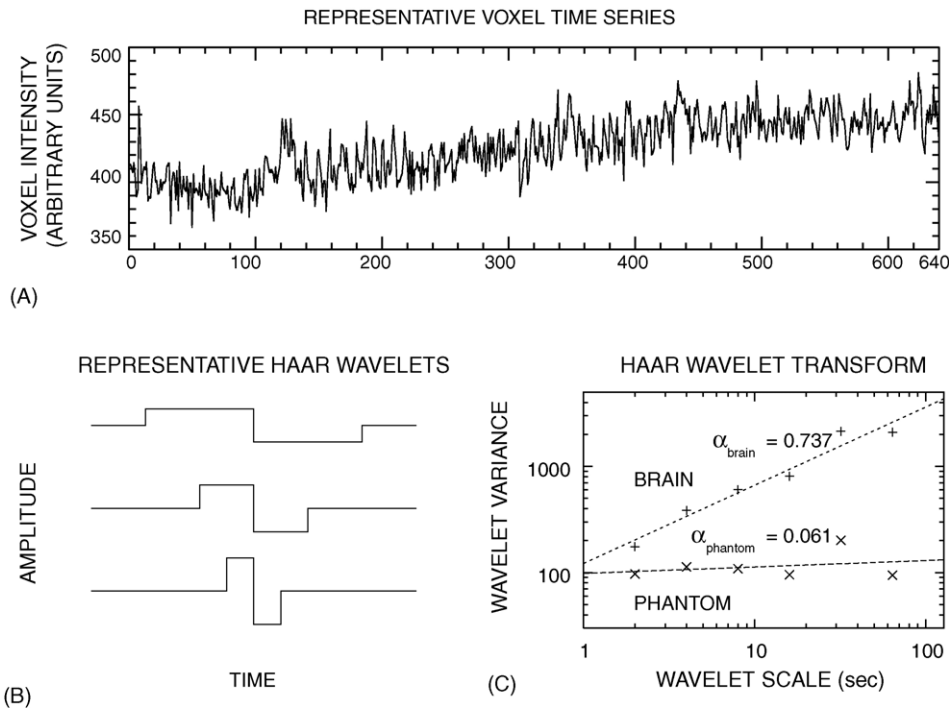


Fig. 1. (A) Plot of the intensity (arbitrary units) of a representative cerebellar voxel time series from subject 1 with a TR = 1 s over 640 s of meditation. (B) Illustration of translated and dilated Harr wavelet functions at different scales, which are sequentially convolved with the voxel time series. (C) A log–log plot of the six wavelet transform variances vs. six wavelet scales for the voxel time series in (A) and a phantom time series (not shown previously). Wavelet fractal exponents α for a given time series were computed from the linear fit to the log–log plot ($\alpha_{\text{brain}} = 0.737$, intercept = 121.781, $r = 0.977$; $\alpha_{\text{phantom}} = 0.061$, intercept = 98.176, $r = 0.27$). By analogy to other complex systems (see Section 4), an exponent $\alpha > 0.5$ for the cerebellum signifies a scaling relationship, characteristically long-range and persistent, during this behavioral state among observed neuronal fluctuations at six timescales. On the contrary, an exponent $\alpha = 0.061$ was computed for potential instrument noise-induced fluctuations in a phantom voxel, indicating significantly fewer long-range correlations at these timescales.

were obtained empirically). This procedure resulted in α maps displayed in column D of Fig. 2. For the first three columns in Fig. 2, monotonically increasing transforms similar to histogram equalization were applied to the data just before generating the images shown, in order to improve visibility.

2.3. Statistical methods

A variety of methods exist for determining whether two distributions differ in mean, median, or other centering measure. Parametric methods depend on the distribution having a particular form, generally Gaussian or normal. The data shown here, like many physiological data, do not follow a Gaussian form (Bassingthwaite et al., 1994; Lowen and Teich, 2005). We therefore employed a non-parametric statistical method: receiver operating characteristic area or ROC (Swets, 1988), functionally equivalent to the Mann–Whitney U -test or Wilcoxon rank-sum test. We define a region of interest (ROI) for two conditions. We then gradually increase a threshold from negative infinity to positive infinity. For each threshold value we plot a point (x, y) where x (respectively, y) is the proportion of values in the first (respectively, second) ROI below the threshold. All curves generated by this procedure start at $(0, 0)$, increase monotonically, and end at $(1, 1)$. For perfect separation the curves pass through the point $(0, 1)$ and have unit area; interchanging the ROIs yields a curve that passes through the point $(1, 0)$ and has zero area. If the data from the two ROIs are indistinguishable, the curve will follow the line $y=x$ and have an area of 0.5. For a given number of voxels in the two ROIs, and the difference between the resulting curve area and 0.5, a significance value emerges.

Fig. 3 displays the significance values computed directly from Fig. 2, columns A–D. For each pixel in Fig. 1 a 7×7 neighbor-

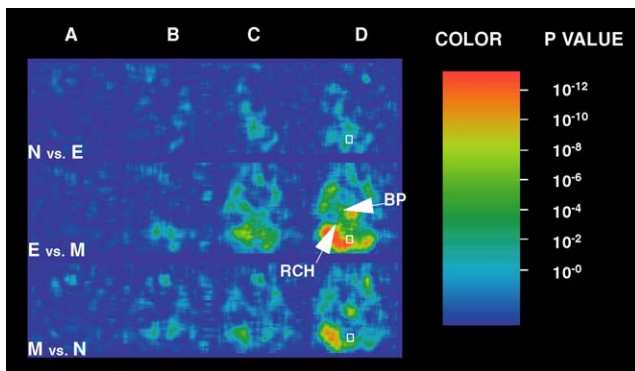


Fig. 3. Receiver operating characteristic (ROC) area significance maps for comparisons of each pixel in the neutral (N) vs. emotional (E) tasks; E vs. meditation (M) tasks; or M vs. N tasks; mean (A), variance (B), Haar wavelet of scale 64 (C) or exponent color maps (D) given for a single slice in Fig. 1. For each pixel in a task image, a 7×7 neighborhood of that pixel formed an ROI (indicated by white box) that was compared with a corresponding ROI in the contrasting task. The bonferroni-corrected difference in ROC curve area for two ROI's combined with the total number of voxels result in significance values that ranged from 1.0 (blue) to 3.5×10^{-11} (red). Significant changes in average slope for the posterior inferior vermis ROI (see Fig. 1) are visually apparent here for the E vs. M and M vs. N comparisons. Significant changes of higher magnitude in other regions, such as the right cerebellar hemisphere (RCH) and basilar pons (BP) are also evident.

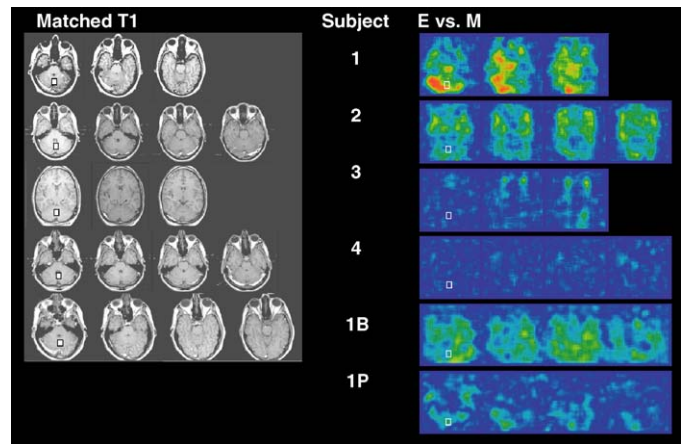


Fig. 4. Matched T1 slices (left) for the ROC color significance maps (right) of the emotional memory (E) vs. meditation (M) contrast for all subjects. Subjects 1, 2 and 1B have higher POMS score totals for the emotional memory task, than did subjects 3, 4 and 1P (see Table 2). The approximate location of the sampled ROI is indicated by the black box in the first column of T1 weighted images and white box in the first column of significance maps.

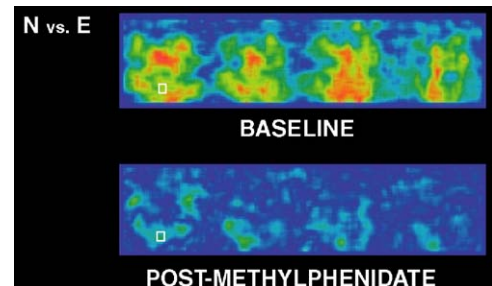


Fig. 5. Illustration of the dramatic reduction of ROC significance for the neutral (N) vs. emotional memory (E) contrasts at 40 min post methylphenidate ingestion (bottom) compared with high ROC significance for the same contrast during the unmedicated baseline state (top). The approximate location of the sampled ROI is indicated by a white box in the first column of significance maps.

hood of that pixel formed one ROI, while the corresponding neighborhood in the row directly below (or at the top, for the last row) formed the other ROI. The corresponding bonferroni-corrected significance from the ROC test appears in the same location in Fig. 3. The P -value ranged from 1.0, corresponding to an ROC area of 0.5 and no statistical significance (displayed as blue) to 3.5×10^{-12} corresponding to an ROC area of 0.0 or 1.0 and maximum statistical significance (displayed as red). Fig. 4 show this significance for all subjects and slices while Fig. 5 depicts the emotional-meditation ROC comparison of fractal exponents in an ADHD subject at baseline and following oral methylphenidate.

3. Results

The algorithms implemented in “C” take less than 5 min per subject to complete motion correction, wavelet exponent fits and ROC analysis on a dual processor 2 GHz personal computer. For subject 1 recall of emotional memories elicited a post-scan score of 8 on the POMS scale, higher than for either neutral memory or meditation (see Table 2). The average wavelet

Table 3

Average wavelet exponent $\{\alpha\}$ \pm standard error by subject and task for a 4×4 ROI centered on the poster inferior vermis (1B = subject 1 baseline; 1P = subject 1 post oral MPH)

Subject	Neutral	Emotional	Meditation
1	0.124 \pm 0.001*	0.055 \pm 0.000##	0.160 \pm 0.001
2	0.044 \pm 0.001	0.023 \pm 0.001#	0.128 \pm 0.001
3	0.097 \pm 0.001	0.097 \pm 0.001	0.154 \pm 0.002
4	0.236 \pm 0.003	0.183 \pm 0.001	0.273 \pm 0.003
1B	0.325 \pm 0.003***	0.084 \pm 0.001####	0.503 \pm 0.005
1P	0.148 \pm 0.001	0.138 \pm 0.002	0.332 \pm 0.004†

Statistical significance for ROC comparisons of $\{\alpha\}$.

* Neutral vs. Emotional: $P < 0.05$.

*** Neutral vs. Emotional: $P < 0.001$.

Emotional vs. Meditation: $P < 0.05$.

Emotional vs. Meditation: $P < 0.01$.

Emotional vs. Meditation: $P < 0.0001$.

† Meditation vs. Neutral: $P < 0.05$.

exponent $\{\alpha\}$, for a 4×4 voxel ROI centered on the poster inferior vermis (see box Fig. 2D) underwent a change from fluctuations with $1/f^\alpha$ spectrum, with $\{\alpha\} = 0.124$ during the recall of neutral memories over 10 min to $\{\alpha\} = 0.055$, over the next consecutive 10 min recalling emotional memories. During the last 10 min (meditation), the spectral form of BOLD fluctuations was characterized by $\{\alpha\} = 0.160$. Fluctuations occurring during the emotional task when compared with the corresponding regions during the meditation task were accompanied by an increase in the ROC significance for large regions of the slice, principally in the right cerebellar hemisphere (RCH; see Fig. 2D).

Results for subject 2 further support the association of elevated post-scan POMS scores of emotional experience (see Table 2) with a similar increase in the spectral slope of $\{\alpha\}$ and in ROC significance for large regions of several slices, predominately temporal lobe regions (see Fig. 4). For $\{\alpha\}$ in a 4×4 ROI positioned over the right temporal lobe all tasks were significantly different using a two-tailed contrast (N versus E: $P < 0.05$; E versus M: $P < 0.00001$; M versus N: $P < 0.01$). In contrast, subjects 3 and 4 had substantially lower POMS ratings of emotional response, consistent with little change in $\{\alpha\}$ (see Table 3) or the ROC statistic across the slices examined (see Fig. 4). However, A 4×4 ROI positioned over the basilar pons in subjects 3 and 4 did detect significant change in the neutral versus meditation tasks (subject 3, $P = 0.0006$; subject 4, $P = 0.002$). When the PIV was examined over all subjects, a correlation between the change in α and total POMS score with task was significant ($r = 0.622$, d.f. = 14, $P < 0.0005$).

Scans for ADHD subject 1 were repeated 2 years following initial test, with and without MPH. A similar change in $\{\alpha\}$ and ROC statistic for the emotional task versus meditation was elicited (see Table 3) for the two medication-free scans, two years apart (see Fig. 4). However, ingestion of MPH abolished task-evoked changes in α and the ROC statistic over all conditions of the task with one exception, meditation versus neutral memory, where α remained relatively large regardless of MPH (see Table 3 and Fig. 5).

4. Discussion

We report a novel and sensitive fMRI method to observe and compare state-dependent $1/f$ -type low-frequency fluctuations. The method utilized long (11-min), continuous sequences of images for processing, which were much longer than both the 10–60 s blocks typically used in standard fMRI experiments and the data sets studied with other wavelet processing methods (Basar et al., 1999; Brammer, 1998; Breakspear et al., 2004; Bullmore et al., 2001, 2003, 2004; Fadili and Bullmore, 2002, 2004; Long et al., 2004; Muller et al., 2003; Ruttimann et al., 1998; Shimizu et al., 2004; von Tscherner and Thulborn, 2001). As such, it is doubtful that subjects would remain in a single stationary mental state for the entire scan period. In fact, all subjects prior to scanning were asked to think of several memories to recall during the task to attempt to maintain a “steady-state” of mental activity during the task condition. Also, the order of tasks was not randomized, the antithesis of standard linear and autoregressive models used for statistical analysis of fMRI data (Bandettini et al., 1993; Bullmore et al., 1996; Locascio et al., 1997; Worsley et al., 2002). A consensus is emerging that the long memory or $1/f$ -type fluctuation characteristics of fMRI time series originates in the fractal nature of brain physiology (Anderson, 2000, 1997, 1998; Anderson et al., 1999; Bullmore et al., 2003), which is the current focus of our methodological development (Illustrated in Fig. 1C). In contradistinction to Bullmore et al. (2003), who place emphasis on the decorrelating properties of the discrete wavelet transform to render time series “white,” the goal of the current fMRI methodology is to accurately sample $1/f$ -type fluctuations during the task. In this framework, these fluctuations can be optimally analyzed and visualized using one wavelet transform per data set, indexed by a single slope, the wavelet exponent α .

Color maps of α condense temporal information in the spatial context of the slice, allowing an overview of relations among brain regions. Furthermore, nonparametric ROC analysis enables pixel-wise comparison of changes in α over similar slices and structures following conditions that involve emotional or pharmacological manipulations.

In general, there are a number of possible scan artifacts, such as scanner stability, which can limit the application of this method. In addition, we did not extensively characterize the influence of low-frequency subject motion artifacts, or respiration and blood pulsations and their possible impact on method sensitivity (Eke et al., 2000). Translation and rotational movement was removed by the DART algorithm (Maas et al., 1996), which is ideally suited to correct these types of motion in the long time series that we collected. How slow, out of plane motion, may influence α is currently unclear. Subject factors, such as fatigue, habituation, weight, age, drug status, and neurological lesions could also substantially influence our particular, and the more general, application of this methodology. All of these concerns, however, were diminished by the robust emotional and pharmacological nature of the regionally selective, fractal scaling of BOLD fluctuations that we observed. However, all these potential confounds would impart similar effects on all voxel time series; it is extremely unlikely that these sources of artifact

would alter time series in so widely differing ways as to yield different fractal exponents across different voxels.

In this preliminary study, using a single wavelet scaling exponent α to succinctly summarize the contributions of fluctuations over a range of time scales, we observed an apparently robust correspondence between changes in $1/f^\alpha$ BOLD fluctuations in brain regions and post-scan subjective ratings of emotional experience in four subjects, one with a diagnosis of ADHD. Also, in the subject with ADHD, oral MPH was observed to substantially reduce ROC significance for fluctuations associated with the recall of an emotional experience in the PIV (see Fig. 5). This observation is concordant with findings by Ruskin et al. (1999), who observed a similar reduction in multisecond oscillations of neural firing rates in the SNpc and GP following MPH, using Morlet wavelets. Walters et al. (2001) have previously reported multisecond oscillations in the rodent cerebellum: however, these oscillations were not consistently altered by the DA agonist apomorphine. Our midline ROI encompassed the PIV: a region rich in the dopamine transporter-IR in the primate (Melchitzky and Lewis, 2000) and [C^{11}]altrone binding “hotspots” in adult human PIV (Anderson et al., 2005). Recently, we have observed rate-dependent alterations of T2 relaxation times (T2-RT) in the vermis of ADHD children who were treated with different pre-scan doses of MPH (Anderson et al., 2002a) and PIV T2-RT in normal adults receiving MPH during scanning (2002b). Also, emotional behavior and aggression in ADHD and fragile X children, both disorders with possible PIV pathology, is dose-dependently modulated by MPH (Casat et al., 1995; Hagerman, 2002; Klein et al., 1997).

The cerebellum, particularly the midline regions, could potentially play a lead role in directing motor system oscillations (Mori et al., 2004a,b, 2000; Yamamoto et al., 2004). By way of fastigial projections to intralaminar thalamus (Okumura et al., 2001; Gonzaloruz and Leichnetz, 1990; Larsell et al., 1972; Melik-Musyan and Fanardjyan, 1998), and pedunculo-pontine tegmental nucleus (PPN; Hazrati and Parent, 1992), the vermis could provide behavioral state-dependent modulation of a critical gaiting region for BG, STN, and PPN (Kimura et al., 2004). The PPN issues collaterals back to the fastigial nucleus (Ruggiero et al., 1997) and is thought to be critical to the effects of fastigial electrical stimulation-evoked cerebrovascular waves coupled with EEG desynchronization (Fadiga et al., 1968; Golanov et al., 2000; Paton et al., 1991).

The midline cerebellum also projects medial-to-lateral across dopamine cell body zones (Ikai et al., 1992, 1994; Snider et al., 1976; Snider and Snider, 1982; Tellerman et al., 1979), possibly synchronizing DA bursting in parallel with efferents from the PPN (Capozzo et al., 2003; Lokwan et al., 1999) which might target DA release via temporal “T-zip codes” to overlapping and interdigitating striato-nigro-striatal BG loop system compartments (Haber, 2003). These compartments are defined by large cholinergic striatal interneurons called tonically active neurons or TANs (Graybiel and Kubota, 2003), which establish a unique T-zip code and a narrow range of time scales (Cromwell and Schultz, 2003) defined by IL and limbic input (Eblen and Graybiel, 1995). TANs appear to lie at striosome-matrix borders, where sensorimotor associations gives rise to the direct

and indirect pathways of the striatum (Graybiel and Kubota, 2003). Mandell and Selz (1993) proposed that observed dynamic information state ranges of bursting brain stem biogenic amine projection neurons (Selz and Mandell, 1991) are reflected in global cortical oscillations, imparting coherence to the EEG, and thus, to behavioral states. The emotional- and pharmacological-state directed shifts in the fractal scaling of midline cerebellar BOLD fluctuations we have observed could impinge on and couple with monoamine fractal clustering mechanisms proposed by Mandell and Selz (1993), by way of fastigio-intralaminar, -PPN, -VTA, -SN, -locus ceruleus, or -rapha influences, manifesting spike sequences in global behavioral $1/f$ -type fluctuations in autonomic, attentional and intentional time series.

The PIV is a multifunctional cerebellar region, evolutionarily enlarged in predatory mammals to facilitate rapid shifts of sensorimotor coupling during the tracking and pursuit of prey in both quadrupeds and sea mammals (Paulin, 1993, 1997; Guillaume et al., 2000). In humans its additional roles include: coordinating balance, breathing, eye tracking, locomotion and vascular tone, especially during the supreme evolutionary challenges of bipedal motion and language production. It has not escaped our notice that many of the behaviors coordinated in whole or in part by the PIV also have long-range power-law scaling characteristics with $1/f$ -type fluctuations (e.g., walking; standing; eye movements; blood flow; breathing; sleep states; language: Aks et al., 2002; Anderson et al., 1998; Bassingthwaight et al., 1994; Duarte and Zatsiorsky, 2000, 2001; Hausdorff et al., 2001; Lo et al., 2004; Voss and Clarke, 1975). In particular, the vermis has an interesting and enigmatic role in emotional expression and motor coordination. For example, surgical lesions of the PIV, performed in the course of removal of fourth ventricle tumors, frequently render children and adults mute for a time following recovery from surgery (Ildan et al., 2002; Schmahmann, 2000; Steinlin et al., 2003). After recovery and the return of speech, the porosity or emotional tone of the speech is lost, and children often also lose emotional coordination (Levisohn et al., 2000; Riva and Giorgi, 2000). Schizophrenia and autism, both psychiatric conditions associated with various forms of midline cerebellar pathology (Heath et al., 1982; Deicken et al., 2001), are also associated with defects in the perception and transmission of emotional information (Ornitz, 1970; Schmahmann, 2000). Our finding of a significant correlation between changes in emotional state and wavelet exponent unique to PIV supports an observation by Shaffer (1981; cited in Wing et al., 2004) that emotions are expressed by intended variations in movement timing (e.g., vocal porosity; musical production; dance: Juslin and Laukka, 2003; Madison, 2000; Manaris et al., 2003) aspects of which display power-laws (Tuller et al., 1997; Voss and Clarke, 1975). Is $1/f$ -type emotional-motor production variability perceived (Bhattacharya et al., 2001, Jeong et al., 1998) and if so, then does it serve the brain as a neurobiological broad-band carrier wave (Lowen et al., 1997, 1999; Teich and Lowen, 1994; Teich et al., 1996) for the reception, translation and retransmission of emotional experience (Jeong et al., 1998)? Perhaps the PIV is a psychologically critical neurodynamic sensory-motor interface, modulating and demodulating brain stem carrier wave oscillations, to be expressed in the coordination of attention, intention,

emotional, motor control, and the observed power-law variation in motor production. Our results would be consistent with emotional and pharmacological modulation of a low-frequency cerebellar carrier wave.

ADHD is also associated with defects in the PIV (Berquin et al., 1998; Castellanos et al., 2001; Bussing et al., 2002) and with difficulties in emotional and physical coordination, balance, hyperactivity and language processing. Many of these defects are ameliorated or eliminated by oral treatment with MPH. We observed that low-frequency oscillations are more extensive in the cerebellum before medication and that, following MPH, the oscillations are greatly diminished in this region. The ROC significance of differences between the baseline and emotional, and emotional and meditation tasks were substantial for the ADHD subject without MPH during both baseline scans, which were two years apart. However, these differences, except for meditation, were completely disrupted by MPH. This may indicate that the PIV, for the reasons discussed above, is a focal site of MPH action and that meditation, as a form of self-initiated internal biofeedback, can potentially augment $\{\alpha\}$ despite the action of MPH. Other ADHD subjects will need to be tested to replicate and extend these observations with this methodology. Additional measures such as baseline activity, the morphology and volume of the PIV and other brain regions, diagnosis, and PIV [C^{11}]altropane binding density could be useful as covariates. Real-time online collection of head movement, eye tracking, galvanic skin resistance, heart rate, and subject responses during scanning could enable characterization of the coherence of BOLD with behavioral fluctuations, and the possible role fractal time processes contribute to brain function and its disruption in ADHD as in well as other psychiatric disorders.

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References

- Aks DJ, Zelinsky GJ, Sprott JC. Memory across eye-movements: 1/f dynamic in visual search. *Nonlin Dyn Psychol Life Sci* 2002;6:1–25.
- Allers KA, Ruskin DN, Bergstrom DA, Freeman LE, Ghazi LJ, Tierney PL, et al. Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. *J Neurophysiol* 2002;87:1118–22.
- Anderson CM. Multi-time scale analysis of fluctuations in BOLD fMRI. *Abstr Soc Neurosci* 1997:1575 [<http://remfractal.mclean.org/hurst1997.pdf>].
- Anderson CM. Fractal fluctuations in BOLD fMRI Dynamical Neuroscience VI; 1998 [<http://remfractal.mclean.org/hurst1998.pdf>].
- Anderson CM. From molecules to mindfulness: how vertically convergent fractal time fluctuations unify cognition and emotion. *Conscious Emotion* 2000;1:193–226 [http://www.benjamins.com/cgi-bin/t_articles.cgi?bookid=C%26E%201%3A2&artid=278008276].
- Anderson CM, Holroyd T, Bressler SL, Nakamura R, Selz KA, Mandell AJ. 1/f-Like spectra in cortical and subcortical brain structures: a possible marker of behavioral state-dependent self organization. In: Handel PJ, Chung AJ, editors. *Noise in physical systems and 1/f fluctuations*. St. Louis: American Institute of Physics; 1993. p. 737–40.
- Anderson CM, Lowen SB, Maas LC, Renshaw PF, Teicher MH. State-of-mind-dependent fractal fluctuations in BOLD fMRI. *Dynamical neuroscience VII*. Florida: Delray; 1999 [<http://remfractal.mclean.org/wave1999.pdf>].
- Anderson CM, Mandell AJ. Fractal time and the foundations of consciousness: vertical convergence of 1/f phenomena from ion channels to behavioral states. In: Mac Cormac E, Stamenov MI, editors. *Fractals of brain, fractals of mind (advances in consciousness research)*. Amsterdam/Philadelphia: John Benjamins; 1996. p. 75–126.
- Anderson CM, Mandell AJ, Selz KA, Terry LM, Wong CH, Robinson SR, et al. The development of nuchal atonia associated with active (REM) sleep in fetal sheep: presence of recurrent fractal organization. *Brain Res* 1998;787:351–7.
- Anderson CM, Polcari A, Lowen SB, Renshaw PF, Teicher MH. Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. *Am J Psychiatry* 2002a;159:1322–8.
- Anderson CM, Silveri MM, Cowan R, Maas LC, Madras BK, Lukas SE, et al. Activation of lobule VIII of the human cerebellar vermis by oral methylphenidate and cue-induced cocaine craving. *Drug Alcohol Depend* 2002b;66:S6.
- Anderson CM, Maas LC, Frederick BB, Bendor JT, Spencer TJ, Livni E, et al. Cerebellar vermis involvement in cocaine-related behaviors. *Neuropsychopharmacology*, published online 12 October, 2005, doi:10.1038/sj.npp.13000937.
- Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med* 1993;30:161–73.
- Basar E, Demiralp T, Schurmann M, Basar-Eroglu C, Ademoglu A. Oscillatory brain dynamics, wavelet analysis, and cognition. *Brain Lang* 1999;66:146–83.
- Bassingthwaite JB, Liebovitch LS, West BJ. *Fractal physiology*. Oxford University Press; 1994.
- Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, et al. Cerebellum in attention-deficit hyperactivity disorder—a morphometric MRI Study. *Neurology* 1998;50:1087–93.
- Bhattacharya J, Petsche H, Pereda E. Interdependencies in the spontaneous EEG while listening to music. *Int J Psychophysiol* 2001;42:287–301.
- Bieberich E. Recurrent fractal neural networks: a strategy for the exchange of local and global information processing in the brain. *Biosystems* 2002;66:145–64.
- Billock VA. Neural acclimation to 1/f spatial frequency spectra in natural images transduced by the human visual system. *Physica D* 2000;137:379–91.
- Billock VA, de Guzman GC, Kelso JAS. Fractal time and 1/f spectra in dynamic images and human vision. *Physica D* 2001;148:136–46.
- Biswal B, DeYoe AE, Hyde JS. Reduction of physiological fluctuations in fMRI using digital filters. *Magn Reson Med* 1996;35:107–13.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995;34:537–41.
- Biswal BB, Ulmer JL. Blind source separation of multiple signal sources of fMRI data sets using independent component analysis. *J Comput Assist Tomogr* 1999;23:265–71.
- Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR Biomed* 1997;10:165–70.
- Brammer MJ. Multidimensional wavelet analysis of functional magnetic resonance images. *Hum Brain Mapp* 1998;6:378–82.

- Breakspear M, Brammer MJ, Bullmore ET, Das P, Williams LM. Spatiotemporal wavelet resampling for functional neuroimaging data. *Hum Brain Mapp* 2004;23:1–25.
- Bullmore E, Fadili J, Breakspear M, Salvador R, Suckling J, Brammer M. Wavelets and statistical analysis of functional magnetic resonance images of the human brain. *Stat Methods Med Res* 2003;12:375–99.
- Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, et al. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. *Hum Brain Mapp* 2001;12:61–78.
- Bullmore ET, Rabe-Hesketh S, Morris RG, Williams SCR, Gregory L, Gray JA, et al. Functional magnetic resonance image analysis of a large-scale neurocognitive network. *Neuroimage* 1996;4:16–33.
- Bussing R, Grudnik J, Mason D, Wasiaik M, Leonard C. ADHD and conduct disorder: an MRI study in a community sample. *World J Biol Psychiatry* 2002;3:216–20.
- Capozzo A, Florio T, Cellini R, Moriconi U, Scarnati E. The pedunculo-pontine nucleus projection to the parafascicular nucleus of the thalamus: an electrophysiological investigation in the rat. *J Neural Transm* 2003;110:733–47.
- Casat CD, Pearson DA, Vandavelaar MJ, Cherek DR. Methylphenidate effects on a laboratory aggression measure in children with ADHD. *Psychopharmacol Bull* 1995;31:353–6.
- Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, et al. Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2001;58:289–95.
- Cromwell HC, Schultz W. Effects of expectations for different reward magnitudes on neuronal activity in primate striatum. *J Neurophysiol* 2003;89:2823–38.
- Deicken RF, Feiwell R, Schuff N, Soher B. Evidence for altered cerebellar vermis neuronal integrity in schizophrenia. *Psychiatry Res* 2001;107:125–34.
- Duarte M, Zatsiorsky VM. On the fractal properties of natural human standing. *Neurosci Lett* 2000;283:173–6.
- Duarte M, Zatsiorsky VM. Long-range correlations in human standing. *Phys Lett A* 2001;283:124–8.
- Eblen F, Graybiel AM. Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. *J Neurosci* 1995;15:5999–6013.
- Eke A, Herman P, Bassingthwaite JB, Raymond GM, Percival DB, Cannon M, et al. Physiological time series: distinguishing fractal noises from motions. *Pflügers Arch* 2000;439:403–15.
- Fadiga E, Manzoni T, Sapienza S, Urbano A. Synchronizing and desynchronizing fastigial influences on electrocortical activity of cat in acute experiments. *Electroencephalogr Clin Neurophysiol* 1968;24:330–42.
- Fadili MJ, Bullmore ET. Wavelet-generalized least squares: a new BLU estimator of linear regression models with 1/f errors. *Neuroimage* 2002;15:217–32.
- Fadili MJ, Bullmore ET. A comparative evaluation of wavelet-based methods for hypothesis testing of brain activation maps. *Neuroimage* 2004;23:1112–28.
- Freeman WJ, Holmes MD, Burke BC, Vanhatalo S. Spatial spectra of scalp EEG and EMG from awake humans. *Clin Neurophysiol* 2003;114:1053–68.
- Gilden DL. Cognitive emissions of 1/f noise. *Psychol Rev* 2001;108:33–56.
- Gisiger T. Scale invariance in biology: coincidence or footprint of a universal mechanism? *Biol Rev Camb Philos Soc* 2001;76:161–209.
- Golanov EV, Christensen JRC, Reis DJ. The medullary cerebrovascular vasodilator area mediates cerebrovascular vasodilation and electroencephalogram synchronization elicited from cerebellar fastigial nucleus in Sprague-Dawley rats. *Neurosci Lett* 2000;288:183–6.
- Gonzalorui A, Leichnetz GR. Connections of the caudal cerebellar interpositus complex in a new-world monkey (cebus-apella). *Brain Res Bull* 1990;25:919–27.
- Graybiel AM, Kubota Y. Understanding corticobasal ganglia networks as part of a habit formation system. In: Bédard M-A, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lespérance P, editors. *Mental and behavioral dysfunction in movement disorders*. Totowa, New Jersey: Humana Press Inc.; 2003. p. 35–50.
- Guillaume A, Goffart L, Courjon JH, Pelisson D. Altered visuo-motor behavior during inactivation of the caudal fastigial nucleus in the cat. *Exp Brain Res* 2000;132:457–63.
- Haber S. Integrating cognition and motivation into the basal ganglia pathways of action. In: Bédard M-A, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lespérance P, editors. *Mental and behavioral dysfunction in movement disorders*. Totowa, New Jersey: Humana Press Inc.; 2003. p. 35–50.
- Hagerman RJ. Influence of stimulants on electrodermal studies in fragile X syndrome. *Microsc Res Tech* 2002;57:168–73.
- Hausdorff JM, Ashkenazy Y, Peng CK, Ivanov PC, Stanley HE, Goldberger AL. When human walking becomes random walking: fractal analysis and modeling of gait rhythm fluctuations. *Physica A* 2001;302:138–47.
- Hazrati LN, Parent A. Projection from the deep cerebellar nuclei to the pedunculo-pontine nucleus in the squirrel monkey. *Brain Res* 1992;585:267–71.
- Heath RG, Franklin DE, Walker CF, Keating Jr JW. Cerebellar vermal atrophy in psychiatric patients. *Biol Psychiatry* 1982;17:569–83.
- Hilker R, Voges T, Weisenbach S, Kalbe E, Burghaus L, Ghaemi M, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. *J Cereb Blood Flow Metab* 2004;24:7–16.
- Honey G, Bullmore E. Human pharmacological MRI. *Trends Pharmacol Sci* 2004;25:366–74.
- Houk JC, Buckingham JT, Barto AG. Models of the cerebellum and motor learning. *Behav Brain Sci* 1996;19:368–83.
- Ikai Y, Takada M, Mizuno N. Single neurons in the ventral tegmental area that project to both the cerebral and cerebellar cortical areas by way of axon collaterals. *Neuroscience* 1994;61:925–34.
- Ikai Y, Takada M, Shinonaga Y, Mizuno N. Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei. *Neuroscience* 1992;51:719–28.
- Ildan F, Tuna M, Erman T, Gocer AI, Zeren M, Cetinalp E. The evaluation and comparison of cerebellar mutism in children and adults after posterior fossa surgery: report of two adult cases and review of the literature. *Acta Neurochir (Wien)* 2002;144:463–73.
- Jeong JS, Joung MK, Kim SY. Quantification of emotion by nonlinear analysis of the chaotic dynamics of electroencephalograms during perception of 1/f music. *Biol Cybern* 1998;78:217–25.
- Juslin PN, Laukka P. Communication of emotions in vocal expression and music performance: different channels, same code? *Psychol Bull* 2003;129:770–814.
- Kimura M, Minamimoto T, Matsumoto N, Hori Y. Monitoring and switching of cortico-basal ganglia loop functions by the thalamo-striatal system. *Neurosci Res* 2004;48:355–60.
- Klein RG, Abikoff H, Klass E, Ganeles D, Seese LM, Pollack S. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry* 1997;54:1073–80.
- Larsell O, Jansen J, Korneliusen H, Mugnaini E. The comparative anatomy and histology of the cerebellum: the human cerebellum, cerebellar connections, and cerebellar cortex. The University of Minnesota Press; 1972.
- Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumor resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 2000;123:1041–50.
- Li SJ, Biswal B, Li Z, Risinger R, Rainey C, Cho JK, et al. Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI. *Magn Reson Med* 2000;43:45–51.
- Linkenkaer-Hansen K, Nikouline VV, Palva JM, Ilmoniemi RJ. Long-range temporal correlations and scaling behavior in human brain oscillations. *J Neurosci* 2001;21:1370–7.
- Linkenkaer-Hansen K, Nikulin VV, Palva JM, Kaila K, Ilmoniemi RJ. Stimulus-induced change in long-range temporal correlations and scaling behaviour of sensorimotor oscillations. *Eur J Neurosci* 2004;19:203–11.
- Lo CC, Chou T, Penzel T, Scammell TE, Strecker RE, Stanley HE, et al. Common scale-invariant patterns of sleep-wake transitions across mammalian species. *Proc Natl Acad Sci USA* 2004;101:17545–8.

- Locascio JJ, Jennings PJ, Moore CI, Corkin S. Time series analysis in the time domain and resampling methods for studies of functional magnetic resonance brain imaging. *Hum Brain Mapp* 1997;5:168–93.
- Lokwan SJA, Overton PG, Berry MS, Clark D. Stimulation of the pedunculo-pontine tegmental nucleus in the rat produces burst firing in A9 dopaminergic neurons. *Neuroscience* 1999;92:245–54.
- Long C, Brown EN, Manoach D, Solo V. Spatiotemporal wavelet analysis for functional MRI. *Neuroimage* 2004;23:500–16.
- Lowen SB, Cash SS, Poo MM, Teich MC. Quantal neurotransmitter secretion rate exhibits fractal behavior. *J Neurosci* 1997;17:5666–77.
- Lowen SB, Liebovitch LS, White JA. Fractal ion-channel behavior generates fractal firing patterns in neuronal models. *Phys Rev E Stat Nonlin Soft Matter Phys* 1999;59:5970–80.
- Lowen SB, Teich MC. Fractal-based point processes. New York: Wiley; 2005.
- Maas LC, Anderson CM, Teicher MH, Renshaw PF. Hurst analysis of physiological fluctuations in functional MRI. In: Third international conference on functional mapping of the human brain, vol. NeuroImage 5. Copenhagen, Denmark; 1997a. p. S [<http://remfractal.mclean.org/hbm1997.pdf>].
- Maas LC, Frederick BD, Renshaw PF. Decoupled automated rotational and translational registration for functional MRI time series data: the DART registration algorithm. *Magn Reson Med* 1997b;37:131–9.
- Madison G. Properties of expressive variability patterns in music performances. *J New Music Res* 2000;29:335–56.
- Magill PJ, Sharott A, Bolam JP, Brown P. Brain state-dependency of coherent oscillatory activity in the cerebral cortex and basal ganglia of the rat. *J Neurophysiol* 2004;92:2122–36.
- Manaris B, Vaughan D, Wagner C, Romero J, Davis RB. Evolutionary music and the Zipf-Mandelbrot law: developing fitness functions for pleasant music applications of evolutionary computing (lecture notes in computer science). Berlin: Springer-Verlag Berlin; 2003. p. 522–34.
- Mandelbrot BB. Multifractals and 1/f noise: wild self-affinity in physics (1963–1976). Springer; 1999.
- Mandell AJ, Selz KA. Brainstem neuronal noise and neocortical resonance. *J Stat Phys* 1993;70:355–73.
- Melchitzky DS, Lewis DA. Tyrosine hydrolase- and dopamine transporter-immunoreactive axons in the primate cerebellum: evidence for a lobular- and laminar-specific dopamine innervation. *Neuropsychopharmacology* 2000;22:466–72.
- Melik-Musyan AB, Fanardjyan VV. Projections of the central cerebellar nuclei to the intralaminar thalamic nuclei in cats. *Neurophysiology* 1998;30:39–47.
- Mitina OV, Abraham FD. The use of fractals for the study of the psychology of perception: Psychophysics and personality factors, a brief report. *Int J Modern Phys C* 2003;14:01047–60.
- Miyazaki M, Nakajima Y, Kadota H, Chitose K, Ohtsuki T, Kudo K. 1/f-Type fluctuation in human visuomotor transformation. *Neuroreport* 2004;15:1133–6.
- Mori F, Nakajima K, Tachibana A, Takasu C, Mori M, Tsujimoto T, et al. Reactive and anticipatory control of posture and bipedal locomotion in a nonhuman primate. *Prog Brain Res* 2004a;143:191–8.
- Mori S, Matsui T, Mori F, Nakajima K, Matsuyama K. Instigation and control of treadmill locomotion in high decerebrate cats by stimulation of the hook bundle of Russell in the cerebellum. *Can J Physiol Pharmacol* 2000;78:945–57.
- Mori S, Nakajima K, Mori F, Matsuyama K. Integration of multiple motor segments for the elaboration of locomotion: role of the fastigial nucleus of the cerebellum. *Prog Brain Res* 2004b;143:341–51.
- Muller K, Lohmann G, Zysset S, von Cramon DY. Wavelet statistics of functional MRI data and the general linear model. *J Magn Reson Imaging* 2003;17:20–30.
- Musha T. 1/f fluctuations in biological systems. In: Meijer PHE, Mountain RD, Soulen RJ, editors. Sixth international conference on noise in physical systems; 1981. p. 143–6.
- Nagao S. Pontine nuclei-mediated cerebello-cerebral interactions and its functional role. *Cerebellum* 2004;3:11–5.
- Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K, et al. Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. *Neuroimage* 2000;12:623–39.
- Okumura T, Czarkowska-Bauch J, Nakajima K, Mori S. Fastigiotalamic projection in the cat: an anterograde BDA tracing study. *Abstr Soc Neurosci* 2001;27:293.8.
- Ornitz EM. Vestibular dysfunction in schizophrenia and childhood autism. *Compr Psychiatry* 1970;11:159–73.
- Paton JFR, Lanoce A, Sykes RM, Sebastiani L, Bagnoli P, Ghelarducci B, et al. Efferent connections of lobule-IX of the posterior cerebellar cortex in the rabbit—some functional considerations. *J Auton Nerv Syst* 1991;36:209–24.
- Paulin MG. The role of the cerebellum in motor control and perception. *Brain Behav Evol* 1993;41:39–50.
- Paulin MG. Neural representations of moving systems: cerebellum and cognition. *Int Rev Neurobiol* 1997;41:515–33.
- Poupard L, Sartene R, Wallet JC. Scaling behavior in beta-wave amplitude modulation and its relationship to alertness. *Biol Cybern* 2001;85:19–26.
- Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;189:369–79.
- Rainer G, Miller EK. Effects of visual experience on the representation of objects in the prefrontal cortex. *Neuron* 2000;27:179–89.
- Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 2000;123:1051–61.
- Ruggiero DA, Anwar M, Golanov EV, Reis DJ. The pedunculo-pontine tegmental nucleus issues collaterals to the fastigial nucleus and rostral ventrolateral reticular nucleus in the rat. *Brain Res* 1997;760:272–6.
- Ruskin DN, Bergstrom DA, Kaneoke Y, Patel BN, Twery MJ, Walters JR. Multisecond oscillations in firing rate in the basal ganglia: robust modulation by dopamine receptor activation and anesthesia. *J Neurophysiol* 1999;81:2046–55.
- Ruskin DN, Bergstrom DA, Shenker A, Freeman LE, Baek D, Walters JR. Drugs used in the treatment of attention-deficit/hyperactivity disorder affect postsynaptic firing rate and oscillation without preferential dopamine autoreceptor action. *Biol Psychiatry* 2001;49:340–50.
- Ruskin DN, Bergstrom DA, Tierney PL, Walters JR. Correlated multisecond oscillations in firing rate in the basal ganglia: modulation by dopamine and the subthalamic nucleus. *Neuroscience* 2003;117:427–38.
- Ruttimann UE, Unser M, Rawlings RR, Rio D, Ramsey NF, Mattay VS, et al. Statistical analysis of functional MRI data in the wavelet domain. *IEEE Trans Med Imaging* 1998;17:142–54.
- Schmahmann JD. The role of the cerebellum in affect and psychosis. *J Neurolinguistics* 2000;13:189–214.
- Selz KA, Mandell AJ. Bernoulli partition-equivalence of intermittent neuronal discharge patterns. *Int J Bifurcat Chaos* 1991;1:717–22.
- Shimizu Y, Barth M, Windischberger C, Moser E, Thurner S. Wavelet-based multifractal analysis of fMRI time series. *Neuroimage* 2004;22:1195–202.
- Snider RS, Maiti A, Snider SR. Cerebellar pathways to ventral midbrain and nigra. *Exp Neurol* 1976;53:714–28.
- Snider SR, Snider RS. Structural and functional relationships between cerebellum and catecholamine systems: an overview. *Exp Brain Res* 1982(Suppl. 6).
- Stam CJ, de Bruin EA. Scale-free dynamics of global functional connectivity in the human brain. *Hum Brain Mapp* 2004;22:97–109.
- Stein JF, Aziz TZ. Does imbalance between basal ganglia and cerebellar outputs cause movement disorders? *Curr Opin Neurol* 1999;12:667–9.
- Steinlin M, Imfeld S, Zulauf P, Boltshauser E, Lovblad KO, Luthy AR, et al. Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. *Brain* 2003;126:1998–2008.
- Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–93.
- Takehara T, Ochiai F, Suzuki N. Fractals in emotional facial expression recognition. *Fractals* 2002;10:47–52.
- Teich MC, Lowen SB. Fractal patterns in auditory nerve-spike trains. *IEEE Eng Med Biol Mag* 1994;13:197–202.
- Teich MC, Turcott RG, Siegel RM. Temporal correlation in cat striate-cortex neural spike trains. *IEEE Eng Med Biol Mag* 1996;15:79–87.

- Tellerman K, Astrow A, Fahn S, Snider SR, Snider RS, Glassgold JM. Cerebellar control of catecholaminergic activities: implications for drug therapy of movement disorders. *Int J Neurol* 1979;13:135–55.
- Thurner S, Lowen SB, Feurstein MC, Heneghan C, Feichtinger HG, Teich MC. Analysis, synthesis, and estimation of fractal-rate stochastic point processes. *Fractals* 1997;5:565–95.
- Tuller B, Ding M, Kelso JA. Fractal timing of verbal transforms. *Perception* 1997;26:913–28.
- von Tscharner V, Thulborn KR. Specified-resolution wavelet analysis of activation patterns from BOLD contrast fMRI. *IEEE Trans Med Imaging* 2001;20:704–14.
- Voss RF, Clarke J. 1/f-noise in music and speech. *Nature* 1975;258:317–8.
- Wagenmakers EJ, Farrell S, Ratcliff R. Estimation and interpretation of 1/f(alpha) noise in human cognition. *Psychon Bull Rev* 2004;11:579–615.
- Walters JR, Bergstrom DA, Molnar LR, Freeman LE, Ruskin DN. Effects of dopamine receptor stimulation on basal ganglia activity. In: Ilinsky KK, Ilinsky IA, editors. International symposium “basal ganglia and thalamus in health and in motor disorders”. New York, Moscow: Kluwer Academic/Plenum Publishers; 2001. p. 135–50.
- Ward LM. *Dynamical cognitive science*. Cambridge, MA: The MIT Press; 2002.
- Wing A, Daffertshofer A, Pressing J. Multiple time scales in serial production of force: a tutorial on power spectral analysis of motor variability. *Hum Mov Sci* 2004;23(5):569–90.
- Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, et al. A general statistical analysis for fMRI data. *Neuroimage* 2002;15:1–15.
- Yamamoto T, Nishimura Y, Matsuura T, Shibuya H, Lin M, Asahara T. Cerebellar activation of cortical motor regions: comparisons across mammals brain mechanisms for the integration of posture and movement. *Prog Brain Res* 2004;143:309–17.
- Zhou YH, Gao JB, White KD, Merk I, Yao K. Perceptual dominance time distributions in multistable visual perception. *Biol Cybern* 2004;90:256–63.