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Dynamics of Pain: Fractal Dimension of Temporal Variability of Spontaneous Pain Differentiates Between Pain States

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Foss, Jennifer M., A. Vania Apkarian, and Dante R. Chialvo. Dynamics of pain: fractal dimension of temporal variability of spontaneous pain differentiates between pain states. *J Neurophysiol* 95: 730–736, 2006. First published November 9, 2005; doi:10.1152/jn.00768.2005. Spontaneous pain is a common complaint in chronic pain conditions. However, its properties have not been explored. Here we study temporal properties of spontaneous pain. We examine time variability of fluctuations of spontaneous pain in patients suffering from chronic back pain and chronic postherpetic neuropathy and contrast properties of these ratings to normal subjects' ratings of either acute thermal painful stimuli or of imagined back pain. Subjects are instructed to continuously rate their subjective assessment of the intensity of pain over a 6- to 12-min period. We observe that the fluctuations of spontaneous pain do not possess stable mean or variance, implying that these time series can be better characterized by fractal analysis. To this end, we apply time and frequency domain techniques to characterize variability of pain ratings with a single parameter: fractal dimension, *D*. We demonstrate that the majority of ratings of spontaneous pain by the patients have fractal properties, namely they show a power law relationship between variability and time-scale length; *D* is distinct between types of chronic pain, and from ratings of thermal stimulation or of imagined pain; and there is a correspondence between *D* for pain ratings and *D* for brain activity, in chronic back pain patients using fMRI. These results show that measures of variability of spontaneous pain differentiate between chronic pain conditions, and thus may have mechanistic and clinical utility.

INTRODUCTION

Chronic pain, by definition, is a state of continuous suffering from ongoing pain, sustained for long durations past healing from the injury that initially may have incited the pain (operationally defined as pain that persists for >6 mo). Besides spontaneous pain, chronic pain patients also exhibit various combinations of mechanical-, heat-, or cold-stimulus-evoked increased pain sensitivities (allodynia and hyperalgesia of various types) as well as other somatosensory abnormalities (Birklein et al. 2000; Clauw et al. 1999; Dworkin 2002). Approximately 10% of adults have severe chronic pain (Harstall and Ospina 2003), and back pain is the largest contributor to this population (Cavanaugh and Weinstein 1994; Deyo 1998).

Spontaneous pain is commonly observed in patients with chronic pain, and its presence is a primary reason for subjects seeking medical care. Clinicians agree that the incidence of spontaneous pain is very high in chronic pain (B. Galer and R. Dworkin, personal communication); yet we find few reports documenting this incidence, ranging from 77 to 100% perhaps varying by type (Birklein et al. 2000; Sindrup et al. 1999; Tasker et al. 1991). Traditionally, clinical pain conditions have been contrasted by questionnaires (Melzack and Katz 1999). This approach, however, is not adequate to study time variability (dynamical properties). Therefore to our knowledge, temporal characteristics of spontaneous pain have remained unexplored.

Unlike other sensory modalities, fluctuations in intensity of pain are slow and highly salient, and as a result patients (Apkarian et al. 2001), and normal subjects (Apkarian et al. 1999; Hardy et al. 1968; Koyama et al. 2004; LaMotte et al. 1984; Strigo et al. 2002), can readily indicate their level of pain on a continuous time scale. Empirical observations in our lab (Apkarian 1999; Apkarian et al. 2001) demonstrate that intensity of chronic pain fluctuates spontaneously, and subjects instructed to indicate their pain intensity on a continuous scale comply readily. This approach allows gathering information about ongoing perceived pain over time and enables investigation of underlying dynamical processes. Here we analyze time series of pain ratings from patients with back pain, postherpetic neuropathy (PHN), and from normal subjects. We observe that the fluctuations of spontaneous pain seem random and lack sinusoidal or Gaussian properties, which implies that they are better characterized by studying their fractal properties.

The concept of a fractal is usually associated with irregular geometric objects that show self-similarity (Bassingthwaighte et al. 1994; Feder 1988; Mandelbrot 1982; Peitgen et al. 1992). Fractal objects are made of subunits (and sub-sub-units, etc.) that look like the structure of the overall object. In theoretical models, this property remains true at all length scales, and as a result they are described as scale-free. Real objects, however, are bounded by their size, which limits the range within which scale-free characteristics apply. Many complicated objects in nature, such as branching trees, corrugated coastlines, and shapes of clouds, are fractal. Anatomical structures also display fractal-like geometries, for example, arterial and venous trees, tracheobronchial tree, and dendritic branchings of neurons (Bassingthwaighte et al. 1994; Goldberger 1996; Goldberger et al. 2002; Kruass et al. 1993). The fractal concept can be applied to complex time varying processes that lack a single scale of time in analogy to fractal geometries that lack a single scale of length. Heart rate variability is perhaps the best example (Ivanov et al. 1999) with many clinical applications. Cortical neural activity has also been studied as fractals (Linkenkaer-Hansen et al. 2001) as well as natural behaviors:

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errors in timing of repetitive motions (Chen et al. 1997), locomotion (Hausdorff et al. 1996), swaying during standing (Collins and De Luca 1995), fluctuations in psychological perceptions (Kniffki et al. 1993), and perceived identity of heard syllables (Ding et al. 1995). Fractal time series generate irregular fluctuations across multiple time scales, analogous to scale-free objects that branch with a fixed ratio across multiple length scales (Goldberger et al. 2002). Fractal objects and fractal time series are characterized by their fractional dimension, *D*. Because ratings of spontaneous pain resemble fractal time series, we systematically study these properties. We test the hypothesis that *D* can be used to characterize temporal variability of spontaneous pain and can differentiate between PHN and back pain spontaneous pain ratings. To demonstrate that *D* reflects brain neural processing, we compare this value in fMRI data across different brain regions, and test the hypothesis that *D* derived from brain regions related to pain should be more similar to the *D* derived from the rating of spontaneous pain.

METHODS

Participants

Eleven back pain (2 males, 9 females; mean age, 37 yr), 14 PHN (7 males, 7 females; mean age, 62 yr), and 23 normal healthy subjects (15 females, 8 males; mean age, 34 yr) participated in the study. They gave written, informed consent to participate, according to the guidelines of the Institutional Review Board at Northwestern University. Many of these subjects were participants in other brain-imaging studies in the lab. Here we mainly examine the temporal fluctuations of their ratings. In five of the back pain patients, we also examine the relationship between brain activity and pain ratings. The fMRI data are derived from a larger data set (Baliki et al. 2004). Back pain and PHN patients were recruited from Northwestern University clinics and newspaper advertisement. Patients with back pain fulfilled IASP criteria (Merskey and Bogduk 1994) and were diagnosed in accordance to recent guidelines (Deyo and Weinstein 2001). Briefly, all back pain patients had unrelenting pain for >1 yr, primarily localized to the lumbosacral region, with or without pain radiating to the leg. We did not distinguish between various etiologies of back pain. Patients with PHN fulfilled IASP criteria (Merskey and Bogduk 1994) and were diagnosed based on standard guidelines (Dworkin and Portenoy 1996). They all had pain along the course of a nerve after the characteristic acute segmental rash of herpes zoster for >3 mo. All patients had ongoing pain, and most PHN patients also had touch-evoked pain (allodynia). Patients refrained from using analgesics for 24 h prior to their pain rating sessions.

Finger-span device for monitoring fluctuations of pain

Subjects indicate their level of pain continuously through a linear potentiometer device that is attached to the thumb and index finger of the dominant hand. Voltage output from the finger device is collected and calibrated by a computer running the software LabView (National Instruments, Austin, TX) (Apkarian et al. 2001). Subjects are seated in front of a computer monitor, which displays the extent of their finger span by a colored bar (*y* axis has an intensity scale of 0–100), providing visual feedback of their rating. Ratings are sampled at 2.5 Hz. This is an analog proprioceptive scale used by others statically in the past (Ahlquist et al. 1984). We have presented preliminary data indicating that in normal subjects such continuous ratings of thermal painful stimuli show a robust relationship between stimulus and pain ratings [$r^2 = 0.8$ between peak temperature on the skin, varying from 44 to 52°C, and peak pain ratings (Baliki et al. 2003)].

Experimental paradigm

Subjects are first trained on the use of the finger-span device. To this end, they are presented with a moving bar on the computer monitor that varies in time and instructed to rate its length with the finger-span device, over a 5-min trial. Only subjects able to follow the bar length at a consistency level that results in correlation coefficient $r > 0.75$ between rating and bar fluctuations are included in the study, within two attempts. More than 90% of subjects achieve this criterion. Patients are then instructed to rate the fluctuations of their own ongoing pain, usually for a period of 6–12 min. They are instructed that maximum thumb-finger span should be used to indicate maximum imaginable intensity of pain (level 100) while thumb and finger touching should indicate absence of pain (level 0). Healthy normal volunteers are instructed to imagine back pain and rate its fluctuations in time. A separate group of healthy subjects ($n = 6$, 2 sessions per subject) rate acute thermal stimulus pain with the finger-span device. Eight noxious thermal stimuli ranging in duration from 10 to 30 s were applied to the lower back (baseline: 38°C, peak temperatures: 46 and 48°C, rise rate: 20°C) via a contact probe (1 × 1.5 cm Peltier device). Durations and intensities of thermal stimuli as well as inter-stimulus intervals (range: 30–60 s, mean = 55 s) were presented in a fixed pseudorandom fashion.

Analysis of ratings

Fractal dimension, *D*, of the time series was determined with two independent approaches: rescaled range analysis and calculation of power spectra. Each approach has its unique advantages and assumptions. Both are well-established techniques and are only briefly described here (Bassingthwaighte et al. 1994; Feder 1988; Mandelbrot 1982; Peitgen et al. 1992). Rescaled range analysis measures the extent to which the range *R* (i.e., maximum minus minimum value) spanned during a fluctuating trajectory depends on the number of steps or time in the trajectory, τ. A characteristic of scale free trajectories is that *R* and τ obey a power law, i.e., $R \propto \tau^{\alpha}$. To empirically compute α, the scaling exponent for a given time series of length *N* samples, we determine the average *R* for different length scale τ subsets of the original sample. τ is varied form the largest possible, when $\tau = N$, to $\tau = 8$ samples. We find the length scale, *R,* by taking the distance between the maximum and minimum values of the sub-series after detrending. We then scale *R* by the SD, *S,* of the step size of this sub-series because series with larger step sizes will naturally have a larger length scale regardless of their scaling properties. We find the average value of *R*/*S* for all sub-series at each time scale (for $\tau = N$, there is only 1 sub-series, for $\tau = N/2$, there are 2 sub-series, etc.) and use them to create the "scaling plot," $\log(R/S)$ as a function of $\log(\tau)$. If the time series exhibits scale-free fluctuations, this relationship is linear with slope α. The fractal dimension *D*, is related to the scaling exponent by the relation $D = 2 - \alpha$ (Feder 1988).

For a given time varying signal, the power spectrum measures power (energy per unit time) of the signal at each frequency. Power spectra were computed with Welch's averaged periodogram method, in Matlab. Time series were first truncated to length 2,048 for PHN, imagined pain and thermal pain, and 1,024 for back pain, detrended, and then windowed with a Hanning window. The power as a function of frequency is plotted on a log-log scale. The fractal dimension *D*, is related to the slope of the spectrum, β, such that $D = 2 + ¼\beta$ (Feder 1988}.

In most examples of fractal behavior, the fluctuation is scale free only in a limited scale range. For each time series therefore, we empirically determine the scaling region as the span of τ or frequency within which the series exhibits scale-free behavior. Typically, the spectra became flatter outside that range. Based on comprehensive inspection of the spectra and scaling plots, initial scaling ranges were established for each data type. For each individual spectrum or scaling

plot, these ranges were then incrementally reduced until a region of maximal slope and maximal regression coefficient was identified. This region was then used to compute the scaling exponent.

Functional imaging and analysis

DATA ACQUISITION. Functional brain images were acquired on a 1.5 T Siemens Vision MRI scanner. Standard clinical quadrature head coil is used to image the entire brain. Functional MRI scans are performed using echo planar gradient-echo acquisition sequence (repetition time, 3.5 s; echo time, 40 ms; matrix, 64 × 64; field of view, 240 mm; flip angle, 90°; 4 mm thick slices with no gap). During each fMRI scan, 124 brain volumes were acquired over ~7 min. A vacuum beanbag was used to immobilize the head.

Experimental paradigm

Five back pain patients were used in fMRI to determine the correspondence between brain activity scaling properties and the scaling properties of their ratings. The finger-span device was implemented in the scanner just as it is used in the psychophysical testing outside the scanner. The computer screen where the subject views his finger-span was back projected into the scanner to provide the participant with continuous visual feedback of the ratings. Just prior to starting an fMRI scan, subjects were instructed to concentrate on his/her ongoing pain and rate it with the finger-span device for the duration of the scan. A trigger pulse from the scanner was used to collect the ratings for every slice acquisition.

In visual-control scans, subjects were instructed to follow as closely as possible fluctuations of a bar projected on a screen in time. This visual tracking provides an adequate visual-motor control because it is similar to the pain rating finger-span task in its cognitive demand, with the important difference being that now the finger movement (i.e., variations in magnitude) is correlated with a visual input rather than pain. Unbeknown to the subjects, the time curve of the bar mimicked the variability that the subjects reported in earlier scans for spontaneous back pain. In addition to the visual control, a surrogate-control was generated by inverting in time the recorded pain rating. This procedure preserves all statistical properties of the original ratings, but scrambles the relationship between the ratings and the actual pain fluctuations, thus controlling for nonspecific activations.

fMRI data analysis

Preprocessing and data analysis were performed using FEAT software (FMRIB Expert Analysis Tool; http://www.fmrib.ox.ac.uk/fsl, Oxford University, UK). The first four volumes of each run were discarded. Preprocessing included: slice acquisition time correction; head motion correction (Jenkinson and Smith 2001); spatial smoothing (Gaussian kernel: 5 mm FWHM); and a high-pass filter (cutoff, 100 s). A linear regression model was used to describe the data. The covariate of interest was the time series of pain ratings convolved with a gamma-variate hemodynamic response function (width, 3 s; mean lag, 6 s). A covariate of no interest was used to further correct head-motion artifacts derived from the motion correction procedure during fMRI data preprocessing. Because patients with pain invariably move during fMRI scans, we use the covariate approach to further diminish the contribution of head motion to fMRI activity. This ensures that brain regions that show activity are not contaminated by head motion at the cost of decreasing sensitivity to detect activity in areas where the signal may be reduced due to the covariate correction (for further discussion see http://www.fmrib.ox.ac.uk/fsl). The fMRI signal was linearly modeled on a voxel by voxel basis with local autocorrelation correction (44).

Given our larger study (where fMRI study procedures are presented in more detail) (Baliki et al. 2002; unpublished data), we extracted time curves from four brain regions. Fractal dimensions for these time curves were correlated with fractal dimensions of corresponding finger-span time curves. We use correlation as a metric for similarity since an exact relationship is not expected between D for brain activity and D for ratings, given the extensive transformations that fMRI data and the vector for which activity is analyzed undergo and, given that fMRI data are contaminated with background noise arising from multiple independent sources. We test the hypothesis that brain regions involved in pain perception should have more similar D-values to the ratings than regions that are not related to pain. Four brain regions are selected, based on the results of Baliki et al. (2002), two areas activated for spontaneous pain and two not related to pain: medial prefrontal cortex at 18, 60, 12 (*x, y, z,* in mm in standard brain space, MNI coordinates www.mrc-cbu.cam.ac.uk/Imaging/, www.bic.mni.mcgill.ca/cgi/), and anterior cingulate at the level of the genu at 10, 22, 28 are the areas activated with spontaneous pain; while right and left temporal cortex at 56, −40, 10 and −54, −44, −8 are not activated with spontaneous pain. In all five back pain patients, we extracted the time-series of brain activity only at these four locations and calculated their fractal dimensions. These were then correlated with pain rating D values.

The brain regions of interest were derived from the analysis for the larger group of back pain patients (Baliki et al. 2002), where brain activity related to back pain was determined from the average activation determined for spontaneous back pain ratings from which visual-control related activity and surrogate-control related activity were subtracted. The primary brain activity that survived was located in the medial prefrontal cortex, extending into the rostral anterior cingulate, at the level of the genu. At a higher level of analysis, individual subject brain activations were covaried with the overall intensity of pain the patients reported at the day of scan. The peaks identified from this analysis are the coordinates used for regions specifically involved in spontaneous pain. The two peaks, located in medial prefrontal cortex and rostral anterior cingulate at the genu, show a highly significant correlation, $r > 0.9$, $P < 10^{-4}$, between brain activity and pain intensity.

RESULTS

Scale-free pain ratings

Examination of the time series generated by the patients indicates a wide random variability with no obvious sinusoidal excursions (Fig. 1, *A* and *B*). In contrast, thermal stimulus ratings are "pulse-like" remaining relatively constant in between the presentation of the painful stimulus (Fig. 1*D*).

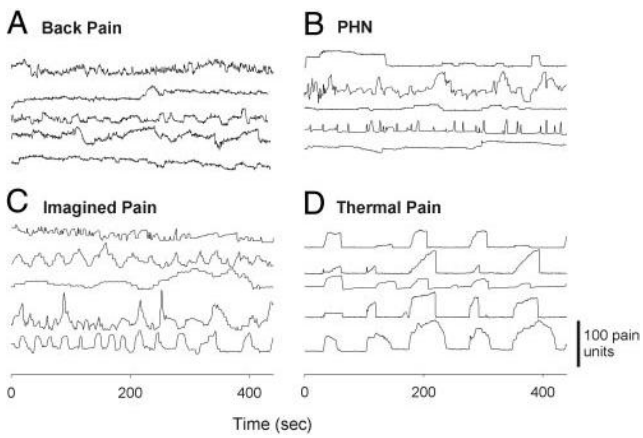

FIG. 1. Example pain ratings. Five example ratings from back pain (*A*) and postherpetic neuropathy (PHN) (*B*) patients, healthy subject imagining back pain (*C*), and healthy subjects in response to thermal stimulation to the lower back (*D*). Pain ratings (vertically shifted for clarity) are plotted at the same scale (shown by the calibration bar in the *bottom right*).

Imagined pain ratings (Fig. 1*C*) seem intermediate between thermal pain and patients' ratings in the amount of fluctuations. Also observe that the time series for the patients look rougher, that is, they show more noncyclic fluctuations, or look noisier, than the curves for the normal subjects. These qualitative impressions can be formalized by computing and comparing their fractal dimension *D*.

Fractal time series exhibit specific properties illustrated in Fig. 2 for pain ratings. Statistical self-similarity at different magnifications is one fundamental property. This is shown for a back pain time series (Fig. 2*A*), and contrasted to rating of thermal stimulation (Fig. 2*B*) where the magnified plots are dissimilar. A related property is the fact that mean and SD of fractal time series do not converge to a fixed value (Fig. 2, *C* and *D*) as more data are included in the calculations. It is typical, as seen in the figure that the mean continues to drift and the SD increases as a power law with an exponent given by its fractal dimension. Shuffling the time series destroys the fractal properties and renders data that behave as a Gaussian distributed sample with well-defined mean and SD.

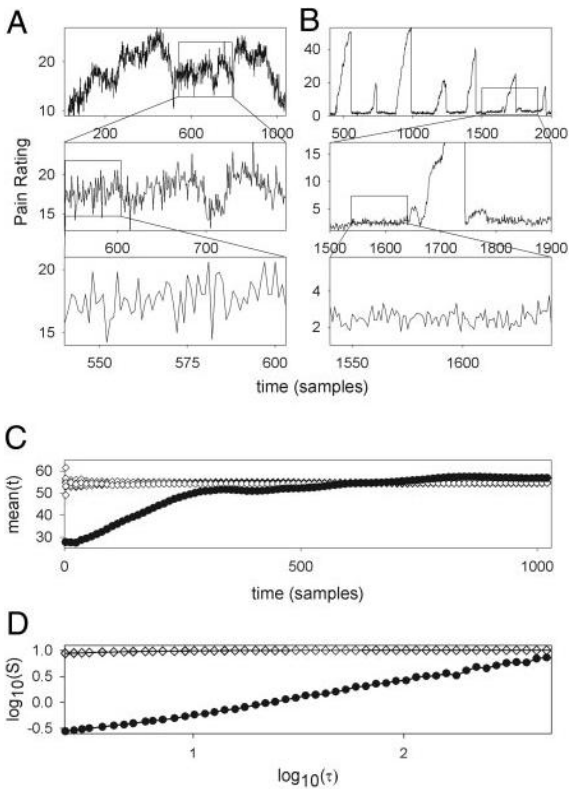

FIG. 2. Properties of fractal pain ratings. (*A*) Statistical self-similarity of a fractal pain rating. A back pain patient's pain rating as a function of time in samples (1 sample = 400 ms) is shown at three different scales. The general time variability pattern is self-similar at all three magnifications. As the horizontal scale is reduced by a factor of 4, the vertical scale is reduced by a factor of 4^{α}, where $\alpha = 0.34$, indicating power law scaling with fractal dimension $D = 2 - 0.34$. The boxes on each plot indicate the ranges in the plot below. (Upper plot has scale 1000 x 18; middle plot has scale 1000*(1/4) x 18*(1/4)$^{\alpha}$, and bottom plot has scale 1000*(1/16) x 18*(1/16)$^{\alpha}$). (*B*) Pain rating from thermal stimulation. Magnifying a rating that is minimally fractal fails to show self-similarity. Scaled as in A, with $\alpha = 0.85$. Note that vertical range is extremely dependent on exact horizontal location. (*C*) Mean does not converge for fractal pain ratings. Mean of successively longer samples of the pain rating time series used in A (solid curve). Open symbols show the means of 10 randomly shuffled surrogates, which quickly converge to a mean. (*D*) Excess of variance for fractal pain ratings. Average SD, S, for all nonoverlapping consecutive sub-samples of size τ as a function of τ, for time series in A (solid symbols). Open symbols show the results of same computation for 10 surrogates created by randomly shuffling the points of the original data series (surrogate data are so similar that they fall on top of each other). The fractal pain rating variance does not converge, but continues to increase by a power law as sample length increases (exponent is 0.64). The surrogates, on the other hand, quickly converge to a fixed variance or SD.

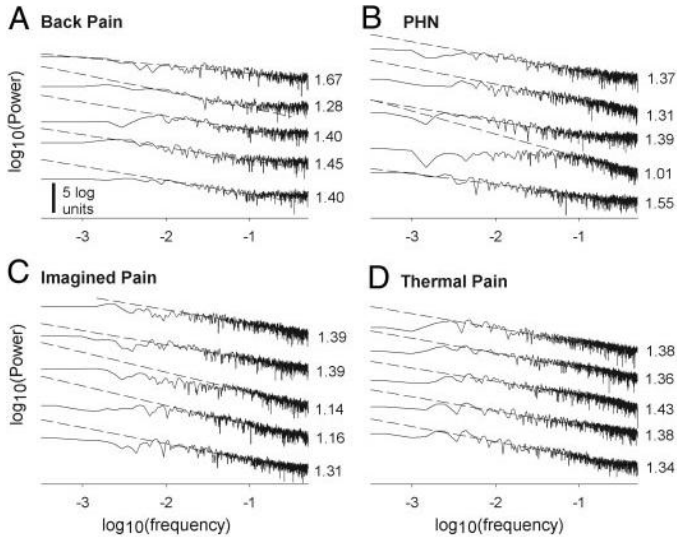

FIG. 3. Power spectra for the same ratings shown in Fig. 1, presented in the same vertical order. Frequency units are in cycles per sample, plotted in log scale. Regression fit lines over the chosen scaling region are also shown (dashed lines). Numbers by each spectrum indicate the fractal dimension *D* derived from the slope β of the linear fit of the spectrum.

We calculated fractal dimension of the ratings from power spectra and rescaled range analysis. Figures 3 and 4 show power spectrum analysis and rescaled range analysis for the corresponding ratings shown in Fig. 1. Resultant *D* values are similar between the two methods of measurement and tend to be higher in the patients. These figures illustrate the range of scales at which power law scaling is exhibited by the two methods. These scale ranges generally correspond between the

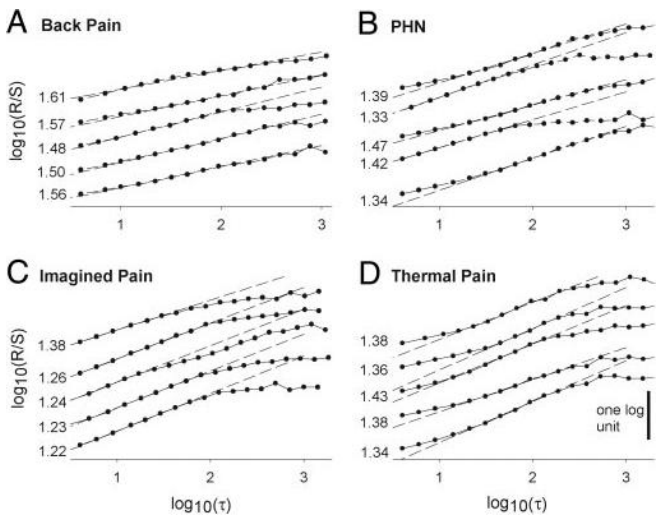

FIG. 4. Rescale range analysis plots for the same time series shown in Fig. 1, presented in the same vertical order. The mean ratio of the range (*R*) to the SD (*S*) at different sample sizes (τ) is shown in log-log plots. Regression lines (dashed lines) were computed from the points in the scaling region. Numbers on each curve indicate fractal dimension *D* derived from the slope of the (R/S) points in the scaling region. τ is in units of samples.

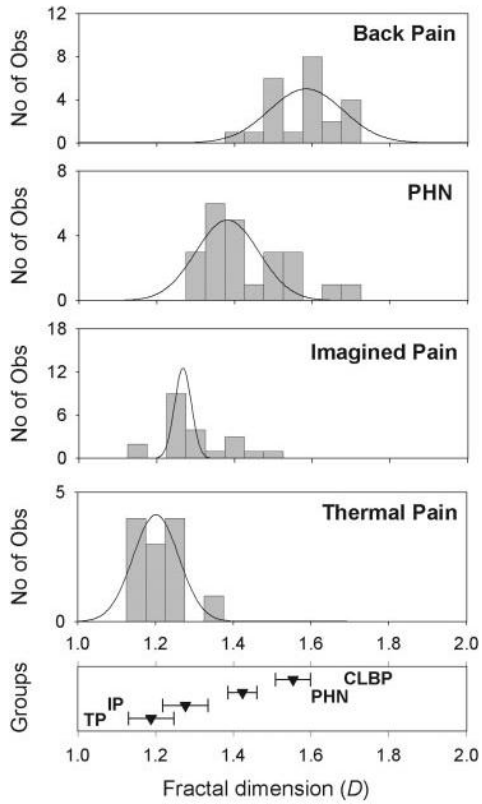

FIG. 5. Distribution of fractal dimension, D, for chronic low back pain (CLBP) and PHN patients, and for normal healthy subjects imagining pain (IP) or rating thermal pain (TP). Spread of D-values and fitted normal distribution for each group is displayed. Bottom panel compares the four data sets by displaying their mean (triangles) and 99% confidence intervals (whiskers). ANOVA between the four groups was highly significant ($P < 10^{-7}$).

two methods, and seem to be larger for patients' rating and smallest for thermal pain ratings (more obvious in time domain, Fig. 4*D*).

Figure 5 shows the distribution of D values for the four groups studied, based on the rescaled range analysis. In back pain patients, average fractal dimension $D = 1.55 \pm 0.08$ (mean $\pm$ SD, $n = 23$); whereas for PHN patients $D = 1.42 \pm 0.11$ ($n = 58$). For ratings in healthy subjects who imagined ongoing back pain and reported its fluctuations $D = 1.28 \pm 0.09$ ($n = 21$) and for healthy subjects ratings of thermal pain $D = 1.19 \pm 0.07$ ($n = 12$; with mean coefficient of the fit $r^2 > 0.99$ for all 4 groups). One-way ANOVA showed a highly significant difference of D across the four groups (back pain, PHN, imagined pain, thermal pain), $F(3,110) = 52.6$, $P < 10^{-6}$. All pairwise planned-comparisons also showed significant differences, with the smallest difference between imagined pain and thermal pain ($F = 8.2$, $P < 0.007$; all other pairwise comparisons had $P < 10^{-6}$).

To test the robustness of our results we compare dimensions determined by the two methods (Rangarajan and Ding 2000). We examine the difference, ΔD determined in time domain by rescale range analysis (D_t) minus D determined in frequency domain by power spectrum (D_f), $D_t - D_f$. The distance from zero of the distribution of this value is used as a measure of confidence regarding fractal properties of the ratings. When a cutoff of two SDs is used, only 5 of the ratings fall outside this threshold, and the group means and SDs remain unchanged. When a cutoff of 1 SD is used, then 10 of the 12 thermal pain ratings are excluded, but >80% of the other ratings remain below the cutoff. Moreover, the D values for the three groups, back pain ($D = 1.53 \pm 0.07$, $n = 16$), PHN ($D = 1.42 \pm 0.10$, $n = 44$), and imagined pain ($D = 1.26 \pm 0.10$, $n = 15$), remain essentially unchanged and statistically significantly different from each other.

Correspondence of scaling properties between pain ratings and brain activity

To test the hypothesis that brain activity in regions involved in pain perception are involved in the generation of fractal ratings, we tested the similarity of fractal dimension D of fMRI brain activity time series to pain ratings. D values of fMRI activity in medial prefrontal cortex and in cingulate at the level of the genu were strongly correlated to pain rating fractal dimensions ($r = 0.96$, $P = 0.008$; and $r = 0.92$, $P = 0.02$, respectively). In contrast, D values of fMRI activity in temporal cortical regions were not related to D of pain ratings ($r = 0.37$, $P = 0.54$; and $r = 0.16$, $P = 0.79$). Medial prefrontal cortex and cingulate at the level of the genu are brain regions activated with spontaneous pain in back pain patients, whereas activity in the temporal cortical areas are not related to fluctuations in back pain (Baliki et al. 2002). Therefore this analysis demonstrates correspondence between D for brain activity in regions involved in ongoing pain of back pain and D for rating of pain.

DISCUSSION

This study is the first to examine temporal properties of spontaneous pain. We found that subjective reports of fluctuations of ongoing pain in chronic back pain and PHN possess dynamic properties that can be characterized with a single parameter. This parameter, fractal dimension D, indicates that pain ratings are scale free. That is they have fluctuations at all time scales within the scaling range studied (Feder 1988). We also show that D is distinct for the two chronic pain conditions studied here and cannot be mimicked by normal subjects imagining pain. In back pain patients where we examined D for pain ratings and for brain activity, we observe a correspondence between them only for brain regions involved in perception of ongoing back pain (Baliki et al. 2002), implying that the scale-free properties of pain variability are a manifestation of neuronal activity involved in pain perception. These results therefore demonstrate that time variability of ongoing pain may be used as a metric for documenting the presence and studying the properties of chronic pain.

Time varying signals have a Euclidean dimension (E) of 1. When they fluctuate nonperiodically they can have fractal dimensions spanning between Euclidean dimensions 1–2. The more rough their fluctuations the higher their fractal dimension. A pure random walk, formed by up-down Gaussian independent steps, would result in $D = 1.5$. Time series are said to be "persistent" when the trajectory during a time period has a higher probability of going in the same direction as in the previous period. This persistency results in values of $1.0 < D < 1.5$. On the other hand, they are called "anti-persistent" when a subsequent period is more likely to be in the opposite direction than in the preceding one, resulting in $1.5 < D < 2.0$

(Feder 1988; Mandelbrot 1982). Thus anti-persistent processes can be thought of as more space filling than persistent processes. It is clear that as time passes, persistent processes on the average make larger excursions than anti-persistent ones because of the increased tendency to go in the same direction. There is a large spread in D computed for different pain patients. However, back pain patients mainly show anti-persistence, meaning that on the average more intense pain is followed by weaker pain. PHN patients instead show both anti-persistent and persistent time series. Healthy subjects attempting to imagine fluctuations of pain generate the most persistent ratings, suggesting that normal subjects assume that pain does not undergo much fluctuation, and these ratings are most similar to thermal pain ratings, which are also the least fractal ratings. Given the extensive peripheral and central re-organization associated with chronic pain (Woolf and Salter 2000), the properties of fluctuations in ongoing pain most likely reflect the interaction between peripheral and central processes inducing the pain and the coping mechanisms that patients develop to deal best with the condition (including use of analgesics and other medications). From this viewpoint, the extent to which a given pain rating is anti-persistent may be interpreted as reflecting the ability of the patient to cope with the condition. One obvious candidate system that can control this parameter is the integrity of descending modulatory pathways, which provides supraspinal feedback control on spinal cord nociceptive neurons and limits nociceptive information transmission cephalad (Fields and Basbaum 1999; Ren and Dubner 2002). Relative potentiation of descending inhibitory and facilitatory pathways in different clinical pain conditions would naturally lead to pain ratings with distinct persistent or anti-persistent scaling properties. Alternative sources of different patterns of fluctuations may be due to the firing characteristics of nociceptive afferents. It may be possible to distinguish between central modulatory fluctuations and peripheral contributions by controlling the pain condition by peripherally or centrally acting analgesics.

It is worthwhile to note that we have been using subjective pain ratings in various chronic pain conditions as a tool to study brain activity (Apkarian 1999; Apkarian et al. 2001). To date, we have asked >100 such patients to rate their ongoing pain and the vast majority readily comply. Only rarely, in $<5\%$, do patients insist that their pain is invariant over the time scale of a few minutes. It is also important to note that the ratings in normal subjects who attempt to imagine pain are strongly dependent on the instruction set, and subtle changes in these instructions may produce different scaling exponents. We reasoned that because back pain is the most common form of sustained pain healthy subjects may experience (Deyo and Weinstein 2001), imagining back pain by healthy subjects had the best chance of mimicking pain ratings in patients. The volunteers tested readily complied with the instruction and yet resulted in ratings that do not match that of back pain patients. Pain ratings were performed after subjects were off medications for 24 h. We do not know if this was critical to the observed results. The influence of analgesics on ratings of spontaneous pain remains to be systematically studied.

Our use of pain ratings in fMRI studies (Apkarian 1999; Apkarian et al. 2001) provides neuronal activity based validation of the approach. It should be mentioned that fractal fluctuations of fMRI signal has been noted by other groups (Bullmore et al. 2004; Zarahn et al. 1997). Here we examined scaling properties of brain activity for regions best related to the pain ratings and found a tight relationship for D between pain ratings and brain activity only for brain regions involved in spontaneous back pain. This is evidence for brain neural activity involved in pain perception being reflected in the fractal patterns of ratings generated by the patients. Still, the number of subjects included in this analysis is small. A larger study remains to be performed to reveal the relationships between D across brain areas and pain ratings.

The list of clinically significant pain conditions is long, and we do not know the extent to which fractal properties can differentiate between them. Still the approach could be useful in disentangling malingerers from real chronic pain patients as well as in assessing efficacy of therapies or medications. We have only studied pain intensity ratings. One could apply the same methodology to examine other dimensions of ongoing pain, such as fluctuations in unpleasantness (affective dimension). It is possible that the latter may reveal different temporal dynamical properties. Moreover, we have only studied fractal properties in the scale of seconds to minutes. The current analyses suggest that power law scaling may be preserved for much longer times (clinically more significant scales of weeks and months), but this remains to be demonstrated. If power law scaling is preserved at longer times, then the commonly used metrics for determining pain levels become questionable because they are all based on the assumption that pain intensity is a Gaussian process. Thus it is imperative that temporal variability of spontaneous pain be documented at larger time scales.

In summary, fractal analysis of pain dynamics over a scale of minutes reveals that perceived ongoing chronic pain fluctuates as a scale-free process. Patients with back pain, of various etiologies, show scaling exponents in the anti-persistent range that may reflect their ability in invoking coping mechanisms to limit the experienced pain. The PHN pain dynamics shows a broader distribution, probably indicating different subtypes (Petersen et al. 2000). We surmise that PHN patients with persistent exponents have a more limited ability to control their pain. The ratings in subjects asked to imagine pain indicate that their expectations do not match reality and that these ratings more closely match acute pain perception ratings. Therefore we demonstrate that temporal properties of pain can reveal novel information with potential mechanistic and clinical significance.

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