A model of multifractality as observed in the neuronal activity of the human basal ganglia

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Abstract

Neuronal signals are usually characterized in terms of their discharge rate. However, this level of description is inadequate to account for the complex temporal organization of spike trains. In particular, fractal and multifractal patterns can be described using methods based on the so-called structure functions. Here, increasing order temporal structure functions are applied to neuronal signals obtained from the globus pallidus interna (GPi) of patients with Parkinson's disease. It is shown that these spike trains exhibit a characteristic multifractal spectrum, which is interpreted as a hallmark of the neuronal activity of the human, parkinsonian basal ganglia. Further, a neural field model is proposed to study the observed multifractality. The model consists of a partial differential equation that relates temporal to spatial activity considering a gradient field and a diffusive term. As the model is perturbed with stochastic initial conditions, the following is observed: 1. multifractality depends on the diffusive term; 2. multifractality is present for a range of diffusion coefficients; and 3. multifractal temporal properties are mirrored in space, which can be explained from the physical properties of the electric field governing neuronal activity. These results predict that passive electric properties of neuronal activity are far more relevant to the human brain than what has been usually considered.

1 Introduction

The basal ganglia are a circuit of densely interconnected subcortical nuclei, whose disease is related to human movement disorders [2]. These disorders include Parkinson's disease, the second most common neurodegenerative pathology following Alzheimer's disease [3]. Due to the aging of the population, the social burden of neurodegenerative disorders is increasing worldwide, deepening the need to understand their pathophysiology. Current models of the basal ganglia are partly successful in the prediction of neurophysiologic alterations occurring in movement disorders. However, no current pathophysiologic model allows to predict and control deep brain stimulation (DBS), one of the major therapeutic approaches to Parkinson's disease [4]. The lack of a description of the complex properties of the basal ganglia neuronal activity might be the cause of this failure. Neuronal spike trains of the basal ganglia are commonly recorded during DBS surgery with clinical purposes; statistical,

frequential, and nonlinear methods have been extensively applied to their study [5-11]. Yet, their characterization is not complete. Here, the presence of a multifractal spectrum in the neuronal discharge of the globus pallidus interna (GPi) from patients with Parkinson's disease is described. This complex geometrical behavior of the human, parkinsonian basal ganglia is interpreted as a hallmark, which must be considered in mathematical models of this circuit.

The fundament of the classic model of pathophysiology of the basal ganglia lies on a description of the discharge rate of their output nuclei: the GPi, and substantia nigra reticulata (SNr) [12, 13]. In primates, GPi and SNr neurons fire in a tonic manner, keeping the motor thalamus inhibited, and momentary reductions of their discharge rate facilitate movement. In humans, movement onset and velocity are positively correlated to the rate of discharge of the motor thalamus, and negatively to the rate of discharge of the GPi, and SNr [14]. These observations seem to confirm the rate hypothesis, but evidence obtained during functional neurosurgery in patients with Parkinson's disease is contradictory (for a detailed discussion see [15] and references therein). The predictions of the classic model of the basal ganglia are inconsistent with the effects of DBS and ablative surgery, raising concerns on the validity of the rate of discharge as a measure of the state of the basal ganglia [16-18].

Nonlinear time series analysis has inspired an alternative view. A growing body of evidence indicates that complex properties are crucial for the understanding and modeling of basal ganglia pathophysiology [15, 19-24]. Accordingly, in previous work we analyzed first order temporal structure functions of basal ganglia spike trains, and identified non-random time patterns [25, 26]. Structure functions were developed initially to describe the behavior of turbulent fields in the inertial range, and have been later applied to the analysis of physiological signals [27, 28]. Interestingly, structure functions exhibit scaling properties that allow classifying a signal as monofractal or multifractal [29, 30]. To that goal, temporal structure functions of order higher than one are calculated now from GPi spike trains, recorded during DBS surgery. Since the GPi is one of the main output nuclei of the basal ganglia, the results obtained from GPi spike trains are representative of the processing of information preformed by the whole circuit.

Further, to simulate the properties observed in the human GPi, a new neural field model is introduced here. The model consists of a nonlinear differential equation that includes a gradient term and a diffusive term. Diffusive properties are present in neuronal processes, given the physical influence of electric fields. However, the role of these so called passive electric properties of neuronal activity is rarely considered in neurophysiology studies, which usually focus on spiking activity. Previous modeling work on the basal ganglia by our group has shown that a diffusion coefficient might be a critical parameter for the control of information transmission and information deterioration in the parkinsonian GPi [31]. The model introduced here shows that: 1. multifractality of neuronal spike trains depends on diffusive properties, and 2. multifractality of temporal activity is reflected on the spatial domain. These results predict that passive (diffusive) properties of neuronal activity determine the structure of temporal and spatial neuronal activity in the basal ganglia, and must be considered in the study and treatment of movement disorders.

2 Methods

2.1 Patients and signal recording

Six patients fulfilling the clinical criteria of the United Kingdom's Parkinson's Disease Society Brain Bank for idiopathic Parkinson's (UK-PDS-BB) disease, Hoehn & Yahr IV, underwent stereotactic neurosurgery and were included in this study [32]. All patients were on chronic treatment with L-DOPA, presented similar motor affectation, with severe dyskinesias and motor fluctuations, and

fulfilled the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT) criteria for inclusion in the surgery program [33]. All patients signed informed consent prior to the procedure, previously reviewed and approved by the institutional ethics committee, and were without medication at the time of the surgery and during data acquisition. Age, gender and other details are not shown to protect patients' privacy.

Details about the recording procedure have been already published elsewhere [19]. Briefly, microrecording, stimulation and neurosurgical procedures were performed in patients awake, under local anesthesia. Surgical targets were planned employing magnetic resonance imaging (MRI) and using a Leksell stereotactic system (Series G, Elekta, Sweden). Microrecordings of neuronal activity were obtained only during the surgery, after the GPi was identified by an expert. Platinum/iridium (Pt/Ir 80/20%) microelectrodes with nominal impedance of 0.8-1.2 megohms (mTSPBN-LX1, FHC Inc) were used. A differential amplifier with a built-in impedance meter (FHC IS-AM-00-01 Iso-Xcell 3 Amplifier) and an isolated stimulus generator (FHC IS-PL-06 Isolated Bipolar Pulsar Stimulator; FHC, Bowdoinham, ME) were connected to a preamplifier remote probe mounted onto a motorized microdrive (FHC 65-00-1 Stepper Drive and ST-M0-00 TMS Controller), located near the electrode tip to minimize pickup of electrical noise. A dedicated acquisition system (1401plus, CED) was employed to amplify, and digitize the signal, filtering with second order 300 to 5,000 Hz bandpass and 50 Hz line notch analog filters. The sampling rate was 50 kHz. The total amplification including probe was set at gain ×10000 (checked with a built-in calibration signal of 1mV at the beginning of each surgery).

2.2 Data analysis

Signals were processed off-line. To obtain single cell recordings, spikes were extracted from raw signals and separated into classes using wavelet analysis and clustering [34]. From these single cell data, time series of interspike intervals (ISI) were constructed. Following that, the temporal structure function was computed as follows. An interval $\mathrm{I(t)}$ is defined as the tth ISI, which is used to calculate the increment $\Delta\mathrm{I}(\tau) = I(\mathrm{t}+\tau) - I(\mathrm{t})$, being τ the time lag, between 1 and 1000. The temporal structure function $\mathrm{S_q}(\tau)$ is

$$\mathrm{S_q}(\tau) = \langle|\Delta\mathrm{I}(\tau)|^{\mathrm{q}}\rangle, \qquad (1)$$

where $\langle\cdot\rangle$ is the statistical average, and q is the order of the structure function, an integer between 1 and 30. Next, $\mathrm{S_q}$ was smoothed by applying a running average over a 30 points window to obtain a smoothed structure function, $\mathrm{S_q^*}$ (30 points shorter than $\mathrm{S_q}$). The behavior of interest here is the scaling behavior of $\mathrm{S_q^*}(\tau)$. Given the general relationship

$$\mathrm{S_q^*}(\tau) \sim \tau^{\varsigma(\mathrm{q})}, \qquad (2)$$

the scaling exponent is a function, $\varsigma_\tau(\mathrm{q})$, which defines the fractal properties of the signal under study. For random processes, $\varsigma_\tau(\mathrm{q}) = 0$. In the case of monofractals the exponent function grows linearly, $\varsigma_\tau(\mathrm{q}) = \mathrm{q}\varsigma(1)$. If the signal is multifractal, $\varsigma_\tau(\mathrm{q})$ is a nonlinear function [29][(1)].

To find $\varsigma_\tau(\mathrm{q})$, $\log(\mathrm{S_q^*}(\tau))$ vs. $\log(\tau)$ was considered, and a linear (scaling) region was looked for.

(1) Different authors use different notations. The function that we call $\varsigma_\tau(\mathrm{q})$ is called $\tau(\mathrm{q})$ in Touchette's work, according to whom the spectrum of singularities $f(\alpha)$ does not need to be concave [1]. A concave $f(\alpha)$ can be calculated as the Legendre transform of $\varsigma_\tau(\mathrm{q})$, whereas a not concave $f(\alpha)$ cannot. In any case, a concave $\varsigma_\tau(\mathrm{q})$ implies multifractality.

The scaling region was defined as the longest range of τ fitting a linear function with non-zero slope ($\varsigma \neq 0$), for at least $1 \leq q \leq 10$. Linear regressions were considered acceptable if $R^2 \geq 0.6$, and regressions with regression coefficients smaller than that were discarded.

2.3 Model and simulations

The neural field model equation is:

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} = \delta\frac{\partial^2 u}{\partial x^2}. \qquad (3)$$

Here, $u(x,t)$ represents spikes' velocity, t is time, x is space and δ is a diffusion coefficient. While it can be thought that spikes travel with constant velocity along axons, the same does not hold for neural tissue at larger scales. Indeed, consider the following simplified situation. Take a single spike S that arrives to a neuronal soma whose membrane potential V is just below the triggering threshold ϑ. If this spike induces an excitation with an amplitude e in the neuron, such that the $V + e > \vartheta$, then the neuron will fire a new spike in response, which is equivalent to saying that the spike S has travelled through the neuron. However, the condition $V + e > \vartheta$ is valid for a range of potentials V. Given the time consumed in the summation process, typically a nonlinear function, the spike triggered in response to the excitation e will be fired faster for membrane potentials that are closer to the threshold, giving place to a higher velocity u. The process described introduces nonlinear variability in the profile of u, which is observed in experimental studies that analyze its inverse I, i.e. interspike intervals or ISI [19, 21]. Therefore, it can be considered that $|u(x,t)| = |1/I(x,t)|$, where I represents a series of interspike intervals.

Two notes are appropriate about the previous description. First, although the velocity u is not commonly considered in neurophysiology, the related variable of neuronal frequency f is present in a large number of neurophysiology studies. Since $u = \Delta x/\Delta t$ and $f = 1/\Delta t$, the relation between both variables is $u = f \cdot \Delta x$. Consequently, for distances $\Delta x = 1$ the module of the velocity $|u|$ has the same value than the frequency. Second, notice that this model takes the form of Burgers' equation, which has been intensively studied in the field of fluid dynamics [35]. In previous work it was proposed that this kind of equations might be useful to study mathematical properties of neuronal activity, which is analyzed with more detail here [20].

Computer simulations were run with custom Matlab and R code. The model was studied numerically in 1D. The discretization scheme selected was a two-step Lax-Wendroff scheme, which is suitable for this kind of study [ref]. The space step was $\Delta x = 0.001$, with a CFL number equal to $CFL = \frac{\Delta t}{\Delta x} = 0.99$, and $u = 0$ at the boundaries of the spatial domain. The initial condition considered was a random distribution of $u(x)$. The temporal evolution of $u(x)$ was studied for n time steps and for a range of diffusion coefficients $0 < \delta < 0.5$, varying δ in increments of 0.05 for $0.05 < \delta < 0.5$ and considering extra points for the range $0 < \delta < 0.05$. Then, the same process that was described in point 2.2 for the analysis of ISI time series was applied to u to obtain a temporal structure function $S_q(\tau)$ at fixed points in space, x, for scales $1 < \tau < l$, where l is the number of time iterations divided by 256. Finally, a spatial structure function $S_q(X)$ was obtained analyzing adjacent points of u for fixed times t and scales $1 < X < d$, where d is the number of spatial points divided by 256. A multifractal spectrum was looked for both in the space ($\varsigma_X(q)$) and time domains ($\varsigma_\tau(q)$), by analyzing the behavior of $S_q(\tau) \sim \tau^{\varsigma(q)}$ and $S_q(X) \sim X^{\varsigma(q)}$ for $0 < q < 2$, respectively.

3 Results

Multifractal properties of neuronal activity in the human basal ganglia

Results for the analysis of clinical data are shown in figures 1 and 2. In total, 22 GPi recordings obtained from 6 patients were analyzed. Time series had a mean length of 5668 ± 773 ISI (mean ± standard error of the mean, SEM). A scaling region of the temporal structure function was found for a minimum range of $1 \leq q \leq 10$ in every neuron. In 15 neurons, the fitting was sufficiently good for q up to 30 ($q_{max} = 24 \pm 2$, mean ± SEM). The length of the scaling interval over τ was 79 ± 25; mean $\pm$ SEM. Figure 1 shows smoothed structure functions of order 1 to 6 and the corresponding scaling region for a sample neuron. In figure 2, the function $\varsigma_\tau(\mathrm{q})$, for sample neurons is shown. In 18 cases (82%) we found a nonlinear $\varsigma_\tau(\mathrm{q})$, implying a multifractal organization of the spike trains analyzed.

Figure 3 shows the results of computer simulations. The left column shows $u(x,t)$ for increasing δ. Note that, as was said before, $|u| = |1/I|$, where u is the velocity field studied and I is the series of interspike intervals both is space and time. Therefore, the results obtained show that the fractal characteristics of the experimental time series obtained from the human brain are reproduced by the fractal properties of the absolute value of the inverse of the equivalent to I for the model, i.e. u. For very small diffusion coefficients initial random conditions are propagated through time with minor spatial changes. As δ is increased, bumps and waves appear in the field of $u(x,t)$. This indicates that a complex dynamics, different than random behavior, is introduced by the diffusive term of the equation. Thus, as time progresses, the behavior of the field becomes different from the random field set at the initial conditions. With respect to the amplitudes of the velocity field, as δ grows the average amplitude of $u(x,t)$ grows up to a point as shocks appear (in the figure δ=0.005), and then diminishes progressively, and thus waves are attenuated (observe $\delta = 0.3$). More importantly, hallmarks of multifractality appear both in space and time as δ increases. The middle column of figure 3 shows typical examples of $\varsigma_\tau(\mathrm{q})$ and the right column shows examples of $\varsigma_X(\mathrm{q})$. Observe that fractality is present for small δ, with linear exponent functions both in space and time. As δ increases, both $\varsigma_\tau(\mathrm{q})$ and $\varsigma_X(\mathrm{q})$ become nonlinear, indicating the presence of multifractality, and resembling the behavior observed in parkinsonian, human neurons.

4 Discussion and conclusion

The focus of this paper is on the structure of spike trains produced by GPi neurons of the human, parkinsonian basal ganglia, and what might be a suitable mathematical model of this neuronal activity. Based on the scaling of structure functions of increasing order, it can be concluded that a multifractal spectrum is characteristic of this system. This level of description is relevant for translational studies, which connect various models of Parkinson's disease to the clinic. Research on Parkinson's disease employs different models, from computational, to animal, and *in vitro* models, each of them tackling different aspects of the disorder [36-46] However, for translational studies in human medicine, the system of interest is no other than the human system, affected by human disease. No model of Parkinson's disease can be more accurate than the more accurate description of the human, parkinsonian basal ganglia. Data obtained during functional neurosurgery offer a unique opportunity to study the parkinsonian basal ganglia directly; mathematical descriptions of complex properties like the one presented here lay the foundation for basic and translational research on Parkinson's disease.

Slowly, it is getting clear that the discharge rate is insufficient to characterize the neuronal activity of the basal ganglia. This approach fails, because it doesn't predict the response of the basal ganglia to DBS, a highly effective therapy to ameliorate parkinsonian symptoms [2, 47-53]. This has motivated the research of other, quantitative features of the neuronal activity of the basal ganglia as candidate

measures of the state of the system. In particular, several authors offered evidence of complex time patterns in the neuronal activity of the basal ganglia (see for example the discussion in [54]). In previous work, we analyzed first order structure functions ($q = 1$) of simulated, animal, and human spike trains, and hypothesized that time patterns and rate-coding properties co-exist in the basal ganglia [25, 26, 31, 55]. Since structure functions of order higher than 1 ($q > 1$) not only allow to characterize the fractal properties of a signal, but have proven useful for the analysis of human neuronal recordings, to continue their study to higher orders was natural. The algorithm used is robust to short, noisy time series and efficient computationally, showing potential for on-line, neurosurgical applications. Alternative methods of multifractal analysis include multifractal detrended fluctuation analysis and wavelet-based methods [28, 56, 57]. A comparison with other methods remains for future studies.

The clinical findings of this work agree with the literature. Zheng et al. used a multiplicative model to reproduce fractal features of human, basal ganglia neuronal activity [58, 59]. Other complex and nonlinear temporal properties are also present in basal ganglia spike trains from rodents, primates and patients with movement disorders [23, 60-63]. The most popular nonlinear measure for the characterization of parkinsonian spike trains is probably entropy, which diminishes due to pharmacological or stimulation treatment, and increases due to alertness [22, 23, 64-67]. Importantly, entropy can be estimated wrongly if the multifractality of a system is not considered [64, 68, 69].

Finally, considering ISI from the perspective of velocity instead of frequency introduces a new concept to the analysis of spiking time series. As was discussed before, interspike intervals (a measure commonly used to characterize neuronal spike trains) can be considered as the inverse of the absolute value of spikes' velocity. Following this idea, neural field models can be introduced that model neuronal activity as a velocity $u(x,t)$, thus relating the spatial and the temporal structure of spike trains. Here, a nonlinear differential equation is introduced that considers $u(x,t)$ as a combination of a nonlinear gradient term and a diffusive term. This kind of coupling between space and time gives place to complex geometrical structures that are mirrored from the time to the space domain: a multifractal spectrum is observed as well in the temporal structure as in the spatial structure of the spike trains, depending on the influence of the diffusive term, and therefore on the diffusion coefficient δ.

In previous work it has already been shown that diffusion plays a critical role in the deterioration of information transmission that occurs in the GPi under Parkinson's disease, and it was pointed out that there are mathematical similarities between neuronal spiking activity of the parkinsonian basal ganglia and turbulence [20, 31]. Based on these premises, here a new neural field model is introduced inspired by Burgers' equation, a well-known equation in the field of fluid dynamics. It is shown that this model captures essential features of neuronal activity of the human brain. The model reproduces multifractality as observed in the neuronal activity of the human, parkinsonian basal ganglia. The main prediction of the model is that diffusive properties can determine the appearance of multifractality in a neural field.

5 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Author Contributions

DSA: study design, data analysis, computer simulations, manuscript preparation

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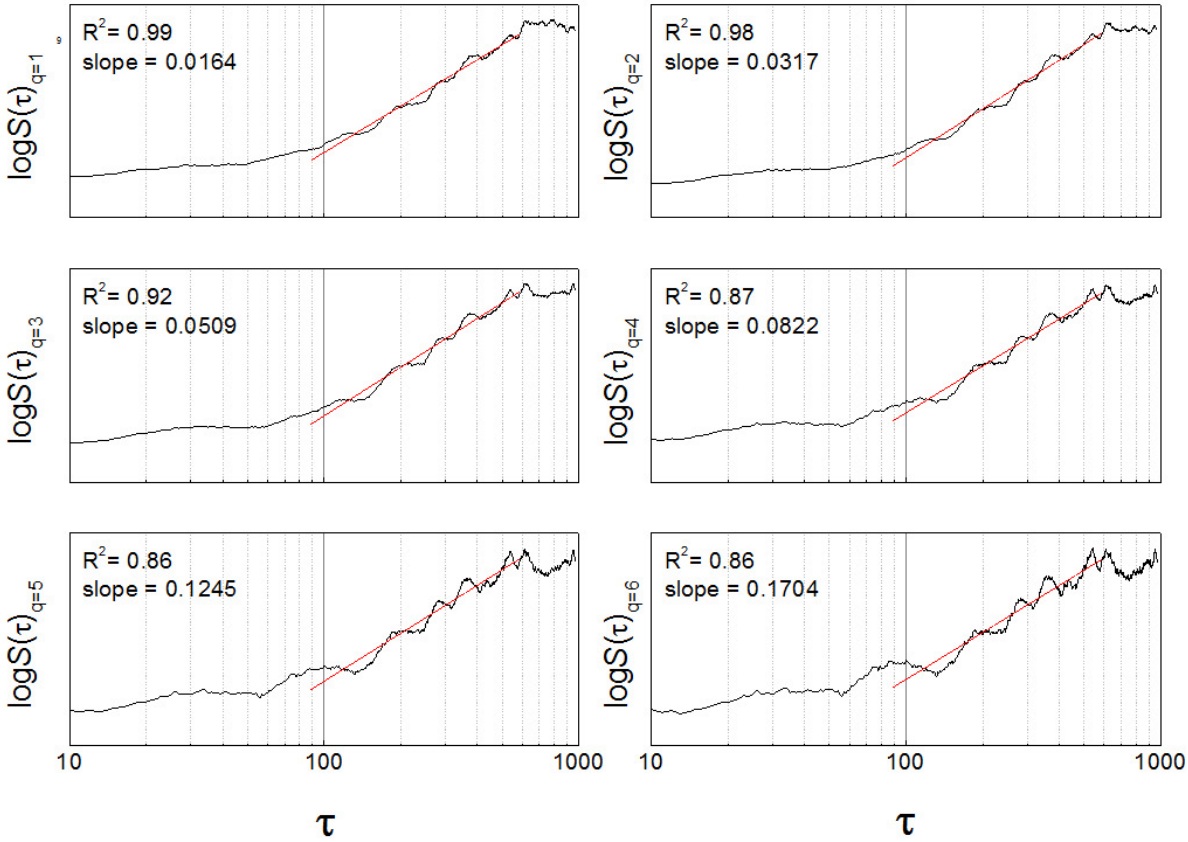
10 Figure captions

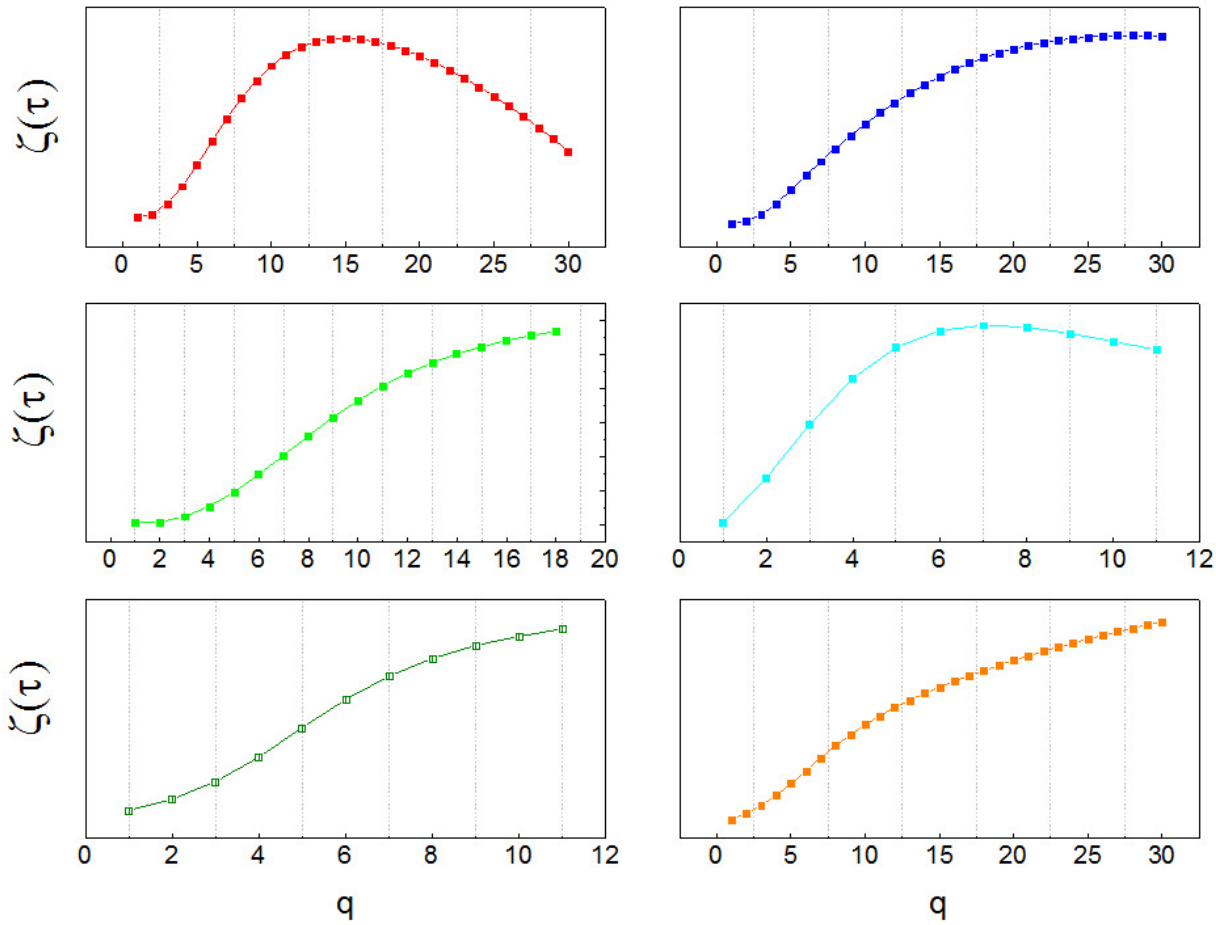
Figure 1) Structure functions of order 1 to 6 for a sample neuron, showing the scaling region (89<τ<589) and corresponding linear fittings.

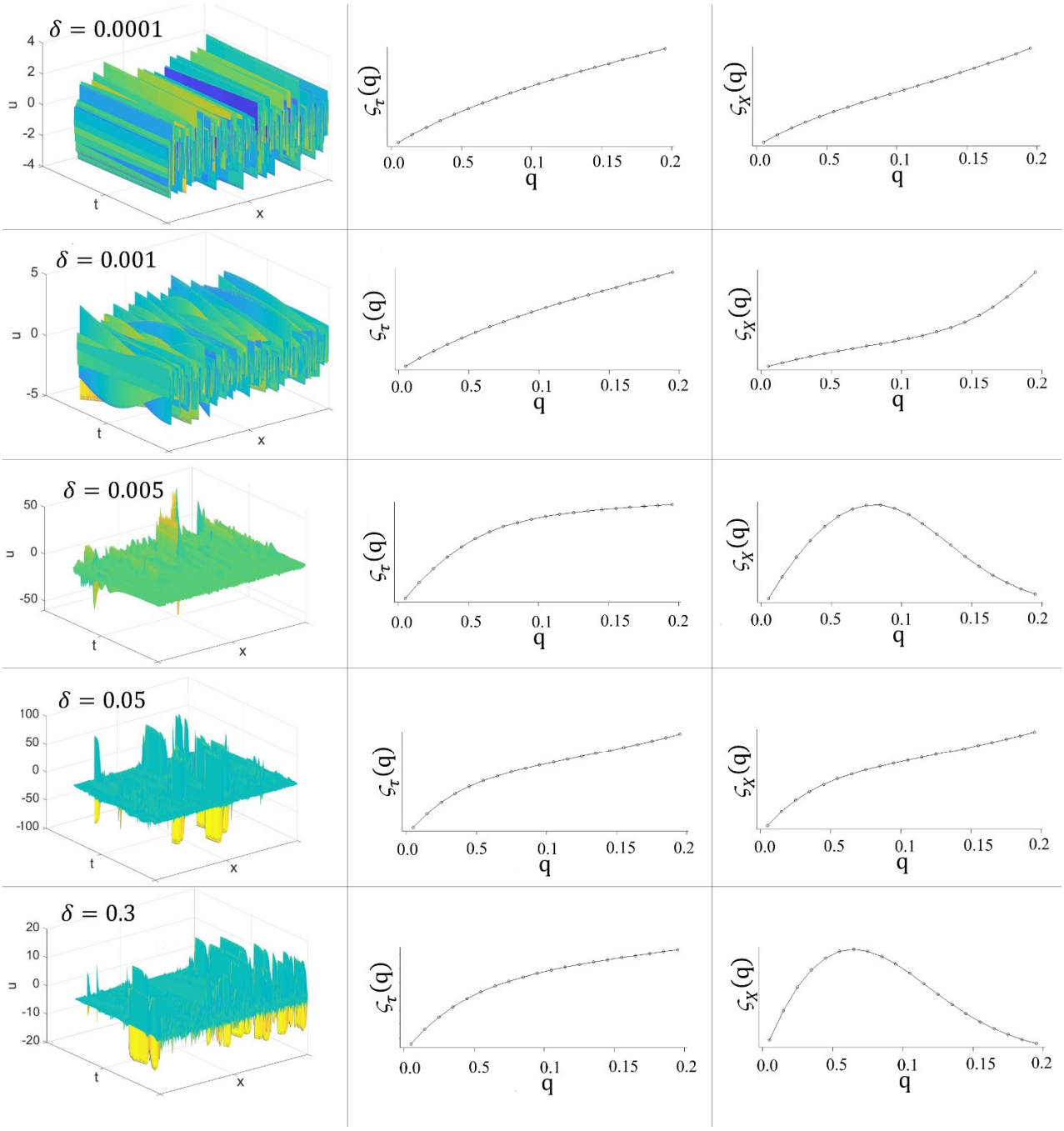
Figure 2) Multifractal spectrum of sample neuronal recordings. The function $\varsigma_\tau(q)$ is built as the slope of the scaling region in $\log S_q(\tau)$, vs. the order in logarithmic scale, q.

Figure 3) Left column: time evolution of $u(x,t)$ as the diffusion coefficient δ increases (from top to bottom). Observe that random initial conditions (along the x axis) are propagated through time with minor changes for small δ. As δ grows, shocks and waves appear, which are then attenuated for even greater values of diffusion. Middle column: The exponent function $\varsigma_\tau(q)$ is linear for simple fractal behavior (upper panels) and becomes progressively nonlinear, indicating multifractality, as δ grows. Right column: The behavior of $\varsigma_X(q)$ is like that of $\varsigma_\tau(q)$. In the space domain as well as in time domain, linearity governs the exponent function $\varsigma(q)$ for small values of δ, while nonlinearity indicates multifractality when diffusion gets stronger.

Multifractal properties of neuronal activity in the human basal ganglia




ζ(τ)
ζ(τ)
ζ(τ)
0 5 10 15 20 25 30
0 5 10 15 20 25 30
0 2 4 6 8 10 12 14 16 18 20
0 2 4 6 8 10 12
0 2 4 6 8 10 12
0 5 10 15 20 25 30
q
q


δ = 0.0001
δ = 0.001
δ = 0.005
δ = 0.05
δ = 0.3
u
t
x
q
0.0
0.5
0.1
0.15
0.2