Published in final edited form as:

J Neurosci Methods. 2015 April 15; 244: 136–153. doi:10.1016/j.jneumeth.2014.07.013.

Multifractal analysis of information processing in hippocampal neural ensembles during working memory under ⁹-tetrahydrocannabinol administration

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Abstract

Background—Multifractal analysis quantifies the time-scale-invariant properties in data by describing the structure of variability over time. By applying this analysis to hippocampal interspike interval sequences recorded during performance of a working memory task, a measure of long-range temporal correlations and multifractal dynamics can reveal single neuron correlates of information processing.

New method—Wavelet leaders-based multifractal analysis (WLMA) was applied to hippocampal interspike intervals recorded during a working memory task. WLMA can be used to identify neurons likely to exhibit information processing relevant to operation of brain–computer interfaces and nonlinear neuronal models.

Results—Neurons involved in memory processing (“Functional Cell Types” or FCTs) showed a greater degree of multifractal firing properties than neurons without task-relevant firing characteristics. In addition, previously unidentified FCTs were revealed because multifractal analysis suggested further functional classification. The cannabinoid-type 1 receptor partial agonist, tetrahydrocannabinol (THC), selectively reduced multifractal dynamics in FCT neurons compared to non-FCT neurons.

Comparison with existing methods—WLMA is an objective tool for quantifying the memory-correlated complexity represented by FCTs that reveals additional information compared to classification of FCTs using traditional z-scores to identify neuronal correlates of behavioral events.

Conclusion—z-Score-based FCT classification provides limited information about the dynamical range of neuronal activity characterized by WLMA. Increased complexity, as measured with multifractal analysis, may be a marker of functional involvement in memory processing. The level of multifractal attributes can be used to differentially emphasize neural signals to improve computational models and algorithms underlying brain–computer interfaces.

Keywords

Cannabinoid; Cognition; Delayed non-match to sample; Electrophysiology; Wavelet leaders; Working memory

1. Introduction and background

1.1. Memory processing in nonlinear hippocampal dynamics

Hippocampal neural ensembles are known to represent crucial information for successful memory performance in a variety of tasks (Berger et al., 2011, 2012; Deadwyler et al., 2013; Eichenbaum et al., 1996; Goonawardena et al., 2010; Hampson et al., 2013; O'Neill et al., 2013; Tayler et al., 2013). The delayed nonmatch-to-sample (DNMS) task requires spatial and nonspatial working memory processing across three timescales: encoding during the sample lever press, retention throughout a variable delay interval, and recall during the nonmatch decision phase (Deadwyler et al., 1996). By analyzing the neuronal discharge rate around these task events, the activity of a subset of task-relevant hippocampal principal neurons, known as functional cell types (FCTs), was shown to represent essential correlates of spatial working memory (Goonawardena et al., 2010; Hampson et al., 1999). FCTs can be identified using their mean firing rate response (calculated as a z-score) during combinations of key behaviorally relevant task events; however, this method involves subjective decisions and cannot completely characterize the full dynamic range of neuronal activity. z-Score calculations require a priori designated behavioral events, selection of a generalizable activity baseline (Hampson et al., 1999), and are prone to high degrees of intra- and inter-session variability. z-Score calculations may miss important features of neuronal information processing occurring around events which have not been identified prior to analysis. By comparing results of z-score-based FCT designation with measures of multifractal complexity, hypotheses concerning dynamic neuronal functionality can be strengthened.

The nonlinear multi-input, multi-output model (MIMO) is an effective predictor of hippocampal memory encoding (Hampson et al., 2012), and it has been successfully used as a neuroprosthetic to improve memory performance in both rats (Hampson et al., 2012) and nonhuman primates (Hampson et al., 2013). FCTs have been shown to significantly contribute to the MIMO hippocampal model (Hampson et al., 2012) suggesting that behavioral correlates of individual hippocampal neurons exhibit nonlinear and possibly fractal features in their spike trains. Hippocampal neuronal ensembles have previously been pre-screened using z-score based FCT identification, but since this method employs subjective decisions during computation, it is hypothesized that multifractal analysis could provide an objective measure of the information processing capacity of hippocampal neurons. This would improve both the speed and accuracy of the current MIMO model (Song et al., 2009) and facilitate translation into the human population. The nonlinearity and

variability of hippocampal interspike interval sequences may carry a significant amount of memory processing information, and multifractal analysis can provide a quantitative measure of these dynamical features. Fractal analysis and $1/f^\alpha$ -power-law-distribution have previously been used to describe dynamics of neuronal avalanches (Beggs and Plenz, 2003, 2004), EEG oscillations (Benayoun et al., 2010; Linkenkaer-Hansen et al., 2001, 2004), cell morphology (Bernard et al., 2001), and interspike intervals (Das et al., 2003; Lewis et al., 2001; Teich et al., 1990). Fractal analysis and $1/f^\alpha$ -power-law-distribution are able to quantify self-similarity of the whole data set but cannot describe local fluctuations in the data occurring over time. We therefore hypothesize that multifractal analysis, which can simultaneously quantify self-similarity and local fluctuations (Zilber et al., 2012), can be used to detect neural information processing relevant for memory performance in hippocampal spike trains based on the distribution of interspike interval variability throughout the DNMS task. The qualitative information provided by FCT classification concerning neuronal information representation can be complemented with multifractal analysis to promote richer interpretations of neurophysiological data.

1.2. Background: Fractal nature of time series data

Fractal analysis quantifies the irregularity, also known as singularities, in objects and signals by detecting correlations among these irregularities across multiple spatial and/or temporal scales. The term “fractal” was originally used to describe “self-similar” objects that contain identical repeating structures at an infinite set of smaller scales (Mandelbrot, 1982). Later the term fractal was expanded to include “self-affine” objects; i.e., objects with structure that is statistically equivalent, but not identical across an infinite set of smaller scales (Mandelbrot, 1985). Self-affinity describes a wider range of natural formations, such as those found in coastlines, clouds, mountain ranges and branching patterns of trees. More recently, fractal analyses have also been used to describe scale-invariant fluctuations occurring over multiple time scales in biological signals, turbulence, sun spot activity, and financial markets (for a review, see Kantelhardt, 2012). In scale-invariant structures, all measurement scales contribute equally to the dynamical activity patterns. Understanding these scaling relationships may provide important details about the underlying information processing mechanisms (Ciuciu et al., 2008).

The singularity spectrum is a succinct way of conveying the scale invariant self-similarity of the data along with local temporal variability. The singularity spectrum plots the local Hölder exponent h , a measure of local variability, versus the fractal (Hausdorff) dimension $D(h)$ of data points with the same local Hölder exponent. Monofractal signals are defined by a single scaling relationship that remains constant for the entire time series. Multifractal signals have regions of high variability interspersed with regions of low variability. As a result of this dispersed variability, multiple scaling relationships form throughout the entire time series. Based on results obtained with multifractal analysis, three representative hippocampal neurons recorded during a working memory task are shown in Fig. 1: a random (uncorrelated) signal, a monofractal signal, and a multifractal signal. The top graphs display the interspike interval sequences of each neuron (Section 2.4.5), while the bottom graph shows their singularity spectra. The most common local Hölder exponent occurs at the apex of the inverted parabola is also called the global Hurst exponent H (Brazhe and Maksimov,

2006; Mandelbrot, 1982). It describes the global self-similarity of the data set and is analogous to the power law exponent obtained from fractal analysis in $1/f^\alpha$ -power-law distributions. If H falls between 0 and 0.5 the system is anti-persistent, H equal to 0.5 corresponds to a random Gaussian process, and a persistent signal has an H from 0.5 to 1. A persistent series is one containing long-term positive correlations (or long-range temporal correlations) and is often referred to as having “long term memory,” while anti-persistent structure indicates negative correlations over time. Since random signals not correlated, the uncorrelated data in Fig. 1 has a global Hurst exponent of 0.5. In this example (Fig. 1), the monofractal signal has long-range temporal correlations and a Hurst exponent of 0.65. In the context of neuronal activity, long-range correlations could be described by repeating series of activity patterns. For example, neuronal bursting will be followed by more bursting, while quiescence will most likely be followed by more quiescence (Hu et al., 2013). In a fractal context, “long-range” refers to correlations to multiple previous data points. For example, one ISI may be correlated with 5 of the immediately prior ISIs, and long-range temporal correlations would arise if numerous occurrences exist throughout a signal. The uncorrelated and monofractal signals should have non-existent spectra width, but the small range of local Hölder exponents is a result of analyzing real data sets of finite duration. The singularity spectrum of the multifractal signal is much wider than those of other signals because the heterogenous distribution of variability can only be quantified by a range of Hölder exponents.

The complex neuronal interactions governing behavior, memory and cognition can be further understood by appreciating the implications of what “multifractality” means in a broader context. Interactivity, both between neurons and between an organism and its environment, is an important feature that can be empirically quantified using multifractal analysis. Recent research drawing from Gibsonian views of ecological psychology has suggested that multifractal properties arise from interactions from many signals across multiple scales (Kelty-Stephen et al., 2013), hence its name: “interaction-dominant theory.” Interaction-dominant theory views a system as resulting from the synergistic, interrelated activity of all parts and postulates that common patterns are extracted and reused throughout the learning process across all contexts (Dixon et al., 2012; Ihlen and Vereijken, 2013). A counter argument, component-dominant theory, states that variability is caused by particular sources and an underlying behavior arises from specific, localized system constituents (Ihlen and Vereijken, 2010, 2013). Earlier work suggested that interaction-dominant phenomena could be dissociated from component-dominant processes based on $1/f^\alpha$ power-law distributions and long-range temporal correlations (Kello et al., 2007; Van Orden et al., 2005), but it is now believed that only multifractal models can disentangle these theories (Ihlen and Vereijken, 2010). Multifractal cascade dynamic theory suggests that scale-invariance and fractal properties can come from “temporally correlated fluctuations of many different sizes” (Stephen et al., 2012). Multifractal dynamics suggests that a signal interacts with other signals, possibly from other local neurons or additional distant brain areas, and the amount of mutual interaction is quantified by the width of the singularity spectrum (Ihlen and Vereijken, 2010).

Many techniques can compute the singularity spectrum, such as Wavelet Transform Modulus Maximus (WTMM; Arneodo et al., 1993), Adaptive Detrended Fluctuation Analysis (AFA; Kuznetsov et al., 2012; Riley et al., 2012), Arbitrary-Order Hilbert Spectral Analysis (AOHSA; Huang et al., 2011), Empirical Mode Decomposition (EMD; Flandrin and Goncalves, 2004; Goncalves et al., 2007), Multifractal Detrended Fluctuation Analysis (MFDFA; Ihlen, 2012; Kantelhardt et al., 2002; Owieczimka et al., 2006), and Wavelet Leaders-based Multifractal Analysis (WLMA; Jaffard et al., 2007; Serrano and Figliola, 2009; Wendt et al., 2007; Wendt and Abry, 2007). WLMA has many advantages over the other methods: it is computationally efficient, it is able to deal with a broader range of singularity types, and it is able to estimate the Hölder exponents in regions of low variability. In the latter case, problems associated with estimating the Hölder exponents may be circumvented by estimating the singularity spectrum directly from the infinite series expansion of the log-cumulants of the scaling exponents. The first three parameters of this expansion c_1 , c_2 , and c_3 describe the singularity spectrum's peak, width, and asymmetry, respectively. The parameterization of the singularity spectrum with these three parameters provides a convenient and efficient means of comparing singularity spectrum along with classifying time signals (Ciuciu et al., 2008, 2012; Wendt et al., 2007).

1.3. Fractal analyses of hippocampal neural spike trains

We used the WLMA to estimate the singularity spectrum from the interspike intervals (ISI) of rat hippocampal (CA3 and CA1) neurons recorded during the delayed nonmatch-to-sample (DNMS) task, a working memory task with spatial and nonspatial components (Deadwyler et al., 1996; Hampson et al., 1999). Neurons were tracked in animals under control conditions and also with delta-9-Tetrahydrocannabinol (THC) administration. The general idea of this paper is that the singularity spectra, a quantitative measure of multifractal properties, will be able to distinguish task-correlated from non-correlated neurons and differentiate between control and THC sessions. We tested this general idea with three specific hypotheses. Our first hypothesis is that functional cell types (i.e., FCTs or FCT neurons – as defined in Goonawardena et al., 2010; Hampson et al., 1999) will have larger long-range temporal correlations than non-FCT neurons. Since FCTs are involved in memory processing, the long-range temporal correlations could arise from their similar and repeating firing patterns during specific behavioral events. Our second hypothesis is that FCTs will contain more multifractal dynamics, possibly due to abrupt, intermittent changes in neuronal activity coinciding with variable DNMS task requirements. THC, the main psychoactive constituent of cannabis (Gaoni and Mechoulam, 1964), disrupts memory function (Hampson and Deadwyler, 2000), sequential processing (Hampson et al., 1989), perception (Atakan et al., 2012), theta power (Ilan et al., 2004; Kuciewicz et al., 2011), hippocampal neural spike-timing (Robbe et al., 2006), and hippocampal neural synchrony (Goonawardena et al., 2011). Therefore, THC can be used as a tool to differentiate the role of hippocampal mnemonic processing during the DNMS task under memory-impairing conditions. And finally, our third hypothesis is that THC administration will reduce multifractal dynamics of all recorded hippocampal principal cells.

2. Materials and methods

2.1. Subjects, training and drug administration

2.1.1. Animals—Subjects were Long–Evans rats (Harlan) aged 4–6 months ($n = 6$) individually housed and allowed free access to food with water regulation to maintain 85% of ad libitum body weight during testing. All animal protocols were approved by the Wake Forest University Institutional Animal Care and Use Committee, in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care and the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 8023).

2.1.2. Apparatus—The behavioral testing apparatus for the delayed nonmatch to sample (DNMS) task is the same as reported in other studies (Hampson and Deadwyler, 2000; Hampson et al., 2012) and consisted of a 43 cm × 43 cm × 50 cm Plexiglas chamber with two retractable levers (left and right) positioned on either side of a water trough on the front panel. A nosepoke device (photocell) was mounted in the center of the wall opposite the levers with a cue light positioned immediately above the nosepoke device. A video camera was mounted on the ceiling and the entire chamber was housed inside a commercially built sound-attenuated cubicle.

2.1.3. Behavioral training procedure—The DNMS task consisted of three main phases: sample, delay and nonmatch. The sample phase initiated the trial when either the left or right lever was extended (50% probability), requiring the animal to press it as the Sample Response (SR). The lever was then retracted and the Delay phase of the task initiated, as signaled by the illumination of a cue light over the nosepoke photocell device on the wall on the opposite side of the chamber (Fig. 2A). At least one nosepoke (NP) was required following the delay interval which varied randomly in duration (1–30 s) on each trial during the session. The Nonmatch phase began when the delay timed out, the photocell cue light turned off and both the left and right levers on the front panel were extended. Correct responses consisted of pressing the lever in the Nonmatch phase located in the spatial position opposite the SR (nonmatch response: NR). This produced a drop of water (0.4 ml) reward in the trough between the two levers. After the NR the levers were retracted for a 10.0 s intertrial interval (ITI) before the next Sample lever was presented to begin the next trial. A lever press at the same position as the SR (Match Response) constituted an “error” with no water delivery and turned off of the chamber house lights for 5.0 s and the next trial was presented 5.0 s later. Individual performance was assessed as % NRs (correct responses) with respect to the total number of trials (80–100) per daily (1 h) sessions.

2.1.4. Drug preparation and administration—Delta-9-THC was obtained from the National Institute on Drug Abuse as a 50 mg/ml solution in ethanol. Detergent vehicle was prepared from Pluronic F68 (Sigma, St. Louis, MO), 20 mg/ml in ethanol. ⁹-THC was added to the detergent-ethanol solution (0.5 ml of either THC), and then 2.0 ml of saline (0.9%) was slowly added to the ethanol-drug solution. The solution was stirred rapidly and placed under a steady stream of nitrogen gas to evaporate the ethanol (~10 min). This resulted in a detergent-drug suspension (12.5 mg/ml THC), which was sonicated and then

diluted with saline to final injection concentrations (0.5–2.0 mg/ml THC). On drug administration days, animals were injected intraperitoneally with the drug-detergent solution (1 ml/kg) ~10 min before the start of the behavioral session. Our experience with these experiments has shown that performance after vehicle injection is not significantly different than no injection, and therefore was omitted during this series of experiments to minimize risk of infection to the animals. At least two no injection days were imposed between each drug-testing session. All drug solutions were mixed fresh each day.

2.2. Hippocampal electrode array surgery

All surgical procedures conformed to National Institutes of Health and Association for Assessment and Accreditation of Laboratory Animal Care guidelines, and were performed in a rodent surgical facility approved by the Wake Forest University Institutional Animal Care and Use Committee. After being trained to criterion performance level in the DNMS task animals were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and placed in a stereotaxic frame. Craniotomies (5 mm-diameter) were performed bilaterally over the dorsal hippocampus to provide for implantation of 2 identical array electrodes (Neurolinc, New York, NY), each consisting of two rows of 8 stainless steel wires (diameter: 20 μ m) positioned such that the geometric center of each electrode array was centered at co-ordinates 3.4 mm posterior to Bregma and 3.0 mm lateral (right or left) to midline (Paxinos and Watson, 1997). The array was designed such that the distance between two adjacent electrodes within a row was 200 μ m and between rows was 400 μ m to conform to the locations of the respective CA3 and CA1 cell layers. The longitudinal axis of the array of electrodes was angled 30° to the midline during implantation to conform to the orientation of the longitudinal axis of the hippocampus, with posterior electrode sites more lateral than anterior sites (Fig. 2C). The electrode array was lowered in 25–100 μ m steps to a depth of 3.0–4.0 mm from the cortical surface for the longer electrodes positioned in the CA3 cell layer, leaving the shorter CA1 electrodes 1.2 mm higher with tips in the CA1 layer. Extracellular neuronal spike activity was monitored from all electrodes during surgery to maximize placement in the appropriate hippocampal cell layers. After placement of the array the cranium was sealed with bone wax and dental cement and the animals treated with buprenorphine (0.01–0.05 mg/kg) for pain relief over the next 4–6 h. The scalp wound was treated periodically with Neosporin antibiotic and systemic injections of penicillin G (300,000 U, intramuscular) were given to prevent infection. Animals were allowed to recover from surgery for at least 1 week before continuing behavioral testing (Berger et al., 2011).

2.3. Multineuron recording of hippocampal ensembles

2.3.1. Electrophysiological monitoring and acquisition of neuronal data—

Animals were connected by cable to the recording apparatus via a 32-channel headstage and harness attached to a 40-channel slip-ring commutator (Crist Instruments, Hagerstown, MD) to allow free movement in the behavioral testing chamber. Single neuron action potentials (spikes) were isolated by time-amplitude window discrimination and computer-identified individual waveform characteristics using a multi-neuron acquisition (MAP) processor (Plexon Inc., Dallas, TX, USA). Single neuron spikes were recorded daily and identified using waveform and firing characteristics within the task (perievent histograms) for each of

the DNMS events (SR, LNP & NR). Only isolated spike waveforms exhibiting firing rates consistent with CA1 and CA3 principal cells (i.e., 0.5–10.0 Hz baseline firing rate) and stable behavioral correlates across sessions were employed for experimental manipulations and model development (Deadwyler et al., 2007; Berger et al., 2011). Hippocampal neuron ensembles used to analyze encoding of DNMS events consisted of 15–32 single neurons, each recorded from a separate identified electrode location on either of the bilateral arrays.

2.4. Hippocampal neural analysis

2.4.1. Identification of functional cell types—Prior studies from this laboratory have identified hippocampal neurons recorded as above by “Functional Cell Types” (FCTs) described by different behavioral correlates of DNMS task-related events such as lever position and/or phase of the task (Hampson et al., 1999; Goonawardena et al., 2010). Individual neurons exhibit firing rate increases in response to Sample and Nonmatch responses (Fig. 2B); however, the defining characteristic an FCT in this context is that the neuron responds by increased firing rate only to a specific combination of events within the trial. Neural firing in response to each Sample (SR) or Nonmatch (NR) response event is analyzed by standard score ($z = (\text{peak firing rate} - \text{mean of the baseline firing rate}) / (\text{std. dev of baseline firing rate})$) using 100 ms bins. The baseline firing rate and standard deviation were computed 2.0–2.5 s prior to the SR, and the peak firing rate was computed ± 1.2 s around the instant of SR or NR. Only neural firing during correct trials was used for z -score calculations. Neurons were then categorized according to simple responses: position cells: Left-lever only, Right-lever only; phase cells: Sample-response only, Nonmatch-response only; conjunctive cells: Right Sample only, Left Sample only, Right Nonmatch only, Left Nonmatch only; or Trial-type cells: Right Sample + Left Nonmatch, Left Sample + Right Nonmatch (Hampson et al., 1999; Goonawardena et al., 2010). In addition, increased neuronal activity during the “last nosepoke” (LNP in Fig. 2A) was also analyzed which allowed for the creation of a new class of FCT: nosepoke-nonmatch cells.

Neurons were classified as FCTs based on the combination of z -scores calculated around sample, last nosepoke, and nonmatch responses. Average firing rate around DNMS events was computed for multiple days to create one overall average for each neuron for each event, and z -scores were calculated based on the overall averages; this was done separately for control and THC sessions. Neurons with z -scores greater than or equal to 3.19 ($p < 0.001$) in control sessions were considered to be FCTs. Designations of FCT (e.g., Conjunctive or Trial-Type) were made by examining which combination of events (six total: sample, nosepoke and nonmatch for both right and left levers) showed significant increases in firing rate. The average z -score and z -score standard deviation were calculated using these six z -score values for each neuron. If neurons had more than three out of six possible significant peaks, only peaks above the “ z -average half std. dev” (z -average half std. dev = average z -score + $0.5 * (z\text{-score std. dev.})$) were considered for FCT group designation. Even when using this criterion, some neurons still exhibited a combination of three significant peaks and were designated as another FCT-group, “3 Peaks.” All neurons were recorded during at least two sessions (days) each under both control and THC conditions (drug conditions), with some being recorded during more than 20 total sessions.

2.4.2. Statistical analysis of FCTs based on multifractal log-cumulants—

Neurons were divided into FCTs groups (as described in Section 2.4.1) and repeated measures ANOVAs were performed with Statistical Analysis Systems (SAS) software (SAS Institute) using each neuron as the subject identifier, each session as a within-subjects effect, and FCT group as the group identifier. Since each session was used as the within-subjects effect, log-cumulants (details in Section 2.4.4) from all sessions from all neurons recorded in at least two sessions of both control and THC (four sessions total) were used (Section 2.4.1). The covariance structure used was compound symmetry. In total, two repeated measures ANOVAs were performed for both c_1 and c_2 as dependent variables while examining main effects of FCT group and drug condition (control or THC) and an interaction between the two. One set of repeated measures ANOVAs was performed with three “FCT-groups:” classic FCTs, new FCTs and non-FCTs (Sections 3.3 and 3.4). Another set of repeated measures ANOVAs was performed after breaking down FCTs into specific FCT-groups (Sections 2.4.1 and 3.5; position, phase, conjunctive, trial-type, nosepoke-nonmatch, and 3 peaks) and comparing a total of 7 “FCT-groups.” Posthoc tests were performed using Tukey-Kramer adjustments for multiple comparisons.

The set of same repeated measures ANOVA procedures were used to perform control analyses with mean firing rate (Sections 3.4 and 3.5) and ISI standard deviation (Section 3.7) as dependent variables. Two repeated measures ANOVAs were performed for each dependent variable; one comparing classic FCTs, new FCTs and non-FCTs and the other analyzing all FCT-groups (7 total groups including non-FCTs).

When examining an effect of hippocampal location (Section 3.6), no FCT-group designations were made and hippocampal location (CA3 or CA1) was used as the group identifier. Main effects of hippocampal location and hemisphere (left or right) were tested, as well as an interaction between them.

2.4.3. Calculation of scaling exponents and multifractal singularity spectrum

—WLMA is described in detail in other sources (Ciuciu et al., 2008, 2012; Jaffard, 2004; Jaffard et al., 2007; Serrano and Figliola, 2009; Wendt et al., 2007), and information concerning multifractal analysis is detailed elsewhere (Kantelhardt, 2012). Therefore, we only briefly highlight the main features of WLMA for calculating the singularity spectrum.

Multifractal analysis may either be done from a global perspective by measuring how the variability of the signal changes across multiple scales or from a local perspective by measuring the variability of the signal at each point in time. The local variability in the signal $X(t)$ may be defined by the local Hölder exponent h , which is the largest h : $h(t_0) = \sup\{h: X \in C^h(t_0)\}$ that satisfies the equation

$$|X(t) - P_{t_0}(t)| \leq C|t - t_0|^h \quad (1)$$

where C is a positive constant and P is an n th degree polynomial with n less than h . This definition comes from the theoretical usage of the Hölder exponent and describes the pointwise regularity of the signal $X(t)$ (Struzik, 2000). The information concerning the

variations in regularity of the Hölder exponents along time can be quantified with the multifractal singularity spectrum, which plots Hausdorff dimension, $D(h)$, of the set of points with the same Hölder exponent. The singularity spectrum may be calculated directly from the log-transformation of the normalized probability distribution function of the local Hölder exponents. However, for real finite data sets with noise calculating the singularity spectrum directly from the local Hölder exponents requires fitting a Taylor polynomial $P(t)$ to every t_0 ; this procedure becomes computationally expensive and prone to high variability (Ihlen, 2012; Struzik, 2000; Wendt et al., 2007).

2.4.4. Estimation of singularity spectrum with wavelet leaders and log-cumulants

—As an alternative, the singularity spectrum may also be calculated from a global perspective by estimating the scaling exponents $\zeta(q)$ of a process with self-similar scale invariant structure such that

$$E|X(at)|^q = |a|^{\zeta(q)} E|X(t)|^q \quad (2)$$

where a is the scaling parameter and q is the statistical moment. For monofractal processes, $\zeta(q)$ is constant. For multifractal processes, $\zeta(q)$ is a range of power-law exponents. The distribution of local Hölder exponents and scaling exponents $\zeta(q)$ are related through a Legendre transform (Wendt and Abry, 2007). WLMA computes the scaling exponents by measuring how the absolute value of the wavelet coefficients d_X changes as a function of scale. The first step in WLMA is to transform the data to the wavelet domain with a Discrete Wavelet Transform (DWT) (Fig. 3A).

$$d_X(j, k) = \int_{\mathbb{R}} X(t) 2^{-j/2} \Psi_0(2^{-j}(t - 2^j k)) dt \quad (3)$$

where Ψ_0 is an appropriately chosen mother wavelet. For this work, a Daubechies wavelet with 4 vanishing moments was used. The wavelet coefficients d_X are extracted from the DWT on a dyadic grid at scales equal to 2^j and time shifts equal to $2^j k$. The wavelet leaders d_L are calculated from the wavelet coefficients for every point on this dyadic grid by finding the maximum wavelet coefficient among the adjacent wavelet coefficients for the current scale and all smaller scales (Fig. 3B and C).

$$d_L(j, k) = \max\{d_X(j', k')\} \quad (4.1)$$

such that

$$(k-1)2^j \leq 2^{j'} k' < (k+2)2^j \quad (4.2)$$

If n_j is the number of wavelet leaders $d_L(j, k)$ available at every scale 2^j for the time series $X(t)$, then the structure function $S(j, q)$ can be defined as:

$$S(j, q) = \frac{1}{n_j} \sum_{k=1}^{n_j} d_L(j, k)^q \quad (5.1)$$

where $k = 1, 2, \dots, n_j$. This function behaves as a power-law over analysis scale 2^j for a set range of scales and for a set range of statistical orders q . The scaling exponent $\zeta(q)$ may be calculated from the structure function $S(j, q)$ to quantify changes in variability as a function of scale j and statistical orders q :

$$S(j, q) = F_q(2^j)^{\zeta(q)} \quad (5.2)$$

where F_q is a constant independent of j . Then, singularity spectrum (Fig. 3E, gray line) can be estimated directly from the scaling exponent using a Legendre transform (Wendt and Abry, 2007).

The scaling exponents may also be rewritten as second characteristic functions, a standard function expansion of the natural log of the time averaged wavelet leaders C_p^j (Fig. 3D). The power law expansion of the first three terms of C_p^j are

$$C_1^j = E[\ln[\hat{d}_L]] = c_1^0 + c_1 \ln 2^j \quad (6)$$

$$C_2^j = E[\ln[\hat{d}_L]^2] - (C_1^j)^2 = c_2^0 + c_2 \ln 2^j \quad (7)$$

$$C_3^j = E[\ln[\hat{d}_L]^3] - 3C_2^j C_1^j - (C_1^j)^3 = c_3^0 + c_3 \ln 2^j \quad (8)$$

The log-cumulants c_1 , c_2 , and c_3 , which are calculated from the slope of C_p^j versus scale (Fig. 3D), correspond to specific attributes of the multifractal singularity spectrum (Wendt et al., 2007; Wendt and Abry, 2007). The singularity spectrum of a one-dimensional time series may be approximated as a polynomial expansion around its maximum (Ciuciu et al., 2012; Wendt et al., 2007) (Fig. 3E, red line).

$$D(h) = 1 + \left(\frac{c_2}{2!}\right) \frac{h - c_1^2}{c_2} + \left(-\frac{c_3}{3!}\right) \frac{h - c_1^3}{c_2} + \dots \quad (9)$$

c_1 is a self-similarity parameter, which measures long-range temporal dependencies. It takes values very closely related to the global Hurst exponent and therefore shares properties as discussed in Section 1.2 (Wendt et al., 2007). c_2 is a function of the width of the multifractal spectrum and acts as a test of mono- vs. multifractal. Monofractal signals are self-affine with a narrow range of Hölder exponents uniformly distributed throughout the signal. Multifractal signals deviate from pure self-affinity by expressing a wide range of nonuniformly dispersed variability throughout distinct regions. c_2 is always negative due to the inverted parabolic shape of the singularity spectrum. As c_2 becomes more negative, it is

indicates that the signal is more multifractal. c_3 is related to asymmetry in the distribution of scaling exponents on either positive or negative end of the singularity spectrum, and can be used to describe more complex multifractal models, such as compound Poisson cascades (Wendt and Abry, 2007). For this paper, we mainly focus on c_1 and c_2 because they describe the main features of the singularity spectrum, location and width, and are the most robust to calculate.

The Wavelet Leaders code was obtained from Wendt's freely available, online MATLAB toolbox, the WLMA Toolbox (Wendt et al., 2007; <http://www.irit.fr/~Herwig.Wendt/software.html>). For all of our analyses, j ranged from $2^j = [2^3-2^8]$ in integer increments, and statistical orders q ranged from 5 to -5 in 0.5 increments (excluding zero). Analyses were performed using this code with MATLAB version R2013a.

2.4.5. Wavelet leaders analysis of hippocampal interspike intervals—The wavelet leaders analysis was performed on a time series of interspike intervals (ISI) from every neuron recorded in either CA3 or CA1 during the DNMS task. In figures with interspike intervals over time (i.e., Figs. 1A, 3A bottom, and 5A), the “ISI Index” on the horizontal axes represents the sequential order of ISIs to illustrate the variability in ISI amplitude as spiking occurs over time. In these graphs, the vertical axes was normalized based on the largest ISI, and the width of ISI data line segments along the horizontal axes were normalized to fit all ISIs obtained during a single recording into one graphic. All recordings included in the analysis were at least one hour in length and contained a minimum of 2048 ISI data points. Log-cumulants were calculated for each neuron recorded during each session. The log-cumulants for the same neurons were averaged within drug conditions to obtain separate values for control and THC sessions used to construct scatter plots (Fig. 8) in Section 3.5. For the overall FCT analysis described in Section 2.4.2 and in Fig. 7, cumulant values obtained for all neurons during all recording session were compared using repeated measures ANOVA.

3. Results

3.1. DNMS task and behavioral performance with cannabinoid manipulations

The delayed nonmatch-to-sample task (DNMS) tests short term memory by requiring rats to retain spatial information acquired during the “Sample phase” throughout a subsequent variable delay period of 1–30 s ending with the “Last nosepoke,” after which they make a decision based on their memory of the sample phase in the “Nonmatch phase” (Deadwyler et al., 1996). Analysis from hippocampal pyramidal cell recordings (CA3 and CA1) revealed that FCTs encode task-specific information regarding combinations of lever position and task phase (Fig. 2B; Hampson et al., 1999). Results using this task have shown that behavior and hippocampal neural processing are impaired by relatively low doses of the cannabinoid receptor type 1 (CB1) partial agonist, delta-9-Tetrahydrocannabinol (THC; Fig. 4). Cannabinoids reduced ensemble information content, increased the number of neurons required to encode the same information as in control sessions, and impaired memory performance by reducing the strength of sample encoding (Hampson and Deadwyler, 2000). The sample encoding strength is a function of the firing rate of specific FCTs during the sample response (Fig. 2A and B), which has been shown to be critically important for

DNMS performance (Hampson et al., 1999, 2012). THC reduced the behavioral complexity by producing stereotyped responding, revealed in the increased behavioral bias, or “preference”, for the same lever in the nonmatch phase (Fig. 4). The important distinction between control and THC can be noted by examining the difference between preferred lever and non-preferred lever selection within the respective drug condition. When challenged with delays > 20 s, subjects in control sessions showed preferred responding, while preferred responding during THC sessions occurred at all delay intervals. Behavior becomes more stereotyped (less complex) during the task after THC administration compared to behavior produced by an uncompromised working memory system in the control condition.

3.2. Multifractal analysis of hippocampal interspike intervals

In time series, multifractal analysis describes the distribution and structure of variability across multiple temporal scales (Makowiec, 2010). Multifractal dynamics are exhibited by complex systems, like the brain (Di Ieva et al., 2013a, 2013b) from macroscopic brain oscillations (Ciuciu et al., 2012; Zorick and Mandelkern, 2013) to an intermediate scale of neuronal spiking (Biella et al., 1999) and to the microscopic scale ion channel fluctuations (Brazhe and Maksimov, 2006). To investigate complex interactions on the intermediate scale, a time series was constructed from the action potential timestamps recorded from individual hippocampal principal cells (CA3 and CA1). The differences between each successive spike were taken to create an interspike interval (ISI) time series to analyze using Wavelet Leaders-based multifractal analysis (Jaffard, 2004; Jaffard et al., 2007; Wendt et al., 2007). By examining the ISI of recorded neurons, it is not readily apparent which neurons are FCTs or not, nor is it possible to determine which neurons were subjected to THC (Fig. 5A and B). The differences between FCTs and non-FCTs are not detected by measuring the average firing rate or standard deviation over an entire behavioral session (population analyses in Sections 3.3, 3.4 and 3.7, respectively). Only after calculating the range of scaling exponents and the multifractal singularity spectrums do differences between these neurons become visually apparent (Fig. 5C). Multifractal analysis quantifies the heterogeneously distributed variability related to active working memory correlates across many spatiotemporal scales (Ihlen and Vereijken, 2010).

The wavelet leaders method produces log cumulant values, c_1 , c_2 and c_3 , which correspond to specific attributes of the multifractal singularity spectrum (see Section 2.4.4; Wendt et al., 2007). Multifractal singularity spectrums were constructed by analyzing ISI sequences of each hippocampal neuron recorded during each DNMS behavioral session. Recordings over all sessions for two FCTs, left and right trial type neurons each recorded from a different rat, are presented in the left plots of Fig. 6. Trial type cells are an FCT that corresponds to specific nonmatch-rule combinations; left trial type neurons discharge during left sample and right nonmatch responses, while the right trial type neurons fire for the opposite combination (Fig. 2B). Each singularity spectrum in the left graphs was computed from one DNMS session from the Hölder exponents h and corresponding dimensionality $D(h)$ values. The average log-cumulant values for each neuron during each condition were used to create average singularity spectra plotted on the right using the Eqs. (6)–(9) in Section 2.4.4. Within neuron drug-induced changes in c_1 and c_2 are seen by differing maximum h values

and spectrum widths, respectively. Both neurons had a statistically significant decrease in c_1 , but insignificant changes in c_2 .

3.3. Multifractal analysis facilitated identification of new FCTs

Previous work identified four different FCT groups: position, phase, conjunctive and trial-type cells. The results of multifractal analysis revealed that some neurons unidentified solely based on combinations of sample and nonmatch lever responses exhibited multifractal dynamics. Further FCT analysis labeled the last nosepoke, which coincides with termination of the delay and extension of levers for the choice phase (methods Section 2.4.1), as another event considered for FCT classification and increased the number of analyzed behavioral events from four to six. This allowed for a new type of phase cell, “nosepoke phase,” two conjunctive cell types, “left nosepoke” and “right nosepoke,” and two more trial-type cells, “left-trial sample-nosepoke” and “right-trial sample-nosepoke” to be identified (Table 1).

The addition of nosepoke events also allowed creation of two new FCT-groups: “Nosepoke-Nonmatch” and “3 Peaks.” These were not previously defined as a distinct FCT-group based on the subjectivity used in defining FCTs (Hampson et al., 1999), but multifractal analysis provided additional insight into the information processing of hippocampal neurons that allowed designation of new FCTs exhibiting significant peaks during the last nosepoke. Twenty-three neurons previously identified as nonmatch conjunctive cells were found to exhibit paired firing rate peaks during the last nosepoke and nonmatch response events; these are now classified as “Nosepoke-Nonmatch” neurons. These cells may be the same cells identified previously as a subset of nonmatch-conjunctive cells that fired in the nonmatch phase of the task as well as in the late (>15 s) portion of the delay (Deadwyler and Hampson, 2004). In addition, five neurons responded significantly to a combination of three out of six behavioral events, and these are now signified as “3 Peaks.” In total, including z-score analysis of the nosepoke event allowed us to classify 48 additional neurons as “new FCTs” that were distinguished by containing at least one significant peak around the last nosepoke event (Table 1).

3.4. Multifractal correlates of FCT designation scheme

Long-range temporal dependences and multifractal properties were examined at a population level by grouping hippocampal principal cells based on FCT firing characteristics as described in Section 2.4.1. 20 non-FCT neurons, 68 classic FCT neurons and 48 neurons exhibiting novel FCT classification were recorded in a total of six animals. Chronic hippocampal single-unit recordings allowed us to measure neuronal activity over many sessions to repeatedly measure activity over multiple control and THC sessions. The neurons within each FCT classification were subdivided by control and THC sessions and average c_1 and c_2 values were calculated (Fig. 7C and E). For c_1 , a repeated measures ANOVA revealed a main effect of drug condition ($F_{(1,133)} = 29.58, p < 0.0001$), an interaction between drug condition and FCT group ($F_{(1,133)} = 3.41, p = 0.036$), but no significant main effect of FCT group ($F_{(1,133)} = 2.24, p = 0.11$). It should be noted that all averaged c_1 values are greater than 0.5, which implies long-range temporal correlations and persistent structure. For c_2 , a repeated measures ANOVA showed main effects of drug condition ($F_{(1,133)} = 33.73, p < 0.0001$), FCT group ($F_{(1,133)} = 3.91, p = 0.022$) and an interaction between the

two ($F_{(1,133)} = 11.72, p < 0.0001$). Large, negative values of c_2 in FCTs indicate inhomogeneous diffusion of interspike interval variability. c_2 is always negative, but for illustrational purposes, we plotted the absolute value $|c_2|$ (Fig. 7E). Five posthoc t -tests were performed for c_1 and c_2 using Tukey-Kramer correction for multiple comparisons; drug effects were examined within each FCT group, and both classic and new FCTs were compared to non-FCTs (control condition only). THC reduced c_1 and $|c_2|$ in both classic FCTs and new FCTs (Fig. 7C and E). In addition, both classic FCTs and new FCTs recorded in the control group had significantly larger $|c_2|$ compared to non-FCTs in the control condition.

As a control procedure, the mean firing rate over the entire session was computed and a repeated measures ANOVA was performed (Fig. 7A). No significant effect of FCT group ($F_{(1,133)} = 0.03, p = 0.97$), drug condition ($F_{(1,133)} = 0.05, p = 0.83$), or interaction between the two ($F_{(1,133)} = 0.97, p = 0.38$) was detected. FCTs could not be distinguished from non-FCTs using mean firing rate as the dependent variable (Fig. 7A).

3.5. Multifractal correlates of FCT groups

Based on the positive results obtained from including nosepoke events, all FCTs were further subdivided into designated groups based on increased firing rate around a combination of task-related events using a standard z -score (Methods Section 2.4.1; Hampson et al., 1999). The neurons exhibiting significant nosepoke peaks were sorted into their respective classifications (Sections 2.4.1 and 3.3) from the classic FCT grouping system (i.e., the nosepoke phase cells were sorted as phase cells, etc.) or labeled as Nosepoke-Nonmatch (NP-NM) or 3 Peaks. This grouping yielded 10 position, 34 phase, 33 conjunctive, 11 trial-type, 23 nosepoke-nonmatch, and five “3 peak” cells that were used for all subsequent analyses in this section.

The first log-cumulant, c_1 , measures long-range temporal correlations in the data and is very similar to the Hurst exponent (Wendt et al., 2007; Ciuciu et al., 2012). Repeated Measures ANOVA for c_1 revealed a significant main effect of drug condition ($F_{(6,129)} = 36.46, p < 0.0001$), and an interaction between FCT group and drug condition ($F_{(6,129)} = 2.25, p = 0.0427$). However, there was not a significant main effect of FCT group ($F_{(6,129)} = 2.1, p = 0.0576$). Two sets of posthoc t -tests were conducted using Tukey-Kramer adjustment for multiple comparisons. Each FCT-group was compared to itself in control and THC conditions, and all control FCTs were compared to control non-FCTs (Fig. 7D). Trial-type and 3 Peaks in the control condition contained significantly greater c_1 values than control non-FCTs. All FCTs, except position and phase cells, showed a significant decrease in c_1 after THC administration (Fig. 7D).

The second log-cumulant, c_2 , quantifies the multiplicative interactions across spatiotemporal scales as indicated by multifractal dynamics. By convention, c_2 is negative, but the absolute value $|c_2|$ was used for graphing purposes (Zilber et al., 2012; Fig. 7E and 7F). Repeated Measures ANOVA for c_2 revealed a significant main effect of drug condition ($F_{(6,129)} = 34.68, p < 0.0001$), a significant interaction between FCT group and drug condition ($F_{(6,129)} = 4.37, p = 0.0005$), but no main effect of FCT group ($F_{(6,129)} = 1.73, p = 0.1181$). The same series of posthoc t -tests as performed for c_1 were done for c_2 . All control FCT-groups,

except position cells, were significantly more multifractal than control non-FCTs (Fig. 7F). All FCT-groups, except position and trial-type cells contained significantly more multifractal complexity in the control condition compared to the THC condition (Fig. 7F).

As a control, the same analysis was also performed using mean firing rate over the entire DNMS session (Fig. 7B). There was no main effects of drug condition ($F_{(6,129)} = 1.79, p = 0.18$) or FCT group ($F_{(6,129)} = 0.62, p = 0.72$). No interaction was detected ($F_{(6,129)} = 0.48, p = 0.82$). FCTs could not be distinguished from non-FCTs by using mean firing rate as the dependent variable.

The effects of THC on the dynamics of the entire recorded neuronal population is illustrated in Fig. 9 by comparing mean firing rate (Fig. 8A), c_1 (Fig. 8B), and c_2 (Fig. 8C and D) across drug conditions. In all of these plots, each neuron is represented by one dot labeled by its corresponding FCT-group. It is visually apparent that THC reduces c_1 , as seen by a larger cluster on the right side of the midline. THC reduces multifractality as indicated by c_2 closer to zero and the clustering toward the left of the midline (Fig. 8C and D). To appreciate the density of data points, neurons with c_2 less than -0.1 (designated by a black square in Fig. 8C) are also shown in a bigger plot (Fig. 8D). THC had no significant effect on mean firing rate since all data points reside near the midline (Fig. 8A).

3.6. Similar multifractal dynamics within hippocampus

Repeated measures ANOVA results looking for an effect of hippocampal location (CA3 or CA1) or hemispheric location (right or left) revealed no significant differences. When comparing c_1 values, there was no effect of hippocampal location ($F_{(1,135)} = 0.49, p = 0.48$) or lateralization ($F_{(1,135)} = 0.68, p = 0.41$). When comparing c_2 values, there was no significant effect lateralization ($F_{(1,135)} = 0, p = 0.97$), but a trend toward an effect of hippocampal location ($F_{(1,135)} = 3.67, p = 0.06$ with CA1 exhibiting slightly greater multifractal properties than CA3 (data not shown). This demonstrates that classifying neurons based on their multifractal properties is more useful than classification based on anatomical location.

3.7. THC increases standard deviation of hippocampal ISIs

Another series of control analyses examined if the standard deviation of ISI sequences could distinguish between FCT and non-FCTs in control or THC conditions. When using three FCT groups from Section 3.4 (non-FCTs, classic FCTs, new FCTs), a repeated measures ANOVA revealed a significant main effect of drug condition ($F_{(1,133)} = 8.53, p = 0.0041$), but no main effect of FCT group ($F_{(1,133)} = 0.02, p = 0.98$) or interaction between the two ($F_{(1,133)} = 0.31, p = 0.28$). When using all 7 FCT groups (Section 3.5), a significant main effect of drug condition ($F_{(6,129)} = 12.77, p = 0.0005$) was found, but FCT groups ($F_{(6,129)} = 0.78, p = 0.58$) could not be distinguished. An interaction could not be detected ($F_{(6,129)} = 0.77, p = 0.59$). In both cases, THC increased ISI standard deviation as measured throughout the entire behavioral session (data not shown). It was not possible to distinguish between FCT groups based on ISI standard deviation alone.

4. Discussion

4.1. Multifractal features of hippocampal FCT neurons

In the present work, we showed that WLMA and corresponding log-cumulants (Wendt et al., 2007) differentiated groups of neurons based on their memory-related responses (FCT characteristics), confirming our first two hypotheses. The ISI trains of hippocampal principal neurons recorded during a working memory task exhibit long-range dependencies and multifractal complexity. The finding that FCTs exhibit very multifractal discharge properties is an interesting property previously unattributed to memory-correlated neurons. It is known that FCTs are essential for sensory processing relevant for task performance (Hampson et al., 1999). Sensory processing occurring over sequential trials and across days may generate correlations in the neuronal response patterns (i.e., bursting sequences) detected by c_1 . FCTs could present increased multifractal dynamics due to the relatively large degree of effective connections necessary to promote successful memory performance. FCTs are known to represent memory processing during the DNMS task, and multifractal analysis provides an empirical method for quantifying their dynamical complexity that could be applied to many other forms of data. Importantly, the differences between FCT neurons and non-FCT neurons were not readily detected by mean firing rate and standard deviation calculations over the entire signal, and this emphasizes the importance of analyzing the structure of ISI variability with multifractal analysis.

Multifractal analysis revealed that some neurons unidentified using previous techniques exhibited a large degree of multifractal complexity, and this finding elicited investigation into their relationship to the DNMS task. Firing rate responses around the last nosepoke event were analyzed which allowed for creation of two new FCT-groups: nosepoke-nonmatch and 3 peaks. Previous work could have identified these neurons as FCTs if nosepoke events were included in the analysis (Hampson et al., 1999), but the subjectivity involved in this classification allowed these cell types to be undetected for 15 years. Grouping neurons with significant nosepoke peaks as new FCTs revealed that they are similar to classic FCTs, as both are more multifractal than non-FCTs and both show significant decreases of log-cumulants after THC administration (Fig. 7E). However, even with the inclusion of the last nosepoke event, FCT designation could not be assigned to all neurons with multifractal dynamics. For example, one non-FCT neuron with a c_2 near -0.3 could have a functional role in the task that was not detected by the standard FCT analysis using z -score (Fig. 8C), such as delay activity or rhythmic modulation, and future work is planned to thoroughly investigate these possibilities.

z -score analysis allowed for qualitative descriptions of FCTs into specific groups, while multifractal analysis allowed us to quantify the information processing capacity of these FCT-groups. We showed that trial-type and 3 peak FCTs groups contained more long-range temporal correlations and exhibited more multifractal complexity than non-FCTs. Phase, conjunctive, and nosepoke-nonmatch cells did not have greater c_1 values than non-FCTs but were more multifractal than non-FCTs (Fig. 7F). Position cells were not distinguished from FCTs by either log-cumulant. The lack of significance may represent an important link to the proposed “functional hierarchy” (Hampson et al., 1999), where position cells are labeled

as least complex. It is hypothesized that connections from position and phase cells converge onto conjunctive and trial-type cells as information becomes more specific (Hampson et al., 1999, 2012). Results from multifractal analysis lend support to this interpretation and suggest that multifractal properties of FCTs may arise from these hypothesized interactions. However, future work combining cross-correlation and multifractal analyses is needed to substantiate this claim.

Five FCT-groups, excluding position cells, were significantly more multifractal than non-FCTs in the control condition (Fig. 7F), but the scatter plot reveals some very interesting information when comparing the magnitude of multifractal complexity to FCT-group designation. Surprisingly, “very multifractal” neurons (i.e., $c_2 < -0.1$) are drawn from all FCT-groups. Previous results from z-score analysis and FCT-group designation (Hampson et al., 1999) suggested that trial-type cells are hierarchically more complex than position and phase cells. Additionally, it has been demonstrated that the MIMO model preferentially extracts trial-type cells to optimally boost performance with electrical stimulation (Hampson et al., 2012). However, our present results show that neurons from all FCT-groups exhibit a large degree of multifractal complexity (Fig. 8C). The absence of clear clustering based on FCT groupings suggests that neurons within specific FCT-group may not contribute equally to the DNMS task and supports the hypothesis that designing models based on FCT group alone might miss important information uncovered with multifractal analysis. The resulting spectrum of neurons with differing degree of multifractal complexity suggests that it may be advantageous to give a “functionality score” based on log-cumulants for neuronal modeling and microstimulation experiments (Berger et al., 2011; Hampson et al., 2012, 2013; Opris, 2013). One of the requirements of an effective MIMO model is recording and stimulation of neurons with high information content (Hampson et al., 2012), and multifractal analysis has allowed us to explore task-relevant neural firing on a deeper level by identifying a spectrum of multifractal neurons with different correlates to the behavioral task. In general, our results showed that 3 peaks are the most multifractal and nosepoke-nonmatch are second (Fig. 7F). However, this grouping still contains variability as it is visually apparent that three of the five FCTs with 3 peaks (left side of Fig. 8C) are more multifractal than the remaining two that can also be seen in Fig. 8D. Since multifractal analysis quantifies the structure of variability occurring throughout the entire recorded DNMS session, it is hypothesized that the FCTs exhibiting greater multifractal complexity than others in the same FCT group may exhibit additional roles undetected with z-score-based FCT classification.

4.2. Multifractality represents interactions across multiple spatiotemporal scales

Hippocampal neurons specifically involved in task-related mnemonic processing (i.e., FCTs) are multifractal and exhibit more multifractal properties than uninvolved neurons, which supports interaction-dominant model (Dixon et al., 2012; Ihlen and Vereijken, 2010) and suggests that these neurons may be involved with more active memory-related interactions than neurons without task-specific activity. The interactions suggested by multifractality may arise from involvement of specific hippocampal neural ensembles with other memory-related brain structures, interactions between frequency components, and/or coordination between macroscopic and microscopic brain processing mechanisms. In future work, it will be very important to examine cross-correlations between recorded neurons and

determine if multifractality arises directly from interactions within the recorded hippocampal population.

The multifractal nature of FCTs may arise from a greater amount of reciprocal connections with other anatomical regions. Interaction-dominant theory states that multifractal properties describe intermittency in signals due to exchange of information within and between cognitive structures across multiple temporal scales (Ihlen and Vereijken, 2010). The DNMS task is a working memory paradigm that necessitates interactions among all three classical memory modalities: memory encoding of the sample position, maintenance or short-term storage throughout a delay interval, and a recognition-based form of memory recall during the nonmatch phase. This “layered” form of memory processing may lead to multifractal dynamics. These three memory modalities are known to be distributed among various cortical and limbic structures, including the entorhinal cortex (Deadwyler et al., 1976; Newmark et al., 2013; Stepan et al., 2012; Talnov et al., 2003), prefrontal cortex (Hyman et al., 2010, 2011), subiculum (Deadwyler and Hampson, 2004, 2006), medial septum (Hasselmo and Stern, 2014; Mitchell et al., 1982; Rawlins et al., 1979) and parahippocampal gyrus (Barredo et al., 2013). It has been shown that the DNMS task involves reciprocal connections from the hippocampus to the subiculum (Deadwyler and Hampson, 2004, 2006) and theta-entrainment of cells in the medial prefrontal cortex during correct responding (Hyman et al., 2010, 2011). Multifractal analysis of simultaneous recordings of neuronal ensembles and local field potentials in these and other memory-related brain structures will enrich our understanding of cognitive processing related to multiscale spatiotemporal interactions.

Multifractal properties could correlate with neuronal bursting events specific to memory processing or bursting induced by endogenously generated brain rhythms, like theta or gamma rhythms. The requirements of the DNMS task synchronize neuronal action potentials (Berger et al., 2011; Hampson et al., 2012) and may elicit neuronal avalanches (Beggs and Plenz, 2004; Palva et al., 2013; Ribeiro et al., 2010) during memory encoding or recall, and this bursting activity could produce the detected power-law distribution of interspike intervals. Specific, recurring spatiotemporal bursts of neuronal activity were shown to possess the diversity and long-term stability required as a memory substrate (Madhavan et al., 2007) activated during both encoding and retrieval (Ji and Wilson, 2007; Nádasdy et al., 1999). Similar spatiotemporal activity patterns may underlie memory transmission and storage mechanisms described as the memory engram (Liu et al., 2014; Ramirez et al., 2013), neuronal avalanches (Beggs and Plenz, 2003, 2004; Ribeiro et al., 2010), and spatial memory encoding during the sample lever press (Berger et al., 2011, 2012; Deadwyler et al., 2013).

It has also been postulated that brain rhythms, specifically theta and gamma rhythms, can coordinate neuronal assemblies by precise temporal modulation of network excitability (Buzsáki and Draguhn, 2004; Buzsáki and Moser, 2013; Chrobak et al., 2000). Theta-entrainment of specific medial prefrontal neuronal populations is known to occur during successful nonmatch responses in the DNMS task (Hyman et al., 2010, 2011). Cross-frequency theta-gamma coupling correlates with memory success in rats (Shirvalkar et al., 2010; Tort et al., 2009) and humans (Axmacher et al., 2010; Canolty et al., 2006). Theta-

gamma comodulation produces “up-states” (Mölle and Born, 2011) during which memory-specific neuronal ensembles can become coordinated as nested representations (Jensen, 2006; Mathis et al., 2012) or bursts within bursts (Linkenkaer-Hansen et al., 2001) across many resolution scales. The notions of nested neuronal resolutions and cross-frequency comodulation can be viewed as comparable to self-affinity, intermittency, scale-invariance, and temporally specific activity patterns characteristic of multifractal dynamics, especially when viewed as evidence for interaction-dominant theory (Ihlen and Vereijken, 2010). All of these phenomena could potentially generate multifractal dynamics in single neurons activated by the memory sequence. Interactions between frequencies have been postulated to represent an exact timing mechanism extractable from local field potentials, while multifractal interactions between temporal scales suggest a precise temporal structure of neuronal interspike intervals. These views from two measurement scales may reflect self-affine timing processes. Multifractal analysis provides a method to understand how macroscopic oscillations interact with neuronal spike trains and could facilitate development of a more coherent timing paradigm through future theory integration.

Fractal processes are described by $1/f^\alpha$ power-law distributions and self-affine patterns appearing over macroscopic to microscopic scales. This relationship can be conceptualized in the brain as the different measurement scales ranging from surface EEG to local field potentials to neuronal spiking and to more microscopic levels of channel currents and biochemical molecular interactions. Modeling of recurrent fractal neural networks (Bieberich, 2002) and topological structure of brain modules and clusters in fMRI data (Gallos et al., 2012a, 2012b) reveal fractal dynamics at the most macroscopic level. Self-organized criticality (metastability) is suggested by the presence of $1/f^\alpha$ power-law distributions (Bak et al., 1987). Networks are “optimized” in the critical state: interpretation of sensory stimuli (Linkenkaer-Hansen et al., 2004), fluctuations between cognitive states (Linkenkaer-Hansen et al., 2001), adaptation to novel circumstances (Alstrom and Stassinopoulos, 1995), neuronal integration within avalanches (Beggs and Plenz, 2003, 2004) and maintenance of large memory repositories (Ribeiro et al., 2010) occurs in an augmented fashion during metastability (Kinouchi and Copelli, 2006). Modeling work predicts coupled neural oscillators in a metastable (critical) state produce long-range temporal correlations and fractal properties of interspike intervals (Fronczak et al., 2006; Usher et al., 1995). We hypothesize that long-range dependencies and multifractal features provide empirical measures of persistent activity structure and increased network interactivity of FCTs compared to non-FCTs. Future experiments are planned to improve upon the current methodology by combining multifractal analysis with spectral, wavelet and unsupervised machine learning algorithms to understand what other aspects of neuronal activity may contribute to the multifractal complexity of FCTs.

4.3. Role of THC in multifractal behavior of neural firing

Tetrahydrocannabinol (THC), the main psychoactive component of cannabis (Gaoni and Mechoulam, 1964), administered prior to the DNMS task reduced memory performance, hippocampal memory encoding (Deadwyler et al., 2007), information content (Hampson and Deadwyler, 2000), long term dependencies and multifractal properties. THC administration disrupts the complexity of responding by evoking a more simplistic, homogenous behavioral

pattern during performance of the DNMS task. The rats adopted a stereotyped performance strategy in an attempt to maximize rewards; they increasingly chose a “preferred” lever during the nonmatch phase during challenging trials with long delays (Fig. 4). The ability of THC to impair behavioral performance seems correlated with its capacity to reduce long-range temporal correlations (Fig. 7C) and multifractal properties (Fig. 7E) in FCTs, which only partially confirms our third hypothesis since non-FCTs were unaffected by THC (Section 1.3). These results highlight the usefulness of multifractal analysis in examining the effects of cannabinoids on brain and nervous system function and provide novel insight into THC’s mechanism of action. The use of THC also provides reciprocal insight into what multifractal complexity of hippocampal neurons could reveal about memory processing. According to interaction-dominant theory (Ihlen and Vereijken, 2010; Kelty-Stephen et al., 2013), it could be hypothesized that THC reduces multifractal complexity of FCTs by inhibiting interactions with other task-relevant neurons or brain areas.

Since non-FCT neurons are not processing much, if any, task-related information, the lack of a THC effect on fractal measures is consistent with the presence of fractal modification only in areas receiving information (Linkenkaer-Hansen et al., 2004). The absence of a THC effect on either log-cumulant of position cells initially seems surprising (Fig. 7D and F), but it could be attributed to a smaller number of neurons within this group (10 neurons). The scatter plot (Fig. 8C) shows at least 3 position cells residing to the left of the midline because THC reduced their multifractal complexity; two position cells clearly show reduced c_1 after THC administration (Fig. 8B). THC did not significantly reduce c_1 of phase cells, but c_2 was significantly reduced by THC in this FCT-group. Trial-type cells showed the opposite effects, where THC reduced c_1 but not c_2 . Before adjusting for multiple comparisons, all 4 of the above differences were detected, and this suggests that with more neurons in these FCT-groups, significance would have been achieved. The scatter plot (Fig. 8C) suggests that THC may preferentially reduce multifractality of very multifractal neurons from all FCT-groups. The lack of an effect of THC on some FCT-groups suggests that a weighting system of scores based on event-related (FCT correlates) activity and fractal properties (log-cumulants) could accurately and objectively capture more relevant interactions than previously used FCT detection methods (Hampson et al., 1999).

In general, THC could be reducing temporally precise activity in the working memory network which was detected as reduced multifractal dynamics of FCTs. The two most commonly reported effects of cannabis use are short term memory deficits and a distorted sense of time (Atakan et al., 2012; Tart et al., 1970). THC disrupts temporally specific information and serial dependence related to sensory processing in the hippocampus (Hampson et al., 1989) and increases the probability of nonmatch information proactively interfering with encoding of the next sample position during the DNMS task (Deadwyler and Hampson, 1997; Hampson and Deadwyler, 1998, 2000). Within the conceptual framework of multiscale temporal processing, THC-induced impairment may predispose retrieval from inappropriate time scales (previous trials), which would be in line with impaired short term memory processing and reduced sequential memory differentiation. THC effectively causes decoupling and reduced cellular synchrony of intrahippocampal activity (Goonawardena et al., 2011). Theta phase-locking correlates with successful DNMS

performance (Hyman et al., 2010, 2011), and in similar spatial working memory tasks, cannabinoid agonists impaired theta phase-locking of medial prefrontal cortical neurons to hippocampal LFP (Kucewicz et al., 2011), decreased theta power, and reduced temporal coordination of hippocampal principal cell ensembles (Robbe et al., 2006). In humans, THC reduces EEG theta power and synchrony (Ilan et al., 2005), working memory speed (Böcker et al., 2010), accuracy, (Ilan et al., 2004), and activation of the working memory network (Bossong et al., 2012). Interesting, it was shown that decreased frontal theta power correlates with increased default mode network (DMN) activity (Scheeringa et al., 2008). DMN activity correlates with stimulus-independent thought (Mason et al., 2007), and activity in this network is inappropriately induced by THC during an executive function task in humans (Bossong et al., 2013). It has been proposed that effects of cannabis, such as mind-wandering, disorganized thought, and memory impairments could be related to the increased default mode network (DMN) activation (Bossong et al., 2013). These studies suggest that THC decreases working memory network function by facilitating DMN network activity, and this phenomenon may reduce interactions and multifractal dynamics of FCTs measured during the DNMS task.

Evidence for fractal dynamics in spike-timing and receptor dynamics exists at a more microscopic level, where cannabinoids modulate channel currents, synaptic plasticity and neurotransmitter release. Ion channel kinetics (Liebovitch and Sullivan, 1987; Lowen et al., 1999), AMPA receptor state transitions (Szárics et al., 2000), and quantal release events (Lamanna et al., 2012) exhibit fractal behavior. Channels have been successfully modeled using chaotic (Bandeira et al., 2008) and multifractal properties (Brazhe and Maksimov, 2006). Endogenous cannabinoids, or “endocannabinoids,” alter synaptic currents by activating CB1-receptors (Mechoulam and Parker, 2013; Morena and Campolongo, 2013). Endocannabinoids can act preferentially on either glutamate or GABA neurons (Domenici et al., 2006), and thereby modulate the “spontaneous” levels of excitation and inhibition (for review, see Diana and Marty, 2004; Lutz, 2004). Endocannabinoids were shown to enhance spike-time precision through selective inhibition of GABAergic neurons (Dubruc et al., 2013). Cannabinoid receptor activation inhibits calcium currents (Twitchell et al., 1997), increases potassium conductance (Mu et al., 1999), and inhibits long-term potentiation (Terranova et al., 1995). These mechanisms demonstrate numerous ways whereby cannabinoids can modulate neurotransmitter release and network excitation. Critical state dynamics are characterized by a balance between network stability and information transfer, and another way to interpret this would be a balance between excitation and inhibition (Beggs and Plenz, 2003). Our data suggests that THC might reduce the criticality of the network as measured by decreased fractal properties, and this may be, in part, due to the modulation of excitation and inhibition at the cellular level caused by exogenous cannabinoid administration (Xu et al., 2010).

4.4. Multifractal analysis as a biomarker

Multifractal analysis could be used as a biomarker for identification, detection and classification of recorded biological signals to improve computational models and predictions based on experimental data. Much evidence exists suggesting that multifractal analysis could be used to improve our understanding of clinically defined disorders.

Multifractal can enhance placement precision of deep brain stimulators needed for Parkinson's disease by distinguishing between brain areas (Zheng et al., 2005). Some indication exists demonstrating the efficacy of patterned spatiotemporal electrical stimulation in suppressing seizures (Osorio et al., 2005; Sandler et al., 2013; Sun et al., 2008). Seizure events measured in mouse and human hippocampus show decreased nonlinearity and reduced multifractal character (Serletis et al., 2012), and together, these results suggest the multifractal analysis might provide critical information relevant for seizure detection, prediction and prevention.

Our data supports the idea that multifractal analysis could be incorporated into brain-computer interface detection algorithms as a biomarker for neurons or signals that might be functioning in the task (Hu et al., 2013). Multifractal analysis describes the temporal evolution of scale-invariant movement patterns over time and across environments (Ihlen and Vereijken, 2013). Understanding how movement patterns are encoded in the motor cortical regions is critically important for advancing the learning rate for users and improving decoder algorithms (Ortiz-Rosario and Adeli, 2013). Multiplicative interactions between temporal scales reflects healthy performance and adaption to external environmental influences (Ihlen and Vereijken, 2013), and integrating naturally occurring modes of movement and adaptation into BCI algorithms should be ideal for mimicking biologically produced motions. By combining multifractal analysis with established BCI algorithms, like band-power features, we believe that improved classification and decoding performance of the technology can be achieved (Brodu et al., 2012).

5. Conclusions

We have shown that the heterogenous distribution of task-relevant hippocampal interspike intervals possesses long-range temporal correlations and multifractal properties, and these results support the interaction-dominant theory. We suggested mechanisms for these interactions: different memory-related brain regions may preferentially connect with FCTs, multifractal ISI distributions may be a cellular correlate of cross-frequency coupling, and/or multifractal ionic currents may alter firing properties. Future work could bridge the gap over spatial scales by relating the multifractal activity of ion channels to the membrane potential of neurons, to action potential intervals, and to interactions between neurons. In addition, combinations of acquisition modalities, including fMRI, EEG, MEG, and multi-unit recording, could improve our understanding of the multifractal interactions occurring within the brain across multiple spatiotemporal scales. Additional sophisticated techniques, like unsupervised machine learning and wavelet coefficient analyses, could also be combined with results from multifractal analysis to generate deeper insight into these mechanisms. One major benefit of multifractal analysis is that it can be applied to previously collected neurophysiology data to further understand its complexity and provide evidence either for or against interaction-oriented dynamics within a given system. Multifractal analysis is a very translational approach, and by capitalizing on this advantage, better clinical theories and treatments may be established. By incorporating multifractal analysis with other proven neuroscience techniques, we will be able to improve data analysis and develop richer interpretations that would advance progress in many clinically relevant areas.

The central theme of the proposed mechanisms generating multifractal complexity in FCTs relies on dynamical interactions across spatial and temporal scales. Previous experiments have shown that the MIMO model relies heavily on information from trial-type neurons (Hampson et al., 2012), but the current results suggest that neurons with the largest degree of information content, as measured by multifractal complexity, may be represented from all different FCT-groups. Information processing relevant for performance of the task can be detected using multifractal analysis, as demonstrated by the reduction in log-cumulants after memory-impairing doses of THC. Multifractal analysis promoted the identification of two new classes of FCTs: nosepoke-nonmatch and 3 peaks. Together, our results show that multifractal analysis can detect neuronal processing relevant for memory performance. We hypothesize that multifractal log-cumulants can provide an objective measure for pre-screening neurons to include in neuroprosthetic models and devices, including MIMO and BCI, which overcomes the subjectivity associated with z -score-based FCT classification.

Acknowledgments

The authors thank Dr. Miaohua Jiang for his time spent thoroughly explaining multifractal analysis and related concepts. The authors appreciate the efforts of Drs. Andrew Sweatt, Cheryl Ann Sexton, Anushka Goonawardena and technical support from Chad Collins. The authors thank both Drs. Sweatt and Sexton for extensive discussions and comments that improved this manuscript. This work was supported by contracts to S.A.D from the DARPA REMIND Program (N66001-C-09-2080 & N66001-C-09-2081, COL. Geoff Ling, Program Manager), NIDA DA07625 and DA006634 (to S.A.D.). This work was also supported by NIBIB grant K25 EB012236-01A1 to S.L.S.

Abbreviations

DWT	discrete wavelet transform
DNMS	delayed nonmatch to sample
FCTs	functional cell types
THC	Delta-9 tetrahydrocannabinol
WLMA	wavelet leaders-based multifractal analysis
ISI	interspike interval

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HIGHLIGHTS

- Multifractal analysis quantifies dynamical information processing characteristics.
- Memory-encoding hippocampal neurons generate multifractal discharge properties.
- Multifractal analysis promoted identification of new “Functional Cell Types”.
- THC reduced memory performance and multifractality of memory-correlated neurons.

Fig. 1.

Comparison of singularity spectra for multiple types of time series. (Top) Three example interspike interval time sequences recorded from the hippocampus (Section 2.4.5). (Bottom) The respective singularity spectra computed for each signal: uncorrelated signal (red), monofractal (green), and multifractal (blue). The singularity spectrum quantifies the distribution of variability in time series. The fractal (Hausdorff) dimension $D(h)$ on the vertical axis is plotted against the range of Hölder exponents h on the horizontal axis (Sections 2.4.3 and 2.4.4). The global Hurst exponent and consequently the peak position on the horizontal axis is 0.5 of the uncorrelated signal. The monofractal and multifractal signals have global Hurst exponents greater than 0.5 indicating long-range temporal correlations in the signal. The multifractal spectrum (blue) is much wider than the others because a larger range of Hölder exponents is needed to accurately describe the heterogenous distribution of variability. The uncorrelated was selected based on results obtained using multifractal analysis because it has a global Hurst exponent of 0.5. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 2.

Delayed non-match to sample (DNMS) task and hippocampal functional cell types. (A) Diagram of different phases of DNMS task: (1) Sample lever presentation (SP) in one of two positions (left or right) and Sample lever response (SR) followed by (2) delay interval of random durations during which delay timeout was contingent on a nosepoke (last nosepoke, LNP) into photocell mounted on opposite wall, followed by (3) simultaneous presentation of both levers (left and right) in Non-match phase in which (4) a Non-match Response (NR) on the lever opposite the spatial position to the prior SR produced, delivery of 0.2 ml of water to the trough between levers for the correct (Non-match) choice or (5) a response on the same lever as the SR shut off houselights for 5 s indicating an incorrect (Match) choice and no reward. Timeline shows sequence of task phases: ITI – intertrial interval; SP – sample lever presentation; SR – sample response; Delay – delay interval; NPs – nosepokes during Delay; LNP – last nosepoke; NR – nonmatch position response; Reinf. – delivery of water (0.2 ml) reward. (B) Examples of functional cell types of hippocampal neurons recorded on same bilateral arrays determined by correlated firing (± 1.5 s) to Sample (SR) and Non-match (NR) task events (0.0 s). Raster and perievent histograms for 4 different types of FCTs, Left and Right Trial Types, Right Sample Conjunctive and Non-match Phase, are shown for each lever position (right or left) and each phase (sample or nonmatch) of the task (Hampson et al., 1999). (C) Hippocampal recording array consisted of eight pairs of stainless steel 20 μ m wires positioned longitudinally within each hippocampus at 200 μ m intervals. For each pair one electrode was positioned in CA3 and the other in CA1 cell field

in a line tangent to the longitudinal axis of the hippocampus. Arrays were implanted bilaterally in each hippocampus providing a total of 32 electrodes per animal.

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Fig. 3.

Illustration of Wavelet Leaders-based Multifractal Analysis. (A) (Bottom) The interspike interval time series of one neuron recorded during on DNMS session (Section 2.4.5). (Top) The continuous wavelet transform of this interspike interval sequence. A continuous wavelet transform is shown here for illustrational purposes only; a discrete wavelet transform was used for all data analysis presented in this paper. (B) The wavelet coefficients are selected on dyadic grid. The measurement scale (bin size) increases moving up the vertical axis, and time is increasing along the horizontal axis. At each point in the dyadic grid, the wavelet leader (circled) is the maximum wavelet coefficient among the wavelet coefficients to the immediate right and left and for all lower scales (the two gray boxes). (C) The wavelet leaders d_L are calculated as a function of measurement scale j . Since wavelet leaders are averaged according to the scale (bin size), this results in the fewer wavelet leader data points at each scale. In order for the scale invariant structure of the wavelet leaders to be seen, the average wavelet leader is plotted according to its bin size. As measurement precision increases from top to bottom, the measurement scale (bin size) decreases. This is why the length of the ISI index does not change and the wavelet leaders appear to have higher resolution (Section 2.4.5). (D) The log-cumulants are derived from the slopes second characteristic functions derived from the natural log of the time averaged wavelet leaders. c_1 is obtained from the slope of the red line, c_2 from the blue line, and c_3 from the green line. (E) The singularity spectrum can be estimated from the log-cumulants (red) or the scaling function (gray). Both methods yield very similar estimates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 4.

Average DNMS task performance during control and THC sessions. Mean ($\pm$ SEM) % correct non-match responses (NRs) summed across animals ($n = 6$) shows significant decline in accuracy ($F_{(5,595)} = 61.79$, $p < 0.001$) as a function of delay duration in 5.0 s blocks. A main effect of drug condition ($F_{(1,119)} = 32.09$, $p < 0.001$) and interaction between drug condition and delay interval ($F_{(5,595)} = 2.36$, $p < 0.05$) were detected. Solid lines show THC significantly impaired performance at all six delay intervals ($p < 0.05$). The dashed lines illustrate correct performance according to lever preferences which demonstrate that stereotyped responding underlies reduction in performance during THC administration. Under THC, there was a larger difference between preferred and non-preferred choices at all delay intervals. Preferred responding begins in the control condition only when delays are greater than 20 s. A within subjects design with at least 2 non-drug days between THC administration was used. All animals were given THC (1.0 mg/kg) for no less than five sessions spaced over multiple weeks.

Fig. 5.

Multifractal differences of interspike intervals quantified by singularity spectra. The first four graphs each show the sequence of interspike intervals recorded during one daily DNMS behavioral session. The ISI amplitude is normalized to one for each session based on the largest ISI and the ISI index represents the temporal ISI pattern (Section 2.4.5). Above each graph, the bracketed numbers signify (in order): the measurement scale, the average firing rate in hertz, and the standard deviation of ISIs. On the right, the singularity spectra are plotted with Hausdorff dimension $D(h)$ on the vertical axis and Hölder exponent h on the horizontal axis. (A) The interspike intervals (ISI) of one FCT (top) and one non-FCT (bottom) recorded over one control session. (B) The ISI of one FCT (top) and one non-FCT (bottom) recorded over one THC session; the same neurons as in (A) are shown in (B) when recorded under THC administration. (C) In the FCT control condition (top, blue), the central location of the spectrum exists at a larger Hölder exponent (signified by larger c_1) and the spectrum is wider (signified by larger c_2) than all other illustrated neurons. THC reduces both c_1 and c_2 , designated by the leftward shift and decreased width, respectively. The fractal characteristics of the non-FCT are unchanged by THC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 6.

Multifractal singularity spectra of Trial-Type Cells during THC administration. Right trial-type cells discharge for the right sample response and the left non-match response, while left trial-types respond during the left sample and right non-match. Together, these cell types provide the most essential information for DNMS performance. In the left graphics, each trace represents the results for that specific neuron obtained during one session. Control sessions are in blue and THC sessions are in green. We used a repeated measures design to collect data from the same neuron on a daily basis while interspersing control and THC days. Each of the two cells was recorded over multiple days from two different rats. The right figures represent the averaged spectrum by condition. The log-cumulant values in the table are averaged for each cumulant over all sessions the neuron was recorded. THC significantly reduces c_1 in these functional cell types ($p < 0.05$). However, THC non-significantly reduces c_2 ($p = 0.12$ for the left trial type and $p = 0.14$ for the right trial type).

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Fig. 7.

Effects of THC by FCT-group designation. (A and B) THC did not significantly affect mean firing rate recorded throughout the entire behavior session using either FCT grouping scheme. (C) THC significantly reduced long-range temporal correlations, as measured with c_1 , in both classic and new FCTs. (D) THC significantly reduced c_1 in Conjunctive, Trial-Type, Nosepoke-Nonmatch and 3 Peak FCT-groups. Recorded in the control condition, Trial-Type and 3 Peaks FCT-groups had significantly larger c_1 values than control non-FCTs. (E) Both classic and new FCTs in the control condition have significantly larger c_2 values compared to non-FCTs in the control condition. THC significantly reduced multifractal complexity in both classic and new FCTs. (F) All FCT groups recorded in the control condition, except position cells, exhibited greater multifractal complexity than non-FCTs from the control condition. THC reduced multifractal properties of phase, conjunctive, NP-NM and 3 Peaks FCT-groups. In all graphs, * $p < 0.05$, ** $p < 0.01$, # $p < 0.0001$.

Fig. 8.

Scatter plots comparison of control versus THC condition. These scatter plots show the entire recorded neuronal population coded by color-symbol patterns based on FCT-group designation. The midline is plotted on all graphs to visually show deviations from equal dependent variables between control and THC conditions. (A) The mean firing rate of the neuronal population did not change due to THC administration, and data points cluster around the midline. (B) THC reduced c_1 in many different neurons across FCT-groups, as noted by the rightward-shifted cluster below the midline. (C) THC reduced multifractal complexity as measured by c_2 values closer to zero. This is visually seen by the clustering of neurons to the upper left of the midline. (D) The “dense” section of (C), designated by the black square, is enlarged with axes limits to -0.1 instead of -0.6 . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1

New FCT classification. By including the last-nosepoke event, a total of 48 new neurons could be identified as FCTs. In Section 3.4, these neurons were classified as “new FCTs.” In Section 3.5, they were designated into their respective FCT-group.

New FCT Classification	# Detected
Nosepoke phase	10
Left nosepoke conjunctive	4
Right nosepoke conjunctive	2
Left sample-nosepoke trial-type	4
Right sample-nosepoke trial-type	0
Nosepoke-non-match	23
3 Peaks	5