Multiplexed coding in the human basal ganglia

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Abstract— **A classic controversy in neuroscience is whether information carried by spike trains is encoded by a time averaged measure (e.g. a rate code), or by complex time patterns (i.e. a time code). Here we apply a tool to quantitatively analyze the neural code. We make use of an algorithm based on the calculation of the temporal structure function, which permits to distinguish what scales of a signal are dominated by a complex temporal organization or a randomly generated process. In terms of the neural code, this kind of analysis makes it possible to detect temporal scales at which a time patterns coding scheme or alternatively a rate code are present. Additionally, finding the temporal scale at which the correlation between interspike intervals fades, the length of the basic information unit of the code can be established, and hence the word length of the code can be found. We apply this algorithm to neuronal recordings obtained from the Globus Pallidus pars interna from a human patient with Parkinson's disease, and show that a time pattern coding and a rate coding scheme co-exist at different temporal scales, offering a new example of multiplexed neuronal coding.**

Keywords— **Neural code, time patterns, structure function, Parkinson's disease, basal ganglia.**

I. Introduction

The concept of neural code is a central paradigm in neuroscience [1-2]. However, a precise definition of what is meant by neural code, or neuronal encoding, can be elusive. A general definition of code can be applied to the particular study of the neural code, defining code as "a set of symbols and the rules for their combination, which can be used to represent a pattern of information in a manner different from that of the original signal" [3]. This definition can also be modified to "the smallest set of symbols" [4]. According to this, two main elements need to be identified in a spike train to be able to characterize its neural code: the symbols (words), and the rules governing their combination (grammar). In this sense, an analysis of the neural code is not necessarily bound to lead to an understanding of the meaning of such code in a given context (semantics), making a theoretical approach possible, independently from specific experimental settings [5].

A novel approach to the problem of finding the basic symbols of the neural code has been recently proposed by our group [6]. Based on the calculation of the temporal structure function, an algorithm was developed that can be used for finding the average word length of the neuronal code in a given spike train. (Our algorithm is publicly available at www.neurostruct.org.) Structure functions were originally applied by Kolmogorov to the analysis of fluids undergoing turbulence [7], and can be calculated in the spatial or the temporal domain. Structure functions have been shown to be robust to noisy and short time series, which makes them suitable for working with neuronal data, often consisting of short, highly variable spike trains [8]. More importantly, mathematical properties of the structure function allow determining if a signal is generated by an underlying monofractal, multifractal, or random process [9]. Of particular interest for the analysis of the neural code is the random case, where the slope of the structure function = 0. It has been argued for a long time that, if it can be assured that a given spike train is generated by a random process, then any kind of coding other than a time averaged measure (most probably a rate code) must be precluded [10]. This is precisely the kind of analysis that can be performed by the calculation of the temporal structure function. In the zero-slope region of this function a stochastic process is bound to generate the neuronal signal analyzed. Therefore, at this temporal scale it can be affirmed that any information transmitted must be necessarily coded in the rate of discharge, or a similar time averaged measure (for a more detailed discussion, see ref. 11). Conversely, regions of the function where a non-zero slope is found correspond to a temporal scale where complex geometrical properties are present (either monofractal, or multifractal). These scales are suitable for the transmission of complex time patterns (and hence, a time code). Furthermore, independent events cannot be transmitted at the temporal scales where a complex behavior is observed, given the high temporal correlation between spikes present at those. This is why any events transmitted within this temporal window are necessarily encoded in the same information unit, ultimately offering a measure of the word length of the code.

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In this work, we propose to apply this kind of analysis to neuronal recordings obtained from the Globus Pallidus pars interna (GPi) from a human patient with Parkinson's disease. The GPi represents a main output center of the basal ganglia, the primary circuit that is altered by parkinsonism. To achieve a better understanding of the neuronal encoding by these neurons might help developing better pathophysiological models of Parkinson's disease, and hence a better treatment of this condition.

II. Materials and methods

A. *Algorithm*

Firstly, the temporal structure function is calculated based on interspike intervals (ISIS) time series obtained from single cell recordings. We define $I(t)$ as the t th interspike interval and $\Delta I(\tau) = I(t+\tau) - I(t)$, where τ is the number of ISIS between $I(t)$ and $I(t+\tau)$, also known as time lag increment. The structure function $S_q(\tau)$ is then calculated as:

$$(1)\quad S_q(\tau) = \left\langle \left| \Delta I(\tau) \right| \right\rangle ,$$

where $\langle \cdot \rangle$ accounts for the statistical average and τ varies between 1 and 1000. Here we only consider the first order structure function (q=1). A smoothing technique is then applied, averaging over a running window of 30 adjacent points. This step of the algorithm has the purpose of softening the effects of the high frequency variability typically present in neuronal signals. Finally, a breakpoint in the temporal structure function is looked for, where the slope abruptly changes from either positive or negative to zero on average. To determine this point, the first derivative of the smoothed structure function is calculated, S'. Then, the first point of S' is eliminated, to account for some cases where a high correlation is only found at a scale of $\tau = 1$, which we do not consider significant. Finally, the breakpoint τ_1 is defined as the smallest τ for which $S' < 0$ for three consecutive τ for cases where the initial part of the structure function is ascending, or the smallest τ for which $S' > 0$ for three consecutive τ , if the initial portion of the structure function is descending. At least 4 consecutive points are required to have either a positive or negative slope to consider an ascending / descending region of the function, respectively, to account for the effects of the high frequency variability. (Computer code is available by request. An online version of this algorithm can be tried at www.neurostruct.org.).

B. Data analysis

a) Neuronal recordings

A patient with Parkinson's disease, Hoehn&Yahr IV, and fulfilling Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT) criteria, was routinely selected to undergo surgical implantation of DBS electrodes at our clinic. (Patient's age, gender and nationality are excluded to protect privacy.) The patient signed informed consent prior to the intervention, which was previously approved by the institutional ethics committee. The patient was not under the effect of any neurological medication at the time of the surgery. Briefly as described elsewhere, microrecording, stimulation, and neurosurgical procedures were performed while the subject was awake and under local anesthesia [12]. The patient underwent surgical target planning employing magnetic resonance imaging (MRI) and using a Leksell stereotactic system (Series G, Elekta, Sweden). Initial GPi targets were planned according to anatomical coordinates and corrected using MRI image fusion techniques. The patient showed a favorable outcome after the surgery.

Microelectrode recordings of the neuronal activity were obtained during the surgery. Microrecording was performed using platinum/iridium (Pt/Ir 80/20%) microelectrodes with nominal impedance of 0.8−1.2 megohms (mTSPBN-LX1, FHC Inc). The signal was amplified, conditioned and digitized with a dedicated acquisition system (1401plus, CED). The sampling rate used was 50 kHz. A preamplifier (remote probe) mounted onto a motorized microdrive (FHC 65-00-1 Stepper Drive and ST-M0-00 TMS Controller) located near the electrode tip to minimize pickup of electrical noise was connected to a differential amplifier with a built-in impedance meter (FHC IS-AM-00-01 Iso-Xcell 3 Amplifier) and an isolated stimulus generator (FHC IS-PL-06 Isolated Bipolar Pulsar Stimulator; FHC, Bowdoinham, ME). Acquired signals were submitted to

a single unit's classification algorithm and separation into unit classes was carried out by means of wavelet analysis and a clustering algorithm (developed by Quian-Quiroga,[13]). Interspike intervals were extracted and used to construct time series of single units.

b) Surrogate data

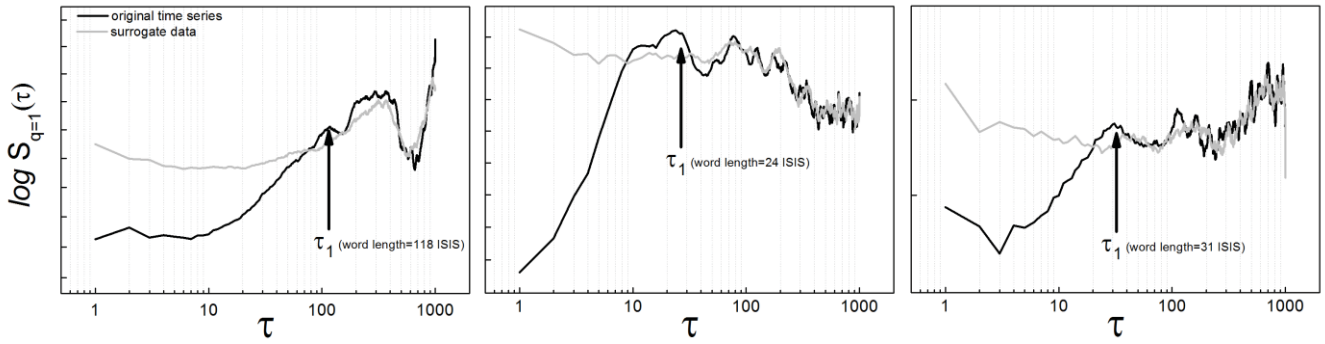

Fig. 1 Temporal structure function calculated for sample GPi neurons and the corresponding surrogate data. The word length (τ_1) can be observed, defined as the first breakpoint were the slope changes from positive to zero on average. The positive slope (related to fractal properties of the time series) is lost in the case of the surrogate data, indicating the dynamic origin of the complex behavior observed.

Surrogate data were generated applying a shuffling technique to the raw ISIS time series, in order to test the hypothesis of a non-random organization in the spike trains. Because our hypothesis states that the neuronal discharge only presents a temporal organization at the scales where the temporal structure function shows a non-zero slope, we shuffled the ISIS specifically at these scales, by changing each ISI for any other, randomly chosen at a distance smaller than τ_1 from the first one. This kind of shuffling preserves the probability distribution function (and all statistical properties) of the time series, while altering any dynamic properties (i.e., properties dependent on the specific temporal order of ISIS). If the temporal structure observed for a scale below τ_1 does depend on dynamic properties, the non-zero slope region should disappear in the analysis of the surrogate data.

III. Results

Nine single cell recordings were obtained from GPi cells. Time series length was 5424 ± 1485 (mean ± SD). Sample temporal structure functions of GPi neurons and the corresponding surrogate data are shown in figure 1. In 7 cases (78%) an initial region of the temporal structure with positive slope was observed, indicating the presence of complex (fractal) properties at small time scales. The rest of the cases presented a zero-slope structure function at small scales, meaning that no complex temporal organization was present at small time scales. Sample temporal structure functions of GPi neurons and the corresponding surrogate data are shown in figure 1.The value of τ_1 was 48 ± 37 ISIS (mean ± SD). The positive slope region disappeared in the surrogate data, proving the dynamic origin of the complex behavior observed.

IV. Discussion

A new paradigm is arising in the field of neuronal encoding, which has been called multiplexed coding. This refers to the simultaneous occurrence of different coding schemes in the same neuronal population, sometimes at different scales, with either complementary or redundant purposes [14-15]. An example of a multiplexed neuronal code at different time scales occurs in the basal ganglia. A rate code is known to play a role in the communication between the basal ganglia and the mo-

tor thalamus and cortex. This is evidenced by the fact that a higher frequency of activity of the output nuclei of the basal ganglia is correlated with a higher level of motor output [16-17]. However, the relevance of a time patterns coding scheme in the basal ganglia - thalamo - cortical circuit has also been proposed by many authors [18-22]. Recently, we reported that a rate and a time code co-exist in output structures of the basal ganglia in healthy and parkinsonian rats [6]. Both coding types were shown to play a role at different temporal scales, and these scales are altered in the parkinsonian animals. Here, we show a similar co-existence of different coding properties at small and large time scales in a human patient with Parkinson's disease. At small scales, a positive slope is observed in the temporal structure function in 78% of the neurons analyzed, which evidences the presence of complex temporal properties with fractal characteristics. This complex temporal organization of the neuronal discharge disappears in the surrogate (shuffled) data, demonstrating its dynamic origin. Regarding the transmission of information, complex time patterns can be transmitted at this scale, although independent information cannot. This obeys to the fact that ISIS are not independent from each other for $\tau < \tau_1$, but strongly correlated. This suggests the presence of a time patterns coding scheme, and allows defining τ_1 as the length of the smallest information unit of the code, or word length. Conversely, at large time scales (i.e., for $\tau > \tau_1$) a zero-average slope is observed, which can only be generated by random processes. In terms of neuronal coding this demonstrates an independence between successive ISIS, precluding any coding scheme different than a time-averaged code, as for example a rate code.

A note is in place regarding the limitations of our study, which are related to the fact that only one patient and few neurons were analyzed. The reliability of our results is enhanced by the fact that similar properties were previously observed in animal and simulated neuronal recordings [11-12]. Nevertheless, a future study including more recordings and patients is mandatory in order to confirm the results presented here.

v. Conclusions

In a majority of human (GPi) neurons with Parkinson's disease, our algorithm was able to detect two main temporal scales with different coding properties. At short time scales time patterns coding takes place, while at longer time scales a rate code is present. This shows the presence of a multiplexed neuronal code in the human basal ganglia. Neurostruct appears as a promising tools for the analysis of neuronal activity, in particular in Parkinson's disease.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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