Entropy measurements in pallidal neurons in dystonia and Parkinson disease.

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INTRODUCTION

Theories on the dysfunction of motor circuits in hyperkinetic disorders such as as dystonia and hypokinetic disorder such as Parkinson's disease (PD) have been based largely on discharge rates and oscillatory activities recorded from basal ganglia (BG) neurons of patients undergoing deep brain stimulation (DBS) or pallidotomy, or from recordings made in animal models of movement disorders. A common assumption of these models is that alterations in BG circuitry are due to shifts in the balance of activity in the excitatory glutaminergic and inhibitory GABAergic inputs to BG neurons and also to the impact of their linear combination (or sum) on the post-synaptic neurons. However, it is questionable whether neuronal systems can be simply described in terms of the sum - or any linear combination - of their individual components. As a consequence of the prevalent use of linear analyses, the activity of BG neurons has often been characterized as being in a steady state and has been described by the firing rate of its nuclei.
For this reason, irregularities in the neuronal data stream have been either neglected or ascribed to random processes.
More recently however, non-linear features have been identified in the data stream of BG neurons of rodents and primate and in Parkinsonian patients. Interestingly, these non-linear features have been found to be modified by DBS of the subthalamic nucleus (STN) in primate models (Dorval et al. 2008) and are controlled by the dopaminergic system in PD patients (Lafreniere-Roule et al. 2010).

These data have led us to hypothesize that facilitation and inhibition of motor activities are controlled by neuronal entropy. However, the lack of data on non-linear features in the BG associated with the hyperkinetic state limits our ability to introduce these findings into functional models of BG.
In this study we compare non-linear features of BG neuronal activity in hypo- and hyperkinetic states to further characterize the pathology of movement disorders and, in so doing, test our model that hypo- and hyperkinesia are associated with high and low neuronal entropy respectively.

METHODS

A total of 36 patients, 26 PD patients (16 males and 10 females, mean age at surgery 61.6 ± 8.3 yrs.) and 10 dystonia patients (8 males and 2 females, mean age at surgery 43.4 ± 14.2 yrs) who have undergone pallidotomy or the implantation of DBS electrodes in the globus pallidus interna (GPi) at Hannover Medical School, Germany and Methodist Hospital, Houston, USA.
All PD patients were idiopathic and the dystonia group comprised of primary generalized (4 patients), primary segmental (3 patients), secondary hemi (1 patient), idiopathic generalized (1 patients) and idiopathic segmental (1 patient) dystonia. All patients signed an informed consent form approved by the respective institution.
All patients were awake during the stereotactic procedures and received local anesthetics only prior to and during surgery, if needed. Standard targeting and mapping procedures were used to localize the posteroventral GPi and GPi neurons were identified by their established neuronal discharge rates and patterns, and their responsiveness to limb movement (Sanghera et al. 2003). Only stable recordings made from those GPi neurons that were located within the central portions of the nucleus were used in the analysis.
Off-line analysis was performed on stable GPi neuronal activity and, where necessary spike sorting procedures were used to separate out different populations of action potentials based on similarities of their morphological characteristics. Time stamps of interspike intervals were imported into Matlab (Mathworks, Natick, MA) and non-linear fractal analysis was conducted under a Matlab environment:

1) Statistical irregularity (Aproximate Entropy; ApEn) was measured following the method of Pincus (1995). ApEn quantifies a degree of complexity in the temporal organization of the data stream: low values are indicative of low irregularity, while high values denote greater complexity (or higher irregularity in the time series).
Three parameters were used in computing the ApEn: the number of spikes in the sequence (*N)*, the embedding dimension (*m*) , and the vector comparsion length (r). Because ApEn is dependent on the record length *N*, analyzed contiguous segments of 500 ISIs was used for all GPi neurons. The embedding dimension *m* was empirically set to 2 and the parameter *r* was calculated for each neuron as 15% of the standard deviation of ISIs (Pincus, 1995; Darbin et al.,2010).

2) Time domain analyses were performed to evaluate the stationarity of the recordings in the two patient groups (Statav; Pincus et al. 1993), the instantaneous frequency (IF) and its dispersion (coefficient of variation, cv).

RESULTS

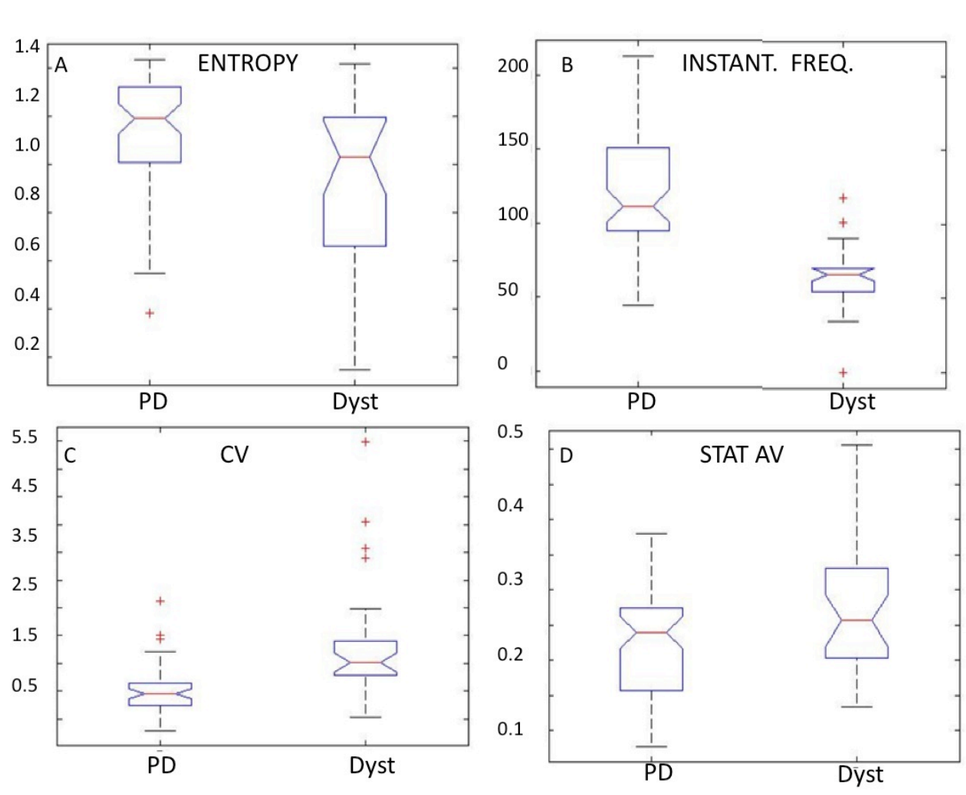
Table 1: Non-linear characteristics of GPi neurons in PD and dystonia

	Patients	Number of GPi neurons	ApEn (raw)	ApEn (shuffled)	Inst. Freq.	CV	Stat Av
PD	17	62	1.19 (1.01 - 1.32)	1.44 (1.40 - 1.49)	111.53 (95.24 - 151.35)	0.95 (0.74 - 1.15)	0.24 (0.16 - 0.27)
Dystonia	6	30	1.03 (0.74 - 1.21)	1.44 (1.24 - 1.51)	66.12 (54.92 - 70.29)	1.51 (1.29 - 1.90)	0.26 (0.20 - 0.33)

$ApEn_{raw}$ - The median ApEn calculated on raw data. Medians are shown at 25th -75th percentiles
$ApEn_{shuffled}$ - The median raw data, shuffled 100 times, at the 1st and 99th percentile
Inst. Freq. - the instantaneous frequency Hz ; CV – coefficient of variation in the Inst. Freq.
Statav - stationarity of discharge.
$P < 0.05$ $ApEn_{raw}$ in PD vs. dystonia (Kruskal-Wallis test)

RESULTS

Figure 1: Non-linear properties of GPi neurons in PD and dystonia



A - Entropy (ApEn raw) for neuronal data stream of GPi neurons from PD and dystonia (Dyst) patients ($p < 0.05$).
B - Instantaneous Frequency ($p<0.05$)
C - Coefficient of variation (CV) indicating the dispersion in the Instantaneous Frequency ($p<0.05$)
D - StatAv describing the stationarity of discharge.

For each patient group, the central red line is the median, the blue horizontal bars on either side of the median represent the 25th and 75th percentile. The black bars show the most extreme data points but which are not outliers. Outlier are plotted individually (red crosses).

DISCUSSION

The findings of this study reveal for the first time that non-linear features in the data stream of GPi neurons differ between Parkinsonian hypokinesia and dystonic hyperkinetic conditions. Our data show that entropy is higher in the data stream of GPi neurons from the PD patients in our study group compared to our dystonia patient group ($P<0.05$) and, in agreement with previous studies, the instantaneous frequency is also higher in the PD group than in the dystonia group. Interestingly, the dispersion of ISIs was higher in the dystonia group than in the PD group, indicating a greater variability in the discharge rate.
These non-linear data suggest that in Parkinsonian hypokinesia, in contrast to dystonic hyperkinesia there is increased entropy in the output nuclei of the BG. Since neuronal entropy refers to a degree of irregularity in the data stream, our data could indicate that facilitation and inhibition of motor activities are controlled by neuronal entropy.
One possible interpretation of this is that higher GPi neuronal entropy (or complexity/noise) decreases the competitiveness of motor information to be selected, filtered and routed to effectors. The opposite may be true in hyperkinetic conditions where reduced GPi entropy increases the relative weight of motor -effective information (overall the cohort of firing activity) and their competitiveness for selection and routing toward effectors. These data may explain the decreases in entropy evoked by DBS and with apomorphine in the PD.

CONCLUSIONS

These data support our hypothesis that hypokinesia, in contrast to hyperkinesia, is associated with increased entropy in the output nuclei of the BG. Although larger populations of GPi neurons from PD and dystonia (as well as from non-motor disorders) must be examined, these data provide a strong basis for revisiting the BG model of movement disorder, with the intention to include non-linear properties of neuronal activity.

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