Entropies 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 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 glutamatergic 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 assigned to random processes. More recently however, non-linear features have been identified in the data stream of BG neurons of rodents and primates 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-Rouleau 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 hypokinetic 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 8 patients (4 males and 4 females), 5 of whom were diagnosed with primary generalized dystonia, while 3 were idiopathic segmental (1 patient) dystonia. All patients signed an informed consent form approved by the respective institutions.

All patients were awake during the stereotactic procedures and received local anesthesia only prior to and during surgery, if needed. Standard targeting and mapping procedures were used to localize the posterior central GPi and GPi neurons were identified by their established neuronal discharge rate 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 (Approximate Entropy; ApEn) was measured following the method of Pincus (1995).
2) Sample entropy is a measure of the number of state sequences of m+1 length that match m-length sequences and is defined as

\[ S_m(r) = \frac{1}{m} \log \left( \frac{\Sigma_{j=1}^{N-m} [I(j,m,r)/I(j,m+1,r)]} {\Sigma_{j=1}^{N-m} [I(j,m+1,r)/I(j,m+2,r)]} \right) \]

where \( I(j,m,r) \) is the number of times a state sequence of m length and difference of r has been matched (for details see Pincus and Goldberger 1994). Sample entropy is defined as the log of the ratio of the conditional probabilities that a state sequence of m length and difference of r occurs in two time series that are similar in m-1 length and difference of r.

These data support our hypothesis that hypokinetic, in contrast to hyperkinesia, is associated with increased entropy in the output nuclei of the BG. Although large 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.

RESULTS

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of</th>
<th>ApEn (raw)</th>
<th>ApEn (shuffled)</th>
<th>Inst. Freq</th>
<th>CV</th>
<th>Stat Av</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>17</td>
<td>1.49</td>
<td>0.95</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.01 - 1.12)</td>
<td>(1.34 - 1.48)</td>
<td>(0.94 - 1.01)</td>
<td>(0.94 - 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>6</td>
<td>1.00</td>
<td>1.49</td>
<td>1.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.80 - 1.23)</td>
<td>(1.22 - 1.54)</td>
<td>(1.34 - 1.57)</td>
<td>(1.30 - 1.84)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

REFERENCES


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 - Stable describing the stationarity of discharge.