Information encoding and pathways in basal ganglia neurons

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INFORMATION ENCODING AND PATHWAYS IN BASAL GANGLIA NEURONS.

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ABSTRACT
The decision making process is a phenomenon which is hard to track using the standard signal averaging methods such as peri-event time histograms (PETHs). Indeed, even if the sequence of the events is controlled during a behavioural task, the inter-event interval duration remains highly variable. We have applied a temporal normalization method such that PETHs can be mapped across all events of a task trial and compared from neuron to neuron and from session to session. We have also applied Shannon mutual information theory to compare neural activity in recorded striatum and GPi neurons in behaving monkeys during a centre-out motor task and investigated individual neuron coding properties. These methods illustrate information pathways and their relative involvement. We also show that the GPi neurons recorded during the decision phase contained more information about the context and choice combination than striatal neurons.

KEY WORDS
Decision making, behavioural task, basal ganglia, information coding

INTRODUCTION
In a visually-guided motor task, decision-making is a distributed neural process which involves the Basal Ganglia (BG) closely interacting with the frontal and prefrontal cortical areas as well as with the dopaminergic system ([1-5]). In a recent electrophysiological study in behaving monkeys, using a multiple choice task, we showed that the encoding of the movement parameter by the neurons of the striatum and the internal Globus Pallidus (GPi) was modulated by the value of the action to be performed ([6]). This provides a mechanism by which motor program selection could be performed under dopamine control. However, the selection process, in itself, is inaccessible using classical electrophysiological analysis methods such as post-stimulus time histograms (PSTHs). This is because, even when a cue is presented at a known time, the actual moment of decision making cannot be observed and so its temporal relationship to the cue and other events cannot be known. To access the neural mechanisms underlying this process, we need to closely link the electrophysiological activity to the behavioural events during the whole task. To do so, we have computed for every neuron a multiple event PETH. Moreover, experimental protocols for decision making assessments (including our own studies) assign a randomly variable duration between task events. This means that the length of time between these events varies from one event to another and from trial to trial for the same event. This, along with the fact that cognitive reaction time varies from trial to trial for each animal, prevents the direct comparison of the time course of the PETHs. To solve this conundrum, we propose a method that allows us to normalize time durations in each trial (see methods). We applied this method to data previously recorded in the main input and output stages of the BG (respectively, striatum and GPi) of 2 monkeys (M1 and M2) during a reward probability based free choice motor task that we designed (Figure 1, see [6] for details). This task encompassed 7 successive events. This normalization method is applied to the whole trial duration because BG activity is notoriously variable and may have dynamic encoding capacities ([7]).

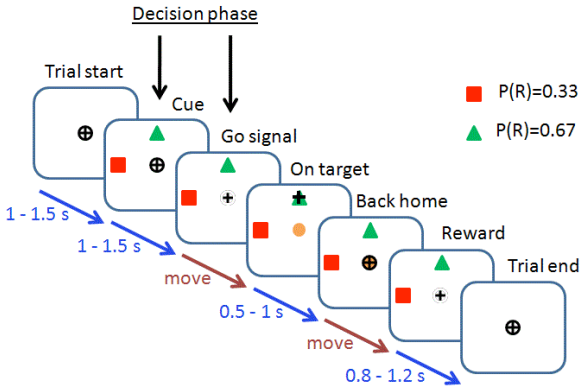

Figure 1: Behavioral paradigm. The reward probability-based free-choice task. 2 different targets associated with reward probabilities (here P(R)=0.33 and P(R)=0.67) are displayed simultaneously during each trial (Cue), in 4 possible positions in random order (6 target combinations) and in random locations (4x3 possibilities).

In our experiments monkeys were over-trained and maximized their payoff by choosing the target with the higher reward value (for details see [6]). This gives 2 possible encoding strategies for the BG. First, it may just encode the chosen target. Secondly, its activity may be related to the sensory context of the trial ([8]). Therefore we then specifically focused our analysis on the possible correlation between the neuronal activity

during the crucial period preceding movement and the context of the task or the ongoing decision: the decision phase (DP). Using these methods, we addressed the question of what the system encodes.

MATERIALS AND METHODS

The reader is invited to refer to the first paper dealing with these data ([6]) for an exhaustive description of materials and methods. Here we provide a summary including only the details necessary to explain the additional analyses and results.

Animal training and surgery

In the task (Figure 1) monkeys were trained to move a custom-made manipulandum in a horizontal plane with their right hand. In each trial of a session, 2 different cue targets (randomly chosen from a set of 4) were displayed simultaneously on the screen. Each cue appeared randomly in one of 4 possible directions and was associated with a specific probability of a reward being delivered at the end of a successful trial (P(R) = 0, 0.33, 0.67 and 1). The reward probability remained the same throughout a session. In order to induce a situation in which there was always a "better" choice, a single trial could not include 2 identical cues or 2 targets in the same location. After a random period (1-1.5 sec), the "go" signal was given and the monkey had to initiate a movement towards one of the 2 targets. Once he reached this position, he had to hold the cursor on the target for another random period (0.5-1.0 sec) after which the animal had to move the cursor back to the initial, central position. The reward was then delivered (fruit juice) according to the probability associated with the selected target. For each successful trial, if the monkey chose the target associated with the highest probability of receiving a reward, her choice was defined as optimal. If not, she could still receive her reward with a probability equal to that for the chosen target. For purposes of analysis of the context dependent choice, we consider that the context in which the animal is making the decision is the combination of 2 targets that are visible during a trial. Thus, with 2 targets selected from 4, there are 6 possible combinations and therefore 6 distinct contexts within which the animal makes a decision on which target to choose.

Recording and data acquisition

Neuronal recording was performed in the dorsolateral striatum and the GPi using an implanted recording chamber ([9, 10]). Data acquisition, spike sorting and storage have been previously described ([6]). The behavioural events were stored simultaneously with the electrophysiological recordings (Figure 1): trial begin (TB), cue presentation (CP), go signal (GS), on target period (OT), back home period (BH), reward/no reward event (RE/NRE) and finally trial end (TE).

Data analysis

The analyses were performed with custom-made Matlab scripts (MathWorks, Natick, MA), C# programs (Microsoft) and NeuroExplorer tools and scripts (Nex Technologies, Littleton, MA).

Global PETH extraction and analysis

PETHs extraction and normalization

The analysis of electrophysiological data coupled with behavioural events often relies on PETHs of single events occurring during the task. Their computation by itself, does not provide a framework for statistical inference ([11]), but despite this intrinsic limitation it remains a widely used reference tool that often provides meaningful insights. To have an overall view of the neuronal dynamics associated with the choice task and to compare both striatal and pallidal activity profiles, we investigate the temporal outline of PETHs across all the steps of the task. Therefore, to focus on the particular involvement of striatum and GPi in these dynamics and their relationship to the experimental conditions, we have implemented an algorithm that can identify behavioural event sequences of interest and extract the spike trains related to these events. Dedicated C# software scrutinizes the spike trains and computes the PETH for every recorded neuron. In a first step, it extracts all the recorded sequences where the monkey completed every event through the course of the trial (the event sequence: TB-CP-GS-OT-BH-RW-ET) and discards sequences where any event was not completed (e.g. where the monkey failed to return the cursor to home). In a second step, all trials in which no reward was gained were discarded. This is because the firing profile in cases where reward is obtained and those where no reward is obtained are necessarily different. Therefore, in the presented results only successfully completed trials where a reward was obtained are shown so that the same behavioural profile is always under consideration. The time normalization of the PETHs is computed as follows: in every trial and for every neuron, the first inter-event interval (IEI) is split into the same number of time bins. The duration of a bin in one trial is thus not equal to that in another trial. For instance, the first IEI is always split into 100 bins. As the duration of this event can vary from 1s to 1.5s, the length of a bin can vary from 10ms to 15ms. Based on this bin size and on the following IEI averaged durations, an average number of bins is allocated for each IEI. Since between different neurons, the IEI average durations are similar (because most of the random durations are generated by the software itself), this time normalization technique allows the comparison of their PETHs. At the same time, amplitude normalization is applied on the PETHs based on the maximum number of spikes observed at any point in time over the whole time course of a trial. Using this method, we have performed new analyses of the data of a previous publication by our team. In this analysis we assume that similarity of form of the PETH over the course of the events of a trial implies similarity of function of the neuron in the decision making process.

PETH analysis

We compare PETH distributions between striatum and GPi. Our main goal is here to find global salient features in the neuronal activity of the 2 structures from a temporal point of view. To achieve this, the correlation coefficient matrixes are computed between every neuron PETH, separately for each monkey. These

analyses are performed separately for the 2 monkeys and for striatum and GPi. All statistical tests used here are student-t tests, p<1%.

Extraction of "Coding neurons"

The monkey's decision occurs after the CP (cue presentation) and before the movement initiation triggered by the GS (go signal). Whilst this period of time, from CP until GS, includes the decision process phase itself, it may also include an amount of time during which the monkey just waits for the GS and it is not easy to differentiate between the two ([12]). We compute this Decision Phase Averaged Firing Rates (DPAFR) for each neuron and for each different context presented to or choice made by the monkey. We first extract the neurons for which significant variations in firing rate are related to any of the 6 different context values or to any of the 3 choice reward probabilities by applying a one-way ANOVA. When the ANOVA is positive, we apply post-hoc methods based on the Tukey's least significant difference procedure. These analyses are performed with the Matlab Statistical toolbox and separately both on the 2 monkeys and on striatum and GPi. We thus obtain tuning curves with preferential choice and/or coding context values for each of these "coding" neurons that are later applied to basic modeling studies.

Signal carried information analysis

We compute mutual information between the firing rates and the context value, for coding neurons. The mutual information, I, between 2 discrete random variables X and Y is given by:

$$I(X;Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \cdot \log\left(\frac{p(x,y)}{p(x) \cdot p(y)} \right)$$

where $p(x,y)$ is the joint probability distribution function of X and Y, and $p(x)$ and $p(y)$ are the marginal probability distribution functions of X and Y respectively. The results are used to investigate the respective involvements of the GPi and of the striatum in the processing of information of context encoding in BG.

Model prediction

For every coding neuron in both structures, the tuning curve exhibits a preferential context/choice value encoding (e.g. one neuron may have its highest DPAFR when the target with 0.66 and the target with 0.33 probability of reward are presented together). For each previously extracted coding neuron, our predictive model thus associates the 6 different reference DPAFRs of the tuning curve with each of the 6 different context values (and respectively the 3 DPAFRs associated with each of the 3 choice values). The model is then used this way: DPAFRs are computed for each trial of a given coding neuron. For every trial, the experimental DPAFR is applied as an input to the tuning curve (core of the model) which returns the most likely context (i.e. that for which reference DPAFR is the closest to the experimental DPAFR). When the theoretical values are the same as the actual, the trial model prediction is considered as successful. Success rates are then computed for context and choice encoding in both monkeys and in both striatum and GPi.

The prediction quality of the model is then compared to random choices based on context and choice respective chance based rates (16.67% and 33.33% to obtain the actual value with a random draw). Using a Kolmogorov-Smirnov test, we first compute the significance of the model retrieval rates compared to the chance based rates. A Wilcoxon rank signed test is then used to compare the power of the model concerning context and choice prediction in order to conclude which one is most efficiently encoded in the recorded structures. Real population coding investigations are not achievable since our data only allow us, at best, 2 or 3 different neuronal spike trains sources during the same session. However, through several examples, we emphasize here some trends of multiple neurons encoding and of their numerical effect on context or choice prediction rates.

RESULTS

PETHs extraction

The software successfully extracts and normalizes both in time and amplitude the global PETHs from all recorded neurons and according to the previously defined sequence of events. The present study is based on 111 striatal cells (53 in M1 and 58 in M2) and 107 pallidal cells (51 in M1 and 56 in M2). Examples of normalized PETH distributions among striatal and pallidal neurons in M1 are given respectively in Figure 2.A and Figure 2.B. They clearly emphasize region dependant disparities among neurons and regarding the activity profile throughout the task. We found the same region dependent disparities in the recordings of M2 (not shown).

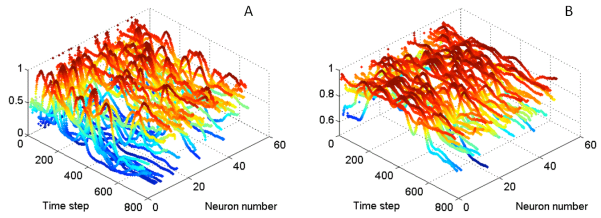

Figure 2: plot of 53 recorded neuron PETHs from the striatum (A) and of 51 neurons from the GPi (B) of M1.

The population activity synchronization differs between striatal and pallidal neurons.

The PETHs correlation coefficients matrices are computed separately for both monkeys and for striatal and GPi neurons. The 3 average correlation coefficient (ACC) combinations (GPi-striatum, GPi-GPi and striatum-striatum) are computed and compared. As predicted after a visual control of Figure 2, clear differences are revealed between the 2 regions regarding the neuronal dynamics, as shown in Figure 3.A and Figure 3.C. The PETHs correlation coefficient values appear higher among GPi neurons than striatal neurons in both monkeys. This demonstrates that there is less dynamic variability between GPi neurons and this is confirmed by the estimate of their ACC values according to the structure. As shown in Figure 3.B and

Figure 3.D, the ACC values differ significantly between the 2 structures. This emphasizes a higher temporal synchronization of GPi neuronal spike trains compared to striatum. This result is the same in both monkeys. Moreover, the lowest absolute value of correlation coefficient occurs in both monkeys when computing the ACC value between GPi and striatum which is another argument in favour of a possible functional dissociation between the 2 structures.

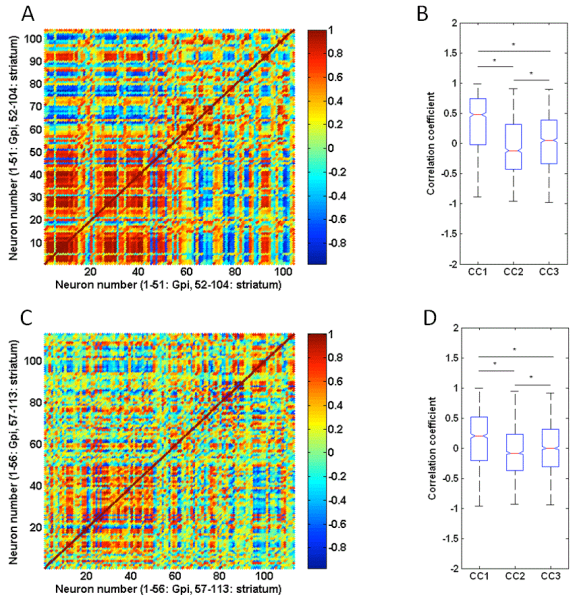

Figure 3: Cross-correlation matrix of all the neurons PETHs for M1 (*A*) and M2 (*C*). Boxplot of ACC values for GPi vs. GPi (*CC1*), striatum vs. striatum (*CC2*) and GPi vs. striatum (*CC3*) of the neurons PETHs for M1 (*B*) and M2 (*D*) (Student t-test, p<1%).

Data modeling by coding neurons

Only those neurons that showed an average firing rate that was dependent on the context or choice during the decision phase were used for analysis of the coding. For M1, 41.51% of the striatum and 21.57% of the GPi neurons and for M2 29.82% and 10.71% displayed such a property.

Mutual information between context/choice values and NFRs during the decision phase was computed. The amount of information carried by striatal neurons is less than that carried by GPi neurons during the DP (Figure 4.A and Figure 4.C). The firing rates of GPi neurons yielded more information on both the context and the choice values than the firing rates of striatal neurons in both monkeys. The GPi neurons thus appear as more reliable encoders. This implies that the context and/or the choice values are refined between the striatal and the pallidal processing stages and therefore suggests an information convergence mechanism between the striatum and the GPi. These results are subsequently confirmed and refined by the modeling studies.

Every context or choice dependant tuning curve of coding neurons is extracted and applied to its originating spike train from which the tuning curve was constructed. This allows us to estimate the efficiency of the model in reconstructing the original choice and context values. Figure 4.B and Figure 4.D summarize these computations. This simple empirical method provides information on both the ability of the model to reconstruct the original data and on its retrieval capability. This allows us to compare the predictive power of GPi and striatal neurons. Considering, firstly, the context or choice prediction rates, we can deduce 2 prominent features. The first is a significant difference between striatal and GPi neuron's success rates.

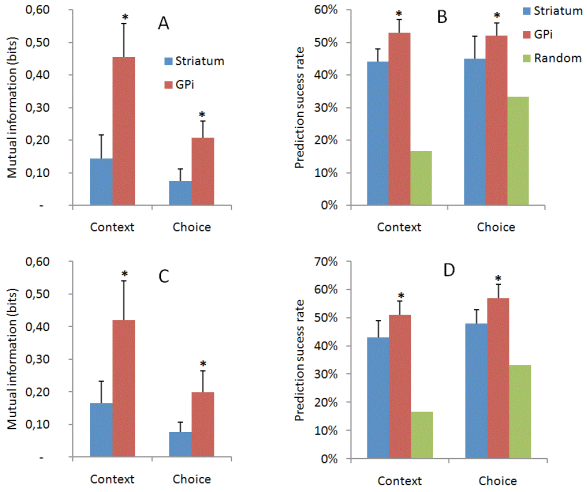

Figure 4: Mutual information between decision phase average firing rate and context and choice values for M1 (*A*) and M2 (*C*). Prediction model success rates for M1 (*B*) and M2 (*D*). The *Random* series represents the success base chance to predict the correct values (respectively 1/6 for context and 1/3 for choice).

The second is a significantly higher retrieval rate for pallidal neurons compared to striatal neurons. This latter result corroborates the previous mutual information outcomes and confirms a greater involvement of the GPi compared to striatum in both context value and choice encoding and thus an information convergence process. The third and last result is obtained by comparing the averaged level of context and choice encoding success rates taking into account their proportion related to chance. From this, we can compare their unbiased respective retrieval success rates. As shown in Figure 4.B and Figure 4.D, the success rate profiles of context and choice encoding are similar between the 2 monkeys. In a first step we compare the actual success rates of the model to the success rates due to chance. For this, the results give a binomial distribution with a success base probability value of 16.67% for context and 33.33% for choice. Kolmogorov-Smirnov tests applied for both monkeys for both striatum and GPi vs. chance give p-values of $p < 1\%$ for both context and choice. These preliminary results confirm that the model predicts both context and choice at a level far greater than chance. In the second step we subtract the success base chance rate from the actual model results to remove bias and compare the predictive power of the model in context and choice encoding ([13]). The Wilcoxon signed rank test is then applied to the unbiased data using an alternative hypothesis of "less" for the choice prediction. For both monkeys and both anatomical structures p-values < 1% are obtained. This suggests that, during the decision phase, the average value of the firing rates of the GPi and striatal neurons preferentially encodes the context rather the choice value.

DISCUSSION

This study presents a novel attempt to shed light on the correlation between BG neuron spike train dynamics and behavioural decision making tasks. It provides evidence that encoding neurons show 2 remarkable properties: i) the firing activity of GPi neurons during the decision phase carries more information on the context and on the choice values than the striatal neurons and ii) both structures preferentially encode the context rather than the choice.

Our study reveals a higher level of synchronization inside the GPi than in the striatum. This feature is evidenced both by the ACC analysis (Figure 3) and the computation of entropy (results not shown here). It confirms our previous work ([6]) where we showed that during the executive part of a choice task, the GPi activity is strongly related to the action performed (encoding mainly movement parameters and action value), while the striatum remains more versatile, encoding different parameters (chosen target value, non chosen target value, motor parameters, action value, etc) at more closely comparable levels. This study confirms these observations and shows that this focus on the action to perform in the output structure of the BG is associated with a high correlation level. These data may seem at variance with another study showing decorrelation between GP neurons in a discrimination task ([14]). However, the Joshua et al. study used a non-instrumental task (the animal has no action to perform in response to the cues), while, in our study, the choice between the 2 options and its expression by a consequent action is an essential aspect of the task. When we consider these 2 studies, it thus reinforces the hypothesis that the very significant and transient synchronized response in the GPi neural population reflects the decision making and action selection processes occurring in the cortico-basal ganglia loop.

When we focused our analysis on the decision period, we used 2 methods to assess the relationship between the neural activity of the BG and the choices performed by the animals (Figure 4). Both reveal a better correlation for the encoding of the context than for the encoding of the choice and both show that the GPi is a much better predictor than the striatum of both parameters. These data imply that during the critical decision phase, when the animal decides which action to perform, the BG are deeply involved in the computation process which leads to the decision. The fact that the input stage (the striatum) is less correlated than the output stage (the GPi) to the actual behavioural parameters is a further confirmation of the importance of the BG in the process. 2 hypotheses can explain why the correlation is higher for the context than for the choice: i) the BG encoded preferentially the context or ii) the BG take into account the context in order to perform a choice. The latter hypothesis has already been proposed by other teams ([15, 16]) and is supported by the fact that the cortico-basal ganglia loop could be considered as a SARSA learning system and encodes the combination of choice made and context within which the choice was made. Unfortunately, because in our task the monkeys optimize their behaviour (thus maximizing their gains), it is impossible to rule out either of these hypotheses.

This work is a first attempt to analyze comprehensively during the full duration of the trial the process of neural computation occurring in the BG during a behavioural task. The high variability of BG neural population firing rates, especially in the output stage makes this solution better than the classical PSTH which reduces the richness of the neural responses. The approach we have adopted allowed us to visualize and analyze the decision period and allowed us to demonstrate the crucial role played by this structure in the decision making process.

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