
Analysis of the neural code for sensory-motor latency in smooth pursuit eye movements reveals general principles of neural variation and the specific origin of motor latency. The trial-by-trial variation in neural latency in MT comprises a shared component expressed as neuron-neuron latency correlations and an independent component that is local to each neuron. The independent component arises heavily from fluctuations in the underlying probability of spiking, with an unexpectedly small contribution from the stochastic nature of spiking itself. The shared component causes the latency of single-neuron responses in MT to be weakly predictive of the behavioral latency of pursuit. Neural latency deeper in the motor system is more strongly predictive of behavioral latency. A model reproduces both the variance of behavioral latency and the neuron-behavior latency correlations in MT if it includes realistic neural latency variation, neuron-neuron latency correlations in MT, and noisy gain control downstream of MT.


Awareness of its rich structural pathways has earned the external segment of the globus pallidus (GPe) recognition as a central figure within the basal ganglia circuitry. Interestingly, GPe neurons are uniquely identified by the presence of prominent pauses interspersed among a high-frequency discharge rate of 50-80 spikes/s. These pauses have an average pause duration of 620 ms with a frequency of 13/min, yielding an average pause activity (probability of a GPe neuron being in a pause) of \( \frac{620 \times 13}{60 \times 1000} = 0.13 \). Spontaneous pause activity has been found to be inversely related to arousal state. The relationship of pause activity with behavioural events remains to be elucidated. In the present study, we analysed the electrophysiological activity of 200 well-isolated GPe pauser cells recorded from four non-human primates (Macaque fascicularis) while they were engaged in similar classical conditioning tasks. The isolation quality of the recorded activity and the pauses were determined with objective automatic methods. The results showed that the pause probability decreased by 9.09 and 10.0%, and the discharge rate increased by 2.96 and 1.95%, around cue and outcome presentation, respectively. Analysis of the linear relationship between the changes in pause activity and discharge rate showed \( r(2) = 0.46 \) and \( r(2) = 0.66 \) upon cue onset and outcome presentation, respectively. Thus, pause activity is a pertinent element in short-term encoding of relevant behavioural events, and has a significant, but not exclusive, role in the modulation of GPe discharge rate around these events.
Selection of a model organism creates tension between competing constraints. The recent explosion of modern molecular techniques has revolutionized the analysis of neural systems in organisms that are amenable to genetic techniques. Yet, the non-human primate remains the gold-standard for the analysis of the neural basis of behavior, and as a bridge to the operation of the human brain. The challenge is to generalize across species in a way that exposes the operation of circuits as well as the relationship of circuits to behavior. Eye movements provide an opportunity to cross the bridge from mechanism to behavior through research on diverse species. Here, we review experiments and computational studies on a circuit function called "neural integration" that occurs in the brainstems of larval zebrafish, primates, and species "in between". We show that analysis of circuit structure using modern molecular and imaging approaches in zebrafish has remarkable explanatory power for details of the responses of integrator neurons in the monkey. The combination of research from the two species has led to a much stronger hypothesis for the implementation of the neural integrator than could have been achieved using either species alone.
stimulus. Especially in motor systems, however, it is equally critical to understand how spike trains predict behavior. Thus, our goal was to compare systematically spike trains in the oculomotor system with eye movement behavior on single movements. We analyzed the discharge of Purkinje cells in the floccular complex of the cerebellum, floccular target neurons in the brainstem, other vestibular neurons, and abducens neurons. We find that an extra spike in a brief analysis window predicts a substantial fraction of the trial-by-trial variation in the initiation of smooth pursuit eye movements. For Purkinje cells, a single extra spike in a 40 ms analysis window predicts, on average, 0.5 SDs of the variation in behavior. An optimal linear estimator predicts behavioral variation slightly better than do spike counts in brief windows. Simulations reveal that the ability of single spikes to predict a fraction of behavior also emerges from model spike trains that have the same statistics as the real spike trains, as long as they are driven by shared sensory inputs. We think that the shared sensory estimates in their inputs create correlations in neural spiking across time and across each population. As a result, one or a small number of spikes in a brief time interval can predict a substantial fraction of behavioral variation.


We have used an analysis of signal and variation in motor behavior to elucidate the organization of the cerebellar and brain stem circuits that control smooth pursuit eye movements. We recorded from the abducens nucleus and identified floccular target neurons (FTNs) and other, non-FTN vestibular neurons. First, we assessed neuron-behavior correlations, defined as the trial-by-trial correlation between the variation in neural firing and eye movement, in brain stem neurons. In agreement with prior data from the cerebellum, neuron-behavior correlations during pursuit initiation were large in all neurons. Second, we asked whether movement variation arises upstream from, in parallel to, or downstream from a given site of recording. We developed a model that highlighted two measures: the ratio of the SDs of neural firing rate and eye movement ("SDratio") and the neuron-behavior correlation. The relationship between these measures defines possible sources of variation. During pursuit initiation, SDratio was approximately equal to neuron-behavior correlation, meaning that the source of signal and variation is upstream from the brain stem. During steady-state pursuit, neuron-behavior correlation became somewhat smaller than SDratio for FTNs, meaning that some variation may arise downstream in the brain stem. The data contradicted the model's predictions for sources of variation in pathways that run parallel to the site of recording. Because signal and noise are tightly linked in motor control, we take the source of variation as a proxy for the source of signal, leading us to conclude that the brain controls movement synergies rather than single muscles for eye movements.

highlight variability generation and regulation as basal ganglia functions.

**2013**


Neural integration converts transient events into sustained neural activity. In the smooth pursuit eye movement system, neural integration is required to convert cerebellar output into the sustained discharge of extraocular motoneurons. We recorded the expression of integration in the time-varying firing rates of cerebellar and brainstem neurons in the monkey during pursuit of step-ramp target motion. Electrical stimulation with single shocks in the cerebellum identified brainstem neurons that are monosynaptic targets of inhibition from the cerebellar floccular complex. They discharge in relation to eye acceleration, eye velocity, and eye position, with a stronger acceleration signal than found in most other brainstem neurons. The acceleration and velocity signals can be accounted for by opponent contributions from the two sides of the cerebellum, without integration; the position signal implies participation in the integrator. Other neurons in the vestibular nucleus show a wide range of blends of signals related to eye velocity and eye position, reflecting different stages of integration. Neurons in the abducens nucleus discharge homogeneously in relation mainly to eye position, and reflect almost perfect integration of the cerebellar outputs. Average responses of neural populations and the diverse individual responses of large samples of individual neurons are reproduced by a hierarchical neural circuit based on a model suggested the anatomy and physiology of the larval zebrafish brainstem. The model uses a combination of feedforward and feedback connections to support a neural circuit basis for integration in monkeys and other species.

**2012**


Reward has a powerful influence on motor behavior. To probe how and where reward systems alter motor behavior, we studied smooth pursuit eye movements in monkeys trained to associate the color of a visual cue with the size of the reward to be issued at the end of the target motion. When the tracking task presented two different colored targets that moved orthogonally, monkeys biased the initiation of pursuit toward the direction of motion of the target that led to larger reward. The bias was larger than expected given the modest effects of reward size on tracking of single targets. Experiments with three different reward sizes suggested that the bias afforded a given target depends mainly on the size of the larger reward. To analyze the effect of reward on directional learning in pursuit, monkeys tracked a single moving target that changed direction 250 ms after the onset of motion. Expectation of a larger reward led to a larger learned eye movement during the acquisition of the learned response and during subsequent probes of what had been learned, implying that reward influenced the expression rather than the acquisition of learning. The specific effects of reward size on learning and two-target stimuli imply that the site of reward modulation is at a level where multiple target motions compete for control of eye movement, downstream from sensory processing and learning and upstream from final motor processing.
Controlling motor actions requires online adjustments of time-varying parameters. Although numerous studies have attempted to identify the parameters coded in different motor sites, the relationships between the temporal profile of neuronal responses and the dynamics of motor behavior remain poorly understood in particular because motor parameters such as force and movement direction often change over time. We studied time-dependent coding of cortical and spinal neurons in primates performing an isometric wrist task with an active hold period, which made it possible to segregate motor behavior into its phasic and sustained components. Here, we show that cortical neurons transiently code motor-related parameters when actively acquiring a goal, whereas spinal interneurons provide persistent information regarding maintained torque level and posture. Moreover, motor cortical neurons differed substantially from spinal neurons with regard to the evolvement of parameter-specific coding over the course of a trial. These results suggest that the motor cortex and spinal cord use different control policies: Cortical neurons produce transient motor commands governing ensuing actions, whereas spinal neurons exhibit sustained coding of ongoing motor states. Hence, motor structures downstream to M1 need to integrate cortical commands to produce state-dependent spinal firing.

2010


Current anatomical models of the cortico-basal ganglia (BG) network predict reciprocal discharge patterns between the external and internal segments of the globus pallidus (GPe and GPi, respectively), as well as cortical driving of BG activity. However, physiological studies revealing similarity in the transient responses of GPe and GPi neurons cast doubts on these predictions. Here, we studied the discharge properties of GPe, GPi, and primary motor cortex neurons of two monkeys in two distinct states: when eyes are open versus when they are closed. Both pallidal populations exhibited decreased discharge rates in the "eye closed" state accompanied by elevated values of the coefficient of variation (CV) of their interspike interval (ISI) distributions. The pallidal modulations in discharge patterns were partially attributable to larger fractions of longer ISIs in the "eye closed" state. In addition, the pallidal discharge modulations were gradual, starting prior to closing of the eyes. Cortical neurons, as opposed to pallidal neurons, increased their discharge rates steeply on closure of the eyes. Surprisingly, the cortical rate modulations occurred after pallidal modulations. However, as in the pallidum, the CV values of cortical ISI distributions increased in the "eye closed" state, indicating a more bursty discharge pattern in that state. Thus changes in GPe and GPi discharge properties were positively correlated, suggesting that the subthalamic nucleus and/or the striatum constitute the main common driving force for both pallidal segments. Furthermore, the early, unexpected changes in the pallidum are better explained by a subcortical rather than a cortical loop through the BG.

Reinforcement learning models of the basal ganglia have focused on the resemblance of the dopamine signal to the temporal difference error. However, the role of the network as a whole is still elusive, in particular whether the output of the basal ganglia encodes only the behavior (actions) or it is part of the valuation process. We trained a monkey extensively on a probabilistic conditional task with seven fractal cues predicting rewarding or aversive outcomes (familiar cues). Then in each recording session we added a cue that the monkey had never seen before (new cue) and recorded from single units in the Substantia Nigra pars reticulata (SNpr) while the monkey was engaged in a task with new cues intermingled within the familiar ones. The monkey learned the association between the new cue and outcome and modified its licking and blinking behavior which became similar to responses to the familiar cues with the same outcome. However, the responses of many SNpr neurons to the new cue exceeded their response to familiar cues even after behavioral learning was completed. This dissociation between behavior and neural activity suggests that the BG output code goes beyond instruction or gating of behavior to encoding of novel cues. Thus, BG output can enable learning at the levels of its target neural networks.

2009


The basal ganglia network is divided into two functionally related subsystems: the neuromodulators and the main axis. It is assumed that neuromodulators adjust cortico-striatal coupling. This adjustment might depend on the response properties and temporal interactions between neuromodulators. We studied functional interactions between simultaneously recorded pairs of neurons in the basal ganglia while monkeys performed a classical conditioning task that included rewarding, neutral, and aversive events. Neurons that belong to a single neuromodulator group exhibited similar average responses, whereas main axis neurons responded in a highly diverse manner. Dopaminergic neuromodulators transiently increased trial-to-trial (noise) correlation following rewarding but not aversive events, whereas cholinergic neurons of the striatum decreased their trial-to-trial correlation. These changes in functional connectivity occurred at different epochs of the trial. Thus, the coding scheme of neuromodulators (but not main axis neurons) can be viewed as a single-dimensional code that is further enriched by dynamic neuronal interactions.


Previous studies have rarely tested whether the activity of high-frequency discharge (HFD) neurons of the basal ganglia (BG) is modulated by expectation, delivery, and omission of aversive events. Therefore the full value domain encoded by the BG network is still unknown. We studied the activity of HFD neurons of the globus pallidus external segment (GPe, n=310), internal segment (GPi, n=149), and substantia nigra pars reticulata (SNr, n=145) in two monkeys during a classical conditioning task with cues predicting the probability of food, neutral, or airpuff outcomes. The responses of BG HFD neurons were long-lasting and diverse with coincident increases and decreases in discharge rate. The population responses to reward-related events were larger than the responses to aversive and neutral-related events. The latter responses were similar, except for the responses to actual airpuff delivery. The fraction of responding cells was larger for reward-related events, with better discrimination between rewarding and aversive trials in the responses with an increase rather than a decrease in discharge rate. GPe and GPi single units were more strongly modulated and better reflected the probability of reward- than aversive-related events. SNr neurons were less biased toward the encoding of the rewarding events, especially during the outcome
Finally, the latency of SNr responses to all predictive cues was shorter than the latency of pallidal responses. These results suggest preferential activation of the BG HFD neurons by rewarding compared with aversive events.


The basal ganglia are known to control behavior using reward information; however, recent experiments have revealed that the basal ganglia contribute to the processing of salient non-rewarding events as well. Here, we suggest that the temporal dynamics of the response of dopaminergic neurons (DANs) enable the basal ganglia to have a dual role. The fast DAN response to salient events is mediated through the brainstem-basal ganglia loop. Forebrain loops enable the second phase of the dopaminergic responses that require highly processed information. The convergent encoding of fast/salient and slow/detailed information suggests that the basal ganglia control the tradeoff between fast and immediate responses to environmental events and slow responses that are only executed after substantial environmental information has been gathered.


Accurate detection of the eye state (i.e., open or closed) of animals during electrophysiological recordings is often crucial for analyzing physiological data. This requires a system which is reliable, and preferably noninvasive and inexpensive. Here we present such a tool incorporating a standard digital camera and a semi-automatic eye state detection (ESD) algorithm that can be used easily in typical primate electrophysiological setups. The ESD algorithm is based on the high light absorbance of the iris and pupil relative to the eyelid and takes advantage of the unique conditions found in primate physiological recordings (minimal area of sclera and head fixation). The ESD algorithm is as accurate as a human observer, and is not vulnerable to variance inherent to human decisions that it requires (i.e., eye location setting, training set classification and threshold setting). The temporal resolution with standard interlaced digital cameras is 17-20 ms. This is sufficient for the detection of eye state changes during electrophysiological recordings including spontaneous blinking and eye blink conditioning, as demonstrated here. Furthermore, the ESD tool can be applied to other physiological areas of research in which changes in eye state are critical to analyzing neuronal activity.

2008


Midbrain dopaminergic neurons (DANs) typically increase their discharge rate in response to appetitive predictive cues and outcomes, whereas striatal cholinergic tonically active interneurons (TANs) decrease their rate. This may indicate that the activity of TANs and DANs is negatively correlated and that TANs can broaden the basal ganglia reinforcement teaching signal, for instance by encoding worse than predicted events. We studied the activity of 106 DANs and 180 TANs of two monkeys recorded during the
performance of a classical conditioning task with cues predicting the probability of food, neutral, and air puff outcomes. DANs responded to all cues with elevations of discharge rate, whereas TANs depressed their discharge rate. Nevertheless, although dopaminergic responses to appetitive cues were larger than their responses to neutral or aversive cues, the TAN responses were more similar. Both TANs and DANs responded faster to an air puff than to a food outcome; however, DANs responded with a discharge elevation, whereas the TAN responses included major negative and positive deflections. Finally, food versus air puff omission was better encoded by TANs. In terms of the activity of single neurons with distinct responses to the different behavioral events, both DANs and TANs were more strongly modulated by reward than by aversive related events and better reflected the probability of reward than aversive outcome. Thus, TANs and DANs encode the task episodes differentially. The DANs encode mainly the cue and outcome delivery, whereas the TANs mainly encode outcome delivery and omission at termination of the behavioral trial episode.


The neurons of many basal ganglia nuclei, including the external and internal globus pallidus (GPe and GPi, respectively) and the substantia nigra pars reticulata (SNr) are characterized by their high-frequency (50-100 spikes/s) tonic discharge (HFD). However, the high firing rate of GPe neurons is interrupted by long pauses. We studied the extracellularly recorded spiking activity of 212 well-isolated HFD GPe and 52 GPi/SNr neurons from five monkeys during different states of behavioral activity. An algorithm that maximizes the surprise function was used to detect pauses and pauser cells ("pausers"). Only 6% of the GPi/SNr neurons versus as many as 56% of the GPe neurons were classified as pausers. The GPe average pause duration equals 0.62 s. The interpause intervals follow a Poissonian distribution with a frequency of 13 pauses/minute. No linear relationship was found between pause parameters (duration or frequency) and the firing rate of the cell. Pauses were preceded by various changes in firing rate but not dominantly by a decrease. The average amplitude and duration of the spike waveform was modulated only after the pause but not before it. Pauses of pairs of cells that were recorded simultaneously were not correlated. The probability of GPe cells to pause spontaneously was extremely variable among monkeys (30-90%) and inversely related to the degree of the monkey's motor activity. These findings suggest that spontaneous GPe pauses are related to low-arousal periods and are generated by a process that is independent of the discharge properties of the cells.


There have been many approaches to the problem of detection and sorting of extra-cellularly recorded action potentials, but only a few methods actually quantify the quality of this fundamental process. In most cases, the quality assessment is based on the subjective judgment of human observers and the recorded units are divided into "well isolated" or "multi-unit" groups. This subjective evaluation precludes comprehensive assessment of single-unit studies since the most basic parameter, i.e. their data quality, is not explicitly defined. Here we propose objective measures to evaluate the quality of spike data, based on
the time-stamps of the detected spikes and the high-frequency sampling of the analog signal of cortical and basal-ganglia data. We show that quantification of recording quality by the signal-to-noise ratio (SNR) may be misleading. The recording quality is better assessed by an isolation score that measures the overlap between the noise (non-spike) and the spike clusters. Furthermore, we use a nearest-neighbors algorithm to estimate the proportion of false positive and false negative classification errors. To validate these quality measures, we simulate spike detection and sorting errors and show that the scores are good predictors of the frequency of errors. The reliability of the isolation score is further verified by errors implanted in real basal ganglia data and by using different sorting algorithms. We conclude that quantitative measures of spike isolation can be obtained independently of the method used for spike detection and sorting, and recommend their reports in any study based on the activity of single neurons.

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