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Lack of Spike-Count and Spike-Time Correlations in the Substantia Nigra Reticulata Despite Overlap of Neural Responses

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Nevet A, Morris G, Saban G, Arkadir D, Bergman H. Lack of spike-count and spike-time correlations in the substantia nigra reticulata despite overlap of neural responses. *J Neurophysiol* 98: 2232–2243, 2007. First published August 15, 2007; doi:10.1152/jn.00190.2007. Previous studies of single neurons in the substantia nigra reticulata (SNr) have shown that many of them respond to similar events. These results, as well as anatomical studies, suggest that SNr neurons share inputs and thus may have correlated activity. Different types of correlation can exist between pairs of neurons. These are traditionally classified as either spike-count ("signal" and "noise") or spike-timing (spike-to-spike and joint peristimulus time histograms) correlations. These measures of neuronal correlation are partially independent and have different implications. Our purpose was to probe the computational characteristics of the basal ganglia output nuclei through an analysis of these different types of correlation in the SNr. We carried out simultaneous multiple-electrode single-unit recordings in the SNr of two monkeys performing a probabilistic delayed visuomotor response task. A total of 113 neurons (yielding 355 simultaneously recorded pairs) were studied. Most SNr neurons responded to one or more task-related events, with instruction cue (69%) and reward (63%) predominating. Response-match analysis, comparing peristimulus time histograms, revealed a significant overlap between response vectors. However, no measure of average correlation differed significantly from zero. The lack of significant SNr spike-count population correlations appears to be an exceptional phenomenon in the brain, perhaps indicating unique event-related processing by basal ganglia output neurons to achieve better information transfer. The lack of spike-timing correlations suggests that the basal high-frequency discharge of SNr neurons is not driven by the common inputs and is probably intrinsic.

INTRODUCTION

The substantia nigra reticulata (SNr) is one of the two major output nuclei of the basal ganglia. The SNr of primates is traditionally associated with orofacial (Inchul et al. 2005) and orientation movements (Basso and Wurtz 2002; Bayer et al. 2004; Handel and Glimcher 1999; Hikosaka et al. 2000, 2006). Physiological studies have indicated that as many as 58% of SNr neurons modulate their firing rate in relation to visual stimuli or saccades (Hikosaka and Wurtz 1983), 60% during the initiation and maintenance of smooth pursuit eye movements (Basso et al. 2005), and 16–25% to orofacial movements (DeLong et al. 1983; Schultz 1986; Wichmann and Kliem 2004). However, the SNr has been shown to be associated with other nonorofacial motor and sensory events (DeLong et al. 1983; Schultz 1986; Wichmann and Kliem 2004). In different studies the percentage of SNr neurons related to forelimb movements ranges between 5 and 46%. In addition, several studies report a significant percentage of SNr neurons with multimodality (Nagy et al. 2005) and more than one event (Schultz 1986; Wichmann and Kliem 2004) responses.

Such similar response properties appear to suggest that many SNr neurons share common functional inputs. This idea is supported by the anatomical characteristics of SNr afferents (Bevan et al. 1996; Francois et al. 1987; Kolomiets et al. 2003). Although neurons driven by common sources are expected to display correlated activity, as indicated by peaks or troughs in their spike-to-spike cross-correlation histograms (Brown et al. 2004; Eggermont 1990; Perkel et al. 1967), an early study of SNr neurons recorded in anesthetized rats reported that SNr spontaneous activity was uncorrelated (Wilson et al. 1977). Recent studies of the SNr of freely moving rats (Deransart et al. 2003) and behaving primates (Nevet et al. 2004) revealed a similar lack of spike-to-spike correlation in the control states.

Most early correlation studies focused on spike-timing (spike-to-spike) correlations (Abeles 1982; Eggermont 1990; Perkel et al. 1967), but other types of correlation between the spiking activity of two neurons can be evaluated. The predominant view today characterizing neuronal encoding by changes in firing rates has inspired new measures of correlation based on rates, or spike count. These were introduced recently and have been used in several brain areas (Averbeck et al. 2006; Bair et al. 2001; Gawne and Richmond 1993; Lee et al. 1998; Prut and Perlmutter 2003; van Kan et al. 1985). The spike-count correlation functions include the signal correlation (correlation between the average responses of two neurons to different events, indicating their tendency to respond similarly) and noise correlation (the correlation between intertrial fluctuations of the neuronal responses). These new measures of correlation also provide the basis for theoretical studies of information processing in the nervous system (Gawne and Richmond 1993; Oram et al. 1998; Panzeri and Schultz 2001; Pola et al. 2003; Schneidman et al. 2003, 2006).

Previous correlation studies of the SNr and other basal ganglia nuclei (Kimura et al. 2003; Levy et al. 2002; Nini et al. 1995; Raz et al. 2000) have concentrated on spike-timing correlations, whereas the novel measures of noise and signal (count) correlations have generally been neglected. In the present

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TABLE 1. *Mean rate and distribution of responses of SNr neurons to task events*

			Pre-Cue, %			Cue, %			Go, %			Reward, %		
Monkey	*n*	Mean Rate, Spikes/s	Inc	Dec	Tot	Inc	Dec	Tot	Inc	Dec	Tot	Inc	Dec	Tot
E	34	59	15	3	18	29	26	55	18	9	27	35	32	67
G	31	57	10	29	39	45	39	84	10	48	58	32	26	58
Mean		58	13	15	28	37	32	69	14	28	42	34	29	63

Only neurons with at least 10 responses to one behavioral event are included. Mean discharge rate is calculated during the ITI at the 500-ms epoch starting 1,500 ms before the Pre-Cue. Percentages are given as the number of significant responses divided by the number of neurons with minimal number of trials recorded for that event. Significant responses were defined as 20% deviation of discharge rate from baseline. Similar results were obtained using a formal Mann–Whitney analysis ($P < 0.05$). Because a single neuron could respond to more than one event, the sum of responses could exceed 100%. Bipolar responses were classified according to the largest response. Inc, increase; Dec, decrease; Tot, total.

study, we conducted multiple electrode recordings of SNr neurons in monkeys performing a probabilistic delayed visuomotor response task and studied the different forms of correlation between simultaneously recorded SNr neurons.

METHODS

Animals

Two female *Macaca fasicularis* monkeys (E and G), weighing 2.5 and 3.5 kg, were used in this study. Care and surgical procedures were

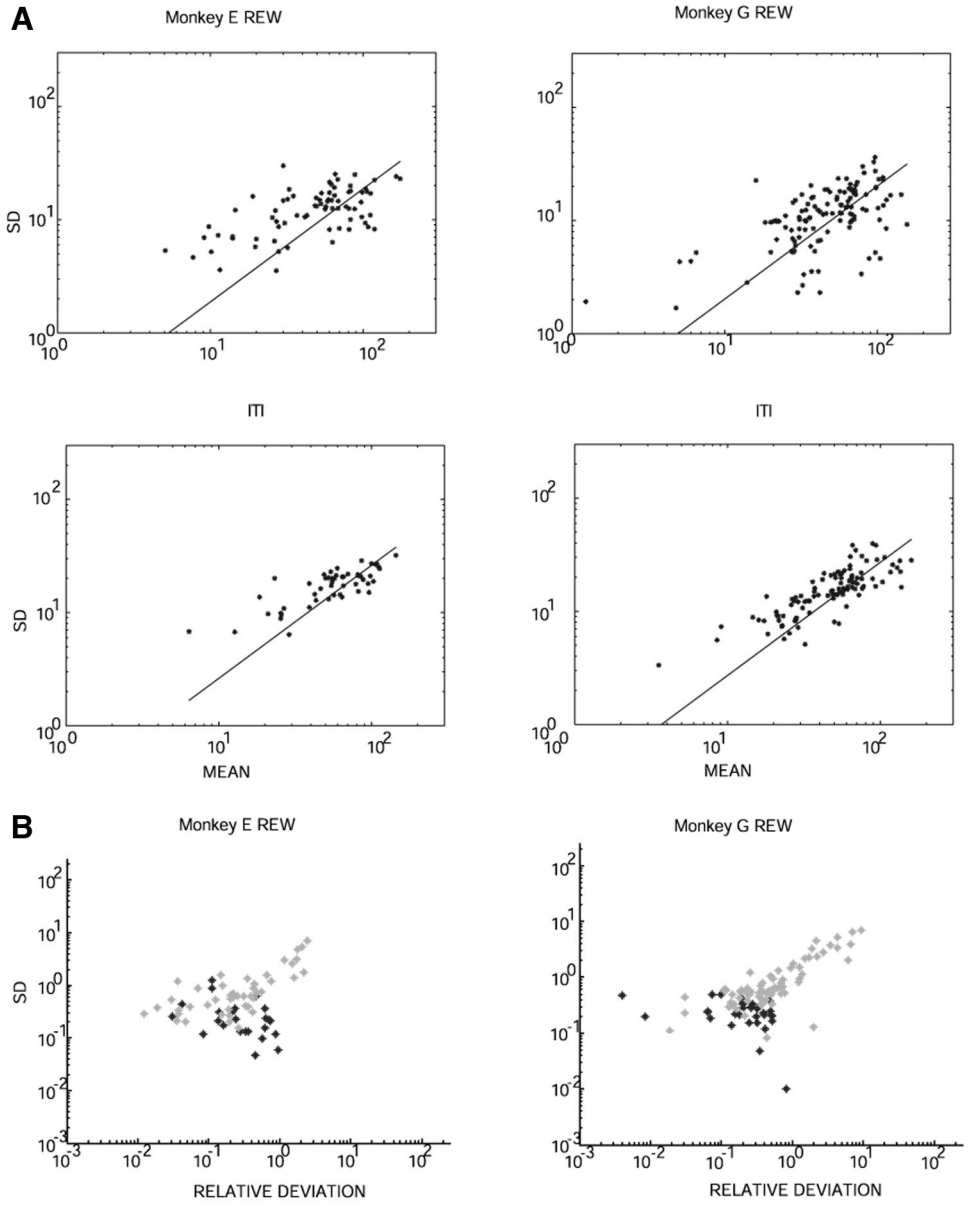

FIG. 1. Substantia nigra reticulata (SNr) discharge variability is proportional to the discharge rate. *A*: log–log plot of the SD vs. average firing rate of neuronal activity during reward and intertrial-interval (ITI) epochs. *B*: log–log plot of the firing variability (SD) vs. the average relative deviation from the baseline during reward epochs. Gray: neurons increasing their activity during the reward relative to baseline activity. Black: neurons decreasing their activity.

in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* (1996) and with the Hebrew University guidelines for the use and care of laboratory animals in research, supervised by the Institutional Animal Care and Use Committee.

Behavioral paradigm

The monkeys were trained to perform a self-initiated probabilistic delayed visuomotor task, in which the probability of receiving reinforcement for correct performance depended on the visual cue presented (for details see Morris et al. 2004). Briefly, during all training and recording sessions, monkeys were seated facing a computer screen, with a panel consisting of three keys in front of them. Trials were initiated when the monkey touched the central key. After a variable delay of 1.5–2.5 s, a visual cue appeared for 350 ms on one side of the screen. The monkeys were overtrained with a set of four possible cues. Each cue was associated with a different probability of reward (0.25, 0.5, 0.75, and 1.0). The cue presentation was followed by a fixed hold period of 1.5 s, after which a Go signal appeared. The monkeys were required to press either the left or the right key to match the side of the visual cue. Correct performance was followed (after an interval of 700 ms) by liquid reward at the probability associated with the visual cue. All trials were followed by a variable intertrial interval (ITI) of 3–6 s, after which the color of the screen changed ("Pre-Cue"), and the central key was enabled. In most cases, the monkey had returned to the central key already within the ITI, and therefore the trial was initiated immediately. The same-duration ITI also followed all trials aborted due to any behavioral errors. All analyses presented here include only the correctly performed trials that met the electrophysiological stability criteria (see following text).

Surgical procedures

A square plastic recording chamber with a 27-mm (inner) side was attached to the skull to allow access to the SNr. In monkey E, the recording chamber was tilted 56° laterally in the coronal plane with its center targeted at the stereotaxic coordinates of the SNr (Martin and Bowden 2000; Szabo and Cowan 1984). In monkey G, the recording chamber was placed with its center dorsal to the stereotaxic coordinates of the SNr. The chamber coordinates were verified with MRI imaging (Biospec Bruker 4.7-Tesla animal system, fast-spin echo sequence; effective TE = 80 ms and TR = 2.5 s, 13 coronal slices 1 or 2 mm wide) by alignment of the two-dimensional MRI images with the sections from the atlas (Martin and Bowden 2000; Szabo and Cowan 1984). A cilux head holder was also attached to the monkey's head to allow for fixation during recording. At the end of the recording period, the chamber and head holder were removed, the skin was sutured, and following a recovery period the monkeys were sent to a primate sanctuary (www.ipsf.org.il). All surgical and MRI procedures were performed under general and deep anesthesia.

Neuronal recording

During recording sessions the monkey's head was fixed by connecting the head holder to an external metal frame. Eight glass-coated tungsten microelectrodes (impedance 0.3–1.2 MΩ at 1,000 Hz), confined within a cylindrical guide (1.65-mm inner diameter), were individually advanced (EPS, Alpha-Omega Engineering, Nazareth, Israel) to the SNr. Signals from the electrodes were amplified with a gain of 10K and band-pass filtered with a 300- to 6,000-Hz four-pole Butterworth filter (MCP+, Alpha-Omega Engineering). Extracellular action potentials were detected and classified on-line using a template-matching algorithm (MSD, Alpha-Omega Engineering). Spike-detection signals (spike trains) and behavioral events were logged to a data acquisition system at 12 kHz (AlphaMap, Alpha-Omega Engineering). Cells were classified as SNr neurons if they were found at the expected stereotaxic coordinates and matched the physiological characteristics typical of SNr neurons: a relatively short-duration action potential and a distinctively high firing rate (DeLong et al. 1983; Schultz 1986). Firing characteristics of neighboring neurons and fibers were also used to guarantee the identification of the target cells as SNr neurons. For example, adjacent to the identified SNr, usually deeper, neurons of the oculomotor nucleus and fibers of the oculomotor nerve were often encountered, displaying a characteristic waveform shape with a dominant positive phase, and prominent changes in discharge rate related to eye movements.

Data analysis

PREPROCESSING. Spike trains were used for analysis only if their spike waveforms could be reliably separated from those of other units during the on-line spike sorting. A critical issue in studying neuronal activity by extracellular recording in behaving animals is to make sure that the spike train recorded is a reliable presentation of a single and

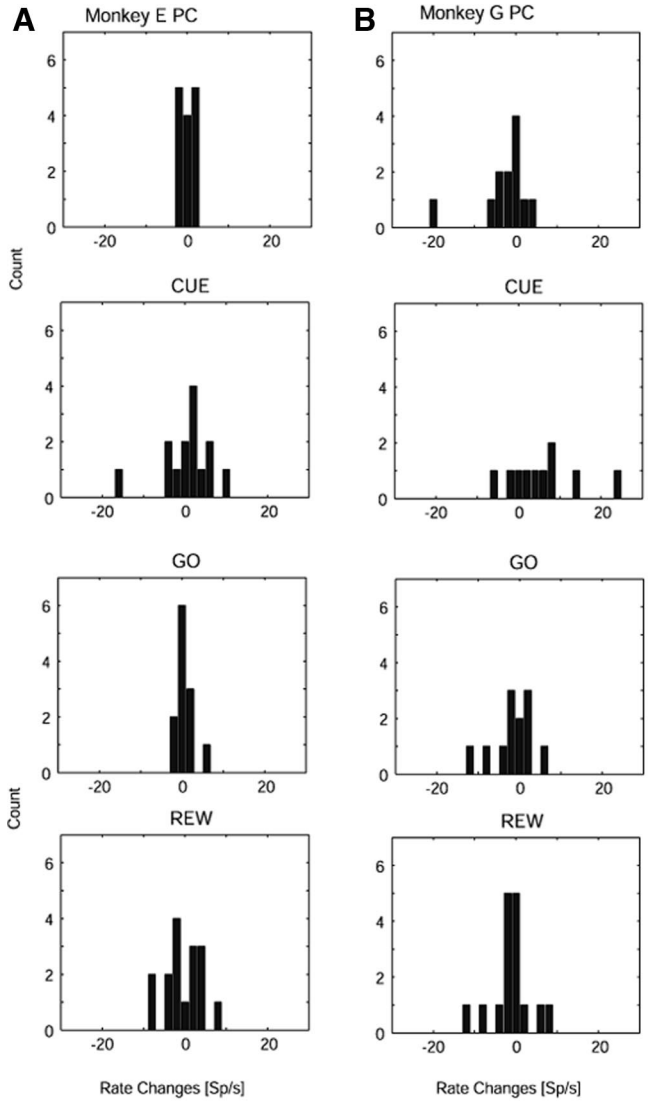

FIG. 2. Distribution of responses (rate changes) of SNr neurons to different events. Responses to events were evaluated by comparing the (negative or positive) peak of the firing rate of the neurons in the 500-ms time intervals starting at the time of the event (response interval) to the average rate in the baseline interval, defined as a 500-ms epoch in the ITI starting 1,500 ms before the Pre-Cue. *A* and *B*: results for monkeys E and G, respectively.

noninjured neuron. Each of the spike trains was therefore analyzed for rate stability. In this analysis, the rate of each unit during all ITI periods was displayed graphically as a function of time for the entire recording session. The underlying assumption is that unnoticed movements of the electrode and recording of another neuron, as well as possible injury to the recorded neuron, would be reflected in a sudden or gradual change in the tonic discharge rate (as reflected in the ITI discharge rate) of the recorded neuron. Only periods of time judged as displaying a stable firing rate were further analyzed. Note that this discharge stability is tested during the ITIs and is therefore not affected by modulation of discharge rate within the trial.

RESPONSES TO BEHAVIORAL EVENTS AND RESPONSE-MATCHES. Neuronal responses to events were evaluated by comparing the (negative or positive) peak of the firing rate of the neurons in the 500-ms time intervals starting at the time of the event (response interval) to the average rate in the baseline interval, defined as a 500-ms epoch in the ITI starting 1,500 ms before the Pre-Cue. The rate responses were calculated in 1-ms bins, averaged over trials, and then smoothed with a Gaussian window (SD = 100 ms). Responses were included in the database only if recorded for at least 10 repetitions of the event. Due to the complexity of SNr response patterns and differences in span and delay of responses, we compared a few methods of evaluation of response significance of the peristimulus histogram (PSTH). A definition of a significant response as a deviation of the peak rate from the baseline exceeding ±20% was found to be closest to our subjective evaluation of a significant response in the PSTH and the raster plots; therefore we used this criterion. However, a more formal criterion, a Mann–Whitney test of the null hypothesis that the rates during the response interval are derived from a distribution similar to the rates during the baseline interval, was also used (significance level $P < 0.05$). In cases of biphasic responses, composed of both increase and decrease in discharge rate, the response with the maximal deviation from the baseline was considered as the representative response to this event.

To examine the overlap between responses of pairs of neurons we calculated the dot-product of the response vectors—the "response-match"—which is a measure of correlation for each time point of each pair of PSTHs. This was performed by scalar multiplication of normalized PSTH vectors. This enabled a pairwise analysis of the overlap between changes in average firing rate during the trials. PSTHs were calculated in 1-ms bins, averaged over trials, and smoothed with a 25- or 100-ms Gaussian window. For this purpose we used PSTH vectors calculated for the whole trial and merged the responses to the Pre-Cue signal, the Cue and the Go signal, the movements, and the Reward, yielding 8,200-ms vectors. Each PSTH vector was normalized so that the baseline would be equivalent to zero and increases and decreases relative to it would be positive and negative, respectively. The normalization was performed as follows: $R(t) = [r(t) - b]/b$, where $R(t)$ represents the normalized PSTH, r is the raw PSTH, and b is the baseline mean (defined earlier). The response-match was defined as $RM(t) = R_1(t) \cdot R_2(t)$, with a single product calculated for each time bin. This way, $RM(t) > 0$ indicates that both neurons displayed an average activity at time t that was either higher or lower than their baseline; $RM(t) < 0$ indicates that one neuron had a higher and the other a lower average firing rate than its baseline at this time point; and $RM(t) = 0$ indicates that at least one of the neurons did not modulate its firing rate in this time period. For each pair, we calculated a reference response-match surrogate vector by randomly shuffling the bins in both PSTHs. A response-match was considered significant if more than three consecutive bins deviated from the mean of the reference vector by >2.5 SDs (SD calculated from the reference vector as well). This criterion was chosen because it yielded <5% correlated pairs when calculated for the surrogate vectors.

SPIKE-TIMING CORRELATIONS. Spike-to-spike cross-correlation functions (Perkel et al. 1967) were calculated with a 1-ms bin size for a time window of ±500 ms. Correlation functions were calculated over the whole duration of stable recording (including all intertrial and trial segments) and for the Reward epoch alone (see following text). The confidence limits of each correlogram were estimated using a resampling (bootstrap) method. This was performed by the calculation of 10 surrogate vectors; in each, every spike was randomly moved 0 to 50 ms forward or backward (Rivlin-Etzion et al. 2006). A cross-correlo-

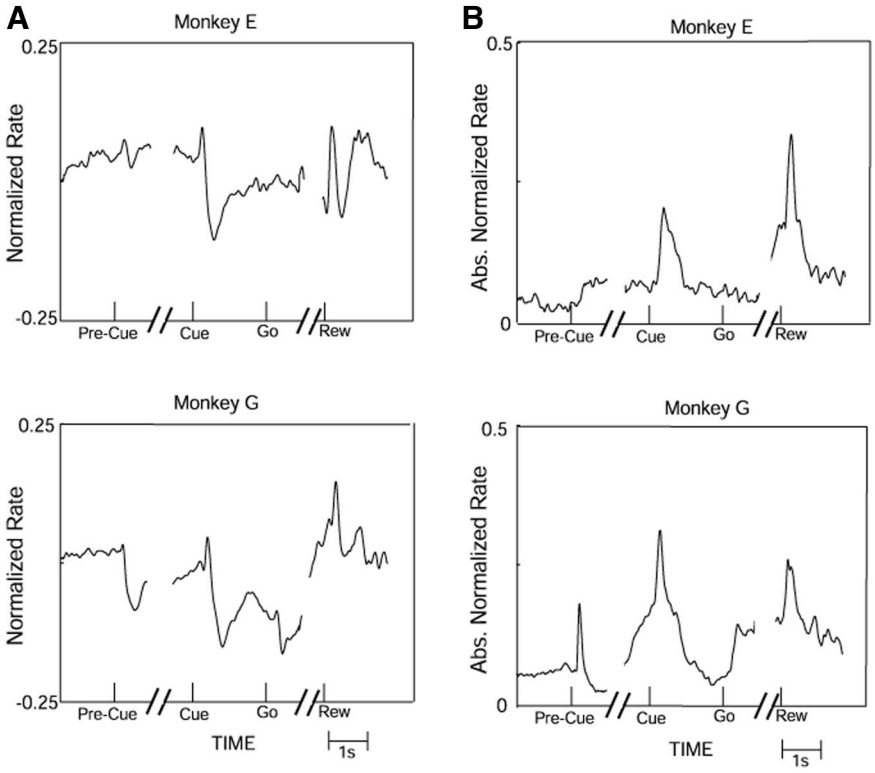

FIG. 3. Population responses of SNr neurons revealed similar response patterns. *A*: population average of peristimulus histograms (PSTHs) of task events presented sequentially. *B*: population average of absolute PSTHs of task events presented sequentially.

gram was considered significant if more than three consecutive bins deviated from the mean of the bootstrap vectors by >1 SD (SD calculated from the surrogate vectors). This criterion was selected because it yielded <5% significant correlations in the surrogate vectors. Only neurons recorded from different electrodes were examined for correlation analysis, to avoid detection of false correlations due to shadowing of coincident spikes (Bar-Gad et al. 2001). In an analysis of three or more simultaneously recorded neurons for correlation, not all comparisons are independent (e.g., if there is a correlation between the neuron pairs AB and BC, one would probably find a correlation between the AC pair). However, although we included correlation analysis for all possible pairs, this did not affect the statistical significance of our findings because we report a negative result.

Cross-correlations in Reward epochs were analyzed only for correct (rewarded) trials following cues that indicated a reward with a probability of 1. These were calculated in the time interval starting 500 ms before the reward until 1,000 ms after the reward and averaged over trials. A shift predictor was computed as the average of 10 surrogate cross-correlations calculated after random shuffling of the trials of one neuron. The shift predictor was subtracted from the original (raw) correlogram to produce the normalized correlogram (Eggermont 1990; Stevens and Gerstein 1976). Confidence levels were calculated as for the raw cross-correlogram (see earlier text).

SPIKE-COUNT CORRELATIONS. Signal correlations are defined as the correlation coefficients between the average responses (defined here as the spike count in the 500-ms time intervals starting at the time of the event) to different events. Signal correlations were calculated for the four-point event vector composed of the Pre-Cue, Cue, Go, and Reward events. Formally, if the average rate in the Pre-Cue, Cue, Go, and Reward is represented by P, C, G, and R, respectively, then for two neurons (1 and 2) the signal correlation (SC) is defined as SC = COV ([P1; C1; G1; R1][P2; C2; G2; R2])/SQRT{VAR ([P1; C1; G1; R1])·VAR ([P2; C2; G2; R2])}, where COV stands for covariance, SQRT for square root, and VAR for variance. Signal correlation can be calculated for simultaneously and nonsimultaneously recoded neurons.

Noise correlations were defined as the correlation coefficients between the number of spikes generated by each of the simultaneously recorded neurons in response to a single type of event (Gawne and Richmond 1993). The correlation coefficient by definition measures the correlation between intertrial fluctuations around the mean response in a single stimulus condition. We calculated noise correlations for the same events used for the calculation of the signal correlations. Formally, if the discharge rate of a unit during event E in trial t is represented by E(t) (E is either Pre-Cue, Cue, Go, or Reward), then for n trials the noise correlation (NC) for two neurons (1 and 2) in event E is defined as NC(E) = COV {[E1(1); . . . ; E1(n)][E2(1); . . . ; E2(n)]}/SQRT{VAR[E1(1); . . . ; E1(n)]·VAR[E2(1); . . . ; E2(n)]}, where COV stands for covariance, SQRT for square root, and VAR for variance. Noise correlation can be calculated only for simultaneously recoded neurons.

Average signal and noise correlations were calculated using Z-transforms to avoid bias from the zero to one range of the correlation-coefficient values.

RESULTS

We recorded the spiking activity of 113 SNr neurons (44 from monkey E and 69 from monkey G), yielding 355 simultaneously recorded pairs (monkey E: 70; monkey G: 285), while the monkeys performed the probabilistic delayed visuomotor response task. Because we required a minimum of 10

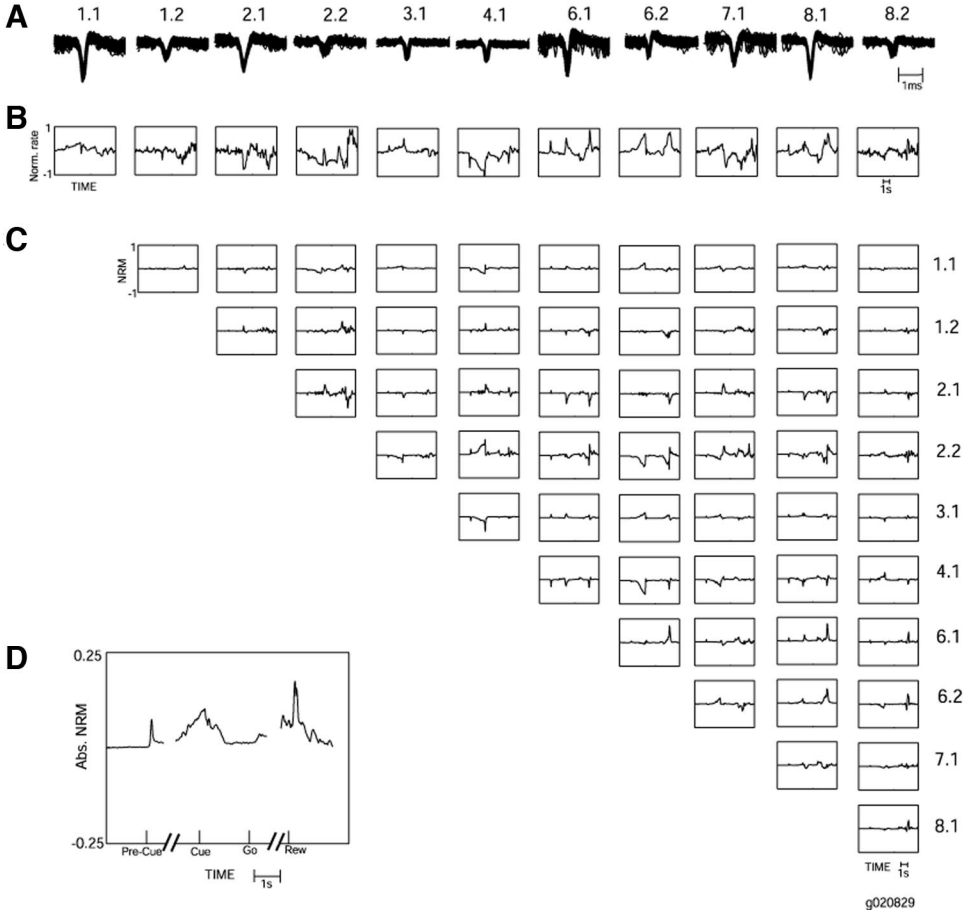

FIG. 4. Responses and response-match analysis of 11 simultaneously recorded SNr neurons. *A*: representative spike waveforms of each neuron. Randomly chosen spikes waveforms are superimposed. First number is the electrode number and the second is the number of the unit in this electrode. Two units were sorted in the recordings of electrode 1, 2, 6, and 8. *B*: normalized PSTHs of all task events presented sequentially for each neuron, smoothed with a 25-ms Gaussian. *C*: response-match vectors calculated by multiplying normalized PSTHs (NRM, normalized response-match). Most of these response-match vectors demonstrate significant deviations from zero, suggesting that these neuronal pairs tend to simultaneously modulate their firing rate. *D*: average of the absolute response-match vectors of these 11 neurons.

trials from each neuron in each analysis, different numbers of neurons or pairs were used for the different analyses. The number of neurons or pairs used in a specific analysis is given along with the results of this analysis. We used this minimum of 10 repetitions so that in an epoch lasting 1 s, an SNr neuron with an average firing rate (58 spikes/s, Table 1) would emit ≥580 spikes in the analyzed period.

Neuronal responses to behavioral events

Most (55%) of the SNr neurons (that passed the inclusion criteria for analysis of responses, $n = 34$ and 31 for monkeys E and G, respectively) responded to multiple events, with a greater tendency to respond to the reward and the instruction cue than to other events (Table 1). As in previous studies of the globus pallidus (Arkadir et al. 2004; DeLong 1971; Turner and Anderson 1997) and SNr (Handel and Glimcher 1999; Wichmann and Kliem 2004) we found that SNr neurons tend to fire at a high (mean = 58 spikes/s, SE = 3.7) tonic discharge rate and to display about equal proportions of responses with increases (48.5%) versus decreases (51.5%) in firing rates (Table 1). Using a formal Mann–Whitney yielded qualitatively similar results.

We considered a change in firing rate as a task-related response if the average change in discharge rate was statistically significant. These changes in the discharge rate may be associated with changes in the variability of the discharge. As in other neuronal structures (Lee et al. 1998) we found that the relationship between the mean and the variability of discharge rates can be fitted well by power functions for both ITI and Reward epochs (Fig. 1*A*). The power functions that fit the actual data best and the corresponding r^2 were: ITI: monkey E, $SD = 0.35M^{0.38}$ ($r^2 = 0.37$) and monkey G, $SD = 0.66M^{0.49}$ ($r^2 = 0.33$); Reward: monkey E, $SD = 0.44M^{0.50}$ ($r^2 = 0.65$) and monkey G, $SD = 0.83M^{0.61}$ ($r^2 = 0.66$). In these equations, M represents the mean and SD represents the SD of the discharge rates, respectively. Because unlike other studied areas, a significant fraction of SNr neurons responded by decreasing their discharge rate (Table 1 and Fig. 2), we also calculated the variability in the discharge rate during the reward period as a function of its deviation from the baseline (absolute value, normalized by the baseline rate). Figure 1*B* shows that the variability in the SNr firing rate was proportional to the magnitude of the positive (higher than baseline) responses. However, the variability of the negative (lower than baseline) responses was smaller than that of the positive responses and less affected by the amount of deviation from the background rate. Thus decoding (read-out by the next stations of the basal ganglia networks) of the neuronal responses of negative SNr responses was enhanced by the reduced variability of lower discharge rate of a Poisson-like firing (Fig. 1*A*), as well as by additional processes leading to stable variability of these responses (Fig. 1*B*).

Many SNr neurons tend to modulate their firing rate to similar events, as evident from the large percentage of neurons responding to each event. The fact that the sum of the percentages exceeds 100% implies that there are groups of neurons that respond to more than one event (Table 1, Figs. 3 and 4*B*). Due to the different polarities of response displayed by SNr neurons (Table 1), this is even more evident in the population average of the absolute deviation from the mean (Fig. 3*B*). We formally tested this by calculating response-match vectors that enabled examination of the overlap of responses between each pair of neurons (Fig. 4, *C* and *D*). Response-match vectors were calculated for the entire population, including pairs that were not simultaneously recorded ($n = 1{,}820$). Using vectors smoothed with a 25- or 100-ms Gaussian, 94 and 80% of the pairs, respectively, had significant peaks in their response-match vector.

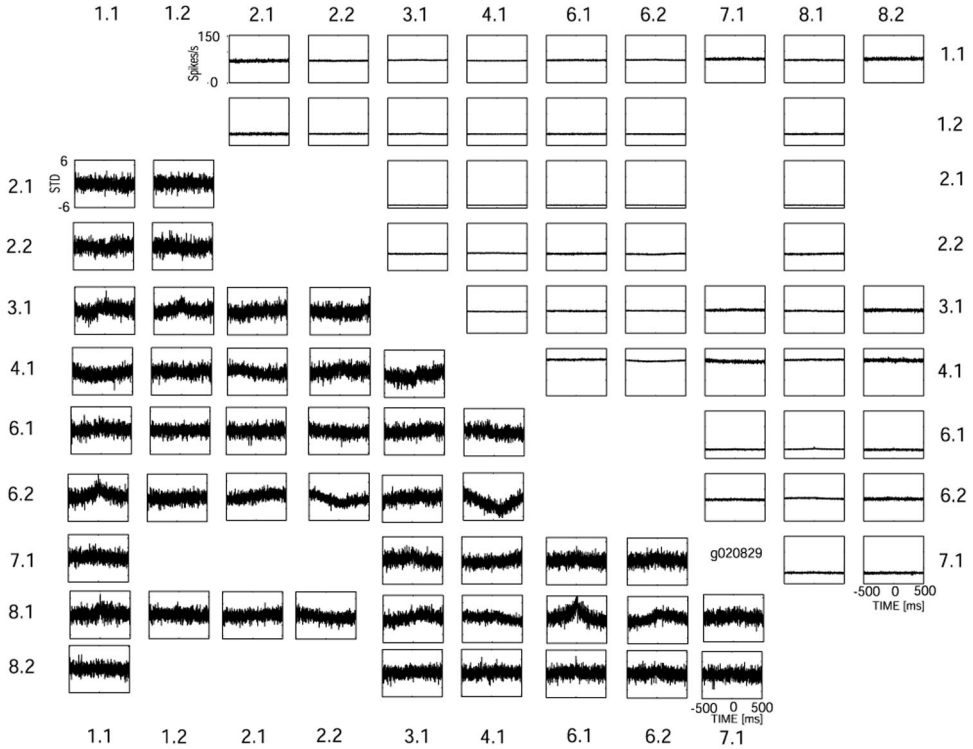

FIG. 5. Spike-to-spike cross-correlation matrix. Spike-to-spike cross-correlation histograms between the 11 simultaneously recorded neurons presented in Fig. 4. In the top right half of the square the ordinate represents the conditional rate (given a trigger spike at *time = 0*, range 0–150 Hz); in the bottom left half the conditional rate is given in SD units. Both parts present the correlations of the same neurons (mirror imaged). Cross-correlation histograms of nonsimultaneously recorded units (e.g., between 1.2 and 7.1) and those between neurons recorded with the same electrode (e.g., 2.1 and 2.2) were excluded.

The high baseline discharge rate of basal ganglia output neurons enables another dimension of neuronal encoding, by assigning a different meaning to increases versus decreases in firing rate. The significant peaks in the response-match vectors suggest that there is a significant overlap between the responses of SNr neurons. Similar (of the same polarity) responses may lead to positive correlations between SNr neurons. On the other hand, if one SNr neuron reduces its firing rate whenever its neighbor neuron increases its firing rate, the SNr correlation functions should be dominated by negative peaks. In the following text we explore the correlation status of the SNr activity given the common responses described earlier.

Spike-timing correlations

In contrast to the similar responses of SNr neurons, spike-to-spike correlations between neurons recorded simultaneously (Fig. 5) were significant in only 2.1% of the cases (monkey E: 6/70; monkey G: 11/285), even less than the 3.8% significant pairs found in surrogate vectors. To isolate possible event-related correlations we also calculated the cross-correlation on Reward epochs (the time interval starting 500 ms before reward until 1,000 ms after reward). Although 63% of the neurons responded to the reward event, and therefore the expected percentage of correlated pairs was $0.63^2 \cong 40\%$, only 10% of the reward epoch correlograms displayed significant peaks or troughs. All of the significant peaks and troughs vanished after normalization with a shift predictor (Fig. 6), indicating that these correlations were not due to precise time correlations in spiking activity, but rather were a consequence of simultaneous rate changes.

Spike-count correlations

Signal correlation values were broadly distributed, showing both positive and negative values. The correlation values were subjected to Z-transformation for analysis of their nontruncated distribution (Fig. 7*E*). The average Z-transform of SNr signal correlations was −0.16 in monkey E and 0.09 in monkey G, both nonsignificantly different from zero ($P < 0.05$, two-tailed *t*-test). The 95% confidence interval calculated for the average signal correlation of both monkeys together was between −0.164 and 0.212.

The average Z-transforms of noise correlation coefficients were also close to zero (Table 2). Figure 7, *A–D* shows the distributions of noise correlation Z-transforms for the different epochs of the behavioral trial. Although the mean values of the noise correlations during the Pre-Cue in monkey E and for the Cue period in monkey G were significantly greater than zero, for the other monkey during the same epochs the results were either less significant (Pre-Cue) or nonsignificant (Cue) and the numbers were very low. Based on confidence intervals it is unlikely that the average Z-transform of noise correlations in the whole population of SNr neurons exceeded 0.056, 0.075, 0.047, and 0.024 for the Pre-Cue, Cue, Go, and Reward intervals, respectively. Results for the ITI varied considerably

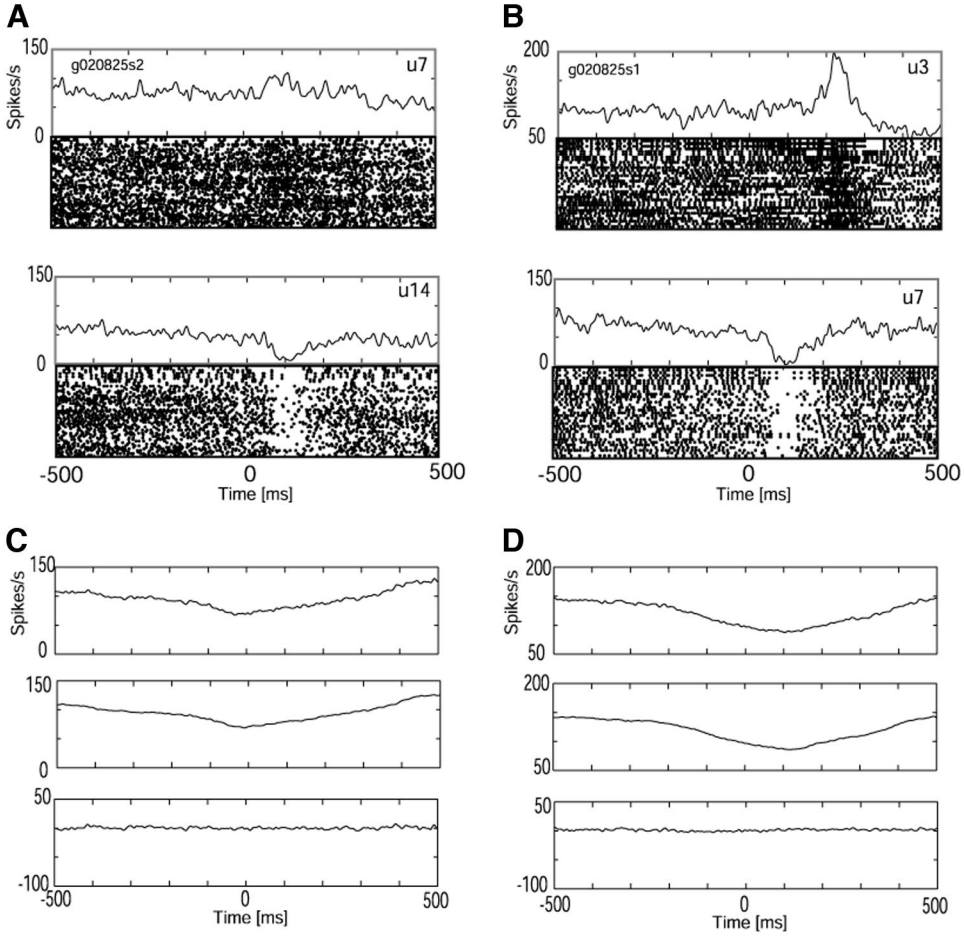

FIG. 6. SNr neurons may have similar responses; nevertheless their normalized correlograms are flat. *A* and *B*: 2 examples of PSTHs and raster displays of activity of SNr neurons aligned around the reward events ±500 ms. *C* and *D*, *top*: Spike-to-spike cross-correlation histograms of the neurons presented in *A* and *B*, calculated for a time interval starting 500 ms before the reward until 1,000 ms after the reward. *Middle*: shift predictor, calculated by shuffling the trials of one neuron 10 times and averaging the shuffled cross-correlation histograms. *Bottom*: normalized cross-correlation histogram obtained by subtraction of the shift predictor from the raw correlograms. PSTHs and cross-correlograms were smoothed with a 25-ms Gaussian.

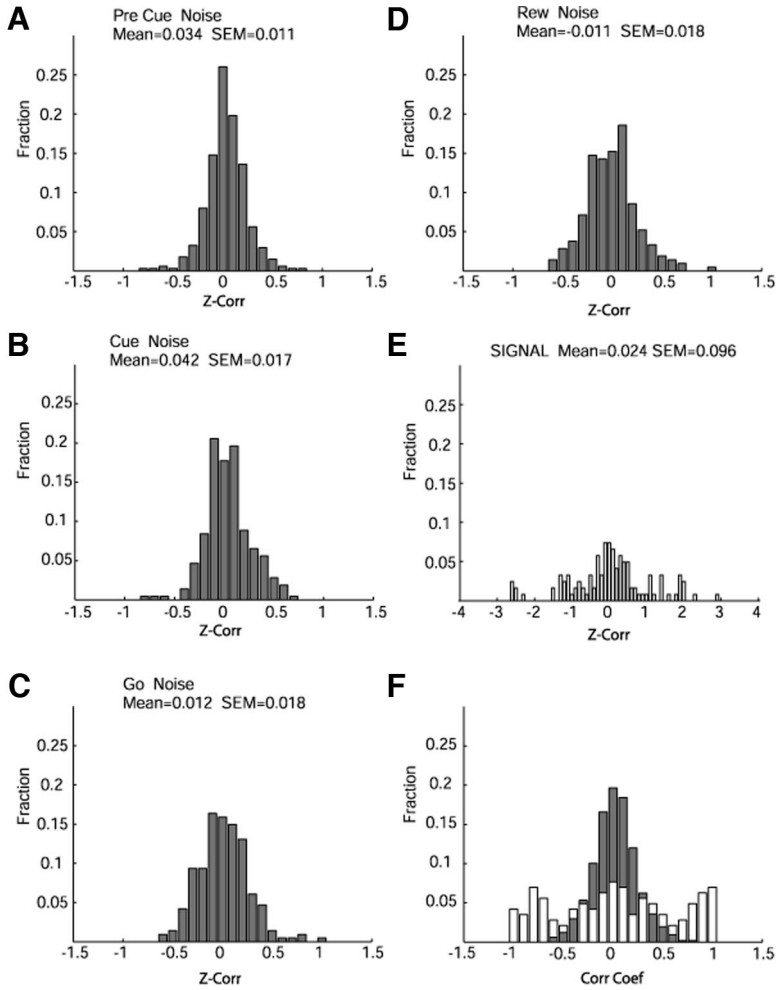

FIG. 7. Histograms of spike-count correlations. *A–D*: distribution of the Z transforms of noise correlations during Pre-Cue, Cue, Go, and Reward, respectively. *E*: distribution of the Z transforms of signal correlations. *F*: distribution of the signal (white bars) and noise (black bars, calculated for all behavioral epochs) correlation coefficient values (without Z transforms).

according to the event aligned for (e.g., Reward of previous trial, Pre-Cue of the next trial). This is probably related to uncontrolled movements or behavior that the monkey may have performed during the ITI (e.g., movements back to the central key or licking of the water reward). These movements may have different temporal correlations with the trial behavioral events and thus might create different "false" correlations due to correlation with a third uncontrolled factor (Ben Shaul et al. 2001; Brody 1999).

The relationships between noise correlations calculated for different behavioral events (Fig. 8) and between noise and signal correlations (Fig. 9) were also evaluated. We found that the noise during the Pre-Cue was correlated to some extent ($R^2 < 0.35$) with the noise in all other events and with the signal correlation, whereas the noise during the Reward epoch was relatively independent of the noise during other events and the signal correlation. The lack of a robust significant correlation between the noise and the signal correlation rules out synergy in the encoding of behavioral events (in our behavioral paradigm) by the population of SNr neurons (Averbeck et al. 2006; Oram et al. 1998). A direct analysis of information coding (Pola et al. 2003; Schneidman et al. 2003) should be performed to further evaluate the mutual information relationships between SNr neurons.

TABLE 2. *Average Z-values of noise correlation coefficients*

	Monkey E		Monkey G	
	Z-Value	Power >80%	Z-Value	Power >80%
Pre-Cue	0.052**		0.029*	
Cue	0.012	Z > 0.35	0.055**	
Go	−0.038	Z > 0.35	0.033	Z > 0.22
Reward	−0.004	Z > 0.35	−0.014	Z > 0.23

Threshold values for statistical power >80% are given for the cases that were not significantly different from zero. *$P < 0.05$ and **$P < 0.01$ indicate that the mean is significantly different from zero.

DISCUSSION

Firing of SNr neurons is uncorrelated despite overlapping responses

Previous studies have indicated that under conditions of normal dopaminergic activity, SNr and pallidal neurons lack spike-to-spike cross-correlations (Nevet et al. 2004; Nini et al. 1995; Raz et al. 2000; Wilson et al. 1977). However, correlations of the response properties of basal ganglia neurons have not been previously examined. The data presented here show analysis of average signal and noise correlations of SNr neurons. Most of the neurons we examined responded to the instruction cue and the delivery of reward, and their response-match vectors were rarely flat. Traditionally, such overlapping

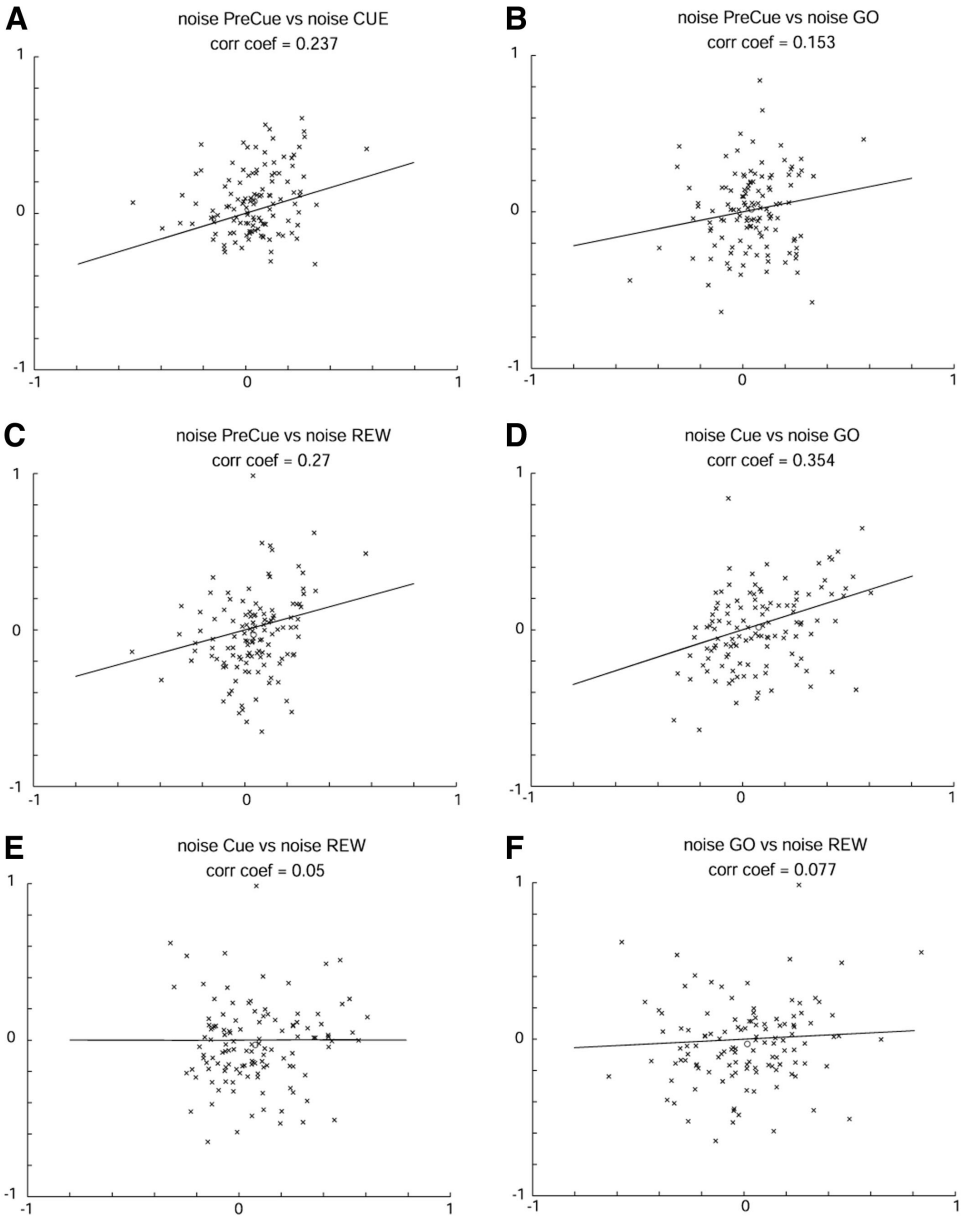

FIG. 8. Correlations between Z transforms of noise correlation coefficients to different events. Each dot represents a single neuron. Lines represent linear regressions.

responses are expected to lead to correlated spiking activity (Eggermont 1990; Perkel et al. 1967). However, all the average measures of spike-count and spike-timing correlations we calculated were close to zero. To the best of our knowledge this is the first CNS structure where the average values of spike-count correlations are not significantly (at $P < 0.05$) different from zero. Although this unique finding could be due to several mechanisms, it still narrows the scope of possible modes of information coding in the basal ganglia and points to specific models of these structures (e.g., sparse connectivity, active decorrelation).

Lack of correlation can improve information transfer

The lack of average signal or noise correlations (compare with Lee et al. 1998) in a small nucleus such as the SNr that receives funneling inputs from much larger structures, including the external segment of the globus pallidus, subthalamic nucleus, and striatum, is surprising. Because most of the SNr neurons are responsive to the same events, the lack of correlation probably serves a purpose and is not fortuitous. The amount of information carried by a nucleus can be bounded by the signal correlation between its neurons (Gawne and Richmond 1993; Samengo and Treves 2001). Therefore keeping low values of the average signal correlations may improve the efficiency of information transfer by the SNr. The tonic background activity of SNr neurons—enabling both increases and decreases in firing rate in responses to behavioral events—probably plays a critical role in creating this equal (around zero) distribution of correlation values resulting in an information-efficient mode of work.

A low level of noise correlation improves the signal-to-noise ratio achieved when averaging multiple inputs. The need to avoid the consequences of correlated noise and redundancy of information (Oram et al. 1998) may favor a selection of

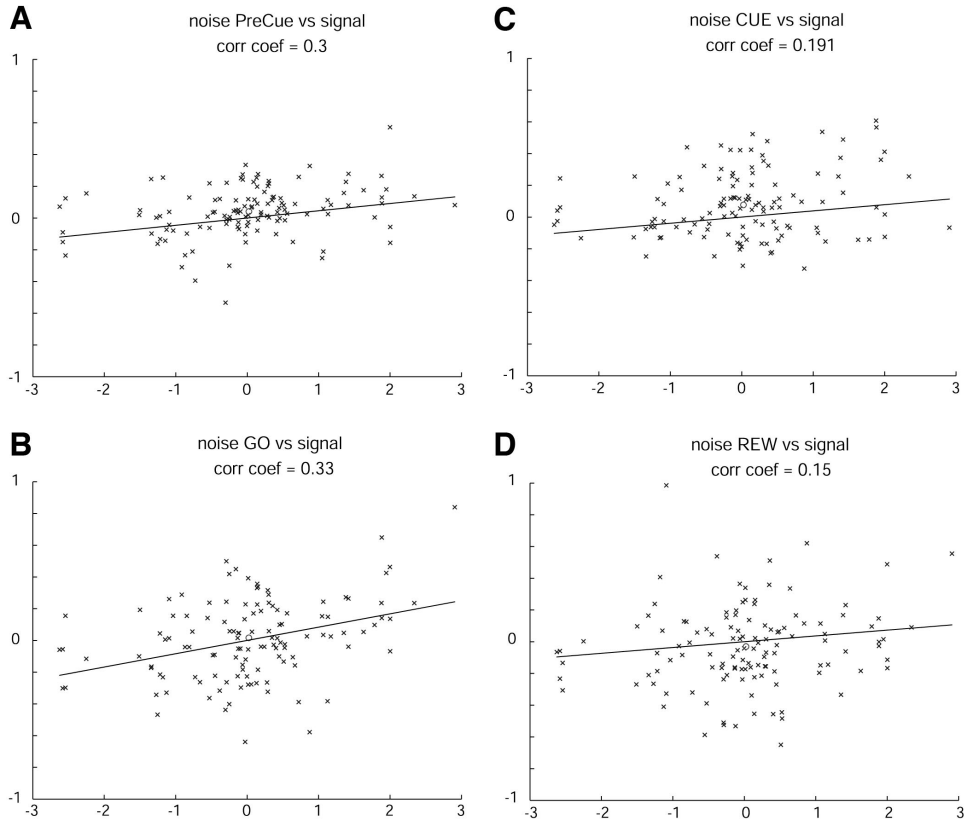

FIG. 9. Correlations between Z transforms of noise (*y*-axis) and signal (*x*-axis) correlation coefficients. Each dot represents a single neuron. Lines represent linear regressions.

connection weights that keeps the responses of adjacent neurons nearly independent for both signal and noise. Neurons sharing common inputs can be decorrelated by different means, including sparse afferent connectivity (Jaeger 2003), various temporal filtering properties of different neurons (Gawne and Richmond 1993), and local Hebbian and anti-Hebbian learning rules as in principal component neural networks (Bar-Gad et al. 2003; Diamantaras and Kung 1996; Foldiak 1990; Oja 1982). Most of these would not result in synergy (a state where the population activity provides more information than the sum of their individual members). The independence of the signal and noise correlation in our study indicates that the basal ganglia networks achieve maximal reduction of redundancy, yet synergy is not observed. Further studies should examine whether

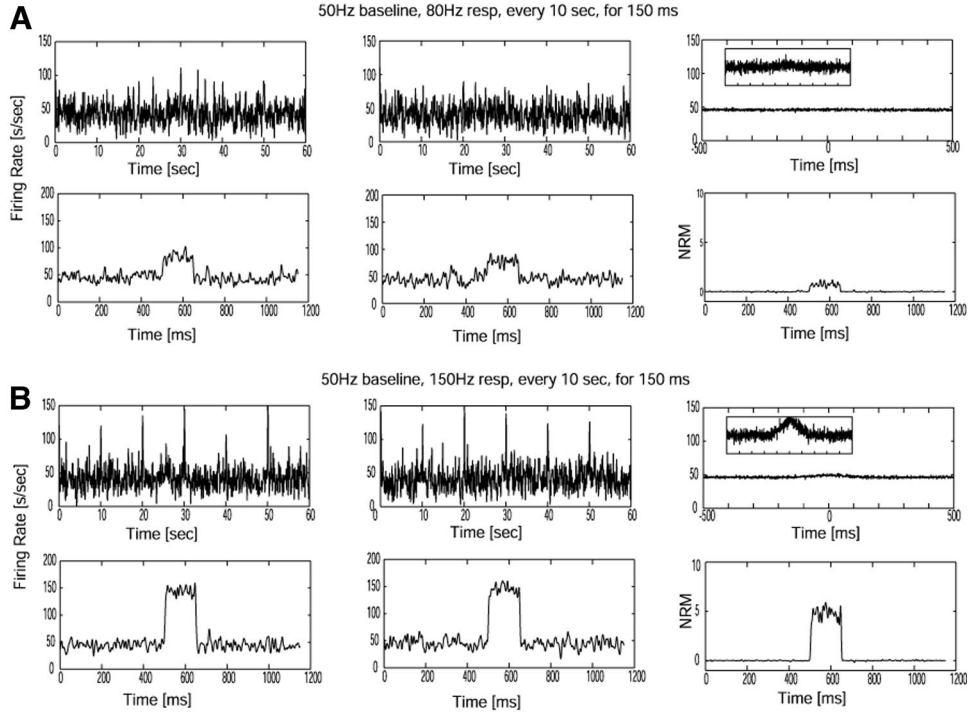

FIG. 10. Effect of overlapping responses on spike-to-spike correlations between neurons with high discharge rates. Neurons were simulated by 2 Poisson-like spike trains with 50-Hz independent spiking activity. Responses (modulation of spiking probability) were induced simultaneously in both neurons every 10 s for 150 ms. *A*: peak responses of 80 Hz (30 Hz above baseline). *B*: peak responses of 150 Hz. *Top*, *left* and *middle*: rate diagrams of representative 60 s from each spike train. Rate was calculated in 1-ms bins and smoothed with a 30-ms Gaussian. *Top right*: spike-to-spike cross-correlation with the ordinate representing conditional rate. *Inset*: ordinate given in SD units (Scale: ±6 SD). *Bottom*, *left* and *middle*: PSTHs (calculated from response onset − 500 ms to response end + 500 ms) of 100 simulated responses. Smoothing was done with a 2-ms Gaussian. *Bottom right*: response-match histogram. NRM, normalized response-match.

this is a property of our limited behavioral paradigm, whether the neuronal machinery of the basal ganglia was not stretched to its maximal capabilities, or whether the neuronal machinery necessary for creating and reading a synergetic code does not exist in the basal ganglia.

The basal high firing rate of SNr neurons is intrinsic

The lack of spike-to-spike correlations (compare with Bair et al. 2001; Gawne and Richmond 1993) supports the hypothesis that the basal high-rate firing of these neurons is intrinsically driven, and thus does not depend on the SNr inputs (Atherton and Bevan 2005; Nakanishi et al. 1987; Stanford 2003; Windels and Kiyatkin 2006). The overlapping responses are superimposed on the uncorrelated basal activity. If the input-driven modulations are rare and weak relative to the basal activity, their influence on the spike-to-spike correlogram will not be significant. In this case no peaks or troughs will be found even without using a shift predictor. A simulation we conducted demonstrates this (Fig. 10) and highlights the differences between correlation studies of neurons with high spontaneous discharge rates versus neurons with low background discharge (Stevens and Gerstein 1976). Therefore we argue that the spontaneous activity of SNr neurons is self-initiated and thus independent, whereas SNr responses are driven by overlapping input sources. The finding that the variability of the positive responses and the ITI discharge rate, but not the negative responses, is correlated with the mean firing rate supports the conjecture that the negative responses of SNr neurons are driven by different mechanisms than the spontaneous activity and positive responses (Gulley et al. 2002; Sato and Hikosaka 2002).

Relevance to Parkinson's disease

Pallidal neurons demonstrate overlapping responses (Anderson and Horak 1985; Arkadir et al. 2004; Brotchie et al. 1991; DeLong 1972; Nambu et al. 1990) without spike-to-spike correlations, like the SNr. The suggestion of independent spontaneous activity modulated by overlapping inputs can therefore be applied to the pallidum as well. However, significant spike-to-spike correlations appear in tremulous Parkinson's disease (PD) patients (Hurtado et al. 1999; Levy et al. 2002) and in primate models of this disease (Heimer et al. 2006; Raz et al. 2000). This phenomenon, not yet tested in the SNr, may reflect a higher dominance of input-driven rate modulations relative to the basal activity of output basal-ganglia neurons in this disease. Signal and noise correlations in the output structures of the basal ganglia of parkinsonian monkeys have yet to be evaluated.

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