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Neural correlates of conflict resolution between automatic and volitional actions by basal ganglia

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Abstract

A dominant basal ganglia (BG) model consists of two functionally opposite pathways: one facilitates motor output and the other suppresses it. Although this idea was originally proposed to account for motor deficits, it has been extended recently also to explain cognitive deficits. Here, we employed the antisaccade paradigm (look away from a stimulus) to address the role of the caudate nucleus, the main BG input stage where the two pathways diverge, in conflict resolution. Using single neuron recordings in awake monkeys, we identified the following three groups of neurons. The first group of neurons showed activity consistent with sensory-driven (automatic) saccades toward a contralateral visual stimulus. The second group of neurons showed activity consistent with internally driven (volitional) saccades toward the contralateral side regardless of stimulus locations. The third group of neurons showed similar firing characteristics with the second group of neurons, except that their preferred saccade direction was ipsilateral. The activity of the three groups of neurons was correlated with behavioral outcome. Based on these findings, we suggest the following hypothesis: the first and second groups of neurons encoding automatic and volitional saccades, respectively, might give rise to the facilitation (direct) pathway and promote saccades toward the opposite directions, which creates a response conflict. This conflict could be resolved by the third group of caudate neurons, which might give rise to the suppression (indirect) pathway and attenuate inappropriate saccade commands toward the stimulus.

Introduction

The basal ganglia (BG) have been implicated in action selection (Redgrave *et al.*, 1999). This hypothesis is supported by the following two types of pathways in the BG: one facilitates motor output and the other suppresses it (Mink, 1996; Hikosaka *et al.*, 2000). This architecture was proposed originally to explain motor deficits in Parkinson's and Huntington's diseases (Albin *et al.*, 1989; DeLong, 1990). This idea has been extended recently to explain cognitive deficits in BG disorders (for a review see Frank *et al.*, 2007). However, this extension has been challenged by clinical studies using a psychophysical paradigm, called the antisaccade paradigm.

The antisaccade paradigm (Hallett, 1978) requires subjects to look away from a visual stimulus (Fig. 1A). This simple requirement creates a conflict between two theoretical saccade commands: an automatic (sensory-driven) saccade toward the stimulus and a volitional (internally driven) saccade away from the stimulus (Everling & Fischer, 1998; Munoz & Everling, 2004). Patients with several BG disorders have difficulties performing antisaccades (Briand *et al.*, 1999; LeVasseur *et al.*, 2001; Chan *et al.*, 2005; Peltsch *et al.*, 2008), suggesting deficits in resolving the conflict between automatic and volitional actions. However, other studies have suggested that antisaccade performance depends only on direct projections from the cerebral cortex to the superior colliculus (SC) bypassing the BG, because BG lesions have no effect on behavioral performance (Gaymard *et al.*, 2003; Condy *et al.*, 2004; Ploner *et al.*, 2005). This suggests an alternative hypothesis that the conflict between automatic and volitional actions imposed by the antisaccade paradigm is resolved by other action selection mechanisms in structures outside the BG, such as the frontal cortex (Cisek, 2007) and SC (Trappenberg *et al.*, 2001) where the winner-take-all networks are implemented presumably by intrinsic circuits.

To begin addressing the issue regarding the role of the BG in conflict resolution, we carried out single neuron recordings in monkey caudate nucleus. The caudate nucleus is the main input stage of the oculomotor BG where the facilitation and suppression pathways diverge (Mink, 1996; Hikosaka *et al.*, 2000), and it has been shown previously that caudate neurons have saccade-related activity presumably correlated with automatic and volitional saccades (Hikosaka *et al.*, 1989, 2000). Furthermore, recent studies have shown that saccade signals in the caudate nucleus are modified by reward in a way

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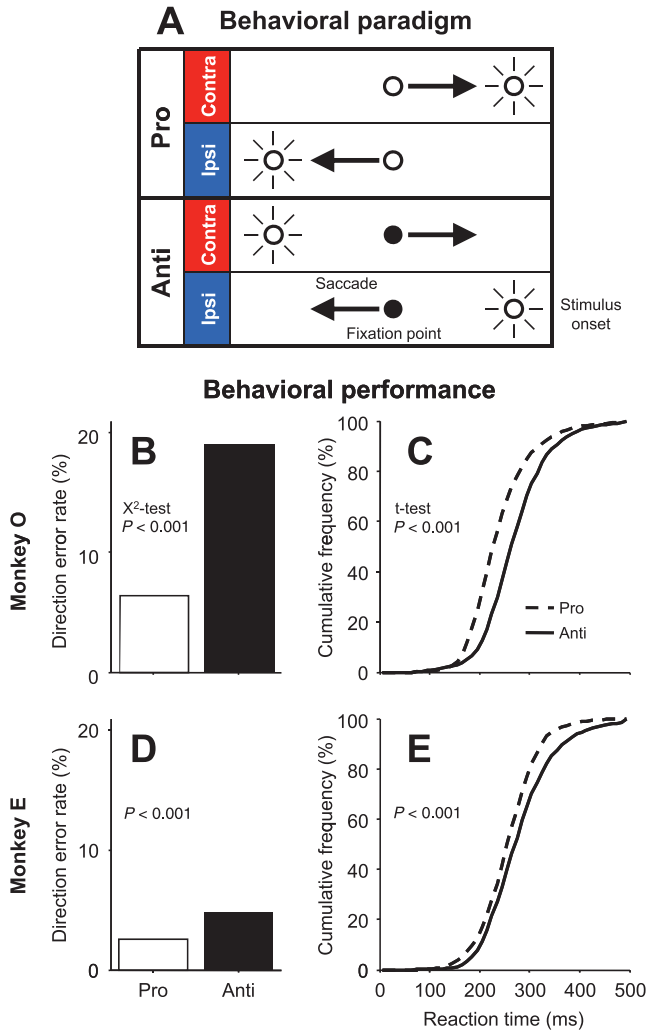

FIG. 1. Behavioral paradigm and performance. (A) Behavioral paradigm. After monkeys fixated on the central fixation point, a peripheral visual stimulus appeared on either the left or the right side. Monkeys generated a prosaccade or an antisaccade in response to stimulus appearance depending on an instruction given by fixation point color. 'contra' and 'ipsi' indicate saccade directions. (B, C) Behavioral performance in one monkey (monkey O): (B) direction error rates; (C) cumulative distributions of saccade reaction times. Similar results were observed in the other monkey (monkey E) (D, E).

to influence behavior (Kawagoe *et al.*, 1998; Hikosaka *et al.*, 2006). Using the antisaccade paradigm, we introduced a conflict between caudate signals encoding automatic and volitional saccade commands and examined whether their activity is consistent with the hypothesis of BG involvement in antisaccade control. Specifically, we asked whether the activity of caudate neurons before saccade initiation carried signals necessary for antisaccade control and was correlated with behavioral outcome.

Methods

General

All experimental procedures were conducted in accordance with the Canadian Council on Animal Care policy on the use and care of laboratory animals and were approved by the Queen's University Animal Care Committee. The evening prior to surgery, the animal was placed under Nil per Os (NPO, water *ad lib*), and a prophylactic treatment of antibiotics was initiated [5.0 mg/kg enrofloxacin (Baytril)]. On the day of the surgery, anesthesia was induced by ketamine (6.7 mg/kg im). A catheter was placed intravenously to deliver fluids (lactated Ringer) at a rate of 10 mL/kg/h to a maximum of 60 mL/kg throughout the duration of the surgical procedure. Glycopyrolate (0.013 mg/kg im) was administered to control salivation, bronchial secretions, and to optimize heart rate (HR). An initial dose was delivered at the start of surgery followed by a second dose 4 h into the surgery. General anesthesia was maintained with gaseous isofluorene (2–2.5%) after an endotracheal tube was inserted (under sedation induced by an intravenous bolus of propofol, 2.5 mg/kg). HR, pulse, pulse oximetry saturation (SpO_2), respiration rate, fluid levels, circulation, and temperature were monitored throughout the surgical procedure. The analgesic buprenorphine (0.01–0.02 mg/kg i.m.) was administered throughout the surgery and during recovery (8–12 h). The antiinflammatory agent ketoprofen (2.0 mg/kg 1st dose, 1.0 mg/kg additional doses) was administered at the end of the surgery (prior to arousal), the day after the surgery and every day thereafter (as required). Monkeys were given 2 weeks to recover prior to onset of behavioral training. Surgical and electrophysiological procedures were as described previously (Marino *et al.*, 2008). Briefly, two male monkeys (*Macaca mulatta*), weighing 13.5 and 10 kg, were implanted with scleral search coils, a head-restraining device and a recording chamber. Horizontal and vertical eye positions were sampled at 1 kHz using the search coil technique (Robinson, 1963; Fuchs & Robinson, 1966; Judge *et al.*, 1980). The onset and end of saccades were identified by radial eye velocity criteria (threshold: 30°/s). Trials with reaction times shorter than 70 ms or longer than 600 ms were excluded from data analyses.

The recording chamber (circular, 19 mm i.d., tilted by 34° laterally and 13° anteriorly in monkey O and 36° laterally in monkey E) was placed on the left hemisphere in both monkeys to cover the head and body of the caudate nucleus. Using the grid system (Crist *et al.*, 1988), we mapped the caudate nucleus as widely as possible in the area allowed by each chamber. Recording sites were verified by magnetic resonance imaging (MRI, 3 T, Siemens) in one monkey (monkey O) whose implant was compatible with MRI (see Fig. 8).

Neurons with fewer than five trials in each condition were excluded from analyses. All quantitative analyses for single neuron recordings were carried out by calculating firing rates using spike counts within temporal windows associated with task events. Additional information, describing experimental systems and details of neural data analyses, can be found in the Supporting information, Appendix S1.

Behavioral paradigm

We trained two monkeys to perform a randomly interleaved prosaccade (look toward a stimulus) and antisaccade paradigm (Fig. 1A). Each trial was preceded by a 600-ms inter-trial interval during which the screen was illuminated with a diffuse light to prevent dark adaptation. After removal of the background light, a fixation point appeared and the monkeys were required to direct their eyes toward the fixation point within 30 s. After they maintained fixation for 900–1200 ms, a red stimulus was presented either 15° left or right from the fixation point and the monkeys generated a saccade either toward the stimulus (prosaccade) or to the opposite direction of the stimulus (antisaccade) within 600 ms based upon fixation point color (red: pro, green: anti). Another 150–350-ms fixation was required on the red stimulus on prosaccade trials or on a green stimulus presented at the mirror position of the red stimulus after saccade onset on antisaccade trials. The monkeys received a liquid reward after each correct

performance. On half of the trials, a 200-ms gap was introduced between fixation point disappearance and stimulus appearance (gap condition). On the remaining half of the trials, the fixation point remained visible until the end of each trial (overlap condition). The pro/anti instructions, gap/overlap conditions and left/right stimulus locations were randomly interleaved in the block of trials (see 'Permutation test' in the supporting Appendix S1 for the control analyses of gap/overlap conditions).

Definition of temporal windows

To quantify firing rates, we adopted the following four time periods: baseline, post-stimulus, pre-saccade and peri-saccade. Here, we describe the definitions of these periods that are linked to specific events in the behavioral tasks.

The baseline period (0–80 ms from stimulus onset) was defined by estimating the shortest latency of caudate neurons to receive spatial information after stimulus onset. We compared activity between contralateral and ipsilateral saccade trials in each instruction separately by two-tailed *t*-tests ($P < 0.05$) with a 60-ms temporal window shifting by 10 ms within 600 ms starting 100 ms before stimulus onset. Because *t*-tests detected occasional statistical significances before 50 ms after stimulus onset, at which point only 5% of neurons in cortical regions projecting to the caudate nucleus show visual responses (Schmolesky *et al.*, 1998), we also calculated saccade direction indices (see 'Classification of task-related neurons' below) and identified a set of criteria to exclude inappropriate statistical detections (five consecutive time points exceeding 0.17 and the maximum value reaching at least 0.33 before falling below 0.17; when a saccade direction index is equal to 0.33, the absolute difference between contralateral and ipsilateral saccades is equal to the RMS_{error}). We detected the earliest saccade direction discrimination at 80 ms after stimulus onset. Shorter temporal windows detected equal or longer latencies. Therefore, we adopted this 80-ms time window starting at stimulus onset as the baseline period.

The post-stimulus period (130–190 ms after stimulus onset on average) was defined for the analysis of correlation between reaction times and firing rates (see Fig. 7A–C). We first created a cumulative reaction time distribution in each condition (systems × monkeys × gap/overlap × instructions × saccade directions, 32 conditions), determined a time point at which the cumulative distribution exceeded 5%, and then defined the post-stimulus period for a 60-ms temporal window ended at 30 ms before the 5% time point (see below for justification of the 30 ms).

To define the pre-saccade (−90 to −30 ms from saccade onset) and peri-saccade (−30 to +30 ms from saccade onset) period, we determined the delay of caudate neurons for saccade control based on several previous findings. Microstimulation of caudate neurons induces inhibitory and excitatory responses in substantia nigra pars reticulata (SNpr) neurons with an average latency of 16.7 ms for both responses (Hikosaka *et al.*, 1993). The latencies of antidromic activation from the SC to the SNpr vary from 0.7 to 2.3 ms (Hikosaka & Wurtz, 1983). Microstimulation of SC neurons during saccades influences saccade trajectories with minimum latency of 8–10 ms (Miyashita & Hikosaka, 1996; Munoz *et al.*, 1996). Therefore, the average latency of caudate neurons to influence eye movements could be as little as 26 ms. For simplicity, we employed 30-ms delay for our caudate neurons. Pro- and antisaccade durations were 51 ± 11 and 58 ± 13 ms (mean ± SD), respectively. Therefore, we took 60 ms as a time for saccade duration for simplicity and defined the peri-saccade period between −30 and 30 ms from saccade onset and the pre-saccade period between −90 and −30 ms from saccade onset. We confirmed our results using another 60-ms time window starting 15 ms earlier than the pre-saccade period to take into account a potential delay for the suppression (indirect) pathway compared with the facilitation (direct) pathway (Tachibana *et al.*, 2008).

Definition of task-related neurons

We defined task-related neurons that changed firing rates depending on task conditions after stimulus onset by the following criteria. We calculated firing rates during the following four periods: 120–180 ms from stimulus onset, 180–240 ms from stimulus onset, −90 to −30 ms from saccade onset (pre-saccade period) and −30 to +30 ms from saccade onset (peri-saccade period). The former two periods were defined for visual responses (peak firing rates were observed approximately at 180 ms after stimulus onset, see supporting Fig. S2). We identified the best window to maximize a difference between two out of the four conditions (2 instructions, pro and anti, × 2 saccade directions, contra and ipsi) using the following equations (DeAngelis & Uka, 2003):

$$\text{Discrimination index} = \frac{C_{\max} - C_{\min}}{C_{\max} - C_{\min} + 2\text{RMS}_{\text{error}}} \quad (1)$$

$$\text{RMS}_{\text{error}} = \sqrt{\text{SSE}/(N - M)} \quad (2)$$

where $C_{\max}$ and $C_{\min}$ indicate the maximum and minimum average firing rates among the four conditions, respectively. SSE is the squared sum error around the average in each condition. N is the total number of trials. M is the number of conditions (2). The index is close to 1 if the difference between the maximum and minimum average firing rates ($C_{\max} - C_{\min}$) is much larger than the variance in firing rates (RMS_{error}), while it is close to zero when the difference between the maximum and minimum average firing rates is negligible compared with the variance in firing rates. Using the temporal window detected by the criterion. We carried out a two-way ANOVA (main factors: instructions and saccade directions, $P < 0.05$). In addition, we compared the maximum average firing rates ($C_{\max}$) and firing rates during the baseline period using a one-tailed *t*-test ($P < 0.05$). For calculation of baseline activity, we chose trials whose instruction was the same as that associated with $C_{\max}$. Trials with two different saccade directions were collapsed for the calculation of baseline activity due to visual latency (see 'Definition of temporal windows'). We assigned neurons to task-related neurons if both two-way ANOVA and *t*-test detected statistical significance. Bonferroni correction was applied to the statistical tests described above to take into account multiple temporal windows.

Of the 320 caudate neurons we encountered (monkey O: 162, monkey E: 158), we identified 72 task-related neurons (monkey O: 42, monkey E: 30) by the criteria described above. We also identified two other neurons (one in each monkey) that changed activity depending on task instructions only (pro/anti) before stimulus onset by another set of criteria (see supporting Appendix S1). We included these two neurons as task-related neurons, but they did not influence our results. The proportion of task-related neurons (23%) was slightly higher than that in the original report (14%) (Hikosaka *et al.*, 1989). This is probably due to our online selection of task-related neurons.

Classification of task-related neurons

We focus here on the majority of task-related neurons that discriminated contralateral and ipsilateral saccades on pro- and/or antisaccade trials by the following criteria. For each instruction (pro- or antisaccade), we compared firing rates on contralateral and ipsilateral

saccade trials during the pre-saccade and peri-saccade periods by calculating the following saccade direction index:

$$\text{Saccade direction index} = \frac{C - I}{|C - I| + 2\text{RMS}_{\text{error}}} \quad (3)$$

where C and I denote the average firing rates on contralateral and ipsilateral saccade trials, respectively. Positive and negative saccade direction indices indicate contralateral and ipsilateral saccade direction preferences, respectively. We identified one of the two windows with larger absolute value of the saccade direction index for the following analyses. We defined neurons discriminating saccade direction if they showed a significant difference between firing rates for contralateral and ipsilateral saccades on pro- and/or antisaccade trials (t-test, $P < 0.05$) and firing rates for the preferred direction exceeded the baseline activity (one-tailed t-test, $P < 0.05$).

We classified task-related neurons with saccade direction preferences into the following two types: contralateral (CN) and ipsilateral (IN) saccade preferred neurons. This classification is straightforward when saccade direction preferences were the same on both pro- and antisaccade trials in individual task-related neurons (the first and third quadrants in Fig. 2).

When saccade direction preferences were the opposite between pro- and antisaccade trials (the second and fourth quadrants in Fig. 2), we compared pro- and antisaccade trials with their own preferred directions by the same procedure described above. For instance, for neurons with contralateral prosaccade and ipsilateral antisaccade preferences (fourth quadrant in Fig. 2), we compared firing rates on contralateral prosaccade trials and ipsilateral antisaccade trials and assigned them as CNs (or INs) if firing rates were higher on prosaccade (or antisaccade) trials. This is similar to adding the third dimension in Fig. 2 and CNs and INs in the second and fourth quadrants are separated along this dimension.

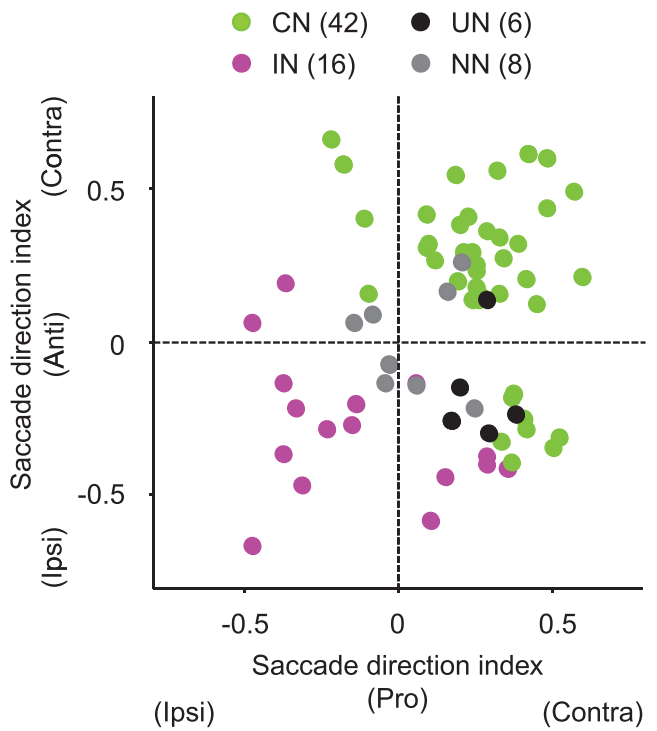

FIG. 2. Classification criteria for task-related neurons. The horizontal and vertical axes indicate saccade direction indices on pro- and antisaccade trials, respectively. For each task-related neuron in each instruction (pro and anti), we calculated saccade direction indices during the pre- and peri-saccade periods and chose indices with higher absolute values for this classification. CN, contralateral saccade-preferred neurons ($n = 42$); IN, ipsilateral saccade-preferred neurons ($n = 16$); UN, unclassified neurons ($n = 6$); NN, no saccade direction-preferred neurons ($n = 8$). See 'Classification of task-related neurons' in Methods for details.

Several neurons showed saccade direction preferences only in one of the two instructions (pro or anti). For these neurons, we applied the same procedure for neurons with opposite saccade direction preferences described above. For instance, if a neuron showed a contralateral saccade direction preference on prosaccade trials, we assigned it as a CN given that firing rates during prosaccades toward the preferred direction were higher than those during antisaccades toward the opposite direction. This excludes the possibility that the strongest activity of this neuron was associated with saccades toward the opposite of the preferred direction on prosaccade trials. Bonferroni correction was applied to the classification criteria described above to take into account the multiple comparisons as well as multiple temporal windows.

Using these criteria, we classified 42 (monkey O: 26, monkey E, 16) and 16 (monkey O: nine, monkey E: seven) task-related neurons as CNs and INs, respectively. There were six neurons (three in each monkey) that showed saccade direction preferences on pro- and/or antisaccade trials but did not meet the criteria. We confirmed similar results when we assigned an unclassified neuron (monkey E) in the first quadrant in Fig. 2 as a CN and five unclassified neurons (monkey O: three, monkey E: two) in the fourth quadrant as CNs or INs, respectively (data not shown). Eight neurons (four in each monkey), including the two neurons detected by the second set of criteria for task-related neurons (see supporting Appendix S1), did not show saccade direction preferences either on pro- or on antisaccade trials.

Activation index

To describe the time courses of task-dependent signals in each group of caudate neurons (Fig. 5), we calculated the following index:

$$\text{Activation index} = \frac{P - P_{\text{min}}}{P_{\text{max}} - P_{\text{min}} + 2\text{RMS}_{\text{error}}} \quad (4)$$

where P indicates the average of firing rates in one of the four conditions (Fig. 1A), and P_{max} and P_{min} indicate the maximum and minimum average firing rates in the four conditions. The number of conditions (M) in Equation (2) is four in this index. Firing rates were quantified using a 60-ms temporal window shifted by 10 ms. This procedure is more advantageous than the population averages of spike density functions because the index normalizes firing rates and takes into account the variance of firing rates in individual neurons before averaging across the population of neurons.

Multiple linear regression analysis

To characterize the pre-saccade activity of caudate neurons, we applied a multiple linear regression analysis to firing rates during the pre-saccade period using the following equation:

$$\text{Firing rate} = b_{\text{stim}} \times [\text{stimulus}] + b_{\text{sac}} \times [\text{saccade}] + b_{\text{inst}} \times [\text{instruction}] \quad (5)$$

where 'stimulus' indicates contralateral (+1) and ipsilateral (−1) stimulus locations, 'saccade' indicates contralateral (+1) and ipsilateral (−1) saccade directions, and 'instruction' indicates prosaccade (+1)

and antisaccade (−1) instructions, respectively. Firing rates were normalized before applying this equation.

Correlation between firing rates and reaction times

We calculated Pearson's partial correlation coefficients between reaction times and firing rates during a post-stimulus period (130–190 ms after stimulus onset on average, see 'Definition of temporal windows'). Other saccade parameters (peak velocity, duration, and horizontal and vertical amplitude) were used as fixed parameters.

Direction error index

To compare activity between correct responses and direction errors (saccade in the wrong direction) on antisaccade trials with the same stimulus location, we calculated the following index similar to the saccade direction index described above (Equation 1):

$$\text{Direction error index} = \frac{C - E}{|C - E| + 2\text{RMS}_{\text{error}}} \quad (6)$$

where C and E indicate average firing rates on correct and direction error trials, respectively. We quantified firing rates on individual trials between stimulus appearance to 30 ms before saccade onset. We confirmed the same result using a fixed pre-saccade window (−90 to −30 ms from saccade onset). We limited this analysis to the conditions of neurons in which five direction error trials were included at least.

Results

Behavior

The behavior of the monkeys was consistent with previous reports in both humans (Hallett, 1978; Fischer & Weber, 1992; Dafoe *et al.*, 2007) and monkeys (Bell *et al.*, 2000) (Fig. 1B and C for monkey O; Fig. 1D and E for monkey E). The rates of direction errors on antisaccade trials were higher than those on prosaccade trials (Fig. 1B and D, χ^2 test $P < 0.001$). Reaction times on correct antisaccade trials were longer than those on correct prosaccade trials (Fig. 1C and E, t-test $P < 0.001$).

Saccade-related neurons

We found 72 task-related neurons in two monkeys (see 'Definition of task-related neurons' above). Of these, we identified 58 neurons that met the criteria for saccade-related neurons (see 'Classification of task-related neurons' above). The firing characteristics of these neurons were consistent with phasically active neurons reported previously based on their phasic activity after stimulus onset (see below) and low firing rates during fixation (200–700 ms after fixation initiation, mean ± SD = 1.2 ± 1.9 spikes/s, no difference between three groups of caudate neurons, see below, one-way ANOVA; $F = 2.1$, d.f. = 2, $P > 0.1$) (Kimura *et al.*, 1984; Hikosaka *et al.*, 1989; Wilson *et al.*, 1990; Aosaki *et al.*, 1995; Apicella, 2007). In the following analyses, we characterize signals issued by these 58 saccade-related neurons.

Contralateral saccade-preferred neurons

Of the 58 saccade-related neurons, we identified 42 that preferred contralateral saccades (CNs). Figure 3A and B shows an example of a CN whose activity is aligned with saccade onset (see supporting Fig. S1 for activity aligned with stimulus onset). On prosaccade trials, this neuron showed stronger activation for contralateral saccades than for ipsilateral saccades. However, on antisaccade trials, activity was higher for ipsilateral saccades than for contralateral saccades (Fig. 3B). Because a stimulus was presented on the contralateral side on ipsilateral antisaccade trials (Fig. 1A), the spatial information carried by this neuron on both pro- and antisaccade trials is consistent with the contralateral stimulus.

Figure 3C and D shows another example of a CN. On prosaccade trials, this neuron showed stronger activation for contralateral saccades than for ipsilateral saccades (Fig. 3C). The key difference of this from the previous neuron is that it maintained contralateral saccade preference on antisaccade trials (Fig. 3D). Accordingly, the activity of this neuron was consistent with contralateral saccades, but not with the contralateral stimulus.

To examine which saccade direction individual CNs support before saccade initiation, we compared activity for contralateral and ipsilateral saccades (Fig. 4). On prosaccade trials (Fig. 4A), the majority of CNs had contralateral saccade preferences (positive saccade direction indices, t-test; $t = 7.2$, d.f. = 41, $P < 0.0001$). However, on antisaccade trials (Fig. 4B), their saccade direction preferences were inconsistent across the population of CNs ($t = 1.2$, d.f. = 41, $P > 0.2$).

Neurons with negative saccade direction indices on antisaccade trials (Fig. 4B), such as the example CN shown in Fig. 3A and B, had higher firing rates for ipsilateral saccades than for contralateral saccades. Because all of these neurons had contralateral saccade preferences on prosaccade trials (positive saccade direction indices, $n = 17$, monkey O: 11, monkey E: 6, mean ± SD = 0.29 ± 0.13, t-test; $t = 8.8$, d.f. = 16, $P < 0.0001$), their activity was consistent with the contralateral stimulus regardless of saccade directions. Because their saccade preferences were incongruent between pro- and antisaccade trials, we call them 'incongruent CNs' (iCNs). The average time courses of task-dependent signals in iCNs are shown in Fig. 5A and B (see supporting Fig. S2 for stimulus-aligned time courses).

By contrast, neurons with positive saccade direction indices on antisaccade trials (Fig. 4B), such as the example CN shown in Fig. 3C and D, had higher firing rates for contralateral saccades than for ipsilateral saccades. Because the majority of these neurons also had contralateral saccade preferences on prosaccade trials (positive saccade direction indices, $n = 25$, monkey O: 15, monkey E: 10, mean ± SD = 0.11 ± 0.15, t-test; $t = 3.8$, d.f. = 24, $P < 0.001$), their activity was consistent with contralateral saccades regardless of stimulus directions. Because their saccade preferences were congruent between pro- and antisaccade trials, we call them 'congruent CNs' (cCNs). The average time courses of task-dependent signals in cCNs are shown in Fig. 5C and D.

Although we divided CNs into iCNs and cCNs based only on the sign of saccade direction indices on antisaccade trials (Fig. 4B), it is important to analyse them separately in terms of the following theoretical aspect of the antisaccade paradigm: the antisaccade requirement dissociates automatic saccade commands toward the stimulus and volitional saccade commands away from the stimulus, while these saccade commands are aligned toward the same direction on prosaccade trials (Everling & Fischer, 1998; Munoz & Everling, 2004). Accordingly, iCNs and cCNs might encode automatic and volitional saccade commands predominantly before saccade initiation (see Discussion).

Ipsilateral saccade-preferred neurons

We identified another group of 16 neurons that had ipsilateral saccade preferences on pro- or antisaccade trials (INs). Figure 3E and F shows

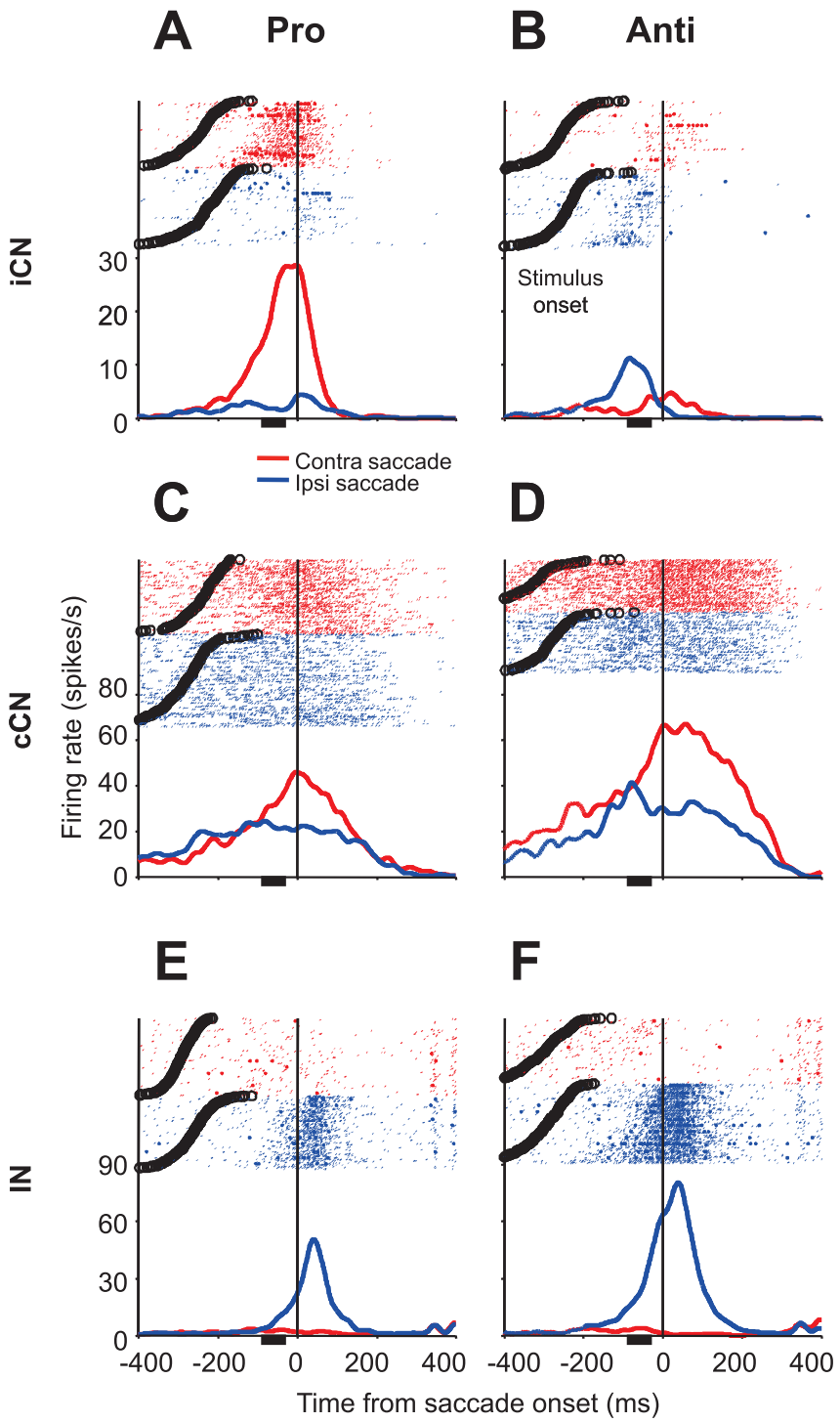

FIG. 3. Activity of three groups of caudate neurons aligned with saccade onset. (A, B) An incongruent contralateral saccade-preferred neuron (iCN). (C, D) A congruent contralateral saccade-preferred neuron (cCN). (E, F) An ipsilateral saccade-preferred neuron (IN). Left (A, C, E) and right (B, D, F) columns indicate prosaccade and antisaccade trials. Black circles indicate stimulus onset. Black bars under the *x*-axes indicate the pre-saccade period (−90 to −30 ms from saccade onset). Although the cCN (C, D) showed relatively higher activity before stimulus onset (see supporting Fig. S1, C and D) compared with the other two example neurons, it stopped firing approximately 300 ms after saccade onset and its activity during fixation was low (< 1 spike/s), consistent with the firing characteristics of phasically active neurons. See supporting Fig. S1 for activity aligned with stimulus appearance.

an example of an IN. On both pro- and antisaccade trials, this neuron showed higher activity for ipsilateral saccades than for contralateral saccades. The population of INs showed a similar tendency, although they seem to discriminate saccade directions better on antisaccade trials than on prosaccade trials (Fig. 5E and F). Indeed, we found that, on prosaccade trials, the population of INs did not show consistent saccade direction preferences (Fig. 4C, *t*-test; $t = -0.9$, d.f. = 15, $P > 0.3$). However, on antisaccade trials (Fig. 4D), the majority of INs showed

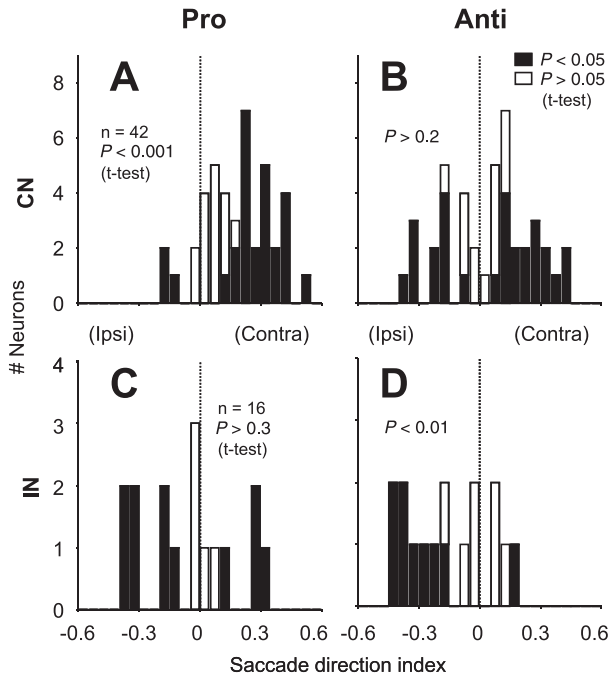

FIG. 4. Saccade direction index for pre-saccade activity (−90 to −30 ms from saccade onset). (A, B) CNs on pro- (A) and antisaccade (B) trials. (C, D) INs on pro- (C) and antisaccade (D) trials. Black bars indicate neurons with statistical difference between firing rates for contralateral and ipsilateral saccades (*t*-test $P < 0.05$). We divided CNs into the following two subgroups based on the signs of saccade direction indices on antisaccade trials: incongruent CNs (iCN, negative indices in B) and congruent CNs (cCN, positive indices in B). See main text for discussion of this classification. There were several CNs with higher pre-saccade activity on ipsilateral saccade trials (including iCNs) and INs with higher activity on contralateral saccade trials. However, they were judged as CNs and INs because the classification criteria did not depend only on their pre-saccade activity on either pro- or antisaccade trials (see 'Classification of task-related neurons' in Methods).

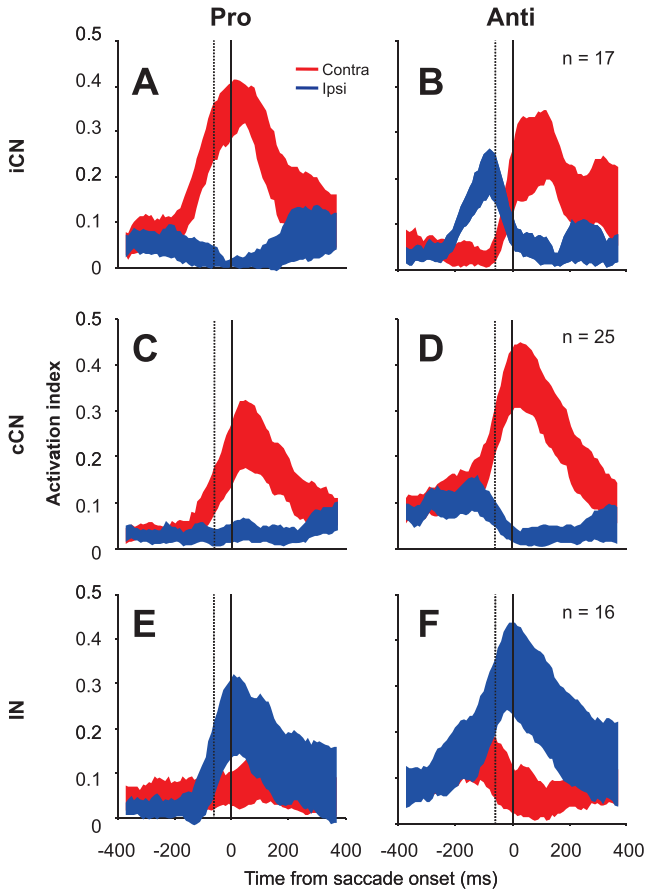

FIG. 5. Time courses of task-dependent signals. (A, B) iCNs; (C, D) cCNs; (E, F) INs. Left (A, C, E) and right (B, D, F) columns indicate pro- and antisaccade trials, respectively. See 'Activation index' in the Methods for the equation of activation indices. See supporting Fig. S2 for stimulus-aligned time courses.

ipsilateral saccade preferences before saccade initiation ($t = -3.0$, d.f. = 15, $P < 0.001$). The consistent saccade direction preferences on antisaccade trials, but not on prosaccade trials, suggest that signals encoded by INs might be somewhat specialized for antisaccade control.

Decomposition of pre-saccade signals

Based on the qualitative inspections of temporal evolution of task-dependent signals in each group of caudate neurons (Fig. 5), it seems likely that the activity of caudate neurons is controlled by the following three task parameters: saccade directions, stimulus directions, and pro- and antisaccade instructions. We decomposed these signals by a multiple linear regression analysis (see 'Multiple linear regression analysis' above). Figure 6 shows the average regression coefficients of the three groups of caudate neurons (see supporting Fig. S3 for regression coefficients in individual neurons). The regression coefficients of saccade directions confirmed contralateral saccade preferences for iCNs and cCNs and ipsilateral saccade preferences for INs (Fig. 6A, *t*-test; iCNs: $t = 4.3$, d.f. = 16, $P < 0.001$, cCNs: $t = 11.6$, d.f. = 24, $P < 0.0001$, INs: $t = -4.3$, d.f. = 15, $P < 0.001$). The regression coefficients of stimulus directions (Fig. 6B) revealed that iCNs showed a strong bias toward the contralateral stimulus ($t = 7.5$, d.f. = 16, $P < 0.0001$), while cCNs and INs did not show consistent biases (cCNs: $t = -1.7$, d.f. = 24, $P > 0.05$, INs: $t = 1.1$, d.f. = 15, $P > 0.2$). The regression coefficients of pro- and antisaccade instructions (Fig. 6C) revealed that cCNs and INs showed antisaccade instruction preferences (cCNs: $t = -3.2$, d.f. = 24, $P < 0.005$, INs: $t = -2.6$, d.f. = 15, $P < 0.05$), while iCNs showed the opposite tendency, although this did not reach statistical significance ($t = 1.8$, d.f. = 16, $P > 0.05$).

These results are consistent with our hypothesis that iCNs facilitate automatic saccades toward the contralateral stimulus, cCNs facilitate volitional saccades toward the contralateral direction and INs are somewhat specialized for ipsilateral antisaccade control.

Correlation with behavior

If the three types of caudate neurons described above contribute to behavioral control, their activity should be correlated with the fluctuations of behavioral outcome on a trial-by-trial basis. Accordingly, we calculated correlation coefficients between reaction times and firing rates (see 'Correlation between firing rates and reaction times'. above). All three groups of caudate neurons showed higher firing rates followed by shorter reaction times (negative correlation coefficients) when saccades were directed toward their preferred directions on both pro- and antisaccade trials (Fig. 7A–C, *t*-test $P < 0.05$, see figure legend for detailed statistical results and supporting Fig. S4 for individual neurons). cCNs also showed significant negative correlation on ipsilateral antisaccade trials, which might reflect non-spatial signals, such as antisaccade instruction (Fig. 6C), arousal and motivation. However, the negative correlation

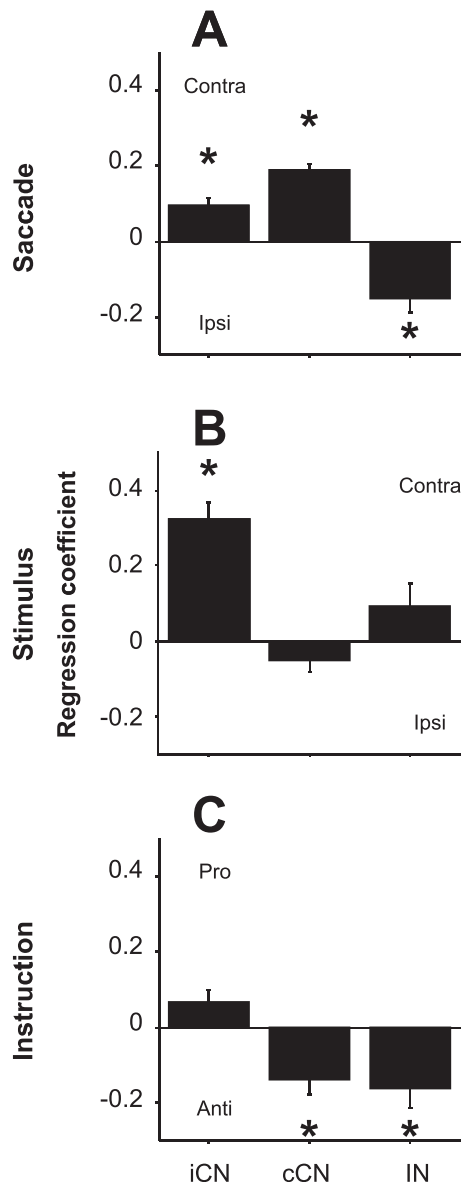

FIG. 6. Linear regression analysis for pre-saccade activity. (A) Average coefficients for saccade directions. (B) Average coefficients for stimulus directions. (C) Average coefficients for pro- and antisaccade instructions. Error bars indicate standard errors. Asterisks indicate $P < 0.05$ (*t*-test). See supporting Fig. S3 for regression coefficients in individual neurons.

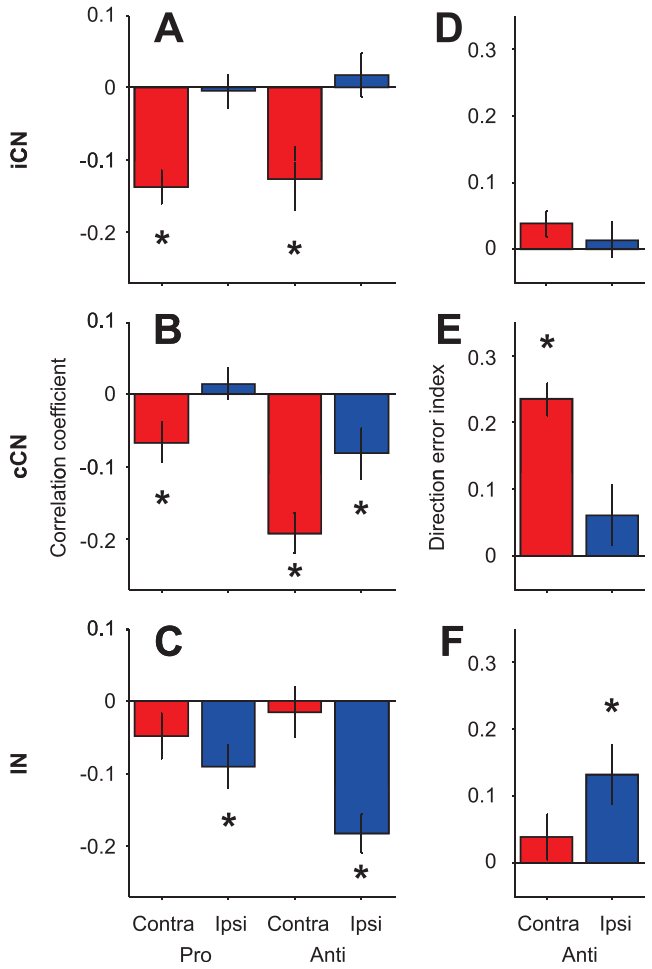

FIG. 7. Correlation with behavior. (A–C) Average correlation coefficients between reaction times and firing rates on correct trials for iCN (A) (*t*-test; d.f. = 16, pro-contra: $t = -5.9$, $P < 0.0001$, pro-ipsi: $t = -0.11$, $P > 0.9$, anti-contra: $t = -2.9$, $P < 0.05$, anti-ipsi: $t = 0.75$, $P > 0.4$), cCN (B) (d.f. = 24, pro-contra: $t = -2.2$, $P < 0.05$, pro-ipsi: $t = -0.5$, $P > 0.6$, anti-contra: $t = -6.7$, $P < 0.0001$, anti-ipsi: $t = -2.8$, $P < 0.01$) and IN (C) (d.f. = 15, pro-contra: $t = -1.5$, $P > 0.1$, pro-ipsi: $t = -3.1$, $P < 0.01$, anti-contra: $t = -0.58$, $P > 0.5$, anti-ipsi: $t = -6.3$, $P < 0.0001$). (D–F) Average direction error indices in the iCN (D) (contra: $t = 1.9$, d.f. = 15, $P > 0.05$, ipsi: $t = 0.54$, d.f. = 10, $P > 0.6$), cCN (E) (contra: $t = 9.7$, d.f. = 21, $P < 0.0001$, ipsi: $t = 1.4$, d.f. = 14, $P > 0.1$) and IN (F) (contra: $t = 1.1$, d.f. = 12, $P > 0.2$, ipsi: $t = 3.0$, d.f. = 13, $P < 0.01$). Comparison was made between antisaccade trials with different behavioral outcomes in response to the same stimulus. 'Contra' and 'Ipsi' indicate saccade directions on correct antisaccade trials. Corresponding error saccades were directed toward the opposite direction. The numbers of neurons in each comparison were as follows. iCN: $n = 16$ (11) and 11 (9), cCN: $n = 22$ (15) and 15 (12), IN: $n = 13$ (9) and 14 (8) for contralateral and ipsilateral antisaccades, respectively. Numbers in parentheses indicate neurons recorded in one monkey (monkey O) whose direction error rates (Fig. 1B) were higher than in the other monkey (monkey E, Fig. 1D). Similar results were observed when the analyses were limited to neurons from monkey O. Error bars indicate standard errors. Asterisks indicate $P < 0.05$ (*t*-test).

on ipsilateral antisaccade trials was not as strong as that on contralateral antisaccade trials (paired *t*-test $P < 0.05$), suggesting that the negative correlation on contralateral antisaccade trials reflects contralateral saccade signals.

Monkeys occasionally made errors in the antisaccade paradigm (Fig. 1B and D) and if neurons in the caudate nucleus are involved in controlling the behavior, their activity should depend on this aspect of behavioral performance. To demonstrate this for caudate neurons, we compared activity on trials with different behavioral outcomes in response to the same stimulus on antisaccade trials (see supporting Fig. S5 for example neurons). The following results were mainly derived from one monkey (monkey O) whose direction error rates (Fig. 1B) were higher than for the other monkey (monkey E, Fig. 1D). In both cCNs and INs, we found higher activation on correct trials than on direction error trials (positive direction error indices, see 'Direction error index' above) when correct antisaccades were required toward their preferred direction and direction errors were generated to the opposite direction ('Contra' condition in Fig. 7E for cCNs and 'Ipsi' condition in Fig. 7F for INs, *t*-test $P < 0.05$, see figure legend for detailed statistical results). However, this enhanced activity on correct antisaccade trials was not observed among iCNs (Fig. 7D, $P > 0.1$). Thus, only cCNs and INs depended on this aspect of behavioral performance (see supporting Fig. S6 for individual neurons).

Recording sites

We reconstructed neural recording sites on magnetic resonance images in one monkey (monkey O) and confirmed that these sites were confined within the caudate nucleus (Fig. 8). The recording sites were mainly in the posterior part of the head of the caudate nucleus (Fig. 8B and C). We did not find differences between the sites of iCNs, cCNs and INs in three-dimensional space (one-way ANOVA, d.f. = 2, $F < 1$, $P > 0.3$ for each dimension defined by principal component analyses applied to the coordinates of neurons).

Discussion

We identified three types of neurons carrying different saccade signals in the caudate nucleus: iCNs, cCNs and INs. These neurons changed activity before saccade initiation in different ways (Figs 4–6). Furthermore, the activity of these neurons before saccade initiation was correlated with behavioral performance (Fig. 7). These results support the hypothesis that the caudate nucleus is involved in the online control of antisaccade initiation. In the following discussion, we link the theoretical aspect of the antisaccade paradigm and BG circuits based on our findings.

Automatic, volitional and suppression commands

As mentioned, the antisaccade requirement dissociates the following two theoretical saccade commands: automatic saccade commands toward the stimulus and volitional saccade commands toward the opposite direction of the stimulus. We speculate that automatic and volitional saccade commands are encoded by iCNs and cCNs in different ways.

The activity of iCNs was higher when a stimulus was presented on the contralateral side (Fig. 5A and B). This could be explained by activation of these neurons in response to the contralateral stimulus (Fig. 6B). However, they also encoded contralateral saccades (Fig. 6A) and their activity was correlated with the reaction times of contralateral saccades on a trial-by-trial basis (Fig. 7A). Accordingly, we speculate that their visual responses correspond to automatic saccade commands toward the stimulus.

In contrast, cCNs showed higher activity for contralateral saccades than for ipsilateral saccades regardless of stimulus directions (Fig. 5C and D). Their activity was correlated with contralateral saccade reaction times on both pro- and antisaccade trials (Fig. 7B). Furthermore, they seem to be important especially for antisaccades because their activity was higher on antisaccade trials than on prosaccade trials (Fig. 6C) and attenuated on direction error trials (Fig. 7E). Accordingly, we speculate that they encode volitional saccade commands required especially for antisaccade initiation.

Automatic and volitional saccade commands encoded presumably by iCNs and cCNs, respectively, could create a response conflict on antisaccade trials, given that they facilitate contralateral saccades. To resolve the conflict, it is necessary to attenuate inappropriate automatic commands. Signals carried by INs might be ideal for this purpose because they are active at the same time with iCNs in the same hemisphere, their activity was stronger on antisaccade trials than on prosaccade trials (Fig. 6C), and their activity was correlated with behavioral outcome on antisaccade trials (Fig. 7F).

Based on these considerations, we suggest the following simple hypothesis: automatic, volitional and suppression commands are encoded by iCNs, cCNs and INs in the caudate nucleus, respectively.

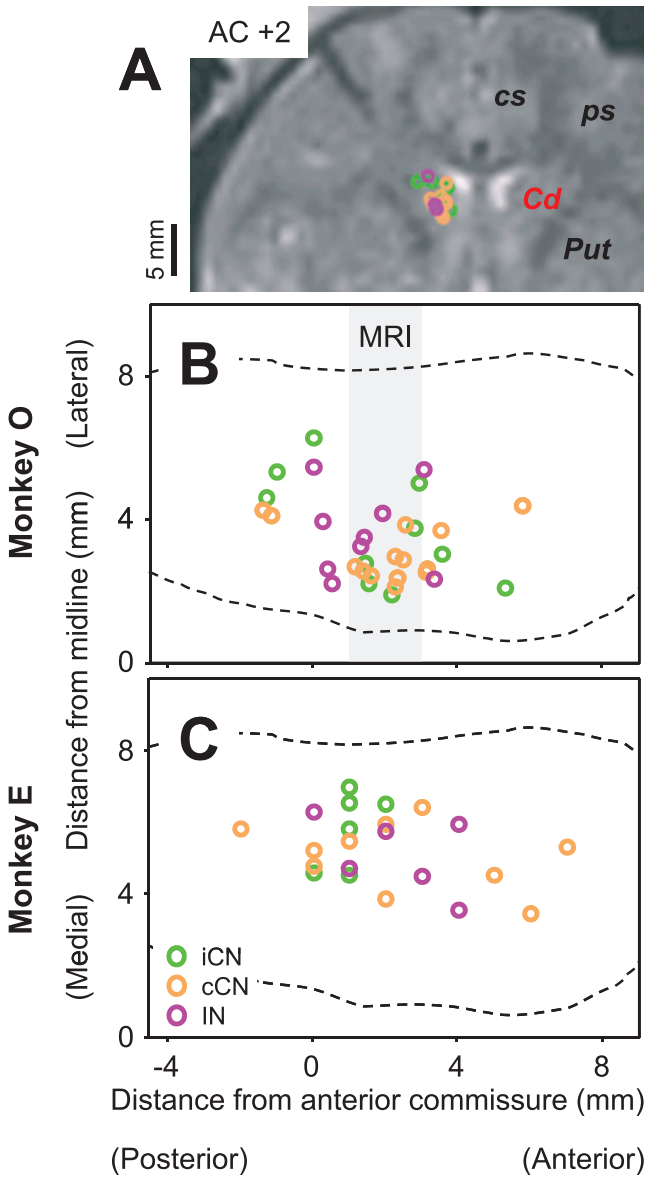

FIG. 8. Reconstructed neural recording sites in the caudate nucleus. (A) MR images (2 mm anterior from the anterior commissure: AC) in monkey O with neural recording sites. *Cd*, caudate nucleus; *Put*, putamen; *cs*, cingulate sulcus; *ps*, principal sulcus. (B, C) Neural recording sites projected on the horizontal plane in monkey O (B) and monkey E (C). Sites included in the gray stripes in B are superimposed on the MR image (A). Broken lines indicate the boundaries of the caudate nucleus (Francois *et al.*, 1996). In monkey E, the level of the anterior commissure is estimated at 19 mm anterior from the intermeatal line (Mikula *et al.*, 2007).

BG pathways

The original BG model established the foundation of the BG in controlling behavior (Albin *et al.*, 1989; DeLong, 1990). Based on the firing characteristics of caudate neurons, we extend the original model by incorporating these neurons (Fig. 9). We simplified this model as much as possible to focus on our findings so that arrows from caudate neurons to the SC indicate polysynaptic pathways (see supporting Fig. S7 for the same model including other BG nuclei). In this model, both iCNs and cCNs give rise to the facilitation (direct) pathway and promote contralateral saccades. Because they are activated in the same hemisphere on prosaccade trials, their

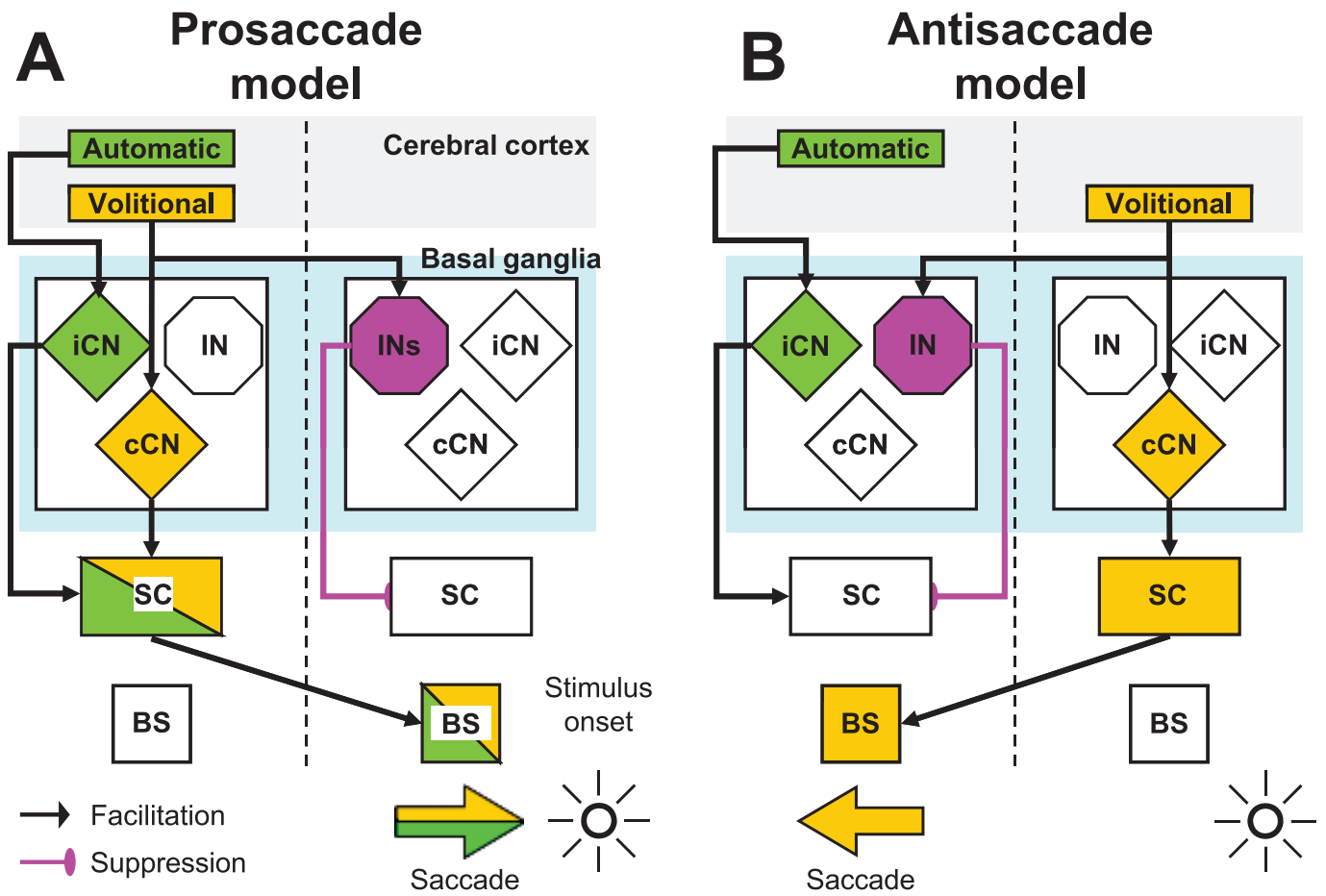

FIG. 9. Hypothetical BG model. (A) On prosaccade trials, automatic and volitional commands activate iCNs and cCNs, respectively, in the same hemisphere to promote a rightward prosaccade through the facilitation pathway. (B) On antisaccade trials, iCN and cCN are activated in the opposite hemispheres. This conflict is resolved by the volitional command recruiting IN to attenuate the inappropriate signal issued by iCN via the suppression pathway. The facilitation and suppression pathways represent polysynaptic pathways from the caudate nucleus to the superior colliculus (SC). BS, brainstem. See supporting Fig. S7 for detailed BG circuits with other nuclei.

signals cooperate with each other to facilitate saccades toward the contralateral stimulus (Fig. 9A). However, on antisaccade trials, iCNs facilitate direction error saccades toward the stimulus while cCNs facilitate correct antisaccades away from the stimulus (Fig. 9B). This conflict is resolved by INs, which give rise to the suppression (indirect) pathway and attenuate the direction error signals.

The simple model nicely links the theoretical aspect of the antisaccade paradigm, the anatomy of BG pathways and the activity of caudate neurons. However, we do not have direct evidence regarding which pathway our recorded neurons give rise to. Furthermore, recent studies have shown that BG circuits are much more complicated than the original BG model (Surmeier *et al.*, 1996; Smith *et al.*, 1998; Aizman *et al.*, 2000; Bar-Gad & Bergman, 2001; Nambu *et al.*, 2002; Levesque & Parent, 2005). In future research, it will be essential to address which pathway recorded neurons project to and how saccade signals issued by caudate neurons are processed through the complicated BG circuits.

Creation of three saccade signals in the caudate nucleus

The antisaccade paradigm has been used to evaluate the functions of cortical neurons (Funahashi *et al.*, 1993; Schlag-Rey *et al.*, 1997; Gottlieb & Goldberg, 1999; Everling & Munoz, 2000; Zhang & Barash, 2000). To create three types of saccade commands observed in the caudate nucleus, the simplest explanation is that the activity of caudate neurons merely reflects cortical input. For example, the activity of iCNs might be created by input from the frontal eye field (Everling & Munoz, 2000) and/or lateral intraparietal area (Gottlieb & Goldberg, 1999), while signals encoded by cCNs and INs might be created by the supplementary eye field (Schlag-Rey *et al.*, 1997) and dorsolateral prefrontal cortex (Funahashi *et al.*, 1993), respectively. Another possibility is that signals encoded by the three types of caudate neurons are created in the caudate nucleus by integrating signals encoding task instructions, stimulus locations and saccade directions. It is reasonable to assume that both mechanisms take place in the intact brain due to the cortex–BG loop circuits (Alexander *et al.*, 1986). Indeed, it has been shown that BG disorders cause disrupted cortical activity before volitional actions (Colebatch, 2007).

The existence of caudate neurons encoding automatic and volitional saccade commands as well as saccade-related neurons with ipsilateral direction preferences have been reported in a seminal study by Hikosaka *et al.* (1989) using a visually and memory-guided saccade paradigm. Accordingly, it is possible that the caudate nucleus includes the three types of saccade neurons we identified regardless of behavioral paradigms monkeys were trained to perform. However, the firing characteristics of saccade neurons in the caudate nucleus might be shaped depending on the history of training. For instance, the enhanced

activation of INs on antisaccade trials than on prosaccade trials (Fig. 6C) might be achieved through the extensive training of the antisaccade paradigm that requires suppression of direction error saccades toward the stimulus while subjects are required to program volitional saccades away from the stimulus concurrently. Although saccade suppression is also required to perform the memory-guided saccade paradigm, INs might not be necessary for this purpose because inappropriate and required saccade commands are not programmed concurrently so that spatially non-specific suppression signals might be more advantageous compared with signals carried by INs to suppress saccades toward the flash of a visual stimulus at an unpredictable location.

BG involvement in conflict resolution

Our neurophysiological evidence in monkey caudate nucleus supports the hypothesis that the BG are involved in conflict resolution between automatic and volitional actions imposed by the antisaccade paradigm. The firing properties of caudate neurons, including their saccade direction selectivity (Fig. 4) and correlation with behavior (Fig. 7) observed before saccade initiation satisfied conditions necessary for antisaccade control. However, to establish fully the direct link between the BG and antisaccade control, further experimental research, including artificial manipulation of neural activity in the caudate nucleus, will be required in future.

Although our results favor the involvement of BG in antisaccade control, we do not exclude the possibility that structures outside the BG, such as the frontal cortex (Cisek, 2007) and SC (Trappenberg *et al.*, 2001), are involved in conflict resolution between automatic and volitional saccades. Such mechanisms might compensate for the function of the BG in patients with BG lesions whose antisaccade performance is intact (Gaymard *et al.*, 2003; Condy *et al.*, 2004; Ploner *et al.*, 2005). Indeed, this idea is consistent with intact antisaccade performance in unaffected relatives of schizophrenia patients without activation in the caudate nucleus, while normal subjects show caudate activation during antisaccades, suggesting their dependence on the BG (Raemaekers *et al.*, 2006).

Because the BG have been suggested to modulate processes controlling behavior occurring outside the BG rather than driving actions directly (Frank, 2005), more sophisticated behavioral paradigms that challenge the modulatory function of the BG might be required to clarify the controversy between the clinical studies. It has been shown recently that the caudate nucleus shows activity specifically when human subjects are asked to switch motor programs from a prosaccade to an antisaccade, but not from an antisaccade to a prosaccade (Cameron *et al.*, 2009). Such a task switching paradigm might be able to detect behavioral deficits in patients with BG lesions.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Activity of three groups of caudate neurons aligned with stimulus onset.

Fig. S2. Time courses of time-dependent signals aligned with stimulus onset.

Fig. S3. Regression coefficients of linear regression analysis in individual neurons.

Fig. S4. Correlation coefficients between firing rates and reaction times in individual neurons.

Fig. S5. Rasters and spike density functions for correct and direction error saccades on antisaccade trials.

Fig. S6. Direction error indices in individual neurons.

Fig. S7. Hypothetical BG model with connections between caudate nucleus and other BG nuclei.

Appendix S1. Supplementary methods.

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Abbreviations

BG, basal ganglia; CNs, contralateral saccade-preferred neurons; cCNs, congruent CNs; iCNs, incongruent CNs; INs, ipsilateral saccade-preferred neurons; SC, superior colliculus; SNpr, substantia nigra pars reticulata.

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