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Title	Enhanced modulation of neuronal activity during antisaccades in the primate globus pallidus.
Author(s)	Yoshida, Atsushi; Tanaka, Masaki
Citation	Cerebral Cortex, 19(1), 206-217 https://doi.org/10.1093/cercor/bhn069
Issue Date	2009-01-18
Doc URL	https://hdl.handle.net/2115/43048
Rights	This is a pre-copy-editing, author-produced PDF of an article accepted for publication in Cerebral Cortex following peer review. The definitive publisher-authenticated version [Cerebral Cortex 2009 19(1):206-217] is available online at: http://cercor.oxfordjournals.org/cgi/content/abstract/19/1/206
Type	journal article
File Information	cc19.pdf



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4 **Enhanced Modulation of Neuronal Activity during Antisaccades**
5 **in the Primate Globus Pallidus**
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21 *Manuscript ID: CerCor-2007-00886.R2*
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25 *Running head: Antisaccade Signals in the Globus Pallidus*
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27 *Key words: antisaccade; globus pallidus; physiology; inactivation; primate*
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31 *Figures: 11*
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33 *Tables: 2*
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35 *Text pages: 37*
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38 *Supplementary Tables: 2*
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40 *Supplementary Figures: 5*
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Abstract

The antisaccade task has been widely used to investigate the neural mechanisms underlying volitional movement control. In this task, subjects suppress reflexive saccades to the sudden appearance of peripheral visual stimuli (prosaccades) and generate a saccade in the opposite direction. Recent imaging studies suggest that the globus pallidus (GP) is involved in the generation of antisaccades. To understand the roles of the GP, we examined single neuron activity and the effects of local inactivation. Monkeys were trained to make either a pro- or antisaccade according to prior instruction provided by the color of the fixation point in each trial. Among 119 saccade-related neurons, 55% showed increased firing rates associated with saccades, while the remaining neurons showed decreased firing rates. For both populations of neurons, the activity modulation was enhanced during the preparation and execution of antisaccades, as compared to prosaccades. Inactivation of the recording sites in the external segment of the GP resulted in an increase in the number of error trials in the antisaccade tasks, suggesting that signals in the GP may play roles in suppressing inadequate prosaccades in the task. Signals in the GP might regulate eye movements through the nigro-collicular descending circuitry and through the basal ganglia-thalamocortical pathways.

Introduction

In many situations, we select one from several possible responses to an external event, depending on internal behavioral goals or imposed task rules. For example, when we drive a car, we usually stop at a yellow light, but sometimes speed up on the same yellow light. The ability to alter the stimulus-response association depending on a given environment is essential for the volitional control of movements. To investigate the neural mechanisms underlying such flexible motor control, many previous studies have adopted the antisaccade paradigm (Hallett, 1978). Typically, subjects are instructed on each block or trial to make a saccade toward (prosaccade) or away from (antisaccade) the sudden appearance of peripheral visual stimuli. Compared to prosaccades, additional neural processes are needed to perform antisaccades correctly: the brain needs to suppress reflexive saccades to the stimulus and, instead, to generate a saccade command in the opposite direction. In humans, impairments in antisaccades have been reported in subjects with a variety of neurological or psychiatric disorders, including the attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease and schizophrenia, as well as those with focal lesions in the frontal and parietal cortices (for reviews, Everling and Fischer, 1998; Munoz and Everling, 2004). Consistent with the deficits in patients with cortical lesions and the basal ganglia diseases, imaging studies have revealed activation during antisaccades in many cortical areas as well as in the lentiform nucleus (the putamen and the globus pallidus) and the thalamus (O'Driscoll et al., 1995; Matsuda et al., 2004; Tu et al., 2006).

The purpose of the present study was to elucidate the roles of the globus pallidus (GP) in the generation of antisaccades. Although a previous clinical study suggested virtually no role when tested with a block of antisaccade trials (Vermersch et al., 1996), recent imaging studies have repeatedly detected significant activation in the GP during antisaccades (Matsuda et al., 2004; Tu et al., 2006). The external segment of the GP (GPe) contains neurons related to saccades (Kato and

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4 Hikosaka, 1995), and has traditionally been viewed as a part of the indirect pathway that relays
5 signals in the striatum to the output nodes of the basal ganglia via the subthalamic nucleus (Alexander
6 and Crutcher, 1990). Recent anatomical data show that neurons in the GPe also have direct access to
7 all other nuclei in the basal ganglia (for reviews, Parent and Hazrati, 1995b; Chan et al., 2005),
8 suggesting that the GPe plays a pivotal role in regulating the signal flow within the basal ganglia. The
9 internal segment of the GP (GPi) has been thought to control somatic rather than ocular movements,
10 but effects of deep brain stimulation in the GPi on eye movements have been reported (Straube et al.,
11 1998; Fawcett et al., 2005). We examined the activities of many saccade-related neurons in the GPe
12 and some in the GPi, when monkeys performed pro- or antisaccades depending on a prior instruction
13 that was provided during each trial. Similarly to neurons in the supplementary eye field (SEF,
14 Schlag-Rey et al., 1997; Amador et al., 2004) and the substantia nigra pars reticulata (SNr, Gore et al.,
15 2005), the firing modulation of GP neurons was greater during antisaccades than during prosaccades.
16 The following inactivation experiments confirmed that signals in the GPe play roles in the generation
17 of antisaccades. Some of these data have appeared in an abstract form (Yoshida and Tanaka, 2007).
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37 **Materials and Methods**

38 *Animal preparation*

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40 Experiments were conducted on two Japanese monkeys (*Macaca fuscata*, one male, 14 kg, and one
41 female, 6 kg). All experimental protocols were approved in advance by the Animal Care and Use
42 Committee of the Hokkaido University School of Medicine, and were in accordance with the *Guide*
43 *for the Care and Use of Laboratory Animals* (National Research Council, 1996). The experimental
44 procedures were similar to those described previously (Tanaka, 2005). Following initial chair training,
45 a pair of head holders was implanted in the skull using titanium screws and dental acrylic under
46 general halothane and pentobarbital anesthesia, and using sterile procedures. Using separate surgical
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4 procedures, a coil of stainless steel wire was implanted under the conjunctiva to record eye
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6 movements. During subsequent training and experimental sessions, the monkey's head was secured
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8 to the primate chair, and horizontal and vertical eye position was recorded using the search coil
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10 technique. After training for eye movement tasks, a recording cylinder was installed over a small
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12 craniotomy under the same surgical conditions. Animals received analgesia with either suppository
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14 acetaminophen or intramuscular injection of pentazocine or ketoprofen after each surgery. Topical
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16 antibiotics were administered around the implant and in the cylinder as necessary. Water intake was
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18 controlled daily so that monkeys were motivated to perform behavioral tasks.
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21 22 *Visual stimulus and behavioral paradigms*

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24 Experiments were controlled by a Windows-based real-time data acquisition system (TEMPO;
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26 Reflective Computing, St. Louis, MO) running on Pentium PCs. All events were updated every 5 ms,
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28 and visual stimuli were presented on a 24-inch cathode-ray tube monitor (GDM-FW900; Sony, Tokyo,
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30 Japan; refresh rate: 60 Hz) that was located 38 cm away from the eyes, and subtended $64 \times 44^\circ$ of
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32 visual angle. A 0.5° square spot served as a visual stimulus. Targets of different colors (gray, white,
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34 red and green) were used for different means in the trials (see below). Experiments were carried out in
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36 a darkened booth. Voltages proportional to horizontal and vertical eye position were calibrated before
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38 each experiment by having monkeys fixate on a stationary target spot at known visual angles.
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40 Thereafter, visual stimuli were presented in individual trials, and monkeys were rewarded with drops
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42 of water or apple juice for maintaining eye position within a 'window' that surrounded the target
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44 position at specific time intervals during each trial. The size of the window was 2° for initial fixation,
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46 and 6° (antisaccade task), 4° (memory saccade task) or 3° (prosaccade task) for the saccade target. A
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48 trial was aborted and followed by a newly selected trial if monkeys failed to maintain eye position
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50 within a specified window. Trials of different types and in different directions were presented in a
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4 random order within a block. The direction of the target step was in any of the 8 directions including
5 four cardinal directions and four 45° oblique directions.
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9 The present study used 3 saccade tasks (Fig. 1). In both the antisaccade task and the prosaccade
10 task, a gray fixation point (10.7 cd/m²) initially appeared at the center of the screen. After 800 ms,
11 color of the fixation point was changed either to green or red in order to instruct monkeys of the trial
12 type. In trials with a green, unfilled fixation spot (4.6 cd/m²), monkeys were required to perform
13 antisaccades in response to the appearance of a peripheral target; in trials with a red spot (8.1 cd/m²),
14 they were required to perform prosaccades. Following the instruction period of 800 ms, the fixation
15 point disappeared and a white target spot (22.6 cd/m²) appeared 16° peripherally. Monkeys were
16 required to make a saccade to the location diametrically opposite to the target (antisaccade task), or to
17 the location of the target (prosaccade task) within 400 ms. Thus, in these tasks, monkeys were
18 required to switch their eye movement responses to the same peripheral target depending on the prior
19 instruction during fixation. In the antisaccade task, the target remained on for 400 ms, and then was
20 relocated to a position opposite the initial location. In the prosaccade task, the target remained
21 stationary. In both tasks, the peripheral target disappeared after a second fixation interval of 900–1200
22 ms, and then, a liquid reward was given. Introduction of the second fixation interval allowed us to
23 temporally dissociate the neuronal responses to eye movements from those to reward. In the
24 memory-guided saccade task, a white target spot appeared 16° peripherally for 200 ms during central
25 fixation of 800–1300 ms. Monkeys were required to remember the location of the target, and to
26 maintain fixation for an additional 800 ms. The color of the fixation point was red throughout the
27 fixation interval in the memory-guided saccade task. Once the fixation point disappeared, monkeys
28 made a saccade to the previously presented target location within 400 ms. The peripheral target
29 reappeared at the same location 400 ms after the fixation point offset, and was visible for an additional
30 1600 ms until the end of the trial. Prior to the present experiments, both monkeys were extensively
31 trained on a variety of memory-guided saccade tasks for another project (Tanaka 2007).
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Procedures for recording and microinjection

A tungsten microelectrode (FHC, Bowdoin, ME) was lowered through a 23-gauge guide tube using a hydraulic micromanipulator (MO-97S; Narishige, Tokyo, Japan). At the beginning of each experimental session, the location of electrode penetration was adjusted using an X-Y stage attached to the top of the cylinder. Signals through the electrodes were amplified, filtered, and monitored using oscilloscopes and an audiomonitor. For each experiment, we were able to locate the dorsal surface of the GP rather easily by recording the characteristic tonically firing neurons with relatively short action potential duration. In some penetrations, we could determine the border of the internal and external segments of the GP by comparing the pattern of baseline firing that was much more irregular in the external segment than in the internal segment, and by the existence of larger, tonic ‘border neurons’ between the segments (DeLong, 1971). Once task-related neuronal activity was encountered, spikes of single neuron were isolated using a real-time spike sorter with template-matching algorithms (MSD; Alpha Omega Engineering, Nazareth, Israel). The occurrence of action potentials was time-stamped, and saved in files with the data of eye movements, location and timing of visual stimuli during the experiments.

When we searched for task-related neurons, monkeys performed a block of 12 randomized trials consisting of 8 memory-guided saccade trials in different directions (45° apart) and horizontal antisaccade trials and smooth pursuit trials. The pursuit trials were included because recent studies show that the basal ganglia are also involved in the control of pursuit. Once a task-related neuron was isolated, we determined the optimal eye movement direction by analyzing the data in the memory-guided saccade trials during experiments. We then configured the block of saccade trials to include tasks only along the preferred axis for the neuron under study. For neurons that showed no clear directional preference, neuronal activity was examined during horizontal eye movements.

After the recording experiments were terminated, the effects of local inactivation were examined in separate experiments. A 30-gauge injection needle connected to a microsyringe was inserted

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4 through the guide tube, and a small amount of the GABA_A agonist (muscimol hydrobromide; 5.0
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6 $\mu\text{g}/\mu\text{l}$ in saline, volume 1.0 μl) was pressure-injected around the recording sites at a rate of $\sim 0.2 \mu\text{l}/30$
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8 s. The effect of inactivation was assessed by comparing eye movements before and 15–60 min after
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10 injection.

11 12 13 14 *Data acquisition and analysis*

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16 Horizontal and vertical eye position signals were directly obtained from the eye coil electronics
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18 (MEL-25; Enzanshi Kogyo, Chiba, Japan). Data were digitized and sampled at 1 kHz, and were
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20 stored in files during the experiments for further off-line analysis that was performed using Matlab
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22 (Mathworks, Natick, MA). For each neuron, data were aligned on either the initiation of saccades or
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24 the onset and offset of visual fixation point. Saccades were detected using automated algorithms.
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26 After applying a 29-point finite impulse response filter to eye position data, horizontal and vertical
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28 eye velocities were obtained by digital differentiation. Saccade onset was defined as the time when
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30 the net eye speed exceeded $40^\circ/\text{s}$, and offset was defined as the time when it crossed $20^\circ/\text{s}$ on the way
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32 back to zero. We determined the velocity criteria for detecting onset and offset of each saccade by
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34 comparing the raw traces of eye position and eye velocity so that the filtering procedure did not shift
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36 the timing of saccade measurements considerably. In some antisaccade trials, monkeys initially
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38 generated a saccade toward the target, but redirected their eyes to the location opposite to the target
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40 within 400 ms ("turn-around saccade"). Since we detected error trials by analyzing eye position
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42 before and 400 ms after fixation point offset during experiments, monkeys were rewarded in such
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44 trials. We detected turn-around saccades off-line and considered them as errors. When we count the
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46 number of error trials (Table 2 and Fig. 9), we also included trials in which the endpoint of primary
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48 saccade following the fixation point offset was deviated $> 8^\circ$ from the goal of the saccade in a given
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50 trial, or eye position 400 ms after the fixation offset was within 6° from the location diametrically
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52 opposite to the endpoint of the required saccade. Other error trials in which monkeys made early
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4 fixation break before the fixation offset, made non-targeting saccade (neither to the target nor to the
5 location opposite to the target), or made no saccade within 400 ms following the fixation point offset
6 were removed from the analysis. For inactivation experiments, we compared the occurrence of early
7 saccades to the cue (within 4°) during the delay period before versus after inactivation, whereas those
8 error trials were not included in the other quantitative measures shown in Fig. 9. During experiments,
9 the error trials were repeated in the recording sessions, but were not in the inactivation experiments
10 unless monkeys maintained fixation until the time of the fixation point offset. Traces of horizontal
11 and vertical eye positions were reviewed with rasters and spike density profiles that were constructed
12 from neuronal data. To obtain spike densities, means of the millisecond-by-millisecond occurrence of
13 action potentials across multiple trials were convolved using a Gaussian filter. The σ of the Gaussian
14 was 15 ms to reveal the time courses of individual neuronal activity and to construct the population
15 activity. Other quantitative measures were performed on the basis of spike counts for specific time
16 windows. Analytical measures are reported in the relevant text in the Results.

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33 Directionality of saccade-related transient activity was quantified by computing the modulation
34 index (MI), which was defined by,

$$35 \quad MI = |Pref - Opp| / (Pref + Opp)$$

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39 where *Pref* and *Opp* indicate the firing rate measured during the 150 ms starting from 100 ms before
40 saccade initiation for trials in the optimal saccade direction and those in the opposite direction,
41 respectively (Fig. 4). The indices were also computed for the 150 ms postsaccadic interval starting
42 from 50 ms after saccade initiation (Supplementary Fig. S2). The MI was close to 0 for neurons
43 showing no directional firing modulation, whereas the value was greater for neurons showing a strong
44 directional modulation. For each neuron, the MIs were computed for both the antisaccade trials and
45 the prosaccade trials. We also examined the time course of directional signals in the population of GP
46 neurons. For each saccade paradigm, the firing rates for trials in opposite directions were compared
47 for every 50-ms window starting from 600 ms before the initiation of saccades to 600 ms after (in
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4 25-ms steps). In this and most of the other analyses, the difference in firing rate was assessed using
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6 Wilcoxon rank-sum test. We also used *t*-test and ANOVA to evaluate statistical significance. Each
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8 statistical test that was applied is stated in the relevant text.
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10 11 *Histological procedures*

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13 The sites of recorded neurons were reconstructed from histological sections for one monkey (monkey
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15 *E*, Fig. 10). The remaining monkey is still in use for another project. At the end of the experiments on
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17 the first monkey, several electrolytic lesions were made by passing a direct current (10–20 μ A)
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19 through the recording electrodes for 30–40 s. The monkey was deeply anesthetized with a lethal dose
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21 of pentobarbital (> 50 mg/kg), and was perfused transcardially with 0.1 M phosphate buffer followed
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23 by 10% formalin. Then, the brain was removed, blocked, and fixed with the same solution overnight.
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25 Once the brain was equilibrated with 0.1 M phosphate buffer containing 30% sucrose, histological
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27 sections were cut from each hemisphere using a freezing microtome. Sections were stained with
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29 cresyl violet.
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36 **Results**

37 **Neuronal and behavioral databases**

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39 Data were collected from three GPs of two monkeys. The data were classified into two groups which
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41 were obtained from either the GPe or the GPi. For one monkey (monkey *E*, two hemispheres), the
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43 locations of recorded neurons were reconstructed from the histological sections. For the other
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45 monkey (monkey *D*, one hemisphere), the border of the segments were determined based on the
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47 stereotaxic coordinates of electrode penetrations, the relative depth from the dorsal surface of the GP,
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49 and the firing pattern of the recorded and nearby neurons (Methods). Among 203 task-related neurons,
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51 159 (78%, $n = 132$ from GPe) neurons modulated their activity associated with saccades, while the
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53 remaining neurons responded to reward delivery, smooth pursuit, and/or visual stimuli. The firing
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4 modulation during pursuit or reward delivery was detected visually and was not analyzed further in
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6 this study. Among 120 neurons that were tested for the three saccade paradigms formally, 119 neurons
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8 showed a significant firing modulation around the time of saccades (the 300 ms period starting from
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10 100 ms before saccade) in one or more tasks as compared to the baseline activity 300 ms before the
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12 cue (memory saccade task) or instruction (other two tasks) onset (Wilcoxon rank-sum test, $P < 0.05$).
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14 This study focused on the activities of these 119 saccade-related neurons. Table 1 summarizes the
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16 number of these neurons and shows that most of the data presented in this study were collected from
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18 the GPe (85%). Slightly more than half of these neurons ($n = 66$, 55%) elevated their firing rates
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20 before and during saccades ('increase-type' neurons), whereas the other neurons reduced the firing
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22 rates associated with saccades ($n = 53$, 45%, 'decrease-type' neurons). As shown in Table 1, some of
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24 these neurons also had properties that were related to the other task events.
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28 Table 2 summarizes the behavioral data obtained during recording sessions for 119
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30 saccade-related single neurons (90 and 29 neurons for monkeys *E* and *D*, respectively). Overall, both
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32 monkeys performed the task correctly in > 94% of trials, and made more errors in the antisaccade
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34 tasks than in the other tasks (χ^2 test, $P < 0.001$). Latencies in correct trials were similar between
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36 antisaccades and prosaccades, and were shortest for memory-guided saccades (latency distributions
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38 are shown in Supplementary Fig. S1). The multiple comparisons revealed that the latencies were
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40 significantly different between any pair of the 3 tasks (Scheffé, $P < 0.001$). The shortest reaction
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42 times for memory-guided saccades might be attributed to the fact that the directional information was
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44 provided during fixation in this task, whereas the direction of upcoming saccade was uncertain before
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46 the fixation point offset in the other tasks. The relatively small difference in latencies between
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48 antisaccades and prosaccades found in both monkeys could be due to the prior extensive training on
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50 the memory-guided prosaccade tasks (Methods), because the training on these tasks is known to alter
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52 saccade latencies in the block of mixed anti/prosaccade trials and to reduce the difference in latencies
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54 between the tasks (Amador et al., 1998). When the distributions of saccade latencies were examined
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(Supplementary Fig. S1), the proportions of early saccades within the ‘express’ range (< 90 ms) were different between the correct prosaccades and the erroneous prosaccades in the antisaccade trials (0.8% vs. 10.5% for monkey *D*, 0.03% vs. 1.4% for monkey *E*), suggesting that the monkeys somehow inhibited the occurrence of reflexive saccades to the target even in the prosaccade trials. When we compared saccade accuracy by measuring the distance between target and eye position at the end of the response period (400 ms after the fixation point offset), the values were significantly different across the paradigms (one-way ANOVA, $P < 10^{-10}$).

Activity during saccades in different paradigms and directions

Many neurons in the GP exhibited a greater firing modulation during antisaccades than during prosaccades or memory-guided saccades. Figures 2A and B plot the data from two representative neurons aligned on saccade initiation. The neuron in Fig. 2A increased the firing rate before, during and after saccades in both directions, while the neuron in Fig. 2B reduced the firing rate. For both neurons, the size of the firing modulation during antisaccades was greatest across the paradigms, irrespective of saccade directions. To assess the firing modulation in the population of neurons, we computed the population activities for trials in the preferred direction that was determined by comparing the activity during antisaccades in the opposite directions. Figure 2C plots the data for neurons that increased (left panel, $n = 66$) or decreased (right, $n = 53$) their activity during saccades, and shows that the firing modulation was enhanced during antisaccades in the population.

To quantify the saccade-related activities in the three paradigms, the firing rates of individual neurons were measured in a 150-ms window starting from 100 ms before saccades in the preferred direction (black bars in Fig. 2C). Figure 3A compares the firing rates of individual increase-type neurons for antisaccades with that for prosaccades. A one-way ANOVA and post hoc comparison revealed that the firing rates of 24 of 66 increase-type neurons (38%) were statistically different between antisaccades and prosaccades (Scheffé, $P < 0.05$, filled symbols in Fig. 3A). For the

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4 population of the increase-type neurons, multiple comparisons showed that the activity during
5 antisaccades was statistically different from that during saccades in the other tasks (Fisher's PLSD, P
6 < 0.05), while the activities during prosaccades and memory-guided saccades were comparable ($P >$
7 0.05). Figure 3B plots the data from individual decrease-type neurons. Among 53 decrease-type
8 neurons, 17 (32%) showed activity that was statistically different between the pro- and antisaccades
9 (Scheffé, $P < 0.05$, filled symbols in Fig. 3B). In the population of the decrease-type neurons, the
10 firing rate during antisaccades was significantly smaller than those during prosaccades and
11 memory-guided saccades (Fisher's PLSD, $P < 0.05$). To examine further the enhancement of
12 neuronal activity during antisaccades, the firing modulation before and during saccades (−100 to +50
13 ms of saccade initiation) relative to the baseline activity (300 ms before the instruction) was measured
14 for individual neurons. The triangular plot in Fig. 3C shows the relative magnitude of the firing
15 modulation across the tasks for individual neurons. To generate this figure, the size of the activity
16 modulation in each task was normalized according to the sum of the activity modulation in the three
17 tasks. The x -coordinate of each data point is the difference in normalized activity between the
18 prosaccade task and the memory saccade task (memory saccade minus prosaccade), and the
19 y -coordinate is the normalized response in the antisaccade task times $\sqrt{3}$ or 1.732 (Koida and
20 Komatsu, 2007). Overall, 66% ($n = 79$) of neurons exhibited the greatest firing modulation during
21 antisaccades across the tasks, while only 21% ($n = 25$) and 13% ($n = 15$) neurons preferred
22 prosaccades and memory-guided saccades, respectively. Thus, activity modulation in the GP was
23 enhanced during antisaccades compared to the modulation seen in the other tasks.
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48 As shown in Figs. 2A and B, many neurons exhibited a similar amount of firing modulation
49 for saccades in opposite directions. This is consistent with the previous study showing that the tuning
50 of directional preference of GP neurons, if any, is generally broad (Kato and Hikosaka, 1995). Indeed,
51 when we tested the directional tuning formally for each of 41 GP neurons (20 increase-type, 21
52 decrease-type neurons) by fitting a Gaussian curve to the means of firing rate during memory-guided
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4 saccades in 8 different directions, the preferred directions could be reliably determined ($r^2 > 0.7$ for
5 the fitted Gaussian) for 22 neurons only (54%). The remaining neurons (46%) showed a similar
6 amount of firing modulation for saccades in all directions, and the magnitudes of the modulation did
7 not correlate with saccade directions (Mardia's circular-linear correlation coefficient, $D < 0.75$, $P >$
8 0.05). Overall, the preferred directions of these neurons ($n = 22$) were distributed contralaterally
9 (Rayleigh test, $P < 0.05$, mean vector length $r = 0.41$), whereas the distribution of preferred directions
10 of either type of neurons alone showed no significant directional bias (Rayleigh test, $r = 0.47$, $P =$
11 0.052 for the increase-type neurons, and $r = 0.37$, $P > 0.10$ for the decrease-type neurons). The full
12 width at half maximum of the firing modulation (computed as $2\sigma\sqrt{2\ln 2}$ or 2.35σ , where σ was derived
13 from the fitted Gaussian) averaged $55.2^\circ \pm 40.0^\circ$ (SD) for the increase-type neurons ($n = 13$) and 75.4
14 ± 70.1 for the decrease-type neurons ($n = 9$).

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28 To assess to what extent neurons in the GP carry directional signals in different tasks, we
29 computed the modulation indices (MIs) from the data for saccades in opposite directions in both the
30 prosaccade task and the antisaccade task. The indices were computed based on neuronal activity
31 during the 150 ms period starting from 100 ms before saccades (Materials and Methods). Figures 4A
32 and B plot the MIs for individual neurons that either increased (open circles) or decreased (filled
33 triangles) the firing rates during saccades. For neurons in the GPe (Fig. 4A), only a minority of
34 neurons showed a significant directional modulation in both the tasks (Wilcoxon rank-sum test, $P <$
35 0.05 , black bars in the histograms). Interestingly, however, the size of the directional preferences was
36 different between the types of neurons. The MIs during prosaccades averaged 0.09 ± 0.10 and $0.15 \pm$
37 0.15 for the increase-type neurons and the decrease-type neurons, respectively, and these values were
38 statistically different (unpaired t -test, $P < 0.05$). During antisaccades, the MIs averaged 0.07 ± 0.07
39 and 0.17 ± 0.17 for the increase-type neurons and the decrease-type neurons, respectively, and these
40 values again were also different ($P < 0.001$). The proportions of neurons showing a directional
41 modulation in either or both tasks (MI > 0.2 , corresponding to 1.5-fold firing modulation) were also
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4 different between the increase-type neurons (15%, $n = 8/54$) and the decreased-type neurons (38%, n
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7 = 18/47, $P < 0.05$). For neurons in the GPi (Fig. 4B), the MIs for the increase-type neurons were
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9 significantly greater than that for the decrease-type neurons during prosaccades (unpaired t -test, $P <$
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11 0.05), but not during antisaccades ($P = 0.07$). As in Fig. 4B, all 4 out of 18 GPi neurons that showed a
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13 significant directional modulation (Wilcoxon rank-sum test, $P < 0.05$, black bars in the histograms)
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15 were the increase-type neurons. Thus, neurons in the GP generally showed no clear directional
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17 modulation before and during saccades, while some decrease-type neurons in the GPe and
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19 increase-type neurons in the GPi carried directional information. A similar tendency was found when
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21 the MIs were computed for the post-saccadic period (50-200 ms after saccade initiation,
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23 Supplementary Fig. S2), though the proportion of directional neurons was much larger during this
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25 time interval (see below).
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29 To examine the time courses of the directional signals carried by GP neurons, we next
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31 compared the firing rates between trials in opposite directions for every 50-ms period starting from
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33 600 ms before saccade initiation to 600 ms after (in 25 ms steps). Figures 4C and D plot the
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35 proportions of neurons exhibiting directional modulation in each of the three tasks (Wilcoxon
36
37 rank-sum test, $P < 0.05$) as a function of time, relative to the initiation of saccades. Because no
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39 directional information was provided during the instruction period in the antisaccade tasks and in the
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41 prosaccade tasks, only a few neurons showed directional modulation > 150 ms before saccades. In
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43 contrast, approximately 10% of GPe neurons showed directional modulation during the delay period
44
45 in the memory-guided saccade task (Fig. 4C). For all three tasks, the number of neurons showing
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47 directional modulation increased just before saccades, and about 23% of GP neurons carried
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49 directional signals at the time of saccade initiation. The directional signals in the population peaked
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51 around 200 ms after saccade initiation, and the proportion of directional neurons was up to 40% of all
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53 saccade-related neurons. Thus, more than half (56%) of the saccade-related neurons in the GP did not
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55 carry directional information in any of the three saccade paradigms. About half of the remaining
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neurons exhibited directional modulation only postsaccadically, suggesting that the majority of neurons in the GP may not provide immediate drive signals for saccades, whereas only a minority of the decrease-type neurons in the GPe and the increase-type neurons in the GPi that showed directional modulation before saccades might play this role.

Context-dependent activity modulation during fixation

On each anti- or prosaccade trial, monkeys were required to alter their eye movement response to the same peripheral target depending on the color of the fixation point. We next examined whether neurons in the GP exhibited activity modulation related to the task instructions. Figure 5 plots the data from two representative neurons aligned on the fixation point offset. Because the saccade target appeared at the time of the fixation point offset, data for trials in opposite directions were combined to examine the firing modulation during the instruction period. The neuron plotted in Fig. 5A showed an increased firing rate during the instruction period, while that in Fig. 5B showed a decreased firing rate. For both neurons, the firing modulation was greater before antisaccades than before prosaccades, while the baseline activity (300 ms before the instruction) was not statistically different between the tasks (Wilcoxon rank-sum test, $P > 0.05$). For the population of neurons, the baseline activity was smaller for the increase-type neurons than the decrease-type neurons (34.2 ± 19.5 versus 46.6 ± 23.8 spikes/s, unpaired t -test, $P < 0.01$; Supplementary Fig. S3).

To quantify the modulation of the instruction-period activity for individual neurons, we measured the firing rates during the 200 ms before the fixation point offset. Figure 6A plots the data for neurons that increased the firing rate before and during saccades. Among 66 increase-type neurons, 29 (44%) displayed instruction period activity that was significantly different between the paradigms (unpaired t -test, $P < 0.05$; filled symbols in Fig. 6A). In the population of the increase-type neurons, the instruction period activity in the antisaccade task was statistically different from that in the prosaccade task (paired t -test, $P < 0.001$). The time course of the population activities plotted in

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4 Fig. 6B demonstrates that the task-dependent firing modulation emerged ~500 ms following the
5 instruction, and became more evident towards the end of the fixed instruction interval (800 ms). A
6 similar tendency was found among the decrease-type neurons. Among 53 neurons, 26 (49%) showed
7 task-dependent firing modulation (Fig. 6C, filled symbols). In the population of the decrease-type
8 neurons, the firing rate for antisaccades was statistically different from that for prosaccades (paired
9 *t*-test, $P < 0.001$), and the traces of the population activities diverged during the latter half of the
10 instruction period (Fig. 6D). When the same analyses were performed for neurons in the GPe and GPi
11 separately, the task-dependent firing modulation during fixation was statistically significant for
12 neurons in the GPe (paired *t*-test, $P < 0.001$, Supplementary Fig. S4), but for neither type of neurons
13 in the GPi ($P > 0.05$). We also found that the levels of individual neuronal activity before the target
14 onset were not correlated with the latencies of antisaccades in the preferred direction, while only a
15 minority of neurons showed a significant correlation ($P < 0.05$, increase-type neurons, $n = 4/66$, 6%,
16 decrease-type neurons, $n = 5/53$, 9%). Correlation coefficients for the increase-type neurons averaged
17 -0.05 ± 0.27 (SD), and those for the decrease-type neurons averaged -0.01 ± 0.32 .

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19 Because the instruction for saccade type was given by changing the color of the fixation
20 point, the task-dependent firing modulation during fixation could possibly be due to the color
21 selectivity of GP neurons, rather than due to a difference in task requirements. To address this issue,
22 we examined the activity of 14 neurons (6 increase-type, 8 decrease-type neurons) during a block of
23 fixation trials. In this task, the color of the fixation point changed as in the antisaccade task (that is.,
24 from gray to green), but the saccade target never appeared and the fixation point remained on until the
25 end of the trial. Monkeys were required to maintain fixation throughout the trial to obtain a reward. If
26 the color of the fixation point was actually responsible for the greater firing modulation in the
27 antisaccade trials, similar changes in neuronal activity would be observed in the fixation tasks. We
28 configured a separate block of fixation trials to include 30 fixation tasks followed by repeated
29 sequences of one horizontal antisaccade trial and 9 fixation trials (Fig. 7A). In almost all antisaccade
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4 trials in the fixation block, monkeys made an erroneous prosaccade to the peripheral target, most
5 likely because they did not prepare for antisaccades in advance during the instruction period. We
6 compared neuronal activity during fixation across three different trials: 1) fixation trials, 2) error
7 antisaccade trials and 3) correct antisaccade trials. Data for the latter two classes were collected from
8 both the fixation block and the preceding randomized saccade block, and then were combined for
9 analysis. Figure 7B compares the magnitudes of activity modulation between the fixation trials and
10 the correct antisaccade trials for the 14 neurons. The size of the activity modulation was measured as
11 the difference in the firing rate between 600–800 ms following (instruction period) and 300 ms before
12 (baseline) the color change of the fixation point. All but two neurons (open triangles) showed greater
13 activity modulation in the correct antisaccade trials than in the fixation trials (multiple comparisons
14 with Scheffé, $P < 0.05$). For the population of neurons, Fig. 7C plots the means (\pm SDs) of firing
15 modulation during fixation across the three different trials. A one-way ANOVA and post hoc multiple
16 comparisons revealed that the instruction period activity prior to correct antisaccades was
17 significantly greater than those before erroneous prosaccades in the antisaccade trials and those in the
18 fixation trials (Scheffé, $P < 0.05$). The time courses of the population activities for both the
19 increase-type neurons (Fig. 7D) and the decrease-type neurons (Fig. 7E) show that the instruction
20 period activity found in the correct antisaccade trials (green traces) almost disappeared in error trials
21 (red traces) and in the fixation trials (blue traces). Thus, neuronal activity during the instruction
22 period was related to the preparation for antisaccades, rather than to the color of the fixation point *per*
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48 We next examined the context-dependent firing modulation during fixation on a
49 trial-by-trial basis. Figure 8A plots the means of firing modulation ($n = 14$) during fixation as a
50 function of the trial number in the fixation block. As before, the level of neuronal activity was
51 computed as the difference in firing rate during the 300 ms before and 600–800 ms after the color
52 change of the fixation point. Although the magnitude of firing modulation was initially comparable to
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4 that measured in the antisaccade trials in the preceding saccade block (Fig. 8A, open square), the
5 firing modulation decreased gradually during the repetition of 30 fixation trials (black circles). In
6 addition, we also found that neuronal activity in the fixation trials was modulated immediately after
7 the error trials. Figure 8B plots the sizes of neuronal activity recorded from the 14 neurons during 9
8 fixation trials prior to and following an error trial in the antisaccade task. The activity was greatest
9 immediately following the antisaccade trial, and decreased progressively during the repetition of the
10 fixation trials. The magnitude of firing modulation in the fixation trial just after erroneous antisaccade
11 was significantly different from that in the fixation trial immediately before the antisaccade trial
12 (paired t -test, $P < 0.05$, $n = 14$). These results again confirmed that neuronal activity during the
13 instruction period was context-dependent, suggesting that the activity was likely related to the
14 preparation for antisaccades.
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30 **Effects of local inactivation**

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32 To explore the causal roles of neuronal signals in the GPe in the generation of antisaccades, we
33 inactivated the recording sites reversibly by injecting a small amount of the GABA_A agonist,
34 muscimol (1 μ l in volume, concentration 5 μ g/ μ l dissolved in saline). Sites of inactivation were
35 selected from those containing saccade-related neurons found in the separate experiments. We
36 performed 4 muscimol injection experiments and 3 saline controls in the left hemispheres of two
37 monkeys. For each monkey, the two inactivation sites were in the same coordinate but at different
38 depth along the penetrations (1.0 mm apart). Figure 9A illustrates the data obtained from a single
39 inactivation experiment (site *DI*). Before inactivation, the monkey made erroneous prosaccades to
40 the target in about 15% of the antisaccade trials in both directions (red dashed traces). Following
41 muscimol injection into the left GPe, the error rate increased significantly in the rightward
42 antisaccade trials (contraversive saccades, χ^2 test, $P < 0.01$), while the error rate remained unchanged
43 in the leftward antisaccade trials ($P = 0.75$). The effects of inactivation did not appear to be biasing
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4 the occurrence of leftward saccades, because the monkey performed saccades correctly in all
5 prosaccade trials in both directions during inactivation, and because the errors of making a reflexive
6 saccade to the peripheral cue in the memory-guided saccades tasks did not increase significantly in
7 both directions (χ^2 test, $P > 0.05$). For this and the other experiments, Figure 9B plots the changes in
8 error rate following muscimol (solid lines) or saline (dashed lines) injections for both anti- and
9 prosaccades. Data connected with thick lines were for the experiment shown in Figure 9A (site *DI*).
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11 In all 4 muscimol experiments, the rate of erroneous prosaccades increased dramatically in the
12 antisaccade trials in one direction (χ^2 test, $P < 0.01$), whereas the error rates remained unchanged
13 following saline injection. In one inactivation experiment (site *EI*), we also found clear deficits in the
14 performance of prosaccades; the monkey made many erroneous *antisaccades* in the ipsiversive
15 prosaccade tasks, in addition to the deficits in the ipsiversive antisaccade trials (Supplementary Fig.
16 S5), as if they failed to assign correct responses for a given instruction. The other saccade parameters
17 for all experiments are summarized in Supplementary Tables 1 (latency) and 2 (accuracy). Although
18 inactivation of the GPe altered saccade latency or accuracy slightly and often significantly, we did not
19 find out any consistent effect.
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38 **Localization of task-related neurons**

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40 Figure 10 illustrates the sites of recording and inactivation in monkey *E*, reconstructed from
41 histological sections. Most saccade-related neurons were found in the anterior part of the GPe, within
42 2 mm from the level of the anterior commissure. Consistent with the previous study (Kato and
43 Hikosaka, 1995), many of the saccade-related neurons were located in the dorsal portion of the GPe.
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45 As summarized in Table 1, 15% of saccade-related neurons were recorded from the GPi. Other
46 task-related neurons (pursuit or reward) were distributed rather sparsely within the GP.
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55 **Discussion**

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4 The present study, for the first time, provides direct evidence for the involvement of the GP in the
5 generation of antisaccades. Neurons in the GPe exhibited significant firing modulation during both
6 the preparation and execution of antisaccades. Since the firing modulation during fixation decreased
7 or even disappeared when the instruction stimulus normally calling for antisaccades was presented in
8 a block of fixation trials, we concluded that the activity during the instruction period was related to
9 the preparation of antisaccades, rather than to the visual feature of the fixation target. We also found
10 that the error rate in the antisaccade task increased modestly following inactivation of the recording
11 sites in the GPe, suggesting that signals in the GPe play roles in the generation of antisaccades.
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22 **Enhanced modulation of transient activity during antisaccades**

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24 The most conspicuous feature of neuronal activity in the GP was the strong enhancement of firing
25 modulation during antisaccades. For 32% of individual neurons (33% of increase-type neurons and
26 30% of decrease-type neurons), the modulation of the firing rate immediately before and during
27 antisaccades was statistically greater than the modulation during prosaccades or memory-guided
28 saccades. Furthermore, for both types of GP neurons, the enhancement of activity modulation during
29 antisaccades was also statistically significant in the population of neurons. Previous studies have
30 shown that the firing modulation in the population of neurons during antisaccades is smaller than or
31 comparable to that during prosaccades in many cortical areas, including the lateral prefrontal cortex
32 (PFC, Everling and DeSouza, 2005), the frontal eye field (Everling and Munoz, 2000), the lateral
33 intraparietal area (Gottlieb and Goldberg, 1999; Zhang and Barash, 2000) and the anterior cingulate
34 cortex (ACC, Johnston et al., 2007), whereas a subset of individual neurons in these areas display the
35 enhanced activity during antisaccades (e.g., Johnston et al., 2007). Similarly, the magnitude of the
36 presaccadic burst of activity in the SC is also smaller during antisaccades than during prosaccades,
37 whereas the saccade-related firing modulation (suppression) of the fixation neurons in the rostral SC
38 appears to be augmented during antisaccades, possibly because the firing rates of these neurons are
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4 elevated during the preparation for antisaccades (Everling et al., 1999). In contrast, most neurons in
5 the SEF (Schlag-Rey et al., 1997; Amador et al., 2004) and SNr (Gore et al., 2005), as well as the
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7 SC-projecting neurons in the lateral PFC (Johnston and Everling, 2006) exhibit greater firing
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9 modulation during antisaccades than during prosaccades, showing a significant enhancement during
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11 antisaccades in the population, just like the neurons in the GP reported in the present study.
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16 The enhancement of firing modulation in the SEF, PFC, GP and SNr suggests a strong
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18 functional linkage between these regions during antisaccades. Anatomically, the SEF sends outputs to
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20 the basal ganglia and receives signals from the basal ganglia via the thalamus (Shook et al., 1991;
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22 Tian and Lynch, 1997). Similarly, neurons in the lateral PFC receive the basal ganglia outputs through
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24 the thalamocortical pathways (Middleton and Strick, 2002). Within the basal ganglia, the GPe
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26 regulates signals in both the GPi and SNr directly or through the subthalamic nucleus (Parent and
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28 Hazrati, 1995a,b; Chan et al., 2005), which in turn send inhibitory projections to the SC and the
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30 thalamus.
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33 What are the roles of the saccade-related, transient signals in these structures? Figure 11
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35 illustrates a hypothetical diagram showing how the signals in the GP could regulate antisaccades.
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37 Although it is plausible that each of the intrinsic pathways in the basal ganglia mediates multiple
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39 signals, each pathway in the diagram is assigned to play a single role during antisaccades for
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41 simplicity. Because only a minority of neurons in the GP exhibited directional firing modulation prior
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43 to saccades (Fig. 4), most GP neurons are unlikely to provide the immediate drive or movement
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45 signals for antisaccades. Instead, one possible function of the pathways through the GP might be the
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47 active suppression of unnecessary prosaccades. The signals in the GP could suppress reflexive
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49 saccades through either or both of two possible pathways. The directional neurons in the indirect
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51 pathway might suppress saccades in particular direction by sending inhibitory signals to the SC and to
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53 the thalamus unilaterally (cf, Peltsch et al., 2008). Alternatively, the signals in the hyper-direct
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55 pathway might suppress saccades omnidirectionally, giving the time to produce the command of
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4 correct antisaccade (Fig. 11; cf, Isoda and Hikosaka, 2007). These hypotheses are consistent with our
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6 findings that inactivation of the GPe increased the occurrence of erroneous saccades toward the target
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8 in the antisaccade task. Similarly to the previous inactivation experiments in the lateral PFC (Condy
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10 et al., 2007), we also found directional antisaccade deficits following inactivation of the GPe (Fig. 9);
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12 however, unlike the PFC data, the impaired direction was different from site to site, while the effects
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14 were consistent during each post-lesional testing that lasted up to 60 min. The laterality of the
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16 antisaccade deficits observed in this study might result from the different inactivation effects on the
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18 crossed or uncrossed innervations from the output nodes of the basal ganglia to the thalamus (Hazrati
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20 and Parent, 1991) or to the SC (Jiang et al., 2003; Beckstead et al., 1981), whereas it remains
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22 unknown whether neurons regulating the crossed or uncrossed projections cluster separately within
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24 the GPe. In addition, the idea that signals from the frontal cortex through the basal ganglia to the SC
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26 and the thalamus suppress the initiation of saccades is also consistent with the previous findings that
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28 inactivation of the SNr increases the occurrence of reflexive saccades in the memory-guided saccade
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30 task (Hikosaka and Wurtz, 1985), that the lesions in the medial frontal cortex shorten the latency of
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32 antisaccades (Boxer et al., 2006), and that stimulation in the medial frontal cortex prolongs saccade
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34 latencies (Isoda and Hikosaka, 2007). The signals at the time of antisaccades might play roles in
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36 suppressing unnecessary reflexive saccades through the projections from the basal ganglia to the SC
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38 as well as to the thalamus.
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44 The other possible role of the transient signals in the GPi might be to boost the commands of
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46 antisaccades in the thalamus and the cortex (Fig. 11). It has been accepted widely that ‘disinhibition’
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48 of the tonic inhibitory outputs from the SNr to the SC is essential for conveying the signals in the
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50 basal ganglia to the brainstem, and for giving access to the SC from the cortex (for review, Hikosaka
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52 et al., 2000). Similarly, the decrease-type neurons in the GPi might transmit non-directional signals to
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54 the thalamus by the disinhibition mechanism, enabling the enhancement of the antisaccade signals
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56 within the reciprocal positive feedback circuitry between the thalamus and the cortex. Unfortunately,
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4 however, we could neither test nor prove the hypothesis in the present study. The hypothesis could be
5 tested by analyzing the effects of inactivation in the GPi or the thalamus during antisaccades in the
6 future studies.
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10 11 **Context-dependent sustained activity during fixation**

12 In addition to the transient activity during saccades, many neurons in the GP also exhibited
13 task-related firing modulation even before the target onset. Similarly to the activity during saccades,
14 the firing modulation during fixation was also enhanced for antisaccades compared with prosaccades.
15 For each neuron, the direction of the firing modulation during saccade preparation was identical to
16 that during saccade execution; the increase-type neurons elevated the firing rates during the
17 preparation for antisaccades, while the decrease-type neurons reduced the firing rates during the
18 preparation for antisaccades (Fig. 6). This pattern of firing modulation was similar to those reported
19 previously in the SEF (Schlag et al., 1997), the SNr (Gore et al., 2005) and the lateral PFC (Johnston
20 and Everling, 2006), but seems to be different from that reported in the rostral SC; the activities of the
21 collicular fixation neurons are strongly suppressed around the time of antisaccades, but the firing rate
22 is elevated during the preparation for antisaccades, as compared to prosaccades (Everling et al., 1999).
23 Although it is possible that the preparatory signals in the basal ganglia regulate the firing of fixation
24 neurons in the rostral SC, the difference in the pattern of firing modulation between the GPe and the
25 SC suggests that the signals in the basal ganglia may not be sent exclusively to the rostral SC to
26 suppress reflexive prosaccades — some of the signals in the basal ganglia may regulate eye
27 movements through the thalamocortical pathways, as discussed in the previous section. The existence
28 of the task-related neurons in the GPi (15% of tested neurons) also supports this possibility. The
29 elevation of regional blood flow in the thalamus during antisaccades (O'Driscoll et al., 1995;
30 Matsuda et al., 2004; Tu et al., 2006) could be due to the signals originating from the GPi and the SNr.
31 Another line of evidence also suggests that signals through the thalamocortical pathways likely play
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4 roles in the initiation of voluntary saccades (Petit et al., 1993; Vermersch et al., 1996; Tanaka, 2006,
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7 2007).

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9 Neuronal activity related to the task instruction has been reported in several cortical areas
10 during antisaccades (PFC, Everling and DeSouza, 2005; ACC, Johnson and Everling, 2007; SEF,
11 Schlag-Rey et al., 1997; Amador et al., 2004), and those activities have been thought to be related to
12 the stimulus-response association in the task (for review, Munoz and Everling, 2004). Similarly,
13 neurons in the GP that discriminate the tasks during the instruction period may also play this role, by
14 sending signals through the thalamus to the cortex (Fig. 11). A recent study showed that error rates in
15 the antisaccade trials were significantly greater for subjects with Parkinson's disease than normal
16 controls when the antisaccade trials were mixed with the prosaccade trials randomly within a block,
17 suggesting that the basal ganglia may play roles in online switching of eye movement responses
18 according to a given instruction (Rivaud-Péchoux et al., 2007, but see Chan et al., 2005).
19 Furthermore, this proposal appears to be consistent with the current view of the neural mechanisms
20 underlying the conditional learning that implicates the basal ganglia-thalamocortical circuitry in the
21 stimulus-response associations (Toni and Passingham, 1999; Brasted and Wise, 2004; Pasupathy and
22 Miller, 2005; Boettiger and D'Esposito, 2005). As suggested in the somatic motor system, the
23 cortico-basal ganglia 'cognitive' and 'oculomotor' loops might also play roles in the evolution of the
24 rule-dependent signals for the generation of voluntary eye movements, including antisaccades. To
25 examine the possible roles played by the thalamocortical pathways in antisaccades, further
26 recording and inactivation experiments in the thalamus are needed.
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Notes

We thank J. Kunimatsu, A. Matsushima and M. Tashiro for their insightful discussions; S. Hirano and T. Shiraishi for technical assistance; and M. Suzuki for administrative help. One animal was provided by the Primate Research Institute of Kyoto University. This work was supported by grants from the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

For Peer Review

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References

- Alexander GE, Crutcher MD. 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* 13:266–271.
- Alexander GE, DeLong MR, Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci.* 9:357–381.
- Amador N, Schlag-Rey M, Schlag J. 1998. Primate antisaccade. I. Behavioral characteristics. *J Neurophysiol.* 80:1775–1786.
- Amador N, Schlag-Rey M, Schlag J. 2004. Primate antisaccade. II. Supplementary eye field neuronal activity predicts correct performance. *J Neurophysiol.* 91:1672–1689.
- Beckstead RM, Edwards SB, Frankfurter A. 1981. A comparison of the intranigral distribution of nigroreticular neurons labeled with horseradish peroxidase in the monkey, cat, and rat. *J Neurosci.* 1:121–125.
- Boettiger CA, D'Esposito M. 2005. Frontal networks for learning and executing arbitrary stimulus-response associations. *J Neurosci.* 25:2723–2732.
- Brasted PJ, Wise SP. 2004. Comparison of learning-related neuronal activity in the dorsal premotor cortex and striatum. *Eur J Neurosci.* 19:721–740.
- Boxer AL, Garbutt S, Rankin KP, Hellmuth J, Neuhaus J, Miller BL, Lisberger SG. 2006. Medial versus lateral frontal lobe contributions to voluntary saccade control as revealed by the study of patients with frontal lobe degeneration. *J Neurosci.* 26:6354–6363.
- Chan CS, Surmeier DJ, Yung WH. 2005. Striatal information signaling and integration in globus pallidus: timing matters. *Neurosignals.* 14:281–289.
- Chan F, Armstrong IT, Pari G, Riopelle RJ, Munoz DP. 2005. Deficits in saccadic eye-movement control in Parkinson's disease. *Neuropsychologia.* 43:784–796.

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57
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60
- Condy C, Wattiez N, Rivaud-Pechoux S, Tremblay L, Gaymard B. 2007. Antisaccade deficit after inactivation of the principal sulcus in monkeys. *Cereb Cortex*. 17:221–229.
- DeLong MR. 1971. Activity of pallidal neurons during movement. *J Neurophysiol*. 34:414–427.
- Everling S, DeSouza JF. 2005. Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. *J Cogn Neurosci*. 17:1483–1496.
- Everling S, Dorris MC, Klein RM, Munoz DP. 1999. Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. *J Neurosci*. 19:2740–2754.
- Everling S, Fischer B. 1998. The antisaccade: a review of basic research and clinical studies. *Neuropsychologia*. 36:885–899.
- Everling S, Munoz DP. 2000. Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *J Neurosci*. 20:387–400.
- Fawcett AP, Moro E, Lang AE, Lozano AM, Hutchison WD. 2005. Pallidal deep brain stimulation influences both reflexive and voluntary saccades in Huntington's disease. *Mov Disord*. 20:371–377.
- Gottlieb J, Goldberg ME. 1999. Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. *Nat Neurosci*. 2:906–912.
- Gore JL, Marino RA, Munoz DP. 2005. Neural correlates associated with pro- and anti-saccades in primate SNr. *Soc Neurosci Abstr*. 35: 167.6
- Hallett PE. 1978. Primary and secondary saccades to goals defined by instructions. *Vision Res*. 18:1279–1296.
- Hazrati LN, Parent A. 1991. Contralateral pallidothalamic and pallidotegmental projections in primates: an anterograde and retrograde labeling study. *Brain Res*. 567:212–223.

- 1
2
3
4 Hikosaka O, Wurtz RH. 1985. Modification of saccadic eye movements by GABA-related
5 substances. II. Effects of muscimol in monkey substantia nigra pars reticulata. *J Neurophysiol.*
6 53:292–308.
7
8
9
10
11 Hikosaka O, Takikawa Y, Kawagoe R 2000. Role of the basal ganglia in the control of purposive
12 saccadic eye movements. *Physiol Rev.* 80:953–978.
13
14
15
16 Isoda M, Hikosaka O. 2007. Switching from automatic to controlled action by monkey medial
17 frontal cortex. *Nat Neurosci.* 10:240–248.
18
19
20
21 Jiang H, Stein BE, McHaffie JG. 2003. Opposing basal ganglia processes shape midbrain visuomotor
22 activity bilaterally. *Nature.* 423:982–986.
23
24
25
26 Johnston K, Everling S. 2006. Monkey dorsolateral prefrontal cortex sends task-selective signals
27 directly to the superior colliculus. *J Neurosci.* 26:12471–12478.
28
29
30
31 Johnston K, Levin HM, Koval MJ, Everling S. 2007. Top-down control-signal dynamics in anterior
32 cingulate and prefrontal cortex neurons following task switching. *Neuron.* 53:453–462.
33
34
35
36 Kato M, Hikosaka O. 1995. Functional of the indirect pathway in the basal ganglia oculomotor
37 system: visuo-oculomotor activities of external pallidum neurons. In: *Age-Related*
38 *Dopamine-Deficient Disorders* (Segawa M, Nomura Y, eds), pp 178–187. Basel: Karger.
39
40
41
42 Koida K, Komatsu H. 2007. Effects of task demands on the responses of color-selective neurons in
43 the inferior temporal cortex. *Nat Neurosci.* 10:108–116.
44
45
46
47 Matsuda T, Matsuura M, Ohkubo T, Ohkubo H, Matsushima E, Inoue K, Taira M, Kojima T. 2004.
48 Functional MRI mapping of brain activation during visually guided saccades and antisaccades:
49 cortical and subcortical networks. *Psychiatry Res.* 131:147–155.
50
51
52
53
54 Middleton FA, Strick PL. 2002. Basal-ganglia 'projections' to the prefrontal cortex of the
55 primate. *Cereb Cortex.* 12:926–935.
56
57
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59
60

- 1
2
3
4 Munoz DP, Everling S. 2004. Look away: the anti-saccade task and the voluntary control of eye
5 movement. *Nat Rev Neurosci.* 5:218–228.
6
7
8
9 O'Driscoll GA, Alpert NM, Matthyse SW, Levy DL, Rauch SL, Holzman PS. 1995. Functional
10 neuroanatomy of antisaccade eye movements investigated with positron emission tomography.
11 *Proc Natl Acad Sci U S A.* 92:925–929.
12
13
14
15
16 Parent A, Hazrati LN. 1995a. Functional anatomy of the basal ganglia. I. The cortico-basal
17 ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91–127.
18
19
20
21 Parent A, Hazrati LN. 1995b. Functional anatomy of the basal ganglia. II. The place of subthalamic
22 nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev.* 20:128–154.
23
24
25
26 Pasupathy A, Miller EK. 2005. Different time courses of learning-related activity in the prefrontal
27 cortex and striatum. *Nature.* 433:873–876.
28
29
30
31 Peltsch A, Hoffman A, Armstrong I, Pari G, Munoz DP. 2008. Saccadic impairments in Huntington's
32 disease. *Exp Brain Res.* (in press, published online PMID:18185924)
33
34
35
36 Petit L, Orssaud C, Tzourio N, Salamon G, Mazoyer B, Berthoz A. 1993. PET study of voluntary
37 saccadic eye movements in humans: basal ganglia-thalamocortical system and cingulate cortex
38 involvement. *J Neurophysiol.* 69:1009–1017.
39
40
41
42 Rivaud-Péchoux S, Vidailhet M, Brandel JP, Gaymard B. 2007. Mixing pro- and antisaccades in
43 patients with parkinsonian syndromes. *Brain.* 130:256–264.
44
45
46
47 Schlag-Rey M, Amador N, Sanchez H, Schlag J. 1997. Antisaccade performance predicted by
48 neuronal activity in the supplementary eye field. *Nature.* 390:398–401.
49
50
51
52 Shook BL, Schlag-Rey M, Schlag J. 1991. Primate supplementary eye field. II. Comparative aspects
53 of connections with the thalamus, corpus striatum, and related forebrain nuclei. *J Comp Neurol.*
54 307:562–583.
55
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59
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3
4 Straube A, Ditterich J, Oertel W, Kupsch A. 1998. Electrical stimulation of the posterioventral
5 pallidum influences internally guided saccades in Parkinson's disease. *J Neurol.* 245:101–105.
6
7
8
9 Tanaka M. 2005. Involvement of the central thalamus in the control of smooth pursuit eye movements.
10 *J Neurosci.* 25:5866–5876.
11
12
13
14 Tanaka, M. 2006. Inactivation of the central thalamus delays self-timed saccades. *Nat Neurosci.*
15 9:20–22.
16
17
18
19 Tanaka M. 2007. Cognitive signals in the primate motor thalamus predict saccade timing. *J Neurosci.*
20 27:12109–12118.
21
22
23
24 Tian JR, Lynch JC. 1997. Subcortical input to the smooth and saccadic eye movement subregions of
25 the frontal eye field in Cebus monkey. *J Neurosci.* 17:9233–9247.
26
27
28
29 Toni I, Passingham RE. 1999. Prefrontal-basal ganglia pathways are involved in the learning of
30 arbitrary visuomotor associations: a PET study. *Exp Brain Res.* 127:19–32.
31
32
33
34 Tu PC, Yang TH, Kuo WJ, Hsieh JC, Su TP. 2006. Neural correlates of antisaccade deficits in
35 schizophrenia, an fMRI study. *J Psychiatr Res.* 40:606–612.
36
37
38
39 Vermersch AI, Muri RM, Rivaud S, Vidailhet M, Gaymard B, Agid Y, Pierrot-Deseilligny C. 1996.
40 Saccade disturbances after bilateral lentiform nucleus lesions in humans. *J Neurol Neurosurg*
41 *Psychiatry.* 60:179–184.
42
43
44
45 Yoshida A, Tanaka M. 2007. Antisaccade signals in the primate globus pallidus. *Soc Neurosci Abstr.*
46 37:398.19
47
48
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50 Zhang M, Barash S. 2000. Neuronal switching of sensorimotor transformations for antisaccades.
51 *Nature.* 408:971–975.
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Figure legends

Figure 1. Sequence of events in the three saccade tasks. In both the antisaccade task and the prosaccade task, the color of the fixation point was initially gray, and it became green (antisaccade task) or red (prosaccade task) for 800 ms. A white target spot appeared 16° eccentrically at the time of the fixation point offset. Monkeys were required to make a saccade toward (prosaccade) or away from (antisaccade) the target within 400 ms. In the memory-guided saccade task, the color of the fixation point was red throughout the trial. A peripheral target was flashed briefly (200 ms) during central fixation, and monkeys were required to maintain fixation and remember the location of the target. After a delay of 800 ms, the fixation point disappeared and monkeys made a saccade to the location of the previously flashed target within 400 ms. All of these trials were randomly interleaved in a block.

Figure 2. Comparison of the responses in the 3 saccade paradigms for representative neurons. **A**, An increase-type neuron. **B**, A decrease-type neuron. In all panels, data are aligned on saccade initiation (vertical line). Trials are sorted by saccade latency, and the rasters are shown for contraversive saccades only, while the spike density traces are shown for both directions. The purple diamond on each raster line indicates the time of the fixation target offset. **C**, Traces of mean spike density for the population of neurons. The dashed traces indicate the mean \pm SE for pro- and antisaccades. The population activity was computed for the preferred direction only. The firing rates of individual neurons measured at the time of black rectangle are shown in Fig. 3. *Anti*, antisaccade; *Pro*, prosaccade; *Mem*, memory-guided saccade.

Figure 3. **A**, **B**, Comparison of the firing rates during antisaccades versus prosaccades for individual neurons. Filled symbols indicate the data showing a significant difference (Scheffé, $P < 0.05$). **C**, Relative magnitudes of the firing modulation. The size of the activity modulation (saccade activity minus baseline) in each task was normalized according to the sum of the activity modulation in the three tasks. Overall, 66% ($n = 79/119$) of neurons exhibited the greatest firing modulation during

antisaccades across the tasks.

Figure 4. Quantification of the directionality during saccades. **A, B,** Comparison of the modulation indices (MIs) computed for the 150 ms period starting from 100 ms before saccade initiation between the antisaccade task and the prosaccade task. Neurons with strong directional preference show greater MI values. Open circles indicate the increase-type neurons and filled triangles indicate the decrease-type neurons. Two outliers (both are decrease-type neurons) have been omitted from the plot in A. Filled bars in the histograms indicate neurons showing a significant directional modulation (Wilcoxon rank-sum test, $P < 0.05$). Note that the directional neurons in the GPe tended to be the decrease-type neurons (A, filled triangles), while all directional neurons in the GPi were the increase-type neurons (B, open circles). **C, D,** Time series analysis of the directionality for neurons in the GPe (C) and GPi (D). The proportion of directional neurons is plotted as a function of the time relative to saccade initiation. The firing rates in a 50-ms window centered at the value on the abscissa were compared for saccades in opposite directions (Wilcoxon rank-sum test, $P < 0.05$). Note that approximately 10% of neurons showed directional activity during the delay period in the memory-guided saccade tasks.

Figure 5. Activity modulation during the instruction period. **A,** An increase-type neuron. **B,** A decrease-type neuron. The color of the fixation point was different for the two saccade tasks during the periods between the two vertical lines (Instruction period). The saccade target appeared at the time of the fixation point offset (time 0). To examine the activity during the instruction, data for saccades in both directions were combined. The blue diamond on each raster line indicates the time of saccades.

Figure 6. Quantitative comparison of the instruction period activity. **A, C,** Activities of individual increase-type neurons (A) and decrease-type neurons (C) are compared between the antisaccade trial and the prosaccade trial. Circle indicates the GPe neurons, while triangles indicate the GPi neurons.

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4 The firing rate was measured for a 200-ms interval immediately before the fixation point offset (black
5 bars in **B** and **D**). Filled symbols represent data showing a significant difference between the tasks
6 (two-tailed t -test, $P < 0.05$). **B**, **D**, Population activities for the increase-type neurons (**B**) and the
7 decrease-type neurons (**D**). Data are aligned on the fixation point offset. Dashed traces indicate plus
8 or minus SEM. Supplementary Fig. S4 plots the population activities for each of the GPe and the GPi
9 neurons separately.
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18 **Figure 7.** Context-dependent modulation of the instruction period activity. **A**, Design of the fixation
19 experiment. Following 30 fixation trials, an antisaccade trial was presented in every nine fixation
20 trials. In the fixation task, the color of the fixation point changed from gray to green as in the
21 antisaccade task, but a peripheral target never appeared throughout the trial (See Materials and
22 Methods). **B**, Comparison of the magnitude of the instruction period activity between the successful
23 antisaccade trials and the fixation trials for individual neurons. Data of successful antisaccade trials
24 were obtained from a separate block, and are the same as those plotted in Fig. 6. Different shapes of
25 symbols indicate different types of neurons. Filled symbols indicate data showing a statistically
26 significant difference (Wilcoxon rank-sum test, $P < 0.05$). **C**, Comparison of the mean firing
27 modulation during the instruction period for successful antisaccade trials ('Correct'), error
28 antisaccade trials ('Error') and fixation trials ('Fixation'). Each data point indicates mean (\pm SD)
29 response sizes across the 14 neurons. **D**, **E**, Time courses of the population activity for the
30 increase-type neurons (**D**) and the decrease-type neurons (**E**). Data are aligned on the fixation point
31 offset. Dashed traces indicate plus or minus SEM.
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49 **Figure 8.** Immediate modulation of the instruction period activity in a block of fixation trials. **A**,
50 Decay of neuronal activity during the repetition of 30 fixation trials. Black circles plot the means of
51 firing modulation as a function of trial number in the block. Open square indicates the magnitude of
52 the instruction-period activity measured from the antisaccade trials in the preceding block of saccade
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4 trials. **B**, Activity modulation following the antisaccade task. Means of activity modulations are
5 plotted for the 9 fixation trials prior to and following the antisaccade task in the fixation block. Note
6 that neuronal activity during the instruction period is minimal in the block of fixation trials, as shown
7 in Fig. 7. The asterisk indicates significant difference in neuronal activity in comparison with that in
8 the fixation trial immediately before the antisaccade trial (paired t -test, $P < 0.05$). For both panels,
9 error bar indicates \pm SEM.
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18 **Figure 9.** Effects of local inactivation on the performance of antisaccades. **A**, Data obtained from
19 antisaccade trials before and after muscimol injection. Eye position traces are aligned on the fixation
20 point offset. Red dashed traces indicate error trials. The number on each panel indicates the
21 proportion of error trials. **B**, Changes in error rate for all injection experiments, including 4 muscimol
22 (solid lines) and 3 saline (dashed lines) experiments. Data connected by thick lines plot the data
23 shown in Fig. 9A. Asterisks indicate significant inactivation effects (χ^2 test, $P < 0.01$). Data for the
24 experiment showing the prosaccade deficits are shown in Supplementary Fig. S5.
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34 **Figure 10.** Sites of the task-related neurons and local inactivation in monkey *E*. Different symbols
35 are used for neurons showing different response properties. Levels of frontal sections are shown as
36 millimeters from the anterior commissure. AC, anterior commissure; GPe and GPi, external and
37 internal segments of the globus pallidus, respectively.
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44 **Figure 11.** A hypothetical diagram showing how the signals in the GP could regulate antisaccades.
45 Plus and minus signs indicate elevation and reduction of firing rates, respectively, for neurons in each
46 structure when neurons in the cerebral cortex are activated. Note that Cx, STN and SC/Thal contain
47 excitatory neurons, while other structures contain inhibitory neurons. About one-third of the
48 decrease-type neurons in the GPe and the increased-type neurons in the GPi showed directional
49 activity modulation (rectangles). Other types of neurons in the GP generally showed non-directional
50 firing modulation before saccades. Although it is possible that each intrinsic pathway in the basal
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4 ganglia plays multiple roles, each pathway is assigned to a single function for simplicity. Cx, cerebral
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6 cortex; Cd, caudate nucleus; Put, putamen; SC, superior colliculus; SNr, substantia nigra pars
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8 reticulate; STN, subthalamic nucleus; Thal, thalamus.
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For Peer Review

Table 1. Number of saccade-related neurons and those also showing other types of task-related activity

<i>Monkey D (29)</i>		
Increased saccade-related activity (13)	GPe (13)	GPi (0)
+ visual	0	0
+ pursuit	5	0
+ reward	1	0
Decreased saccade-related activity (16)	GPe (14)	GPi (2)
+ visual	1	0
+ pursuit	5	1
+ reward	2	1
<i>Monkey E (90)</i>		
Increased saccade-related activity (53)	GPe (41)	GPi (12)
+ visual	2	1
+ pursuit	12	5
+ reward	10	5
Decreased saccade-related activity (37)	GPe (33)	GPi (4)
+ visual	1	0
+ pursuit	12	1
+ reward	13	1

Number in parenthesis indicates subtotal.

Table 2. Comparison of saccade parameters during recording sessions.

	Anti	Pro	Mem
Monkey D			
N (correct/all)	1249/1418	1298/1331	1318/1322
Error rate (%)	11.9	2.5	0.3
Latency (ms)	183 ± 35	174 ± 36	143 ± 34
Accuracy (deg)	2.2 ± 1.3	0.9 ± 0.5	1.5 ± 0.8
Error latency (ms)	151 ± 47	233 ± 47	150 ± 26
Monkey E			
N (correct/all)	3349/3769	3704/3901	3677/3718
Error rate (%)	11.1	5.1	1.1
Latency (ms)	213 ± 38	207 ± 36	174 ± 34
Accuracy (deg)	2.8 ± 1.6	1.1 ± 0.7	1.5 ± 0.9
Error latency (ms)	201 ± 53	239 ± 39	158 ± 79

Each entry shows mean ± SD.

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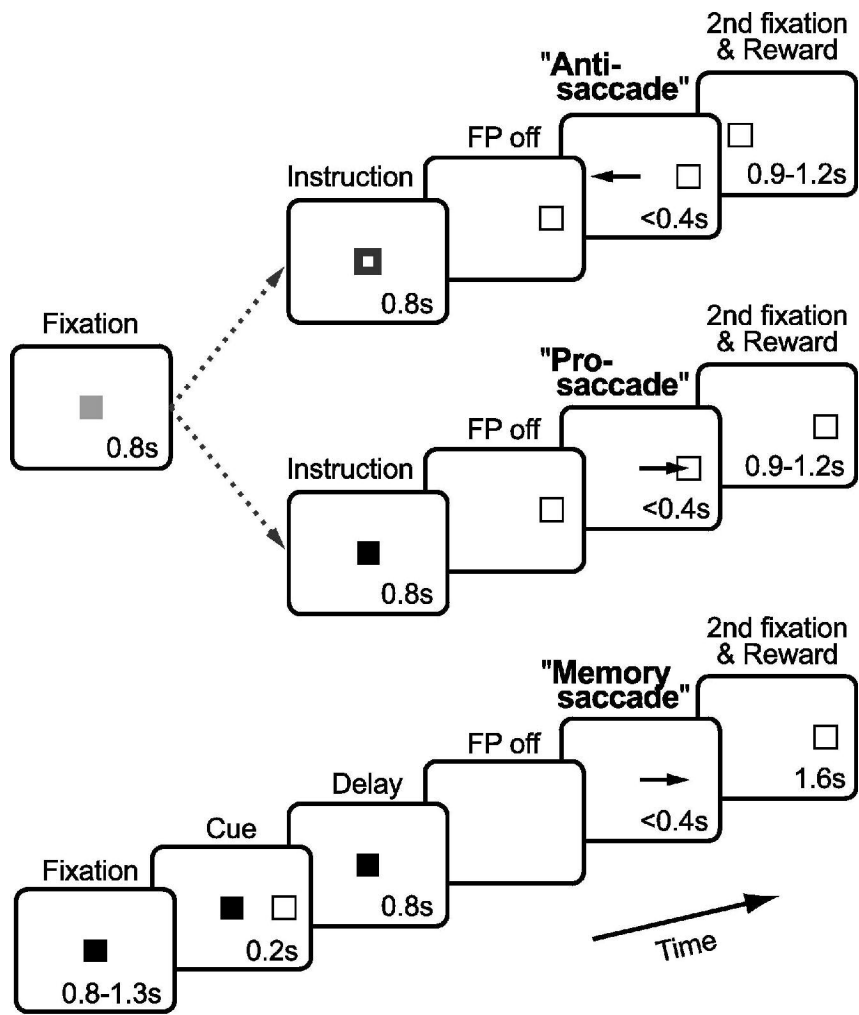


Figure 1, Yoshida & Tanaka

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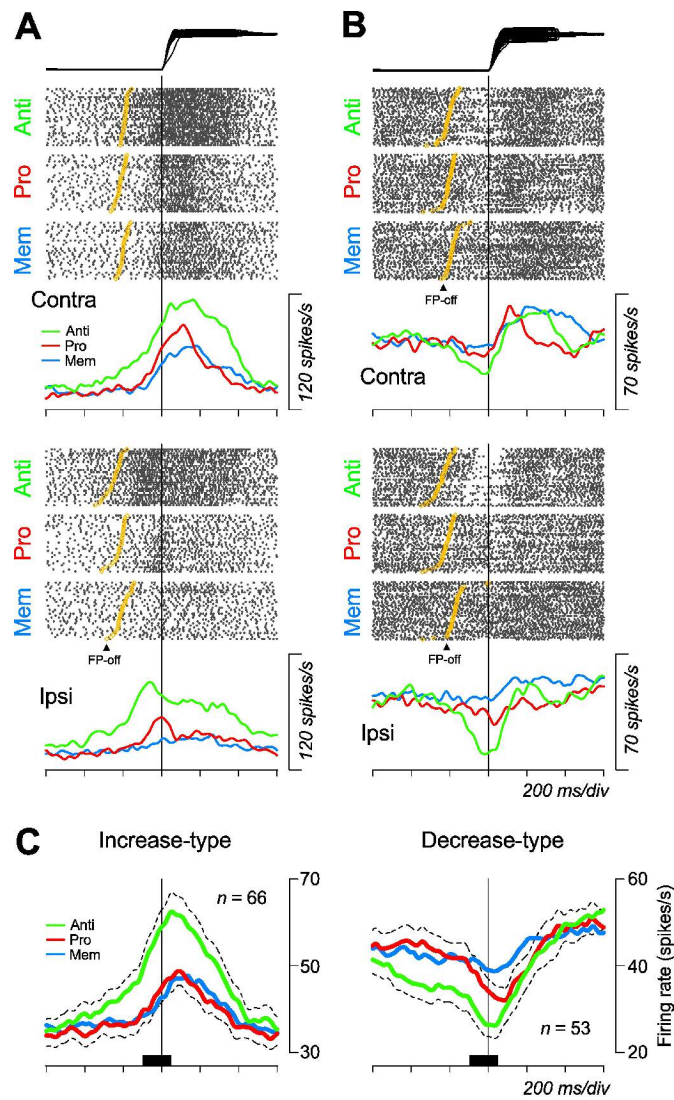


Figure 2, Yoshida & Tanaka

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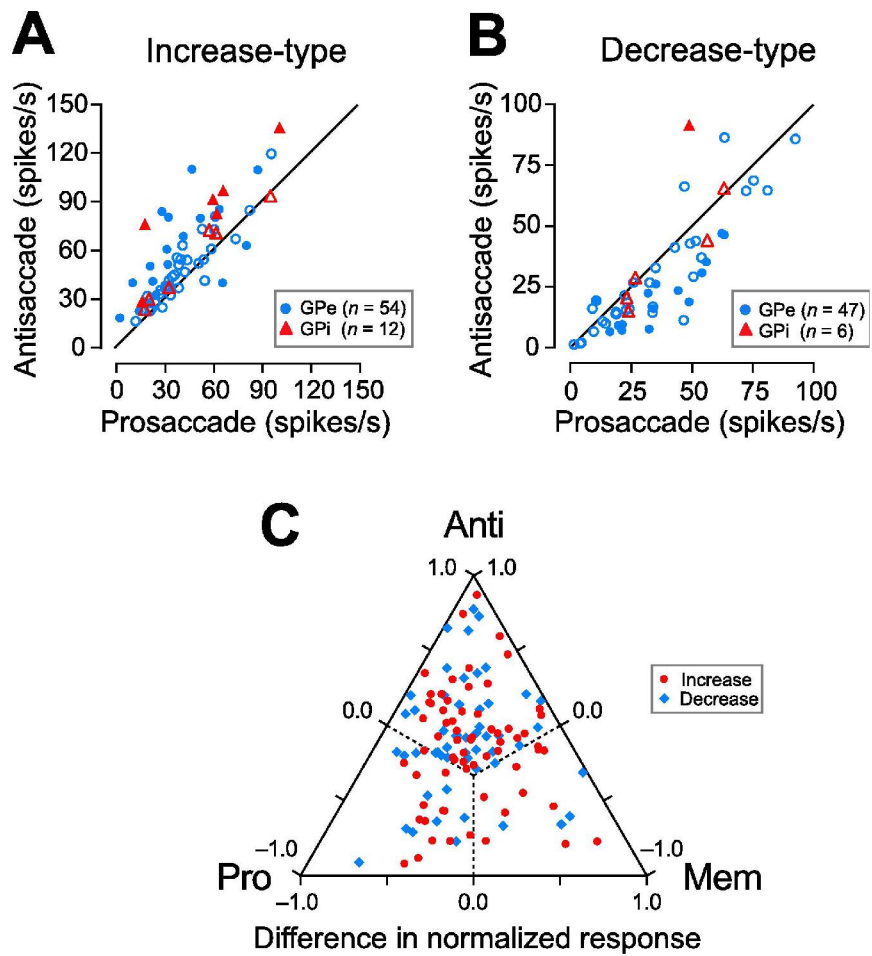


Figure 3, Yoshida & Tanaka

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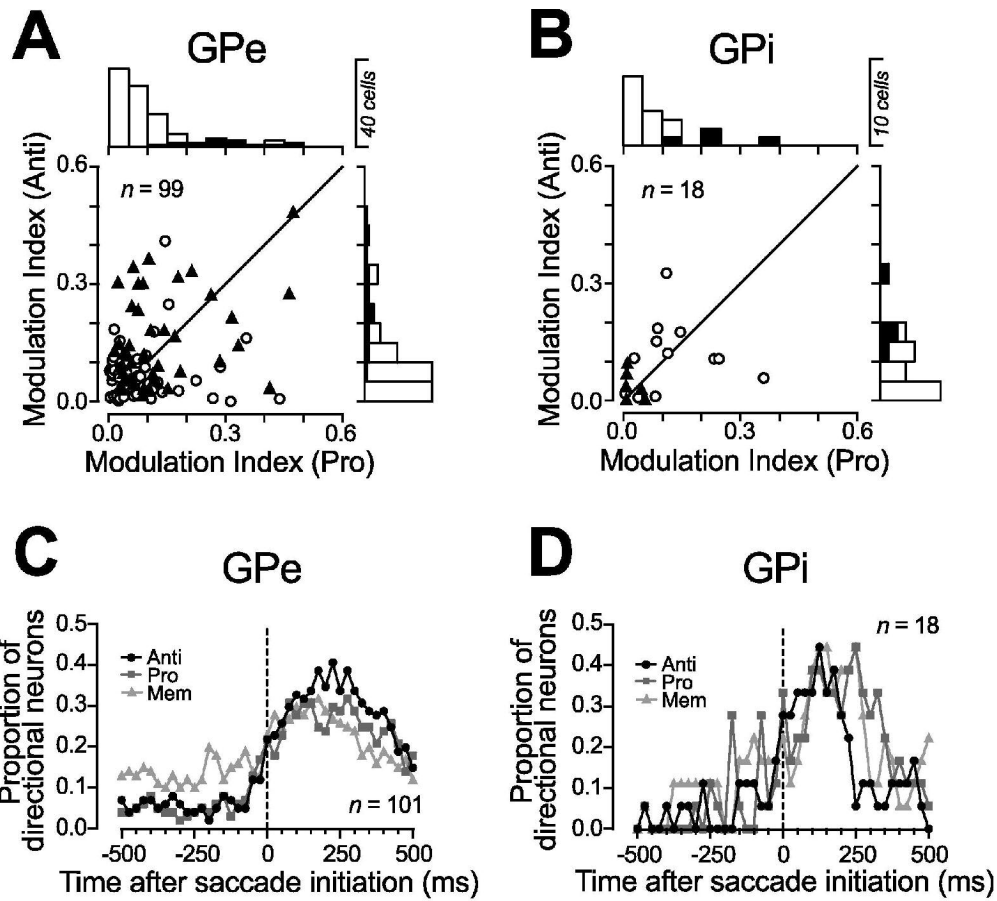


Figure 4, Yoshida & Tanaka

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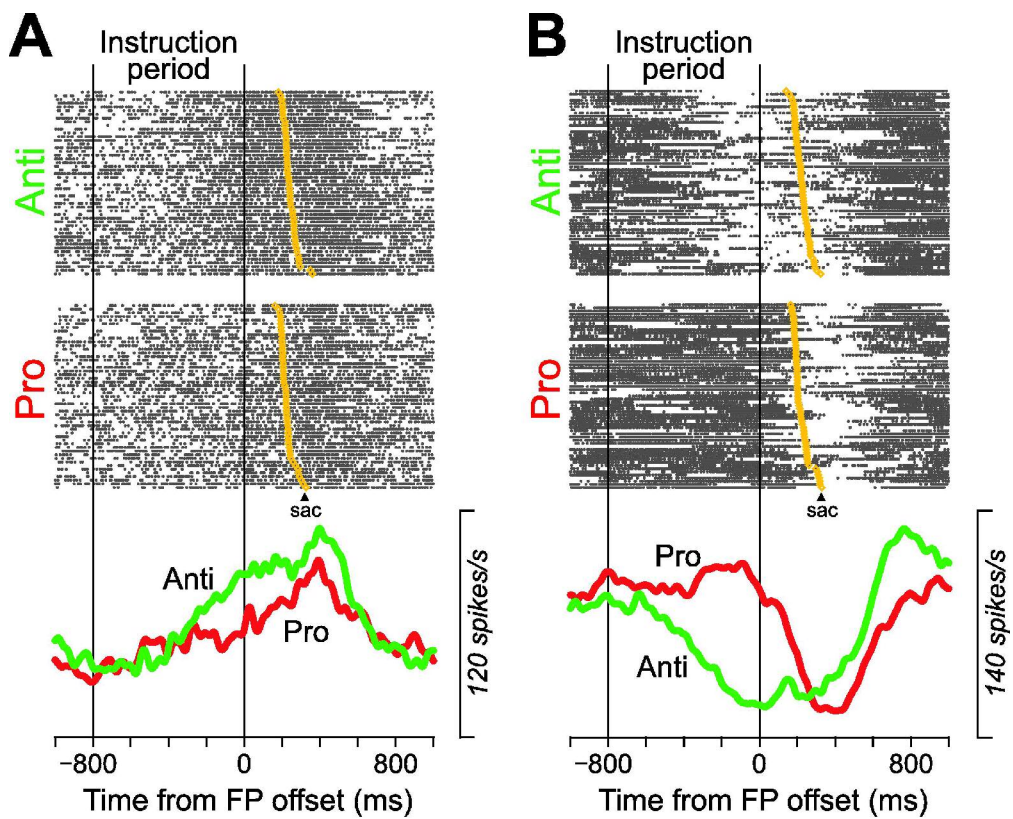


Figure 5, Yoshida & Tanaka

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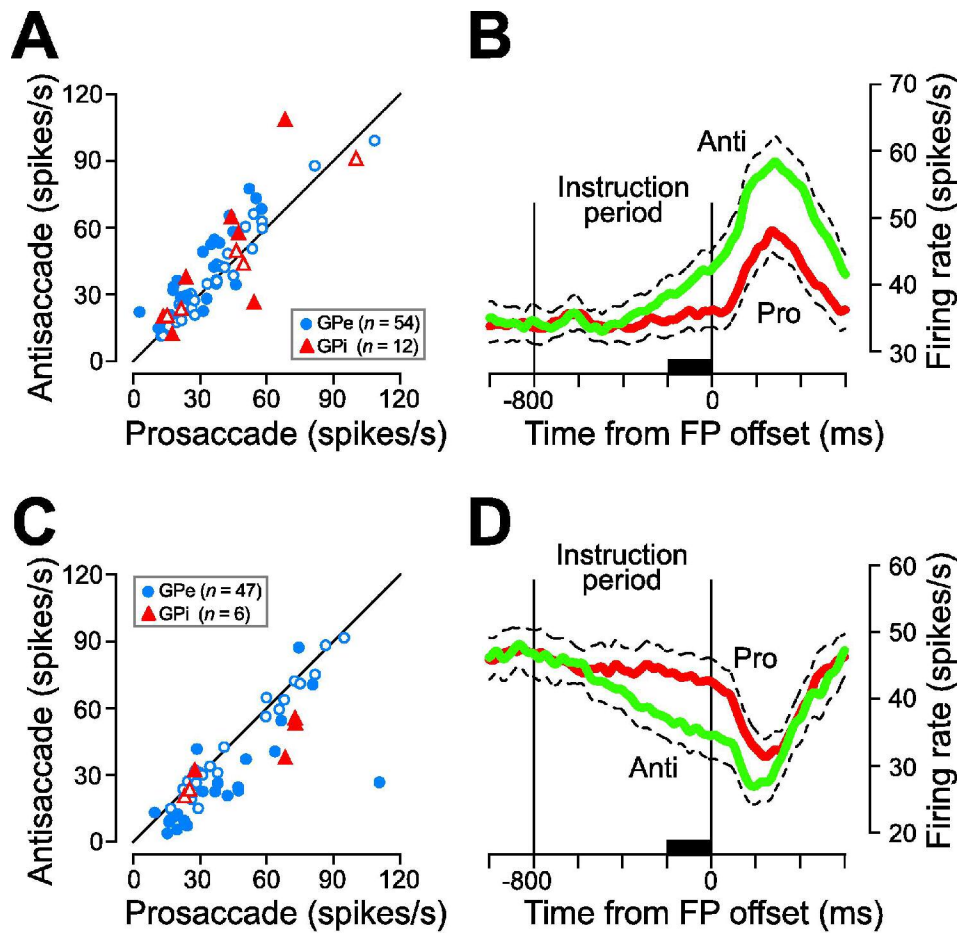


Figure 6, Yoshida & Tanaka

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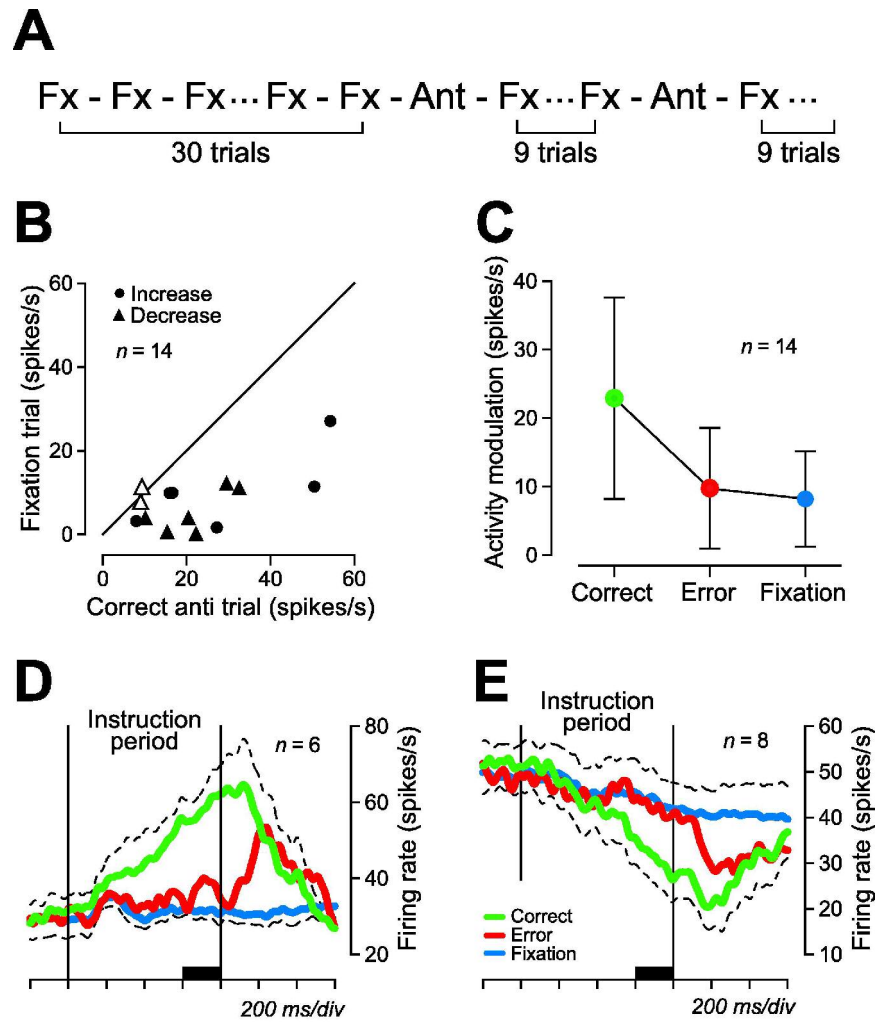


Figure 7, Yoshida & Tanaka

85x119mm (600 x 600 DPI)

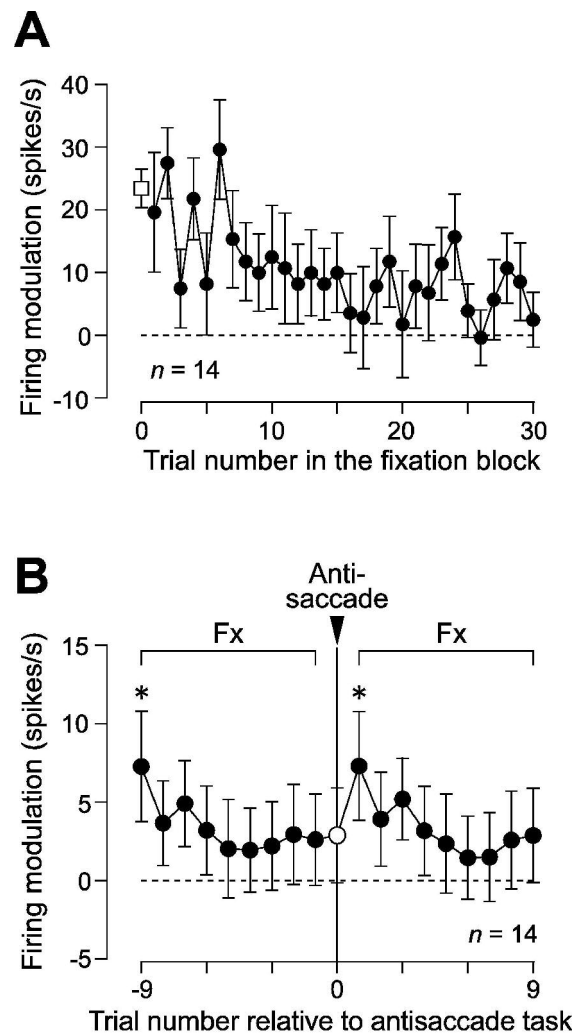


Figure 8, Yoshida & Tanaka

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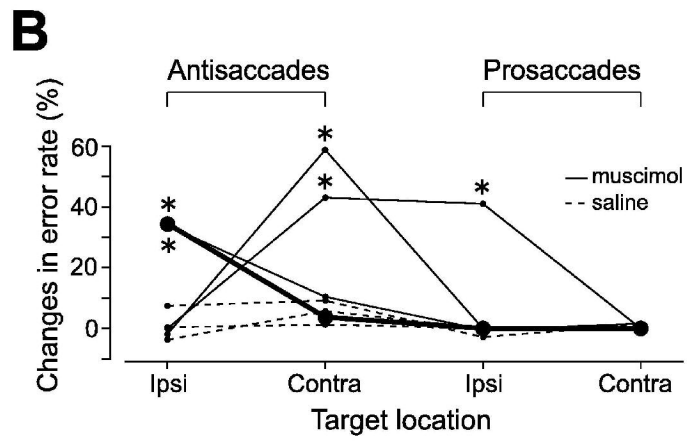
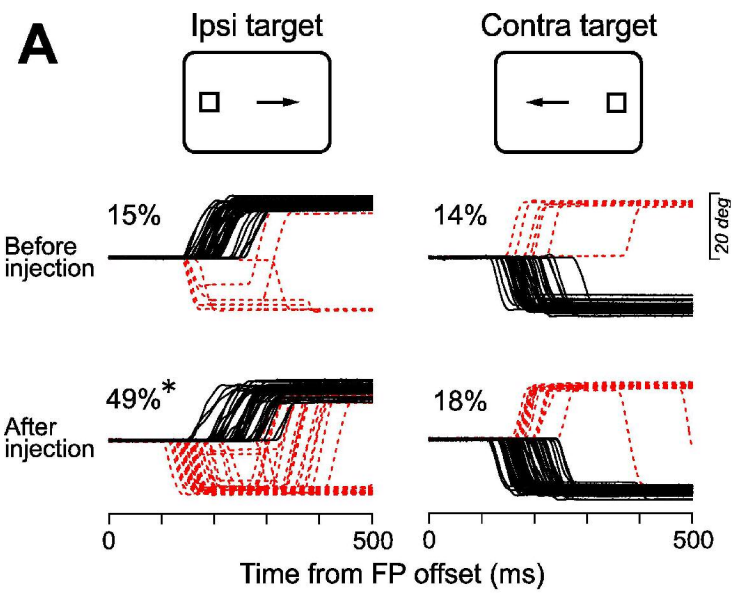


Figure 9, Yoshida & Tanaka

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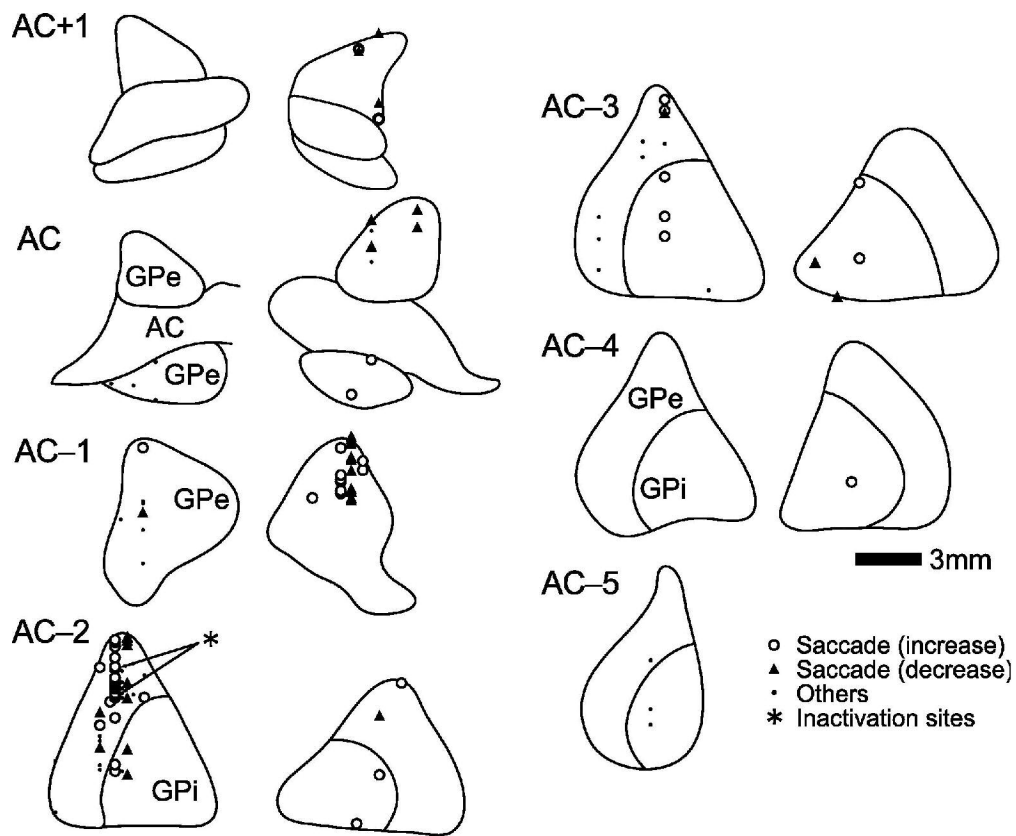


Figure 10, Yoshida & Tanaka

87x92mm (600 x 600 DPI)

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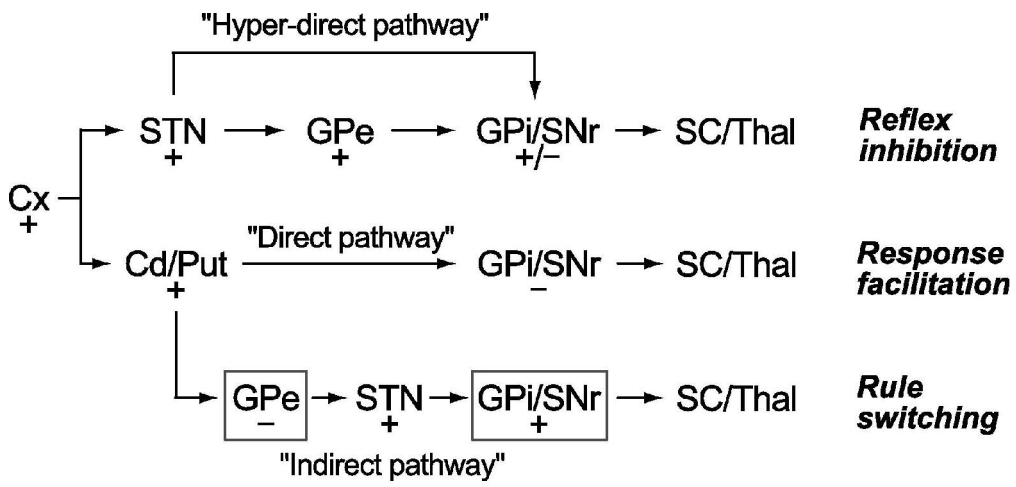
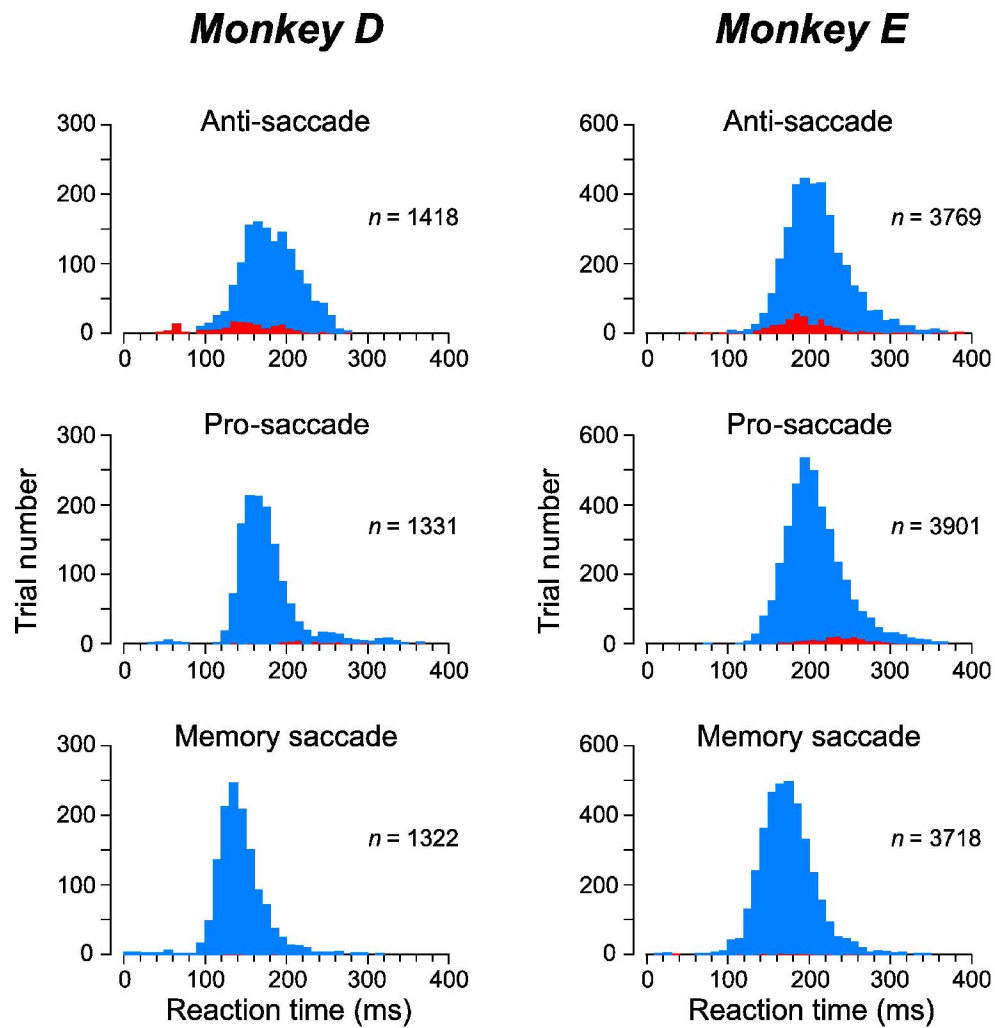


Figure 11, Yoshida & Tanaka

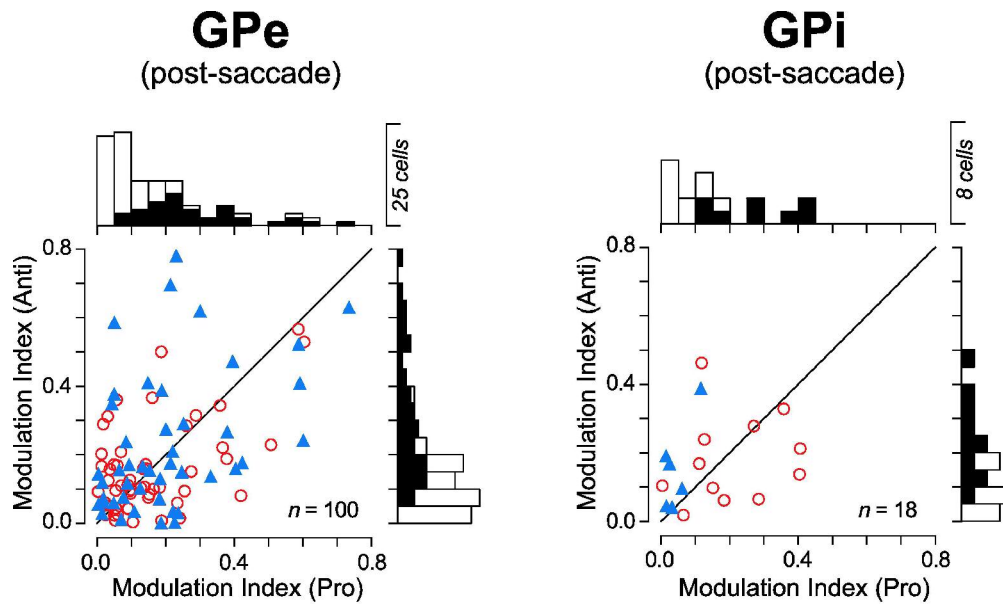
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review

**Supplementary Figure S1**

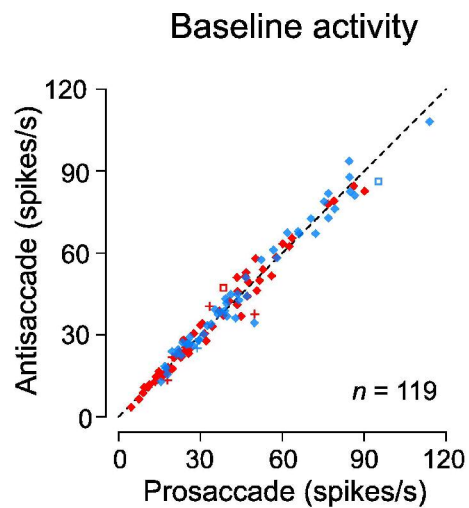
Distributions of saccade latencies for different tasks and monkeys. Blue bars indicate the data for correct trials, while red bars indicate those for error trials.

117x144mm (600 x 600 DPI)

**Supplementary Figure S2**

Modulation indices computed for the post-saccadic activity (50-200 ms after saccade initiation). Red circles and blue triangles are the data for the increase-type neurons and those for the decrease-type neurons, respectively. For the data of GPe neurons, one outlier (decrease-type) has been omitted. Note that the range of both axes are different from that in Figs. 4A and B.

127x109mm (600 x 600 DPI)



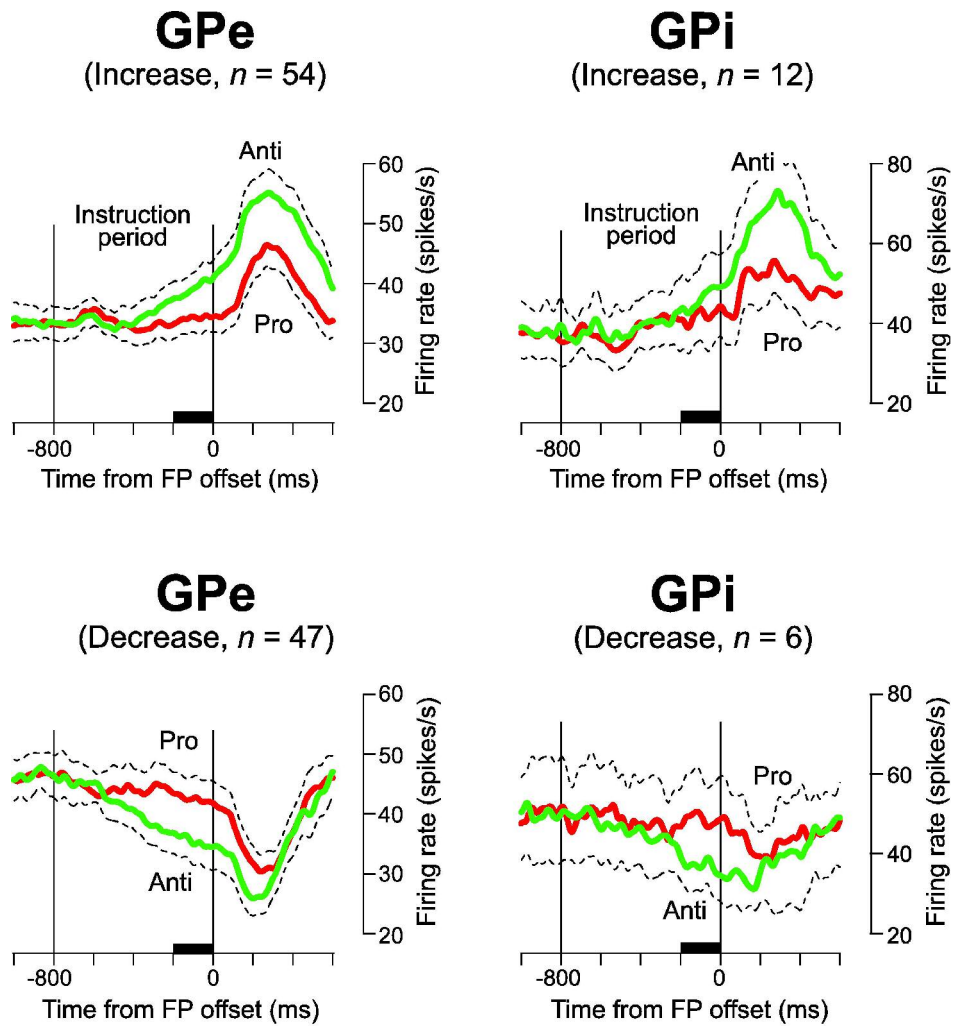
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Supplementary Figure S3

29 Comparison of the baseline activity 300 ms before the instruction between the
30 decrease-type neurons (blue symbols) and the increase-type neurons (red
31 symbols). Despite significant overlap, the baseline firing tended to be less for
32 the increase-type neurons than the decrease-type neurons. Five out of 119
33 neurons showed differential activity between the tasks (cross, Wilcoxon rank-
34 sum test, $P < 0.05$). Open squares indicate the data for the neurons shown in
35 Fig. 5.

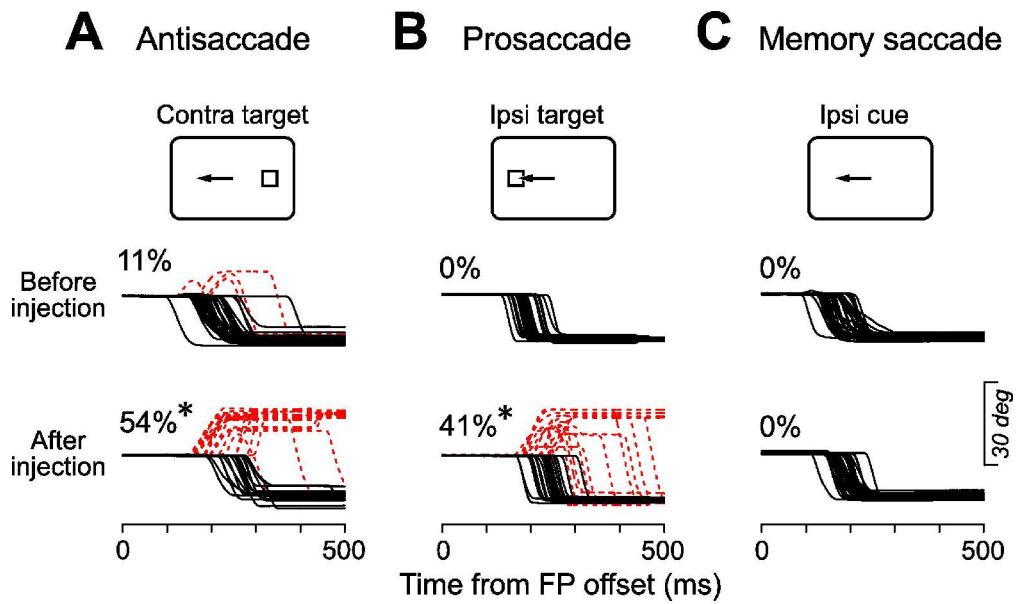
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**Supplementary Figure S4**

Comparison of the population activities between neurons in the GPe and the GPi.

117x150mm (600 x 600 DPI)



Supplementary Figure S5

Deficits in prosaccades following inactivation of GPe (*site E1*).

108x80mm (600 x 600 DPI)

review

Supplementary Table 1. Saccade latencies before and after injection.

		Target location					
		Ipsi			Contra		
Monkey D		Anti	Pro	Mem	Anti	Pro	Mem
1 (MUS)	Pre	190 ± 5	187 ± 6	120 ± 4	166 ± 6	156 ± 2	117 ± 3
	Post	237 ± 7 ^{***}	158 ± 2 ^{***}	119 ± 4	167 ± 4	172 ± 2 ^{***}	129 ± 5 ^{**}
2 (MUS)	Pre	263 ± 11	168 ± 3	142 ± 7	200 ± 6	192 ± 4	175 ± 7
	Post	268 ± 9	170 ± 4	172 ± 4 ^{***}	237 ± 11 ^{**}	178 ± 2 ^{**}	164 ± 6
3 (saline)	Pre	211 ± 10	175 ± 10	131 ± 14	196 ± 14	167 ± 4	162 ± 7
	Post	216 ± 6	165 ± 4	124 ± 7	188 ± 7	151 ± 2 ^{***}	138 ± 6 [*]
Monkey E		Anti	Pro	Mem	Anti	Pro	Mem
1 (MUS)	Pre	162 ± 3	179 ± 3	150 ± 5	194 ± 8	175 ± 4	158 ± 3
	Post	177 ± 5 [*]	221 ± 6 ^{***}	170 ± 4 ^{**}	243 ± 9 ^{***}	193 ± 5 [*]	177 ± 4 ^{***}
2 (MUS)	Pre	211 ± 6	207 ± 6	169 ± 6	221 ± 6	168 ± 3	158 ± 4
	Post	232 ± 10 [*]	202 ± 6	178 ± 9	237 ± 11	195 ± 6 ^{***}	177 ± 8 [*]
3 (saline)	Pre	196 ± 5	191 ± 5	150 ± 7	224 ± 10	187 ± 7	174 ± 6
	Post	208 ± 6	199 ± 5	167 ± 9	201 ± 6	190 ± 9	173 ± 7
4 (saline)	Pre	205 ± 4	185 ± 3	162 ± 6	205 ± 6	162 ± 4	172 ± 5
	Post	201 ± 7	185 ± 4	159 ± 9	205 ± 8	187 ± 9 [*]	164 ± 6

Each entry shows mean ± SD. MUS indicates muscimol injection. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$, Wilcoxon rank-sum test.

123x109mm (600 x 600 DPI)

ew

Supplementary Table 2. Saccade accuracies before and after injection.

		Target location					
		Ipsi			Contra		
Monkey D		Anti	Pro	Mem	Anti	Pro	Mem
1 (MUS)	Pre	1.5 ± 0.12	0.8 ± 0.04	1.7 ± 0.1	1.4 ± 0.13	0.8 ± 0.05	1.1 ± 0.09
	Post	1.9 ± 0.19	1.0 ± 0.03***	1.1 ± 0.08***	1.4 ± 0.07	0.8 ± 0.03	1.1 ± 0.08
2 (MUS)	Pre	2.2 ± 0.30	0.6 ± 0.04	1.1 ± 0.09	1.5 ± 0.15	0.8 ± 0.10	1.6 ± 0.12
	Post	1.5 ± 0.11	0.8 ± 0.04***	0.8 ± 0.05*	1.4 ± 0.19	0.6 ± 0.05	1.2 ± 0.08*
3 (saline)	Pre	2.5 ± 0.46	1.3 ± 0.06	1.0 ± 0.09	2.6 ± 0.22	0.8 ± 0.04	2.2 ± 0.19
	Post	2.2 ± 0.21	1.7 ± 0.05***	1.4 ± 0.09*	2.4 ± 0.15	1.2 ± 0.06***	2.5 ± 0.14
Monkey E		Anti	Pro	Mem	Anti	Pro	Mem
1 (MUS)	Pre	1.9 ± 0.16	0.6 ± 0.05	1.1 ± 0.10	2.0 ± 0.19	1.4 ± 0.07	2.0 ± 0.14
	Post	1.9 ± 0.15	0.8 ± 0.06	1.2 ± 0.11	2.6 ± 0.34	1.2 ± 0.08*	1.7 ± 0.18*
2 (MUS)	Pre	2.5 ± 0.21	0.7 ± 0.05	1.2 ± 0.09	2.4 ± 0.22	0.8 ± 0.05	1.1 ± 0.12
	Post	3.4 ± 0.42	0.6 ± 0.06	1.6 ± 0.20	3.1 ± 0.44*	0.8 ± 0.06	1.4 ± 0.19
3 (saline)	Pre	2.6 ± 0.33	0.9 ± 0.05	0.9 ± 0.09	1.8 ± 0.40	0.7 ± 0.08	1.4 ± 0.13
	Post	2.2 ± 0.22	0.9 ± 0.07	1.1 ± 0.14	2.8 ± 0.48	1.1 ± 0.14	1.5 ± 0.15
4 (saline)	Pre	2.2 ± 0.17	0.7 ± 0.05	1.0 ± 0.08	1.7 ± 0.22	0.6 ± 0.05	1.1 ± 0.10
	Post	1.7 ± 0.17	0.5 ± 0.07	1.0 ± 0.12	2.4 ± 0.42*	0.6 ± 0.08	1.2 ± 0.18

Each entry shows mean ± SD. MUS indicates muscimol injection. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$, Wilcoxon rank-sum test.

123x108mm (600 x 600 DPI)

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