Involvement of the Dorsolateral Prefrontal Cortex of Monkeys in Visuospatial Target Selection

MICHIO IBA AND TOSHIYUKI SAWAGUCHI
Laboratory of Neurobiology, Hokkaido University Graduate School of Medicine, N15W7, Sapporo 060-8638; and Core Research for Evolutional Science and Technology, Japan Science and Technology, Saitama 332-0012, Japan

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INTRODUCTION

Visuospatial target selection, a form of selective attention, is an important cognitive function that allows us to select a relevant target from among distractors, e.g., selecting a familiar face in a crowd. A visual search paradigm has frequently been used to assess this cognitive function in human psychological studies including brain activation studies (Donner et al. 2000; for reviews, see Kinchla 1992; Treisman 1988), lesion studies in monkeys (Latto 1978; Schiller et al. 1987), and single-neuron recording studies in the monkey frontal eye field (FEF) to test saccade target selection (Schall and Hanes 1993; Schall et al. 1995; for a review, see Schall and Thompson 1999). These studies have demonstrated that the posterior parietal cortex and FEF are responsible for the target selection.

Dorsolateral areas of the prefrontal cortex (PFC), rostral to the FEF, might also be involved in target-selection/selective attention processes. The dorsolateral PFC is well known to play a major role in spatial working memory (for reviews, see Funahashi and Kubota 1994; Goldman-Rakic 1995), and this function has been demonstrated to be associated with spatial selective attention in human cognitive psychological studies (for a review, see Awh and Jonides 2001). Indeed, the involvement of the dorsolateral PFC in the attentional mechanism has been extensively demonstrated in brain imaging studies in humans; this area is activated during a shifting attention task (Corbetta et al. 1993), divided attention task (Corbetta et al. 1991) and sustained attention task (Coull et al. 1998). Further, the dorsolateral PFC is activated during the performance of the n-back task, in which the subject must control temporally presented distractors and pick out the target using working memory (Carlson et al. 1998). These findings support the hypothesis that the dorsolateral PFC plays a role in the target-selection/selective attention process by which items are picked out from among distractors. Indeed, Hasegawa et al. (2000) used a visual search paradigm in monkeys and demonstrated that neurons in the dorsolateral PFC are involved in target selection, and this was confirmed by our recent study at the neuronal level (Iba and Sawaguchi 2002). However, there is still very little direct evidence that the PFC is involved in visuospatial target selection, and the functional organization of the PFC to represent this cognitive function is still almost completely unknown.

To address these problems, we combined an oculomotor visual search (OVS) paradigm with local inactivation using muscimol in monkeys. The OVS task employed in this study has some advantages: i.e., precise control over the presentation of the visual stimulus in the visual field, precise control over the subject’s behavior and precise measurement of behavioral parameters such as onset latency, velocity and accuracy of the visual search (Chelazzi et al. 1993, 1998; Hasegawa et al. 2000; Schall and Hanes 1993; Schall et al. 1995). Reversible inactivation with muscimol has been demonstrated to be useful for examining normal functions of the frontal cortex of monkeys (Dias and Segraves 1999; Kurata and Hoffman 1994; Sawaguchi and Iba 2001; Sommer and Tehovnik 1999). In the present study, we found that the injection of muscimol into the dorsolateral PFC produced a specific deficit in the OVS task and the affected target location varied with the injection site but was biased to the contralateral visual field. Preliminary

Address for reprint requests: T. Sawaguchi, Laboratory of Neurobiology, Hokkaido University Graduate School of Medicine, N15W7, Kita-ku, Sapporo 060-8638, Japan (E-mail: toshi-sw@med.hokudai.ac.jp).

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results have been presented in abstract form (Iba and Sawaguchi 1998, 2000; Iba et al. 1998).

METHODS

Subjects

Two rhesus monkeys (Macaca mulatta, male “S”, ~9 kg, and female “N”, ~6 kg) were used. Monkey S had been used for a few years in another study with the oculomotor delayed-response task (Sawaguchi and Iba 2001) before starting the present study. The animals were treated in accordance with the “Guidelines for the Care and Use of Laboratory Animals” of the National Institutes of Health (1985) and the guidelines of our institute. Monkeys were housed in individual cages and supplied with food ad libitum. On training days, their water intake was restricted, and they obtained water as a reward with task performance. They received water ad libitum at least twice a week.

Behavioral procedures

Preliminary surgery was performed under pentobarbital anesthesia (~25mg/kg iv) and aseptic conditions. Two head-holding devices (hollow rods, 8 mm ID) were implanted on anterior and posterior portions of the skull using stainless-steel bolts (3 mm diam) with dental acrylic. To prevent infection, prophylactic antibiotics were applied intramuscularly on the day of surgery and daily for 7 days after surgery.

A few weeks after surgery, each monkey was trained to perform behavioral tasks. During task performance, the monkey sat on a primate chair with its head fixed in a dark room, facing a 21-in CRT monitor (PC-TV471, NEC) positioned ~32 cm from its eyes. The eye position (horizontal and vertical coordinates) was monitored by an infrared eye-camera system (R-21-C-A, RMS, Hiroaki, Japan). The monkeys were trained to perform an OVS task (Fig. 1A). In this task, while the monkey fixated on a central spot (white square, 0.2 × 0.2”) for 2 s, one target stimulus and seven distractors appeared at eight peripheral locations (0, 45, 90, 135, 180, 225, 270, and 315°; eccentricity 15°) as a stimulus array, and the fixation spot disappeared. When the monkey made a saccade to the target location (5° window) within a response period of 0.7 s, it obtained a drop of apple juice or water as a reward. When the first saccade during the response period did not fall within the prescribed window or when the monkey failed to respond within the allotted 0.7 s, the reward was defined as an error and was not rewarded. The target was usually a red cross (“original” target), and most of the data presented in RESULTS are based on this condition. However, in some sessions, we changed both the color and shape of the target; i.e., from a red cross to a green square (“reversed” target). As a “standard” condition, we used distractors that differed from the target only with regard to shape (i.e., red square for the original target but green cross for the reversed target, 1.5 × 1.5°) or color (i.e., green cross for the original target but red square for the reversed target). In addition, to examine the effect of target salience, we introduced a “conjunction” condition, in which two types of distractors, which differed from the target with regard to either shape or color (i.e., a red square and green cross), appeared in the mix. In the conjunction condition, we used only the red cross as a target. We used an OD task as a control task (Fig. 1A, bottom). The OD task was exactly the same as the OVS task except that only a target was presented as a stimulus. At the final stage of training sessions, the monkeys performed these tasks with a correct-response rate of close to 100%.

Injection of muscimol and experimental procedures

After training was completed, a stainless-steel cylinder (20 × 40 mm) was implanted under pentobarbital sodium anesthesia (~25 mg/kg iv) and aseptic conditions. An oval opening (~20 × 40 mm) was made in the skull with a trephine to expose the dura covering the frontal cortex, and the stainless-steel cylinder was positioned over the dorsolateral PFC with dental acrylic. Prophylactic antibiotics were injected intramuscularly on the day of surgery and daily for 7 days after surgery.

In each daily experimental session, muscimol hydrochloride (RBI-Funakoshi, Tokyo, Japan), dissolved in physiological saline (5 mg/1 ml), was injected into the dorsolateral PFC. The dose of muscimol was usually 1 μg (5 μg). Muscimol was administered with a 22-gauge needle attached to a 5-μl syringe. The methods of injection were similar to those in our previous study on the monkey PFC (Sawaguchi and Iba 2001). Briefly, the needle was inserted into the dorsolateral PFC through the exposed dura and lowered to a depth of 3–4 mm from the surface of the dura. This positioning of the needle was achieved with a micromanipulator attached to the cylinder and a plastic grid with numerous holes (0.7 mm ID, 1.5 mm apart). This method allowed us to precisely control the location of the injection and its relocation in subsequent sessions. Furthermore, the needle of the syringe was coated with polyurethane, and multiple neuronal activities at the injection site were recorded using the tip (resistance, 0.2–0.5 MΩ). Thus we were able to confirm that the tip of the needle was located within the gray matter of the cortex.

Each experimental session began with six predrug blocks of OVS and OD trials (Fig. 1B). Each block was associated with either the OVS or OD task and lasted for 10 min. OVS blocks were offered twice as often as OD blocks because we focused on the OVS task and did not consider deficits occurred for the OD task (see RESULTS). Testing was then interrupted while muscimol was injected for 2–3 min. As in the predrug trials, postdrug trials were segmented into blocks of OVS and OD trials that lasted for 10 min, and again there were twice as many OVS blocks as OD blocks. Postdrug trials lasted for ≥1.5 h. Only one injection was made in each daily experimental session.

Data analysis

The effects of muscimol injection were assessed in two ways: by comparing pre- and postdrug performance and by comparing postdrug OVS trials to postdrug OD trials. We analyzed the following data: the two-dimensional trajectory of eye movement, the discrepancy between the endpoint of the first saccade and the target location, the onset latency, and the search time. The onset latency was defined as the time from the appearance of the stimulus to the beginning of the saccadic eye movement, and the search time was defined as the time from the appearance of the stimulus array to the end of the search during the response period. Each parametric measurement (discrepancy, onset latency, and search time) in the predrug trials was pooled as an OD block for comparison with the measurement in each postdrug block. However, because the effect of muscimol usually peaked at ~40–60 min after injection (see RESULTS), generally only the data from 30 to 60 min after muscimol injection (i.e., “postdrug” period) are given in RESULTS, and Mann-Whitney’s U test was used for this analysis. Further, because no significant differences in the behavioral parameters were observed between the shape and color conditions in the standard OVS task during the predrug period (for a typical experimental session, onset latency: 159 ± 39 ms for shape and 154 ± 24 ms for color; discrepancy: 3.6 ± 4.3° for shape and 3.6 ± 4.6° for color; search time: 204 ± 42 ms for shape and 198 ± 24 ms for color), we pooled these data to reflect the “standard” condition in all analyses except the brief analysis to examine possible difference in the effect of muscimol injection between these two conditions (see Independence of target physical properties).

ICMS and histology

To make injections in the dorsolateral PFC outside the FEF, we applied intracortical microstimulation (ICMS, a train of 22 cathodal
pulses of 300 μs duration at 333 Hz, ≤100 μA) at several sites in the lateral frontal cortex before the experimental session while the monkey was fixating on the fixation point. When saccadic eye movement was induced by ICMS, the sites were considered to be in the FEF (Bruce and Goldberg 1985; Bruce et al. 1985). We did not inject muscimol into the FEF, and all injection sites were outside the FEF (see Fig. 2).

After the experiments were completed, the monkeys were deeply anesthetized with an overdose of pentobarbital sodium and perfused with physiological saline followed by formalin. After the brain was removed, it was photographed and the injection sites were reconstructed based on the coordinates of the grid used for injection. Figure 2 shows the injection sites on the surface of the left and right hemispheres of monkey N and the left hemisphere of monkey S. The injection sites were scattered throughout the periaqueduct region and the caudal half of the periprincipal sulcal region; i.e., areas 8, 9, and 46 (mainly area 46). Because all of the injections were made at a depth of 3–4 mm from the surface of the dura, they were distributed in the cortex outside the sulcus.

RESULTS

General

During performance of the OD and “standard” OVS tasks (with the “original” target), muscimol (5 μg/μl, 1 μl) was injected into a total of 157 sites in the dorsolateral PFC of the two monkeys (both hemispheres for monkey N and the left hemisphere for monkey S). Of these 157 sites, muscimol induced a specific deficit in the standard OVS task, but not in the OD task, at a total of 77 sites; the remaining sites were not associated with any significant effects in either the OVS or OD task (Fig. 2). For each effective site, the error was characterized by the disordering of eye traces for some (mostly a few) particular target locations and by an increase in the discrepancy. Further, in most cases, these errors were accompanied by a significant prolongation of the search time of saccades. In some cases (n = 10), saline was injected into approximately

![Diagram](http://jn.physiology.org/)

**FIG. 1.** A: diagrammatic representation of an oculomotor visual search (OVS) task and an oculomotor detection (OD) task trial event. After the monkey fixated on a central fixation spot for 2 s, a stimulus array that contained 1 target and 7 distractors appeared over 8 locations. The monkey then made a saccade to the target location within 700 ms. The OVS task consisted of the “standard” condition in which the distractors differed from the target with regard to color or shape and a “conjunction” condition in which 2 types of distractors, which differed from the target with regard to either color or shape, appeared. In the standard OVS task, the target was usually a red cross (“original” target), but sometimes it was changed to a green square (“reversed” target). The OD task was exactly the same as the OVS task except that the stimulus array contained only a target. B: schematic diagram of the experimental timetable. The OVS and OD tasks were divided into 10-min blocks. There were twice as many OVS blocks as OD blocks.
Effects of muscimol on the OVS and OD tasks

Figure 3 shows an example of the effect of muscimol injection on the standard OVS task and illustrates eye traces (horizontal and vertical components), two-dimensional trajectories of the saccade for each of eight target locations, separately for the pre- and postdrug periods. In this case, muscimol was injected into the right PFC (Fig. 3, inset). As shown in Fig. 3, OVS task performance was impaired by muscimol injection, and this impairment was mainly restricted to the upper-left (135°) and upper (90°) target locations: most evident for 135°. Significant numbers of saccades to these locations were disordered after muscimol injection, whereas only a few saccades to other directions were affected. The frequency of errors in postdrug trials was highest for the 135° direction (12/28, 43%) then the 90° direction (9/24, 38%); both values were significantly higher (0/28 for 135° and 0/26 for 90°) than those in predrug trials (Fisher’s test, \( \chi^2 = 12.83, df = 1, P < 0.001 \) for 135°; \( \chi^2 = 9.49, P < 0.001 \) for 90°). The error frequency for other directions in the postdrug trials was much less and not significant compared with that in the predrug trials: 4% (1/26 vs. 0/31; \( \chi^2 = 0.008, P = 0.46, \) NS) for 0°, 9% (2/22 vs. 0/28; \( \chi^2 = 0.81, P = 0.19, \) NS) for 45°, 0% (0/21 vs. 0/28; NS) for 180°, 0% (0/27 vs. 0/32; NS) for 225°, 5% (1/19 vs. 0/28; \( \chi^2 = 0.039, P = 0.40, \) NS) for 270°, and 5% (1/21 vs. 0/27; \( \chi^2 = 0.016, P = 0.44, \) NS) for 315°. Figure 4 shows the data for the OD task during the same experimental session as in Fig. 3. As shown, muscimol induced no deficits in the OD task; eye movements were normal after injection for all target locations including the upper-left and upper target directions. The impairments in the OVS task were also characterized by changes in quantitative measurements of saccades (Table 1). Discrepancies were significantly increased for both the 135° and 90° directions in the OVS task, and the search time also significantly prolonged for these directions. No significant differences were found between pre- and postdrug for the onset latency of the OVS task. Any measurements for the OD task did not significantly change after the injection. The time course of changes in discrepancy is shown in Fig. 5A (for the 135° location). In this figure, to examine overall changes in discrepancy, correct and error trials were pooled. As shown, the increase in discrepancy in the OVS task began within 20 min after injection and reached a peak at ~60 min after injection. This increase persisted during the postdrug period. No significant changes in discrepancy were seen in the OD task throughout this experimental session.

To examine whether these changes in saccade parameters in the OVS task were due to a deficit in eye movement itself, we examined eye velocity. In Fig. 5B, the mean velocity of the first saccade for the most impaired direction (135°) in the OVS task is plotted against its amplitude for predrug trials (●), postdrug correct trials (○) and postdrug error trials (●). As shown, the velocity in the OVS task was similar among these trials.

To further examine the nature of the deficit, the endpoint of the saccade was examined, and the data are shown in Fig. 6. In Fig. 6, data for predrug trials, postdrug correct trials, and postdrug error trials for the most strongly impaired target location (135°) are shown separately. As shown in Fig. 6A, the endpoints of the first saccade during the predrug period fell within the allotted 5° window (discrepancy, mean ± SD, 1.5 ± 1.2°, \( n = 30 \)). In the postdrug period, the first saccades in correct trials were directed toward the target as in the predrug trials (1.8 ± 1.4°, \( n = 16 \); Fig. 6B), whereas those in error trials were always misdirected (28.2 ± 6.9°, \( n = 12 \); Fig. 6C). These misdirected saccades appeared to be directed toward distractors rather than to random locations. In most error trials (n = 10), additional second saccades were observed during the response period (see Fig. 3), and we plotted the endpoint of the second saccade during the response period for these trials (Fig. 6D). As shown, endpoint of these second saccades in the error trials frequently fell around the target location (n = 8), although they were less accurate (4.8 ± 3.8°).

Thus the deficit in the OVS task was characterized by disorder of the first saccades for a few particular target locations, which appeared to be directed toward distractors and were associated with a prolongation of the search time.

Summary of deficits

Muscimol injection produced similar effects for all of the other effective sites (n = 77). Only a couple of target locations were impaired in most cases (1 direction, n = 10; 2 directions,
n = 48), although some sites were associated with three (n = 18) or four (n = 1) target directions. When more than one target location was impaired, the affected location was always nearby, as shown in the example in the preceding text. For all of these effective sites, we calculated the percent changes, compared with predrug trials, in discrepancy (of the 1st saccade) and search time for the most impaired direction. The discrepancy was significantly increased for all of the effective sites (n = 77, mean ± SD, 300 ± 137%). The search time was also significantly increased for most sites (n = 59, 124 ± 18%), although the onset latency did not change for the most sites (n = 58, 108 ± 9%).

Bias of the impaired direction to the contralateral visual field

The target location affected by muscimol in the OVS task was biased to the visual field contralateral to the injection sites. Figure 7 shows the relationship between the injection site and the impaired target direction in the OVS task for selected sites. As shown, injection into the left hemisphere usually induced disordering of eye movement in the right visual field (Fig. 7, A and C), and injection into the right hemisphere was usually associated with impairment of the left visual field (Fig. 7B). Some sites were associated with vertical (up or down) target locations. To examine the distribution of the impaired direction statistically, we calculated the target location with the most prominent impairment. The impaired direction was not distributed evenly across the eight directions (right, n = 4; upper-right, n = 8; upper, n = 17; upper-left, n = 20; left, n = 12; lower-left, n = 4; lower, n = 9; lower-right, n = 3; 1-sample χ² test, χ² = 28.9, df = 7, P < 0.01), and these were biased to the visual field contralateral to the injection site (contralateral, n = 36 vs. ipsilateral, n = 15; 1-sample χ² test, χ² = 5.14, df = 1, P < 0.05). Impairment in the vertical direction, and particularly the upper direction, was also frequently found.

To examine the relationship between the injection sites and impaired directions in detail, we plotted the most impaired direction for each site on the surface of the PFC (Fig. 8). For monkey N, there appears to be a gross topographical relationship between them with presumable horizontal and vertical meridians, although it was not so clear-cut. For monkey S,
which had been used for a few years in our previous study to reveal the “memory-map” with the oculomotor delayed-response paradigm (Sawaguchi and Iba 2001), there was not such a clear relationship.

Effect of a higher dose of muscimol

In some cases (n = 5), we injected a higher dose of muscimol (10 μg, 2 μl) near the same site that was examined with a “standard” dose (5 μg, 1 μl) in a different daily session. Figure 9 shows an example of the data. In this case, injection of a standard dose of muscimol into the left hemisphere of monkey N (Fig. 9, inset) induced a deficit for the right direction (0°). The saccades toward this target were disordered (Fig. 9A), and the discrepancy was significantly increased (1.8 ± 0.7°, n = 43, predrug; 5.6 ± 5.1°, n = 36, postdrug, P < 0.01). Saccades to other directions were not affected with a standard dose of muscimol. When a higher dose of muscimol was injected into approximately the same site in a different daily session, impairment was seen for both the same right location and additional nearby target locations (Fig. 9B). The discrepancy was significantly increased in the right (0°) direction (2.3 ± 0.7°, n = 26, predrug; 5.4 ± 4.4°, n = 26, postdrug, P < 0.01), the upper-right (45°) direction (1.7 ± 0.6, n = 19, predrug; 10.9 ±

![Image](53x324)

FIG. 4. The effect of muscimol injection on the OD task. The data are for the same session as in Fig. 3. Note that saccades to the upper-left and upper directions, which were associated with impairment in the OVS task (Fig. 3), were not affected by muscimol. Abbreviations are the same as in Fig. 3.

TABLE 1. Quantitative measurements of saccadic eye movements in a typical session

<table>
<thead>
<tr>
<th>OVS (135°)</th>
<th>OVS (90°)</th>
<th>OD (135°)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discrepancy, °</strong></td>
<td><strong>Search time, ms</strong></td>
<td><strong>Onset latency, ms</strong></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>1.5 ± 1.2</td>
<td>13.6 ± 14.2</td>
<td><strong>2.4 ± 1.9</strong></td>
</tr>
<tr>
<td>227 ± 36</td>
<td>355 ± 176</td>
<td><strong>236 ± 34</strong></td>
</tr>
<tr>
<td>191 ± 35</td>
<td>191 ± 38</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are from the same session shown in Figs. 3 and 4. Values are means ± SD. Numbers of movements for oculomotor visual search (OVS) in the 135 and 90° directions are 30 and 28 and 25 and 22 in the pre- and post drug conditions, respectively. The number of movements for oculomotor detection is 20 and 21 for pre- and postdrug conditions, respectively. * P < 0.05; ** P < 0.01.
Thus the deficits in the OVS task appeared to be independent of the physical properties of the target/distractors.

**Effects of “pop-out” and “non-pop-out”**

To investigate target salience, i.e., so-called “pop-out”, we introduced a “conjunction” condition (Fig. 1A) in addition to the standard condition (see METHODS). The standard condition was considered the pop-out condition and the conjunction condition was considered the non-pop-out condition. Before the examination of muscimol injection, we examined the onset latency of saccadic eye movement from the appearance of the stimulus array and found that it was significantly longer for the conjunction condition than for the standard condition for each subject (Table 4).

Of the total of 157 sites for which both standard and conjunction conditions were examined, muscimol injection induced significant effects at 77 sites. Although a few sites (5/77, 6%) were associated with deficits only in the conjunction OVS task, muscimol generally induced deficits for both the standard and conjunction conditions (72/77 sites, 94%), and the affected target location was always the same in these conditions. An example is shown in Fig. 11, which shows two-dimensional trajectories of eye movements to the affected target location. As shown, eye trajectories were largely disordered for both the standard (Fig. 11A, left) and conjunction (Fig. 11A, right) conditions of the OVS task.

The quantitative data for discrepancy and search time before

Independence of target physical properties

To examine whether the deficits depended on the physical properties of the target, we changed both the shape and color of the target in some sessions (n = 15), i.e., from a cross to a square. Exactly the same results as with the original target were obtained with this “reversed” target, and Fig. 10 shows typical data. In this case, muscimol was injected into the right hemisphere of monkey N (inset) and the eye traces toward the upper-left target location (i.e., 135°) were disordered with regard to both shape and color conditions for the original target (Fig. 10A). When the target was changed to a square, a similar distortion of eye traces was observed (Fig. 10B). The parameters of saccadic eye movements for this target location also showed similar changes with the original and reversed targets (Table 3); both discrepancy and search time were significantly increased after muscimol injection for all of these conditions.

![Image](https://example.com/image.png)

**FIG. 5.** A: time course of discrepancy for the OD and OVS tasks. Data are for the upper-left direction (135°) in Fig. 3. ○, data for the OVS task; ●, data for the OD task, means ± SE; **, significant increase compared with predrug trials, P < 0.01. B: relationship between amplitude and mean velocity of the 1st saccade during the response period in the OVS task. Data are for the upper-left direction in the case shown in Fig. 3. *, data before injection; ○, data for postdrug correct trials; ●, data for postdrug error trials. The relationship between amplitude and velocity was similar between predrug trials and postdrug correct and error trials.

12.3°, n = 28, postdrug, P < 0.01), and the upper (90°) direction (0.9 ± 0.7°, n = 23 predrug; 14.0 ± 13.4°, n = 26 postdrug, P < 0.01). Similar results were observed at four of the five injection sites examined (Table 2); i.e., a higher dose of muscimol usually induced deficits in saccades to the target location affected by the standard dose as well as additional surrounding/nearby target locations.

![Image](https://example.com/image.png)

**FIG. 6.** Endpoint of the saccades in the OVS task. Data for the most strongly impaired direction (135°) for the case in Fig. 3 are shown. Endpoints of the 1st saccade in the predrug trials (A), postdrug correct trials (B), and postdrug error trials (C) and the 2nd saccade in postdrug error trials (D) are shown separately. Central square indicates the fixation spot (0.2 × 0.2°), peripheral squares are distractors (1.5 × 1.5°) and the upper-left cross indicates the target (1.5 × 1.5°).
and after muscimol injection in the preceding case are shown in Fig. 11B. The discrepancies for the OD task and the OVS task with each condition for the affected target location (90°) in the OVS task are illustrated separately for the predrug and postdrug periods. As shown, the discrepancy was significantly increased for both the standard (predrug, 2.1 ± 1.5°; postdrug, 10.0 ± 12.8°, n = 37) and conjunction (predrug, 1.5 ± 0.8°, n = 13; postdrug, 9.7 ± 12.5°, n = 25) conditions (U test, \( P < 0.01 \) for each), and the increased discrepancy was not significantly different between these conditions (\( P > 0.05 \), NS). In contrast to the OVS task, discrepancy in the OD task did not change after injection (predrug, 2.3 ± 3.2°; postdrug, 2.2 ± 3.8°; \( P > 0.05 \), NS). Thus the local injection of muscimol affected both the standard and conjunction conditions to a similar degree. Indeed, for effective sites with deficits in both conditions (\( n = 72 \)), the percent increase in discrepancy for the conjunction OVS task (for the most impaired direction) was significantly and positively correlated with that for the standard OVS task (\( r = 0.80, t = 11.1, df = 70, P < 0.001 \)), as shown in Fig. 12.

**DISCUSSION**

In the present study, we demonstrated that the local injection of muscimol into the dorsolateral PFC induced specific deficits in the OVS task but not in the OD task. The impaired target directions were biased to the visual field contralateral to the injection sites. Furthermore, the OVS deficit was not associated with target saliency; i.e., both the standard (pop-out) and conjunction (non-pop-out) conditions were similarly affected by muscimol injection. These findings suggest that the dorsolateral PFC is involved in target selection with pop-out and non-pop-out conditions.

**Involvement of the PFC in target selection/selective attention**

The local injection of muscimol induced a disturbance of saccadic eye movement for some (mostly a few) particular target locations in the OVS task; i.e., the subject frequently made a misdirected first saccade, which appeared to be directed toward a nontarget stimulus (i.e., distractor) rather than the target, and the discrepancy between the endpoint of the first saccade and the target location was significantly increased. The frequency of errors was also significantly increased after injection for some particular target locations, which were characterized by the misdirection of first saccade rather than under- or overshoot toward the correct target location (see Fig. 6C). Accompanying this impairment, search time was significantly prolonged in most cases. In contrast to the OVS task, performance in the OD task, in which only the target appeared, was not affected at all, indicating that the deficits in the OVS task do not involve impairments in simple perception or saccade-generation/control mechanisms. While the OVS task requires selection of the relevant target among distractors, the OD task does not. Indeed, the onset latency of saccadic eye movements was significantly longer for the OVS task than the OD task. Therefore the OVS deficit is likely to be associated with a target-selection process by which the target is picked out from among distractors.

The deficits in the OVS task appeared to be independent of the physical properties of the target and/or distractors; every color- and shape- “original” and color- and shape—“reversed” condition was impaired; this also supports the notion that the OVS deficit was associated with target selection rather than simple visual perception of the stimulus array/target. Further, the subject often made additional second saccades in postdrug error trials, and their endpoints sometimes fell around the target, indicating that the
subject sometimes could find the target after shifting its gaze. Therefore it is unlikely that the subject forgot the target itself. Impaired memory regarding the target features can be excluded as a possible cause of the deficit in the OVS task; again, the results suggest that the OVS deficit is associated with target selection. Furthermore, this finding regarding the additional second saccade is consistent with the finding that misdirected first saccades in the postdrug error trials were mostly limited to a few specific target locations; also suggests that the deficits in the OVS task are associated with relative (retinotopic), rather than absolute (craniotopic), spatial coordinates. A similar nature of relative coordination has been observed in deficits in memory-guided saccades induced by the local injection of muscimol into the dorsolateral PFC of monkeys (Sawaguchi and Iba 1998). In addition, the target location affected was biased to the contralateral visual field. Similar bias has also been demonstrated at the deficits in memory-guided saccade in previous study with muscimol injection (Sawaguchi and Iba 2001) or focal lesions (Funahashi et al. 1993).

As has been demonstrated previously, local injections of muscimol induced inactivation of the injected site in the frontal cortex of monkeys (Dias and Segraves 1999; Kurata and Hoffman 1994; Sawaguchi and Iba 2001; Sommer and Tehovnik 1999). Because the intracerebral injection of a few microliters of muscimol suppresses the activity of neurons within a few millimeters of the injection site for several hours (cf. Kurata and Hoffman 1994; Martin 1991), the present method is useful for mapping the normal function of a small region of the cerebral cortex. One microliter of solution injected into cerebral tissue has been demonstrated to spread ~1 mm in diameter (Myers 1966). Furthermore, the effect of muscimol was dose-dependent; a higher dose of muscimol (10 μg, 2 μl) had a larger effect. We assume that this was due to the greater spread of muscimol because additional nearby target locations were usually impaired by the high dose. In addition, although the error frequency for some particular target locations in the OVS task was significantly higher in postdrug period than in the predrug period, the subject sometimes made correct responses for those locations in postdrug trials. This would be due to the fact that only 1 μl of solution was usually injected and neuronal activity within a limited region was suppressed to affect the behavioral response. The small amount of solution would also contribute to the spatial limitation of affected target locations in each injection; neuronal activity within a limited, particular region of the dorsolateral PFC should be responsible for correct saccades toward some particular target locations in the OVS task.

**FIG. 8.** Relationship between the injection site and impaired direction, illustrated on the surfaces of 3 hemispheres of 2 monkeys. Each color indicates a direction (red, right; orange, upper-right; yellow, upper; green, upper-left; blue, left; cyan, lower-left; purple, lower; pink, lower-right). “H” and “V” are putative horizontal and vertical meridians, respectively. L, left hemisphere; R, right hemisphere.
Thus the present findings indicate that local inactivation at a particular site in the dorsolateral PFC makes it difficult for the subject to find/select the target in some (mostly a few) particular locations among distractors, mainly for the contralateral visual field, and this deficit was not due to impairment of the saccade-generation/control mechanism itself or of simple perception/memory for the target. A specific site in the dorsolateral PFC is likely to be involved in target selection for a particular visuospatial, probably retinotopic, coordinate. As is well known, the dorsolateral PFC is involved in working memory tasks like n-back tasks, which require the subject to pick out items from short-term memory; i.e., internal world (Carlson et al. 1998; Cohen et al. 1997). The present study suggests that the dorsolateral PFC is involved in the process by which items are picked out from distractors, which are present

### TABLE 2. Impaired directions with standard and higher doses of muscimol

<table>
<thead>
<tr>
<th>Injection No.</th>
<th>Injected Hemisphere</th>
<th>Standard Dose (Impaired Direction), °</th>
<th>Higher Dose (Impaired Direction), °</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Left</td>
<td>0</td>
<td>0, 45, 90</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>135</td>
<td>90, 135</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>90</td>
<td>45, 90, 135</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>225</td>
<td>180, 225, 270</td>
</tr>
<tr>
<td>5</td>
<td>Left</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* The injection site shown in Fig. 13.

**FIG. 9.** Dose-dependent effect of muscimol on the OVS task. Standard (5 μg, 1 μl) and higher (10 μg, 2 μl) doses of muscimol were injected into the same site in different daily sessions (inset). A: effect of a standard dose of muscimol on OVS task performance. Two-dimensional trajectories of saccades are shown separately for predrug (Pre) and postdrug (Post) periods at each target location. The central square indicates the central fixation spot and the closed circles at the 8 peripheral locations are target locations. B: effect of a higher dose of muscimol on OVS task performance.
in the external world. Therefore it is likely that the dorsolateral PFC is involved in the selection of items from both the internal and external worlds.

The visual search paradigm used in this study required the subjects to select a target from among distractors, and some attentional mechanisms should be involved in this process. Indeed, the visual search paradigm is known to be suitable for assessing visual selective attention (for reviews, see Egeth and Yantis 1997; Treisman 1988). Further, previous human brain-imaging studies have demonstrated that the PFC is involved in attentional mechanisms (Corbetta et al. 1991, 1993; Coull et al. 1998). In addition, the dorsolateral PFC plays a major role in spatial working memory (for reviews, see Funahashi and Kubota 1994; Goldman-Rakic 1995), and this cognitive function

| TABLE 3. Saccade parameters for the OVS task using the “original” and “reversed” targets in a typical experimental session |
| --- | --- | --- | --- |
| Discrepancy, ° | Search Time, ms |
| | Pre | Post | Pre | Post |
| Original Shape | 2.15 ± 0.57 | 10.50 ± 12.40 | ** | 197 ± 20 | 357 ± 86 |
| n | 10 | 14 | ** | 191 ± 11 | 388 ± 186 |
| Color | 1.04 ± 0.41 | 8.48 ± 11.47 | ** | 222 ± 25 | 330 ± 129 |
| n | 13 | 18 | ** | 301 ± 128 | 397 ± 97 |
| Reversed Shape | 10.20 ± 12.59 | 18.80 ± 16.68 | ** | 36 ± 129 | 330 ± 186 |
| n | 26 | 24 | ** | 301 ± 128 | 397 ± 97 |
| Color | 6.58 ± 5.37 | 10.1 ± 2.60 | ** | 36 ± 129 | 330 ± 186 |
| n | 24 | 25 | ** | 301 ± 128 | 397 ± 97 |

Values are means ± SD. ** P < 0.01.
has been demonstrated to be associated with spatial selective attention (Awh et al. 2000; for a review, see Awh and Jonides 2001). The present findings are consistent with these previous findings, suggesting that the dorsolateral PFC is involved in visuospatial selective attention, and “attentional scotoma” mainly for the contralateral visual field might occur following local inactivation in the dorsolateral PFC. However, because we did not change the number of distractors or use a large variety of target/distractors, further studies are required to clarify this problem.

FIG. 11. Effect of muscimol on the OVS task with the standard and conjunction conditions. A: 2-dimensional trajectories of eye movement toward the affected target location (90°) are shown for the standard and conjunction OVS tasks. B: effect of muscimol injection on discrepancy (mean ± SE). Pre, predrug period; Post, postrdrug period. *, P < 0.05; **, P < 0.01. Inset: injection site (monkey N, right PFC).

FIG. 12. Correlation between the percent increase in discrepancy in the standard and conjunction OVS tasks. The percent increase in discrepancy in the conjunction OVS task is plotted against that in the standard OVS task for the most strongly impaired direction for each effective site associated with deficits in both tasks.

CONTRIBUTION OF THE PFC TO "PASSIVE" AND "ACTIVE" TARGET SELECTION

The injection of muscimol induced deficits in both the “standard” and “conjunction” conditions, which are considered pop-out and non-pop-out conditions (Hikosaka et al. 1993; Treisman and Gelade 1980), or efficient (effortless) and inefficient (effortful) search (Leone et al. 2000; Schall and Thompson 1999), respectively. The characteristic degree of OVS deficits was similar for almost all of the cases for which both conditions were examined. Pop-out is considered to be a feature search for space and/or object, whereas non-pop-out is considered to be a conjunction search for feature integration (Treisman and Gelade 1980). Further, the pop-out condition has been suggested to be controlled by a bottom-up (“passive”) -driven attention system, whereas the non-pop-out condition is controlled by a top-down (”active”) -driven attention system (Hikosaka et al. 1993). Therefore the dorsolateral PFC may be involved in both bottom-up (passive)- and top-down (active)-driven target-selection systems; this area may play a role in specifying the target by controlling various interfering information to enable an appropriate goal-directed behavior in a given situation.

TARGET-SELECTION NETWORKS AND THE ROLE OF THE DORSOLATERAL PFC

The dorsolateral PFC appears to be involved in both active and passive target-selection processes as described in the preceding text, and we suggest that this area is involved in selective attention processes associated with target selection. However, we do not conclude that this is the only area that is important for target selection/selective attention. Previous studies have demonstrated that the posterior parietal cortex (Bushnell et al. 1981; Corbetta et al. 1991, 1993, 1995; Steinmetz et al. 1994) and frontal eye field (FEF) (Donner et al. 2000; Schall et al. 1995) are also involved in target selection. To attend to a relevant visual stimulus in clutter, cortical networks may be activated to perceive the stimulus and act accordingly. The dorsolateral PFC has strong neuronal connections with the posterior parietal cortex (Petrides and Pandya 1984) and FEF (Arikuni et al. 1988; Watanabe-Sawaguchi et al. 1991). The dorsolateral PFC may work together with these
other brain regions during target-selection processes; i.e., these areas may form target-selection networks/systems to work together.

However, the dorsolateral PFC appears to have a unique position because it has been suggested that this area is hierarchically the highest among neocortical areas (Flemmle and Van Essen 1991) and links sensory input with motor output (Fuster 1998). Therefore it is likely that the dorsolateral PFC links target-selection processes with motor output/execution and thus plays a role in guiding goal-directed behavior (i.e., a role of motor-programming/planning) by using target-selection processes; i.e., by controlling various interference information.

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