Inactivation of Parietal and Prefrontal Cortex Reveals Interdependence of Neural Activity During Memory-Guided Saccades

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Chafee, Matthew V. and Patricia S. Goldman-Rakic. Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J. Neurophysiol.* 83: 1550–1566, 2000. Dorsolateral prefrontal and posterior parietal cortex share reciprocal projections. They also share nearly identical patterns of neuronal activation during performance of memory-guided saccades. To test the hypothesis that the reciprocal projections between parietal and prefrontal neurons may entrain their parallel activation, the present experiments have combined cortical cooling in one cortical area with single-unit recording in the other to more precisely determine the physiological interactions between the two during working memory performance. The activity of 105 cortical neurons during the performance of an oculomotor delayed response (ODR) task (43 parietal neurons during prefrontal cooling, 62 prefrontal neurons during parietal cooling) was compared across two blocks of trials collected while the distant cortical area either was maintained at normal body temperature or cooled. The mean firing rates of 71% of the prefrontal neurons during ODR performance changed significantly when parietal cortex was cooled. Prefrontal neurons the activity of which was modulated during the cue, delay, or saccade periods of the task were equally vulnerable to parietal inactivation. Further, both lower and higher firing rates relative to the precool period were seen with comparable frequency. Similar results were obtained from the converse experiment, in which the mean firing rates of 76% of the parietal neurons were significantly different while prefrontal cortex was cooled, specifically in those task epochs when the activity of each neuron was modulated during ODR performance. These effects again were seen equally in all epochs of the ODR task in the form of augmented or suppressed activity. Significant effects on the latency of neuronal activation during cue and saccade periods of the task were absent irrespective of the area cooled. Cooling was associated in some cases with a shift in the best direction of Gaussian tuning functions fit to neuronal activity, and these shifts were on average larger during parietal than prefrontal cooling. In view of the parallel between the similarity in activity patterns previously reported and the largely symmetrical cooling effects presently obtained, the data suggest that prefrontal and parietal neurons achieve matched activation during ODR performance through a symmetrical exchange of neuronal signals between them; in both cortical areas, neurons activated during the cue, delay, and also saccade epochs of the ODR task participate in reciprocal neurotransmission; and the output of each cortical area produces a mixture of excitatory and inhibitory drives within its target.

INTRODUCTION

Our recent interest (Chafee and Goldman-Rakic 1998) has been a comparison of patterns of activity evoked in parietal area 7ip and prefrontal area 8a neurons during an oculomotor delayed-response (ODR) task. The motivating hypothesis has been that neurons in parietal and prefrontal cortex interact during the ODR task, and as such this task may serve as a model for parietal-prefrontal interaction whenever a spatial datum derived from visual input is loaded into working memory. The interaction between prefrontal and posterior parietal neurons is predictable on several grounds. First, numerous investigators have described the large and reciprocal corticocortical projection extending between prefrontal and posterior parietal cortex (Andersen et al. 1985a, 1990a; Barbas 1988; Barbas and Mesulam 1981; Cavada and Goldman-Rakic 1989; Petrides and Pandya 1984; Schall et al. 1995; Schwartz and Goldman-Rakic 1984; Stanton et al. 1995). Second, their output is tightly linked, efferent projections from the two cortical areas travel in parallel to target the same $\geq$15 cortical and subcortical targets, where they terminate either in interdigitating columns or alternating cortical lamina (Selemon and Goldman-Rakic 1988). Finally, distinct but related functions have been ascribed to both regions. Posterior parietal cortex is believed to combine both retinal and extraretinal signals to build a three-dimensional representation of visual space (Andersen and Mountcastle 1983; Andersen et al. 1985b, 1987, 1990b; Brotchie et al. 1995). In addition, parietal cortex is believed to contribute to motor command signals moving the eyes (Andersen et al. 1987; Barash et al. 1991a,b; Gnadt and Mays 1995; Mazzoni et al. 1996; Mountcastle et al. 1975) and hands (Johnson et al. 1996; Mountcastle et al. 1975; Snyder et al. 1997, 1998) to points defined in this space. The dorsolateral prefrontal cortex also has been associated with the spatial guidance of both eye and arm (Butters and Pandya 1969; Niki 1974a,b; Niki and Watanabe 1976) movements, but has been associated particularly with spatial working memory (Goldman-Rakic 1987, 1988, 1995); in this context, the internal representation of a spatial coordinate to direct these movements when none is specified by a currently available stimulus (Funahashi et al. 1989, 1993; Sawaguchi and Goldman-Rakic 1991 particularly). It would be advantageous to know what principles might govern the physiological interaction between parietal and prefrontal neurons suggested by these facts, in that these subsequently may indicate how distributed representations in the visuospatial domain emerge and are stored by the concerted action of groups of interacting cortical areas.

Interestingly, it does not appear to be the case that parietal and prefrontal neurons exhibit categorically different patterns of activity during such a process (Chafee and Goldman-Rakic 1998; Quintana and Fuster 1992) in spite of the prediction to the contrary that lesion studies would seem to support. For

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example, the effects of lesions of parietal and prefrontal cortex have been considered to exemplify a "double dissociation" because damage to parietal cortex rarely has been associated with memory problems (Butters and Pandya 1969; Jacobsen 1936; Pu et al. 1993; although see Quintana and Fuster 1993), and perceptual difficulties are uncommon after prefrontal lesions (Goldman et al. 1971; Jacobsen 1936; Pohl 1973; Ungerleider and Brody 1977). However, a direct comparison of activity within neuronal populations in parietal area 7ip and prefrontal area 8a has indicated that the two cortical areas contain the same heterogeneity of defined neuronal types while monkeys performed the ODR task (Chafee and Goldman-Rakic 1998). The patterns of activation characteristic of each of these subpopulations were matched to a greater extent (Chafee and Goldman-Rakic 1998) than could be gleaned from independent studies of the two populations using similar, but not identical, tasks (Andersen et al. 1990b; Bruce and Goldberg 1985; Funahashi et al. 1989–1991; Gnadt and Andersen 1988). This would suggest that whatever physiological principles drive the interaction between neurons in these two cortical areas, the net result appears to be that changes in neuronal activity within them are virtually coincident during at least some behaviors. Contributions made by either prefrontal or parietal neurons to their aggregate activity might only become evident when the normally integrated system is perturbed. Thus a more direct examination of physiological interaction between prefrontal and parietal cortices at a neuronal level seems warranted to address the contribution made to the activation of neurons in each cortical area by the operation of the network in which both are embedded.

Toward this end, single-unit recording and reversible cryogenic inactivation are combined in the present experiments to determine whether changes in the activity of parietal neurons during ODR performance depend on the normal function of prefrontal cortex and vice versa. This approach has been adopted previously in two studies using cryoinactivation to address interactions between prefrontal and parietal (Quintana et al. 1989) and inferotemporal (Fuster et al. 1985) cortex during the performance of a task in which the color rather than the spatial location of a cue stimulus was stored in working memory. The present experiments sought to extend these data by addressing the operation of the parietal-prefrontal system when the visuospatial dimensions of a stimulus were critical to task performance. Parietal and prefrontal neurons are nearly identical in their activation during ODR performance (Chafee and Goldman-Rakic 1998). It remains a possibility that the activities of these distant neuronal populations are brought into register by the operation of corticocortical projections between them as a result of the exchange of neuronal signals throughout distributed systems in the cortex (Mountcastle 1978, 1995, 1998). The present experiments are intended to reveal whether such an exchange between parietal and prefrontal cortex might take place and what patterns of activity it might include during ODR performance.

METHODS

The neurons presently described represent a subset of those the activity of which during the ODR task was the subject of a previous report: the effects of cortical cooling on the activation of these neurons are addressed here. Additional detail regarding the surgical and single-unit recording methods can be found in that earlier study (Chafee and Goldman-Rakic 1998). All procedures conformed to the Guiding Principles for Research Involving Animals and Human Beings of the American Physiological Society. Briefly, using aseptic surgical procedures, two male rhesus macaque monkeys (7 and 9 kg) were implanted (in stages) with a head-restraint device, a scleral search coil (Judge et al. 1980), and recording chambers positioned over parietal and prefrontal cortex in the right cerebral hemisphere. A Peltier cryothermode (see following text) or a microelectrode (glass-coated Elgiloy or varnish-coated tungsten: FHC, part 120-110-1, Brunswick, ME) could be introduced into either recording chamber to cool the underlying cortex or to record single-unit activity from within it. The microelectrode signal was amplified (BAK MDA-4, BAK Electronics, Germantown, MD) and filtered (Khrone-Hite 3700, Khrone-Hite, Avon, MA) before being input to a PC-based waveform discrimination system (8701 waveform discriminator, Signal Processing Systems, Prospect, South Australia). A PDP 11/73 computer ran a program (generously made available by C. J. Bruce) controlling the experiment. This program generated visual stimuli via a Graph-11 graphics card (Pacific Binary Systems) that were presented on a video monitor (NEC DM3000P, NEC Technologies, Itasca, IL) 57 cm in front of the monkey. The program also collected digitized samples (ADAC, Woburn, MA: 0.1° resolution) of the horizontal and vertical eye position outputs of the eye coil system at a frequency of 500 Hz. Saccades were recognized on-line, and the time as well as horizontal and vertical positions of each saccade start and end point were saved to the data file. The occurrence of the discriminated action potentials of up to two simultaneously recorded units also were sampled at 500 Hz.

ODR task

Two visual stimuli were presented on each trial: a small (0.1°) stimulus always appearing at the center of the monitor (the fixation target) and a larger (0.5°) stimulus (the cue) presented in the visual periphery. Both stimuli were square and solid white in color. The trial began with the presentation of the fixation target (Fig. 1*A1*). The monkey was required to fixate this target for an initial period of 500 ms (Fig. 1*A2*), after which the peripheral cue was presented for an additional 500 ms (Fig. 1*A3*) at one of eight possible locations, equally spaced on a circle 13° in radius centered on the fixation target (Fig. 1*B*). The location of the cue among these eight possible locations was chosen pseudorandomly each trial and was therefore unpredictable. After cue offset, the fixation target remained visible for a fixed 3-s delay period (Fig. 1*A4*). Continual fixation of the fixation target (within a central 4–6° eye position window) was required during both cue presentation and the subsequent delay period, a break in fixation terminated the trial. After the end of the delay period, signaled by the offset of the fixation target, the monkey was allowed 500 ms to complete a memory-guided saccade in the dark (Fig. 1*A5*). If that saccade brought the eyes to within 4–6° of the *x-y* location where the peripheral stimulus appeared before the delay (Fig. 1*A3*), the response was rewarded with a drop of juice. Relatively large eye position windows were made necessary by systematic errors in memory-guided saccades; nonetheless the average saccade of *monkeys JK* and *AR* began within 2° of the fixation target and ended within ≤3° of the actual cue location (Chafee and Goldman-Rakic 1998).

Unit recording and cortical cooling

A cryoprobe (described below) that could be mounted temporarily within either the prefrontal or parietal recording chambers was used to cool the brain. The cryoprobe was mounted firmly against the tissue at the bottom of each recording chamber and fixed in place with set screws in the walls of the chamber. This was necessary for cold to penetrate the volume of thickened dura and

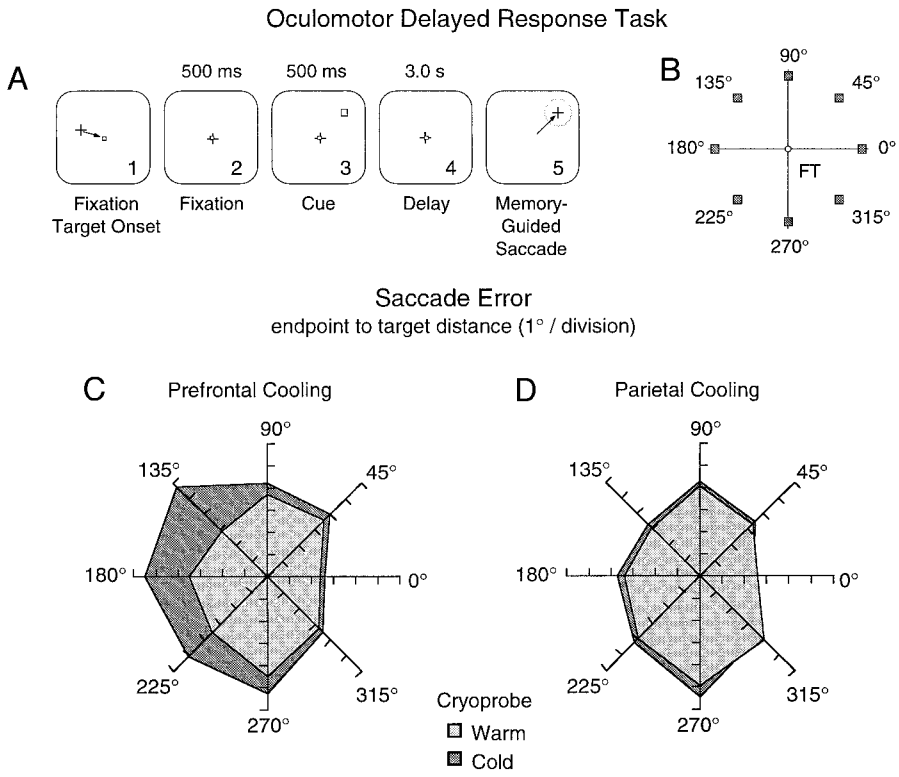

FIG. 1. Oculomotor delayed response (ODR) task. *A*: sequential events of the ODR trial. Monkey's gazing location is represented by the cross symbol in all panels. Monkey initiated the trial by acquiring fixation of a central target (*1*). After maintaining fixation for 500 ms (*2*) and while continuing to fixate the central target, a cue stimulus was presented at a peripheral location for an additional 500 ms (*3*). If the monkey broke central fixation to foveate the peripheral cue the trial was terminated. After extinction of the peripheral cue, the central fixation target remained, and the monkey continued fixation for a 3-s delay period (*4*). At the end of the delay, extinction of the central target provided a go signal for the memory-guided saccade. If the monkey executed a saccade in the dark (*5*) the end point of which fell within an eye-position window (not visible to the monkey) centered on the peripheral cue location (dotted circle), the trial was rewarded. *B*: cue array. ODR cue appeared in 1 of the 8 locations (shaded squares) indicated, selected pseudorandomly each trial. *C*: polar plots represent the mean distance in degrees of visual angle (saccade error) between the endpoint of each saccade and its corresponding target (indicated by the directional coordinate on each axis). Saccade errors observed when prefrontal cortex was cooled (dark gray) exceed those when the prefrontal cortex was at normal temperature (light gray). *D*: saccade errors when parietal cortex was cooled (dark gray) did not differ significantly from those observed when parietal cortex was at normal temperature (light gray).

granulation tissue present in both monkeys at the bottom of the recording chamber. As one cortical area was cooled, single-unit activity was collected from the other. Locations of recording and cooling were switched between parietal and prefrontal cortex on subsequent days. A search for neuronal activity was conducted by lowering the electrode into the chosen brain area while the cryoprobe mounted in the other chamber was maintained at normal body temperature (37°C). Once the activity of a unit was isolated, its activity was recorded for ~8–10 ODR trials per cue location. In general, cooling was reserved for units showing clear changes in activity during one or more epochs of the ODR task. If isolations were stable and the activity clearly task-related, the temperature of the cryoprobe was then lowered from 37°C to between 2 and 5°C in ~1 min and held at this temperature (±0.5°C). During the cooling procedure, care was taken to assure the stability of the unit isolations by comparison of incoming wave forms against samples stored at the beginning of the run. Once the cold temperature had been achieved, data collection resumed after a 5-min waiting period, allowing some time for brain temperature to stabilize and the physiological response to cold to develop. The monkeys performed the ODR task throughout the transition from warm to cold temperatures without interruption and did not show any overt signs of discomfort during this interval. The activity of the neuron then was recorded for a second set of between 8 and 10 ODR trials per cue location. Some isolations lasted long enough to enable collection of additional trials after the temperature of the brain had been returned to normal, and a few allowed for multiple cooling cycles.

Cryoprobe and brain temperature

The cryoprobe (Fig. 2*A*) consisted of a lower cylindrical piece of gold-plated copper made to fit within the recording chamber (16 or 20 mm ID) to which a vertical rectangular piece of copper was soldered to provide a mounting surface for two Peltier thermoelectric cooling devices (CP Series, Melcor, Trenton, NJ) connected in series and mounted on either side of the vertical copper piece. A ±4 A DC power supply used in conjunction with a control circuit adjusted both the amount and polarity of the current delivered to the Peltier devices so that the cryoprobe could be either cooled or warmed (by reversing the direction of current) and small adjustments in current could maintain any desired set temperature. This circuit employed the difference between a desired set temperature and the temperature of the cryoprobe measured by a small (0.010 in) copper-constantan thermocouple (Omega 5TC-TT-T-30-36, Omega Engineering, Stamford, CT) cemented to its under surface, at the interface between the cryoprobe and underlying tissue within the chamber. Excess heat accumulating at the outer face of each Peltier device during the cooling of the cryoprobe was removed by water circulating within copper heat sinks (Fig. 2*A*). To serve as a secondary temperature measurement device, a bead thermistor (YSI 44033, YSI, Yellow Springs, OH) was connected to a telethermometer (YSI) and cemented close to the dura at the bottom of a hole drilled through the long axis of the cryoprobe.

At the end of these experiments, the temperature within the brain underneath the cryoprobe was measured in one animal. To make these measurements, the bead thermistor in the central hole within the cryoprobe was removed. While the cryoprobe was mounted within the chamber and maintained at 2°C, a needle temperature probe (Physitemp, Clifton, NJ) attached to the telethermometer was lowered through the hole along the central axis of the cryoprobe into the brain and the temperature within the tissue directly measured at 1-mm intervals. This relationship was essentially linear at depths between 3 and 10 mm, temperature increasing on average an additional 2.8°C/mm beneath the cryoprobe (Fig. 3*A*). Below a depth of 10 mm, the temperature gradient was less steep, warming 1.3°C/mm. Measurements within prefrontal cortex were on average within 0.8°C of parietal measurements at each depth (the largest discrepancy between the 2 being 1.7°C, data not shown). Temperature measurements obtained with this technique were likely to underestimate actual brain temperature because the temperature of the tip of the probe would reflect both the ambient temperature of the brain and also the temperature of the shaft of the needle probe cooled directly along its course through the cryoprobe. To establish an approxi-

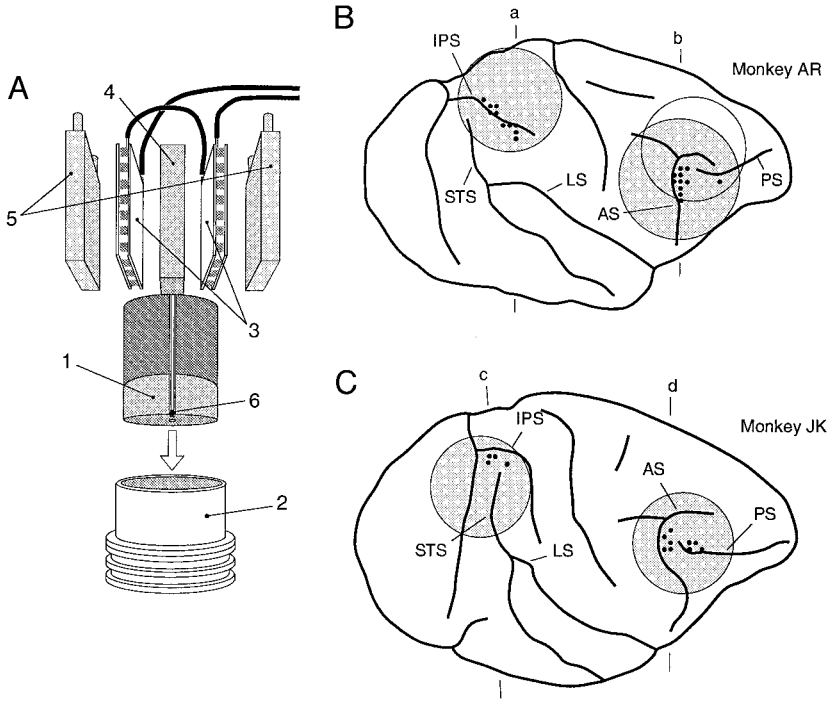

FIG. 2. Cryoprobe and electrode penetration sites. *A*: design of the cryoprobe. A cylinder of gold-platted copper (1) fit inside the recording chamber (2) and was cooled by 2 Peltier thermoelectric coolers (3) mounted on either side of a vertically oriented gold-plated copper fin (4) silver soldered to the top surface of the cylinder. Heat from the warm face of each Peltier device was removed through water circulating in copper heat sinks (5). Heat sinks, Peltier devices, and copper cryoprobe were bolted together with heat sink compound applied to opposing surfaces in the orientation shown. Temperature of the cryoprobe was measured by a thermocouple cemented to a groove in its lower surface (6). *B* and *C*: electrode penetration sites (●) and areas of cortex covered by cryoprobes ([gcirc]) in the 2 monkeys studied in the present experiments (*monkey AR, B; monkey JK, C*). a–d, levels of sections represented in corresponding panels of Fig. 4. In *monkey AR*, the prefrontal recording chamber was moved midway through the experiment (original location indicated by ○ at more medial location over prefrontal cortex), and a larger cryoprobe employed. Sulci are labeled IPS, intraparietal sulcus; STS, superior temporal sulcus; LS, lateral sulcus; AS, arcuate sulcus; and PS, principal sulcus.

mate measure of this inaccuracy, the needle probe was lowered by 1-mm increments through the cold (2°C) cryoprobe into either a cold (2°C) or warm (37°C) oil bath. Errors in the warm bath (considered a boundary condition reflecting maximal error) fell off with greater probe depth (Fig. 3*B*). Below a depth of 5 mm, the error was <3°C.

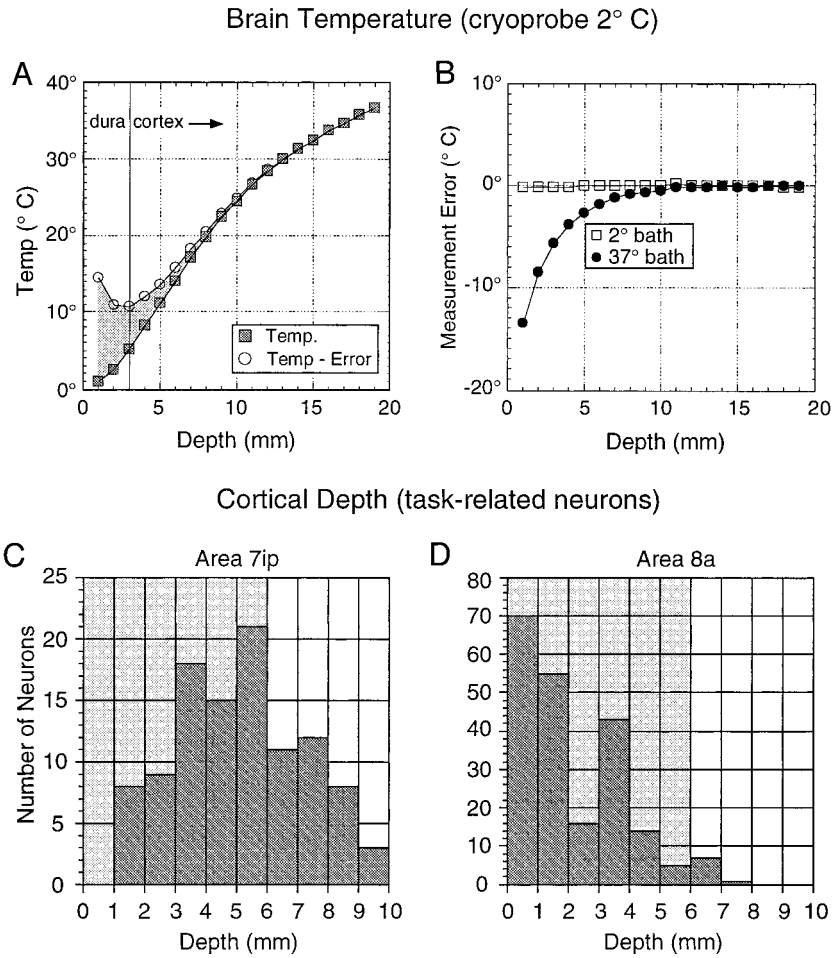

FIG. 3. Measurements of brain temperature, and depths of recorded units in parietal area 7ip and prefrontal area 8a. *A*: temperatures (shaded squares) measured at 1-mm intervals by a needle temperature probe passed through the cryoprobe and into the underlying brain while the cryoprobe was cooled to 2°C. Temperatures corrected for measured error (open circles) define a (shaded) region of uncertainty for actual brain temperature. Cortical surface was located 3 mm below the lower surface of the cryoprobe, the intervening space was occupied by thickened dura and granulation tissue. *B*: accuracy of temperature measuring system. Needle probe was passed through the cryoprobe as it was maintained at 2°C into a stirred oil bath maintained at 1 of 2 known temperatures (37 or 2°C). Errors in measurement obtained in cold (open squares) and warm (filled circles) oil baths are indicated and were a function both of the depth of the needle probe and of the difference in temperature between the cryoprobe and underlying medium. *C*: depths relative to the cortical surface of area 7 ip neurons. *D*: depths relative to the cortical surface of area 8a neurons. Both distributions (*C* and *D*) include only neurons the activity of which was significantly modulated during ODR performance. Some of the neurons included in both area 7ip and 8a distributions were not presently tested during cortical cooling but were recorded in the same monkeys (*JK* and *AR*) as described in an earlier report (Chafee and Goldman-Rakic 1998). Lightly shaded region of each distribution spans cortical depths <6 mm, where cortical temperatures during cooling were <23°C.

Statistical analysis of cooling effects on neuronal activity

Trials were segregated according to cue direction and cryoprobe temperature. Then within each group of trials, neuronal firing rates were measured in five time windows, within the cue, delay, early-saccade, late-saccade, and intertrial periods. The cue and delay windows were coextensive with the corresponding 500 and 3,000 ms periods in the ODR trial. The boundaries of early (100–400 ms after fixation target offset)- and late (400–700 ms after fixation target offset)-saccade period windows were adjusted to coincide with the average timing and duration of pre- and postsaccadic neuronal activity (Chafee and Goldman-Rakic 1998). These windows in the saccade period were not defined relative to saccade initiation because variability in the on-line recognition of saccades could vary the number of trials recognized in a minority number of cases, and the ANOVA we employed required a constant number of trials across each of the repeated measures (trial periods). The window in the intertrial period was the last 2,000 ms of the 2,500-ms intertrial interval (in a minority of the data, a shorter 2,000-ms intertrial interval occasionally was included, and the window spanned the entire period). The monkey was free to make eye movements during the intertrial period, and this occasionally may have included the centering saccade the monkey made after reward delivery (typically this saccade was completed within 500 ms of reward and so would not be included in the bulk of the data with the longer intertrial interval).

Thus three factors described each neuronal firing rate measurement; these were task period (5 levels), cue direction (8 levels), and cryoprobe temperature (2 levels, this analysis was limited to the firing rates observed while the brain was at normal temperature before cooling was initiated, and firing rates observed during the subsequent set of trials administered while cooling was in effect). A three-way repeated measure ANOVA (as implemented in the SYSTAT computer statistics package) was used to analyze the data. Task period was treated as a repeated measure. If the F statistic for the main effect of trial period in the overall analysis was significant, the neuron was defined as task-related. In these cases, additional tests isolated which trial periods contained significantly modulated activity. Four planned comparisons contrasted the mean firing rates in cue, delay, and early- and late-saccade periods each to the intertrial interval. Depending on which of these yielded significance, neurons were assigned a combination of C (cue), D (delay), or S (either early or late saccade) designations. If the F statistic for the main effect of temperature in the overall analysis was significant, the significance of this effect for each of the repeated measures was examined to determine whether cryoprobe temperature impacted firing rates in each trial period. An alpha level of $P \leq 0.05$ was employed throughout. The analysis was limited further only to those trial periods in which neurons exhibited significantly modulated activity. Thus cooling effects were identified as cases where two conditions were met; neuronal firing rates within a given trial period were significantly different from the intertrial interval and the main effect of temperature was significant on firing rates within the same trial period. In this way, the analysis was focused on cooling induced changes in task-related activity. The significance of the main effect of temperature on activity within the intertrial period assessed whether cooling had an overall effect on background activity. This was determined for each neuron. The magnitude of cooling effects was defined as the ratio of the mean firing rate during a given task epoch when the brain was cold, to the mean firing rate during the same epoch when the brain was warm (after Sandell and Schiller 1982). This ratio was <1 when cooling lowered firing rates and >1 when cooling elevated firing rates. Recovery of cooling effects was assessed in a separate three-way repeated measures ANOVA directly analogous to the analysis described in the preceding text, with the exception that neuronal firing rates during cooling were compared with firing rates after the brain had been returned to normal temperature.

Latencies of neuronal activation were defined with the method of MacPherson and Aldridge (1979) based on confidence intervals established around a spike density function of each neuron's activity. We employed Gaussian curves to measure the spatial tuning of neuronal activity. Within each trial period containing significantly modulated activity, the mean neuronal firing rate was measured across the eight cue/saccade directions tested. Then a reiterative curve-fitting algorithm determined the parameters defining the Gaussian curve that best fit these eight mean firing rates (separate fits were made to data collected during warm and cold conditions). Only cases in which the curve fitting procedure provided an F-statistic significant at the $P \leq 0.05$ level were included in subsequent analyses. Further details of both latency and spatial tuning analyses were described previously (Chafee and Goldman-Rakic 1998). Changes in the spatial tuning of neuronal activity were defined as the difference in the best direction or width parameters of the Gaussian tuning functions fit to warm and cold data sets for a given neuron. Two separate two-way analyses of variance then were conducted on the populations of these difference measures each using trial period and cortical area as factors. This addressed whether the mean shift in either spatial tuning parameter varied depending on which cortical area was cooled (main effect of area), and which task period was considered (main effect of trial period).

RESULTS

Database

A total of 105 neurons were isolated and their activity recorded within one cortical area as the monkeys completed two full sets of ODR trials, one conducted while the other cortical region remained at normal body temperature and a second set while the temperature of that region was lowered. Forty three of these neurons were located in parietal cortex (Fig. 2, *B* and *C*), and their activity collected while prefrontal cortex was subjected to cold. The majority of these (31 neurons) were located in parietal area 7ip (LIP) in the lateral bank of the intraparietal sulcus (Fig. 4, *A* and *C*), but a few also were located in area 7a (7 neurons) in the inferior parietal gyrus and also in area DP in the dorsal prelunate gyrus (5 neurons). Conversely, 62 of the neurons in the database were located in prefrontal cortex (Fig. 2, *B* and *C*), the majority of which (52 neurons) was located in area 8a in the anterior bank of the arcuate sulcus (Fig. 4, *B* and *D*), in the approximate location of the FEF, whereas the remainder (10 neurons) was located in the principal sulcus, in area 46.

The results of the repeated-measure ANOVA indicated that 90% of neurons within the database were task responsive and directionally selective. (i.e., the main effects of trial epoch and cue direction, or their interaction, were significant in the analysis, see Table 1). Using a set of planned comparisons (METHODS), the present analysis recognized seven types of neuron on the basis of whether significant activity modulation occurred during the cue, delay, and/or saccade periods or in combinations of these periods. Neurons tested during cooling in both parietal and prefrontal cortex included examples from most of these types (Fig. 5, *A* and *B*).

Extent of cryoinactivation

Cortical cooling involved a group of areas in parietal and prefrontal cortex (Fig. 2, *B* and *C*), with the coldest temperatures existing within the more superficial cortex immediately beneath the cryoprobes (Figs. 3*A* and 4, *A–D*). Progressively warmer brain temperatures occurred at greater depths. At a

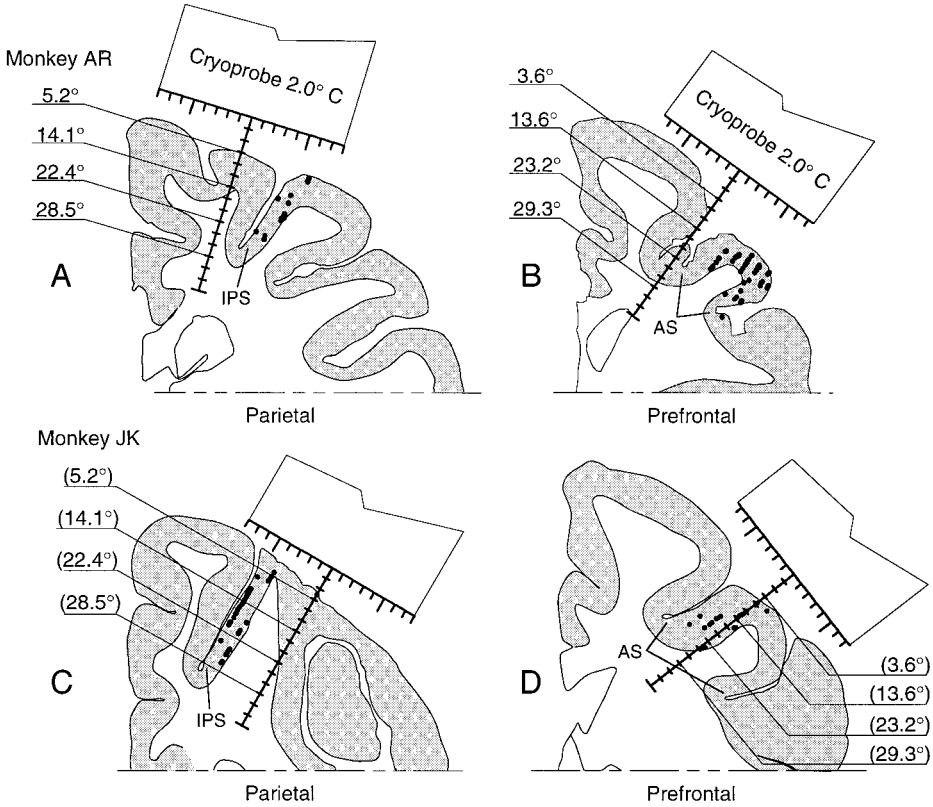

FIG. 4. Reconstruction of levels of cooling and recording sites within the brain. ●, locations of a subset of the neurons in the present database. *A–D*: sections through the brain beneath the cryoprobes in parietal (*A* and *C*) and prefrontal (*B* and *D*) cortex, in *monkeys AR* (*A* and *B*), and *JK* (*C* and *D*). Units were recorded primarily from the cortex of the lateral bank of the intraparietal sulcus (IPS) in parietal cortex (*A* and *C*), and from the anterior bank of the arcuate sulcus (AS) in prefrontal cortex (*B* and *D*). Brain temperatures measured in *monkey AR* (*A* and *B*) are indicated at 3-mm intervals. Same temperature levels are projected onto the reconstruction of *monkey JK* (*C* and *D*, brain temperature was not measured in this animal). Axes underneath each cryoprobe are presented for scale (1-mm divisions).

cryoprobe temperature of 2°C, cortical temperatures at depths of 3, 6, and 9 mm beneath the surface of the brain were 14, 23, and 29°C, respectively (Figs. 3*A* and 4, *A–D*). The lateral spread of cooling was not measured in the present experiments but was likely to extend beyond the boundaries of the cryoprobe (Fuster and Bauer 1974). Thus cooling established a gradient of subnormal temperature and functional inactivation across considerable portions of parietal and prefrontal cortex. Changes in the activity of area 7ip neurons resulted therefore not only from the cooling of area 8a, but of an expanse of prefrontal cortex which included it. Similarly, changes in the activity of area 8a neurons resulted from the cooling of a portion of parietal cortex that included area 7ip but was not limited to this cortical area. The degree to which the volume of cooled cortex involved areas 7ip and 8a can be estimated from the depths of neurons in these areas the activity of which was significantly modulated during ODR performance (Chafee and Goldman-Rakic 1998) and from the temperature measurements made at these depths (Fig. 3*A*). Most ODR task-related neurons in *monkeys JK* and *AR* sampled in area 7ip (Fig. 3*C*) and nearly all of those sampled in area 8a (Fig. 3*D*) were located at cortical depths <6 mm (lightly shaded region, Fig. 3, *C* and *D*), where the temperature of the cortex was <23°C (Fig. 3*A*). It has been shown that whereas colder temperatures are required to block neuronal responsiveness entirely, the response of V1 neurons to an optimal visual stimulus is reduced by ~80% at a temperature of 20°C (Girard and Bullier 1989). Thus cooling in the present experiments would be expected to substantially reduce the activity and output of a large portion of the neurons in parietal area 7ip and prefrontal area 8a. Because neurons in area 8a that were driven during ODR performance were more superficially located, the degree of functional inactivation achieved in area 8a was likely to exceed that in area 7ip.

In parietal cortex, cooling involved a group of cortical areas, which included, in addition to area 7ip in the lateral bank of the intraparietal sulcus, portions of area 5 in monkey AR (Fig. 2*B*),

TABLE 1. *Neurons with significant main effects and their interactions*

	Direction	Temperature	Epoch	Direction × Temperature	Direction × Epoch	Temperature × Epoch	Direction × Temperature × Epoch
Parietal							
Significant	41	33	40	8	42	27	18
Not Significant	2	10	3	35	1	16	25
Total	43	43	43	43	43	43	43
Prefrontal							
Significant	56	44	61	13	58	26	16
Not Significant	6	18	1	49	4	36	46
Total	62	62	62	62	62	62	62

Numbers of neurons for which cue direction, cortical temperature, and oculomotor delayed response (ODR) trial epoch, or their interaction, were significant factors ($P \leq 0.05$) effecting firing rate as determined by a three-way repeated-measures ANOVA of neuronal activity obtained in parietal and prefrontal cortex.

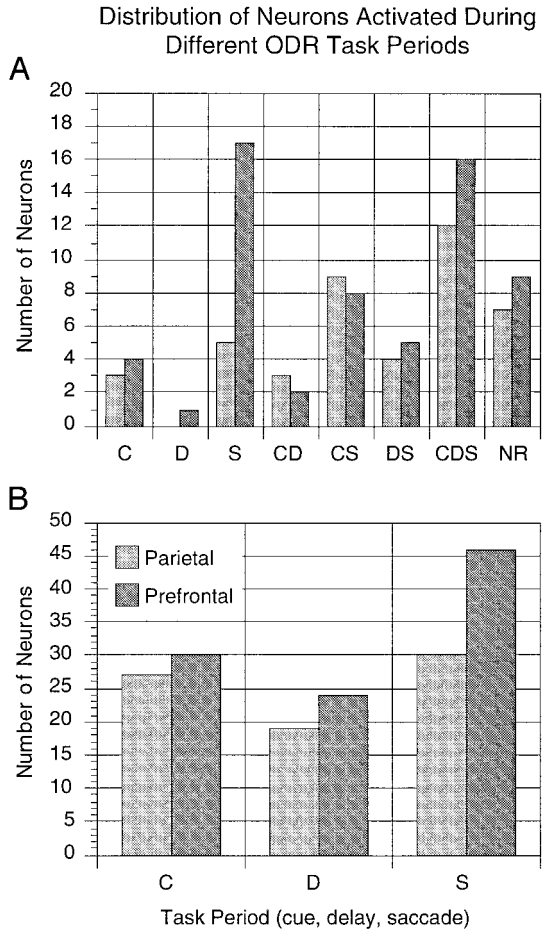

FIG. 5. Distribution of neurons recorded during cortical cooling in the present database by response class. *A*: C, D, and S designations indicate neurons the activity of which was elevated significantly relative to the baseline level during cue, delay, and saccade ODR task periods, respectively, as assessed by a 3-way repeated-measures ANOVA (See METHODS. Combinations of letters indicate neurons the activity of which was elevated during combinations of corresponding task periods). *B*: total numbers of neurons the activity of which was elevated significantly in each task period collapsed across the combinations indicated in *A*.

as well as the dorsal prelunate gyrus (including area DP) and parts of striate cortex in *monkey JK* (Fig. 2*C*). Parts of area 7a were cooled in both animals. In prefrontal cortex, cooling included not only area 8a in the anterior bank of the arcuate sulcus but also portions of area 46 in the posterior principal sulcus, posterior portions of the dorsolateral and inferior prefrontal convexities, and area 6 (Fig. 2, *B* and *C*).

Effect of cold on ODR performance

Cooling prefrontal cortex produced an impairment in memory-guided saccade performance (Fig. 1*C*). In a two-way ANOVA on the mean error distance between the endpoint of memory-guided saccades and their respective visual cues (with cue direction and cortical temperature as factors), error distance increased during cryogenic depression of prefrontal cortex–both the main effect of temperature (F_{temp} =149.47, df = 1, $P < 0.001$) and the interaction between temperature and direction ($F_{temp*dir} = 15.01$, df = 10, $P < 0.001$) were significant in this analysis. This behavioral deficit was confined largely to saccades toward targets appearing contralateral to the cooled prefrontal hemisphere (Fig. 1*C*). During cooling, monkeys would maintain fixation of the central target until its disappearance but then frequently make inaccurate saccades (sometimes into the visual hemifield opposite the target). These trials were interspersed with others in which comparatively accurate saccades were made. Cooling parietal cortex produced a much smaller impact on the accuracy of memory-guided saccades (Fig. 1*D*), failing to significantly effect the mean error between memory-guided saccade endpoints and their targets ($F_{temp} = 3.41$, df = 1, $P = 0.065$; $F_{temp*dir} = 1.50$, df = 10, $P = 0.131$).

Effect of cold on neuronal firing rate

Cooling affected the intensity of activation of neurons in various ODR trial epochs in both parietal and prefrontal cortex. The parietal area 7ip neuron illustrated in Fig. 6*A* exhibited sustained delay period activation when the cue appeared in the upper (90°) and upper left (135°) locations before the prefrontal cortex was cooled. When the activity of the same neuron was recorded with the prefrontal cortex cooled, delay period activity was attenuated sharply in the 135° direction (Fig. 6*B;* $F_{temp} = 45.99$, df = 1, $P < 0.001$), and early-saccade period activity also was suppressed significantly ($F_{temp} = 25.69$, df = 1, $P < 0.001$). The activity in the cue period also was affected but less strongly and not significantly ($F_{temp} = 0.357$, df = 1, $P = 0.551$). The delay period activity of nine additional parietal area 7ip neurons significantly changed during prefrontal cooling (4 neurons suppressed, 5 augmented; Fig. 9*C*).

Comparable effects were observed among prefrontal neurons while cooling parietal cortex. Figure 7*A* illustrates a neuron in the principal sulcus (area 46) recorded during cryogenic inactivation of the parietal cortex. Like the parietal neuron described in the preceding text, the activity of this prefrontal neuron was reduced significantly by cooling (Fig. 7*B*), in this instance during the cue period ($F_{temp} = 99.29$, df = 1, $P < 0.001$). There was also a general suppression of the level of activity during the intertrial interval in this case ($F_{temp} = 108.60$, df = 1, $P < 0.001$). Six additional prefrontal neurons (1 in area 46 and 5 in area 8a) similarly exhibited reduced cue period activation when parietal cortex was cooled, whereas augmented cue period activation was observed in 11 prefrontal area 8a neurons (Fig. 9*B*). Thus whereas the illustrated cooling effects fit well those that prefrontal mnemonic and parietal visuospatial functions would predict (namely the reduction of cue period activity in prefrontal neurons and delay period activity in parietal neurons), counter examples were equally numerous. For example, delay period activity of several prefrontal area 8a neurons was altered by parietal cooling (9 neurons, Figs. 9*D* and 11, *E–H*), and prefrontal cooling altered the activation of parietal 7ip neurons in response to the visual stimulus (9 neurons, Fig. 9*A*). Neurons whose primary activation during ODR performance occurred during the saccade period also were impacted by cooling either area (17 parietal 7ip neurons, 25 prefrontal 8a neurons, Fig. 9, *E* and *F*). Thus prefrontal cooling could reduce the presaccadic activation of neurons in area 7ip (Fig. 8, *A* and *B;* $F_{temp} = 34.54$, df = 1, $P < 0.001$), and cooling parietal cortex could augment the presaccadic activation of neurons in prefrontal area 8a (Fig. 8, *C* and *D;* $F_{temp} = 34.89$, df = 1, $P < 0.001$). In general, both

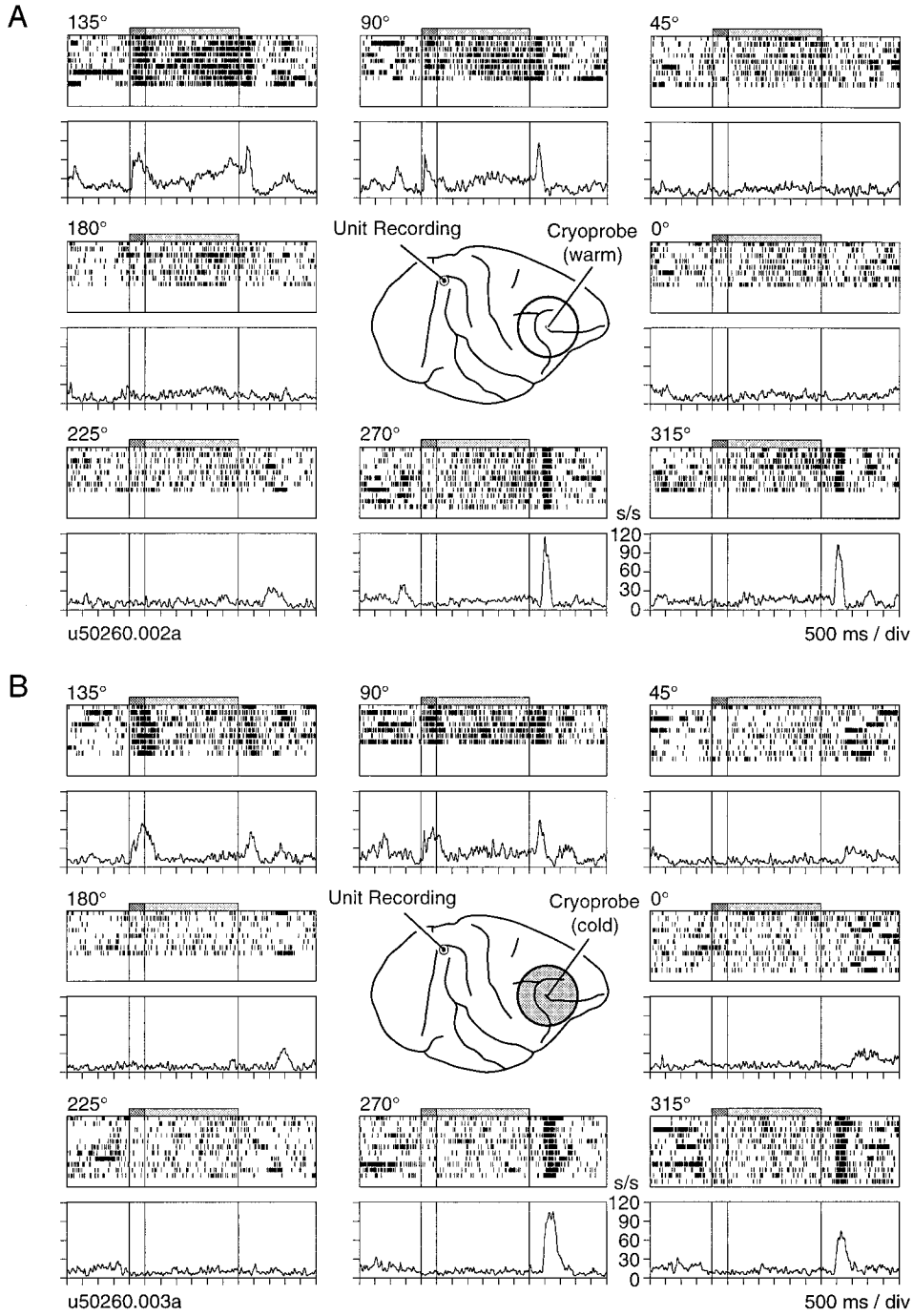

FIG. 6. Delay period activity recorded from a neuron in parietal area 7ip during cooling of prefrontal cortex. Point of entrance of the electrode penetration from which the neuron was recorded is indicated in the central drawings of the right cerebral hemisphere. Circle over prefrontal cortex denotes the area of brain underneath the prefrontal cryoprobe. Eight rasters in each group (*A* and *B*) show activity on ODR trials in which the cue appeared in a single location, corresponding to 1 of the 8 cue locations illustrated in Fig. 1*B*, each indicated by the directional coordinate at the *top left*. In each raster, the duration of the cue (dark gray bar) corresponds to the 500-ms interval between the 1st and 2nd vertical lines. Duration of the delay period (light gray bar) corresponds to the 3-s interval between the 2nd and 3rd vertical lines. Memory-guided saccade was made within the 500-ms immediately after the end of the delay period (3rd vertical line). A spike density function formed by convolution of the corresponding histogram with a Gaussian function accompanies each raster. *A*: activity of this parietal area 7ip neuron while prefrontal cortex was maintained at normal temperature. Activity increased after the onset of the cue in the upper (90°) and upper left (135°) locations, and persisted after cue offset throughout the delay period, ending with an additional burst in activity immediately before initiation of the memory-guided saccade. Later activation on 270 and 315° trials is most likely due to the centering saccade made in the intertrial interval after these trials in anticipation of the reappearance of the fixation target. *B*: activity of the same parietal area 7 ip neuron recorded while the cryoprobe over prefrontal cortex was cooled to 2°C. Delay period activity, particularly in the 135° location, is sharply attenuated.

enhanced and suppressed levels of activation were observed in all task periods after the transient inactivation of either cortical area (Fig. 9, *A–H*).

MAGNITUDE AND FREQUENCY OF EFFECTS. In the case of significant suppressive cooling effects, the mean cooling index was quite constant both across trial period and cortical area (Fig. 10*A*). In this population of neurons, firing rates were reduced by ~40% of their level of activation seen at normal brain temperature. It was not the case that cooling one area produced stronger suppressive effects than cooling the other or that stronger suppressive effects were seen in some trial periods. In a two-way ANOVA of the cooling indices of suppressed neurons (cortical area by trial period), neither the main effects of area or trial period nor the interaction between them were significant ($F_{area} = 0.10$, df = 1, $P = 0.75$; $F_{period} = 0.37$, df = 4, $P = 0.83$; $F_{area*period} = 0.19$, df = 4, $P = 0.94$). Similarly, in the case of enhancing effects, neither the main effects of area ($F_{area} = 0.89$, df = 1, $P = 0.35$) or trial period ($F_{period} = 1.47$, df = 4, $P = 0.22$) were significant, although the interaction term was ($F_{area \times period} = 2.72$, df = 4, $P = 0.03$). Both early- and late-saccade period activities were more strongly augmented in parietal units under prefrontal cooling than the converse (Fig. 10*B*).

Most often, cooling impacted firing rates in a given trial

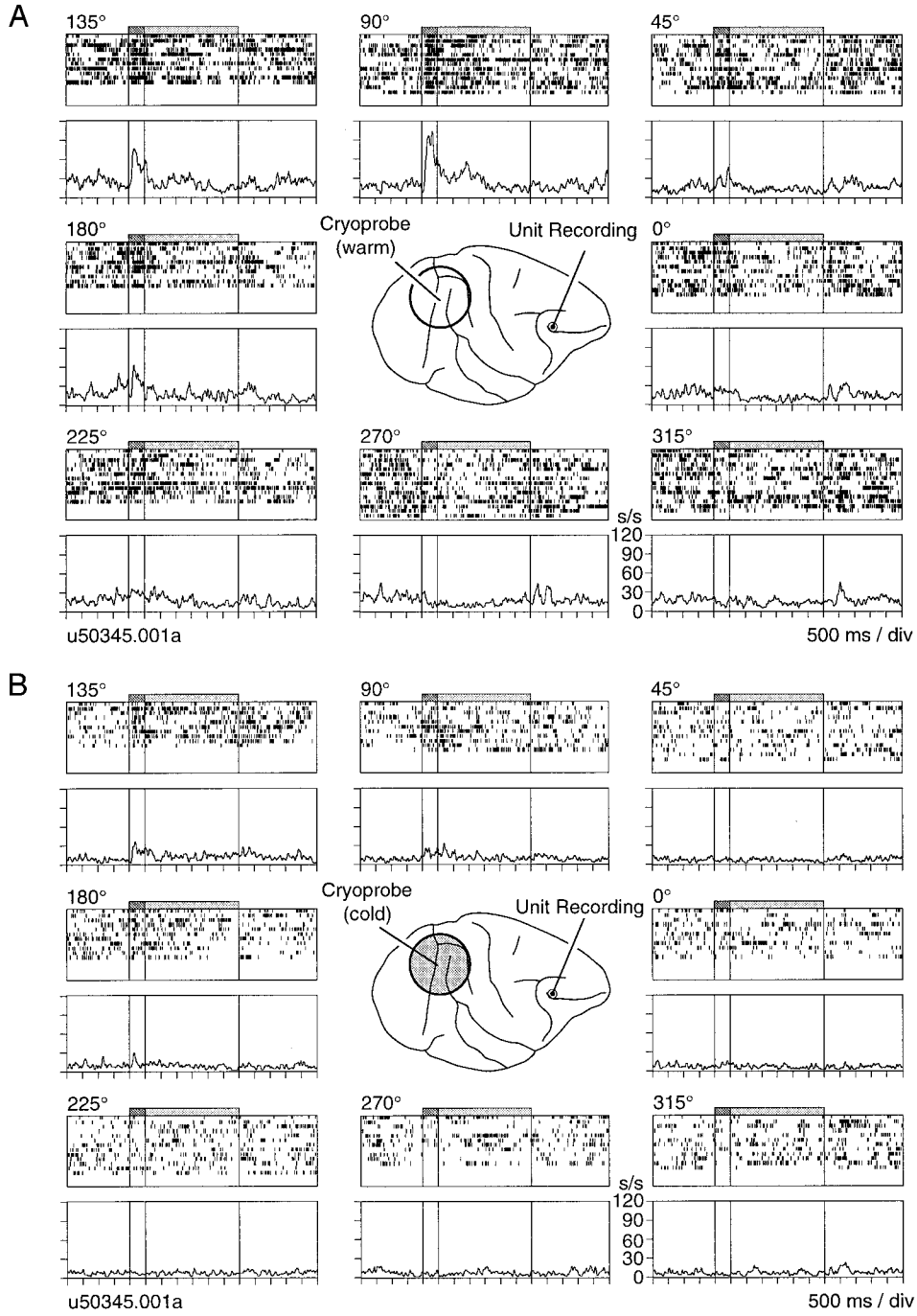

FIG. 7. Cue period activity recorded from a neuron in prefrontal area 8a during cooling of parietal cortex (conventions as in Fig. 6). *A*: firing rate increases during the cue period, and trails into the delay period, when the cue appears in upper (90°) and upper left (135°) locations. *B*: activity of the same neuron after parietal cortex had been cooled. Increase in activity during the cue period is reduced.

epoch equally across trials of different cue and saccade direction. This is indicated by the fact that the interaction between temperature and direction in the ANOVA applied to neuronal firing rates (METHODS) was significant in a minority of neurons (19% of parietal neurons, 21% of prefrontal neurons, Table 1). On the other hand, a significant interaction was found between cortical temperature and trial epoch in a larger proportion of the sample, in 62% of parietal neurons, and 42% of prefrontal neurons (Table 1). This finding indicates that firing rates in different task epochs changed by different amounts. Cooling effects such as these, as well as others that were observed across multiple cooling cycles (Fig. 11), would be difficult to ascribe to spurious sources such as changes in the overall level of activity of a neuron or changes in the quality of the isolation of its activity. Comparable fractions of the neurons activated during the cue, delay, or saccade periods of the ODR task had their activity augmented or suppressed irrespective of which cortical area was cooled (Fig. 9, *A–H*). Thus transient inactivation of parietal and prefrontal cortex produced largely symmetrical effects on the patterns of neuronal activity distributed between them.

REVERSIBILITY OF EFFECTS. The activity of 52 neurons was recorded after the brain had been returned to normal temperature. A repeated-measures ANOVA similar to the original analysis (METHODS) was performed on these neurons to deter-

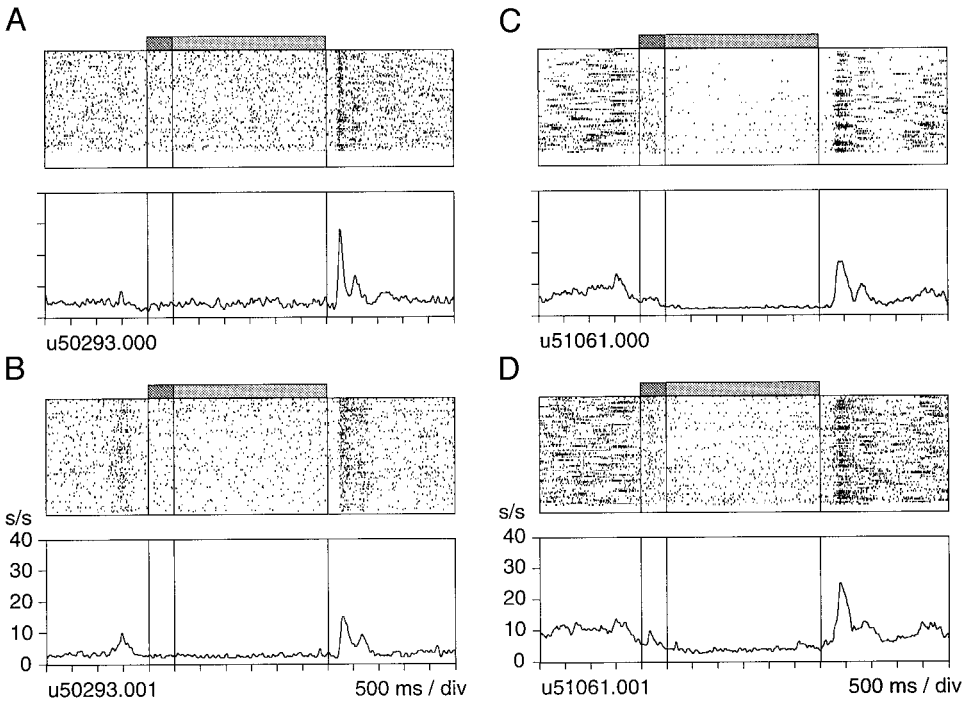

FIG. 8. Saccade period activity recorded from neurons in parietal area 7ip (*A* and *B*) and prefrontal area 8a (*C* and *D*). Trials in each of the 8 different cue directions are displayed together in each raster and spike density function. Other conventions as in Fig. 6. *A* and *C*: neuronal activity recorded in area 7ip (*A*) and area 8a (*C*) when the alternate cortical area was at normal temperature. In both cases, bursts in activity that are evident after the end of the delay period precede the initiation of the memory-guided saccade. *B* and *D*: activity of the same 2 neurons after the remote cortical area had been cooled. In the case of the parietal neuron, the saccade related burst is markedly reduced (*B*). In the case of the prefrontal neuron, saccade period activity is augmented (*D*).

mine whether changes seen under cooling reversed on warming the brain. Nine of the 33 neurons (27%) whose activity was augmented by cooling, and 9 of the 19 neurons (47%) whose activity was suppressed by cooling, exhibited significant changes in activity in the opposite direction when the brain was returned to normal temperature. Thus significant recovery was more common among those neurons suppressed by cooling. In other neurons, changes in activity seen on cooling did not immediately reverse on warming the brain within the period of time over which that activity was sampled. In some neurons, changes in activity were consistently observed across multiple cooling cycles. For example, cooling prefrontal cortex had a reversible and repeatable impact on the activity of the neuron located in parietal area 7ip (Fig. 11, *A–D*, same neuron as in Fig. 6). Before cooling, the firing rate of this neuron was elevated during the delay period (Fig. 11*A*). During the first cooling of prefrontal cortex, the delay period activation was reduced (Fig. 11*B*) and then after the brain was warmed back to normal temperature, rebounded to a level greater than that originally seen before cooling was initiated (compare Fig. 11, *C* and *A*). Delay period firing rates were again suppressed a second time when prefrontal cortex was again cooled (Fig. 11*D*). The neuron in prefrontal area 8a exhibited a tonic excitation during the delay period (Fig. 11*E*) that was attenuated when parietal cortex was cooled (Fig. 11*F*), regained its original strength when parietal cortex was warmed (Fig. 11*G*), and was attenuated again when parietal cortex was cooled a second time (Fig. 11*H*).

Cooling effects on spatial tuning

The technique employed to quantify the spatial tuning of neuronal activity (METHODS) provided for each neuron the parameters of the Gaussian curve representing the best fit to the mean firing rates observed in each of the eight cue/saccade directions tested. Significant Gaussian fits were obtained to the activity of 19 parietal neurons and 32 prefrontal neurons in at least one ODR task period in both warm and cold conditions. Comparison of tuning curves fit with the activity of these 51 neurons within a given trial period across temperature indicated whether cooling affected the breadth of tuning (Td parameter of the Gaussian equation) or the best direction (D parameter) of that activity. The best directions of fits to cue, delay, and saccade period activities shifted $<10°$ in the large majority of neurons (Fig. 12*A*, neurons contributed multiple shift values to this distribution if they were activated in >1 ODR task epoch). However, larger shifts occasionally were seen. For example, after cooling prefrontal cortex, the best direction of the saccade period activity of an area 7ip parietal neuron shifted counterclockwise (leftward) by 28° due largely to opposite changes in mean firing rate observed at off-peak 45 and 135° directions (Fig. 13*A*). In a neuron in prefrontal area 8a, a 26° clockwise (rightward) shift in the preferred direction of saccade period activity was seen (Fig. 13*C*). Comparing the size of the shifts in best direction across parietal and prefrontal cooling in a two-way ANOVA with cortical area and task epoch as factors, the main effect of cortical area was significant ($F_{\text{area}} = 5.08$, df $= 1$, $P = 0.027$), indicating that larger shifts in best directions were associated with cooling parietal than prefrontal cortex (Fig. 12*A*). The size of the shift in best direction did not vary with task period ($F_{\text{epoch}} = 1.89$, df $= 2$, $P = 0.157$). Cooling also could affect the width of tuning (Td parameter; Fig. 12*B*), and a minority of neurons exhibited considerable shifts. The best direction of the saccade period activity of the illustrated area 8a neuron remained constant as the width of tuning changed markedly (Fig. 13*B*). Cooling parietal and prefrontal cortex did not differentially impact this measure ($F_{\text{area}} = 0.64$, df $= 1$, $P = 0.424$), which was comparable across task epoch ($F_{\text{epoch}} = 0.32$, df $= 1$, $P = 0.724$).

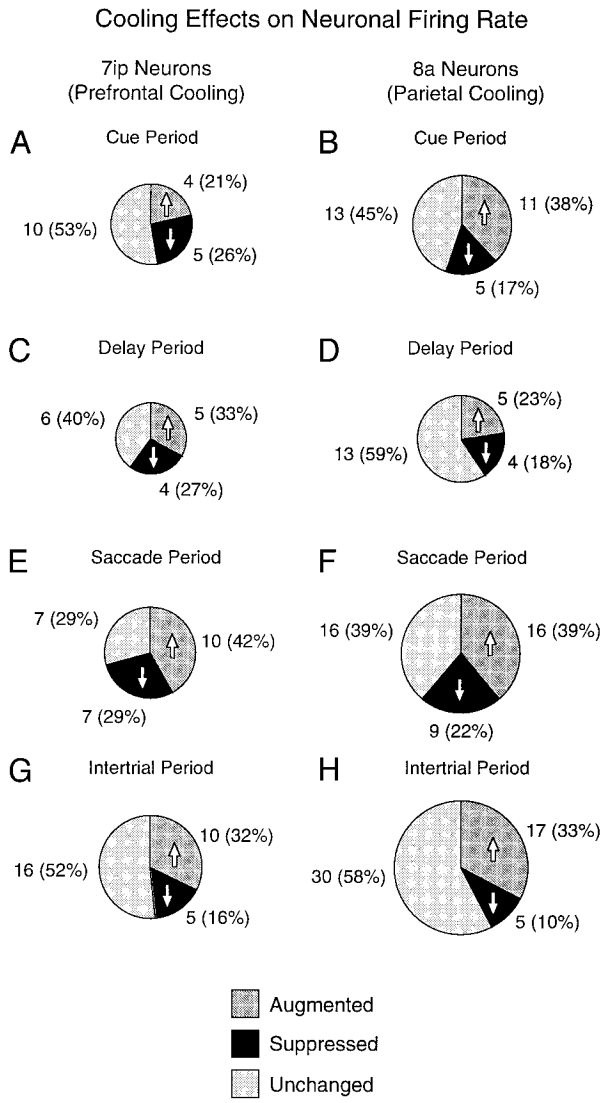

FIG. 9. Frequency of significant cooling effects obtained in a repeated-measures ANOVA (methods) of neuronal firing rates. Numbers and proportions of neurons for which cooling suppressed, augmented, or did not change the activity level within a given task period are shown. Area of the circle in each case is proportional to the number of neurons represented. Cooling effects on neuronal activity during cue (*A* and *B*), delay (*C* and *D*), saccade (*E* and *F*), and intertrial (*G* and *H*) periods of the ODR task are indicated separately on the left for parietal area 7ip neurons during prefrontal inactivation (*A, C, E,* and *G*) and on the right for prefrontal area 8a neurons during parietal inactivation (*B, D, F,* and *H*).

Cooling effects on neuronal latency

Cooling neither prefrontal nor parietal cortex had an appreciable impact on delaying the activation of neurons during the cue and saccade periods. Recruitment curves illustrating the percentage of the populations of neurons activated during cue and saccade periods as a function of time relative to cue onset (Fig. 14, *A* and *B*) or saccade initiation (Fig. 14, *C* and *D*) largely overlap, indicating that on average the activation of these populations followed a similar time course whether the brain was cold or at normal temperature. In both parietal (Fig. 14*A*) and prefrontal (Fig. 14*B*) cortex, there is a tendency for neuronal activation late in the cue period to be delayed during cooling, such that recruitment curves diverge ~100 ms after cue onset; however, neither the mean onset time of cue (parietal: paired $t = -1.43$, df = 18, $P = 0.169$; prefrontal: paired $t = -0.55$, df = 24, $P = 0.585$) or saccade period activation (parietal: paired $t = 0.91$, df = 14, $P = 0.38$; prefrontal: paired $t = 0.38$, df = 36, $P = 0.943$) differed significantly as a function of cortical temperature in either cortical area.

DISCUSSION

Neuronal activity in both prefrontal and parietal cortex increases during the primary ODR trial epochs that separate sensory stimulation, working memory operation, and response execution in time. The population of neurons activated in both cortical areas can be divided into several distinct groups on the basis of which combination of these task epochs include elevated activity (Fig. 5), and the large majority of neuronal types so defined were found to exist simultaneously in both parietal and prefrontal cortex (Chafee and Goldman-Rakic 1998). Thus several subpopulations of neurons in parietal and prefrontal

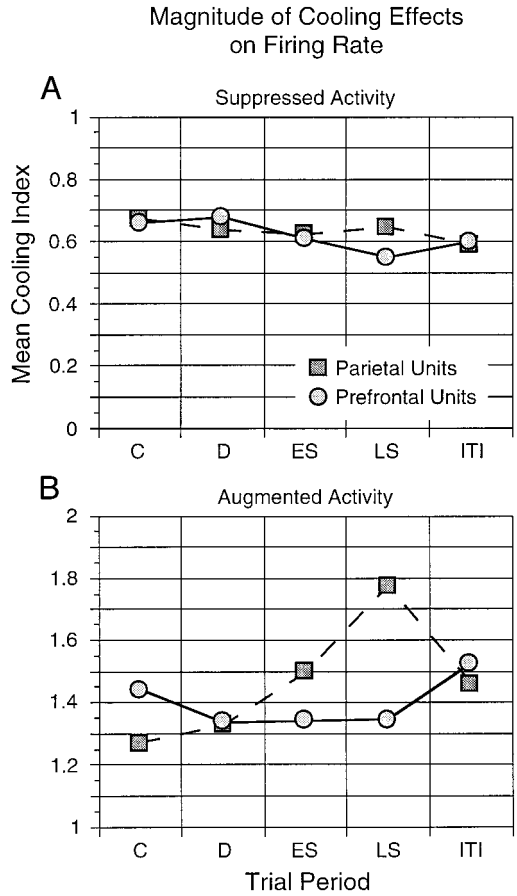

FIG. 10. Magnitude of cooling effects observed in parietal and prefrontal neurons. For each neuron, a cooling index was calculated as the ratio between the mean firing rate observed in a given task epoch on trials collected at cold and warm temperature. *A*: mean cooling index associated with suppressive cooling effects in all neurons in parietal (dark gray squares) and prefrontal (light gray circles) populations activated during each ODR task epoch are shown. *C*, D, ES, LS, and ITI designate the cue, delay, early-saccade, late-saccade, and intertrial periods, respectively. Suppressive effects were of comparable size across all task epochs, irrespective of whether parietal or prefrontal cortex was cooled. *B*: mean cooling index associated with augmenting cooling effects in parietal (dark squares) and prefrontal (light circles) neurons. Activity during the saccade period was augmented in parietal neurons during prefrontal cooling more than the converse.

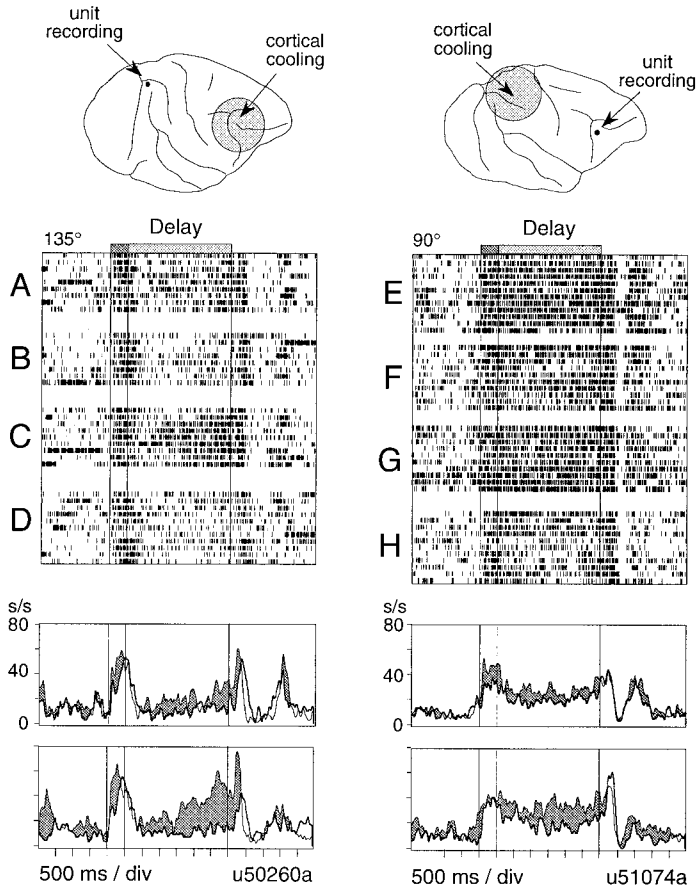

FIG. 11. Repeatability of cooling effects. Activity each of the 2 illustrated neurons was elevated during the delay period on preferred direction trials (only preferred direction trials are shown). Trials in each raster are segregated into 4 groups, collected during a particular temperature condition. Four groups correspond a warm (*A* and *E*), cold (*B* and *F*), warm (*C* and *G*), and cold (*D* and *H*) temperature sequence. Pairs of spike density functions (SDF) below each raster compare activation on the 1st (*top*) and 2nd (*bottom*) cooling cycles. In each panel, the SDF at normal temperature is shaded, whereas the SDF during cooling is open. Other conventions as in Fig. 6. *A–D*: delay period activity of an area 7ip neuron observed after the cue appeared in the 135° location was repeatedly suppressed through 2 cycles of cooling prefrontal cortex (the activity of this neuron across all target locations is depicted in Fig. 6). *E–H*: similar observations in a prefrontal area 8a neuron.

cortex appear to be physiologically synchronized in the sense that the levels of their activity rise and fall together throughout the ODR trial. The present experiments were intended in part to address the mechanisms through which this parallel activation might come about, specifically whether reciprocal neurotransmission between these cortical areas may be involved. The known projection between parietal neurons in area 7ip and prefrontal neurons in area 8a (Andersen et al. 1990a; Cavada and Goldman-Rakic 1989; Schall et al. 1995; Stanton et al. 1995) implies that activity is exchanged between these neuronal populations during ODR performance but not whether this exchange is symmetrical or asymmetrical nor whether it equally includes neuronal activation during the cue, delay, and saccade epochs of the task. As some of these signals (specifically neuronal activity sustained throughout the delay period) appear to effect the retention of a spatial datum defined by the location of a visual stimulus in working memory, the question is of interest as to how prefrontal cortex may engage, and in turn be engaged by, other cortical areas as working memory operates. Our results included the following observations: *1*) neurons the activation of which occurred during periods of sensory input, working memory operation, or saccade execution were equally vulnerable to the effects of cooling. *2*) The effects of cooling parietal versus prefrontal cortex were largely equivalent (with a few exceptions discussed in the following text). *3*) The average change in neuronal activity associated with cooling was on the order of 40% of the firing rate observed in each trial epoch at normal temperature and tended to be equally strong across all cue/saccade directions tested. And *4*) both the suppression and enhancement of activation were observed. How these findings might bear on the nature of the interaction between prefrontal and posterior parietal neurons during the ODR task will be considered in turn. It should be noted that using the current technique it is not possible to conclude whether cooling effects were mediated by direct monosynaptic projections between parietal and prefrontal neurons or via multisynaptic pathways involving other cortical or subcortical areas.

Neuronal activity in all ODR task epochs was affected

The similarity that parietal and prefrontal neuronal activities achieve during ODR performance might arise through any one of several different mechanisms. One possibility is that this similarity is the consequence of a redundancy of oculomotor

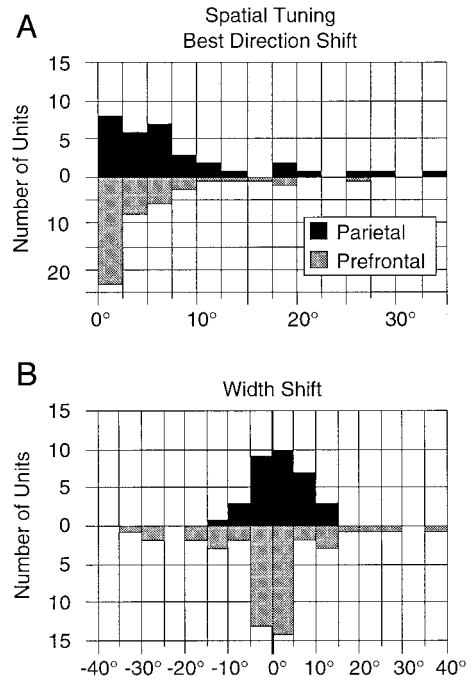

FIG. 12. Effects of cold on spatial tuning. Gaussian curves fit to the mean firing rate observed across cue direction in a given task epoch provided a measure of the width (Td parameter) and best direction (D parameter) of spatial tuning. For each neuron, separate Gaussian functions were fit to data from trials collected at normal brain temperature and during cooling, and the absolute difference between the best directions of these functions (D parameters) was determined along with the absolute difference between their widths (Td parameters). Data obtained from 17 parietal and 32 prefrontal neurons are illustrated. *A*: distribution of the changes seen in best directions of parietal neurons (■) and prefrontal neurons (▤) associated with cooling. Best directions of the large majority of neurons changed $<10°$. *B*: distribution of the changes seen in the width of tuning of parietal neurons (■) and prefrontal neurons (▤) during cooling.

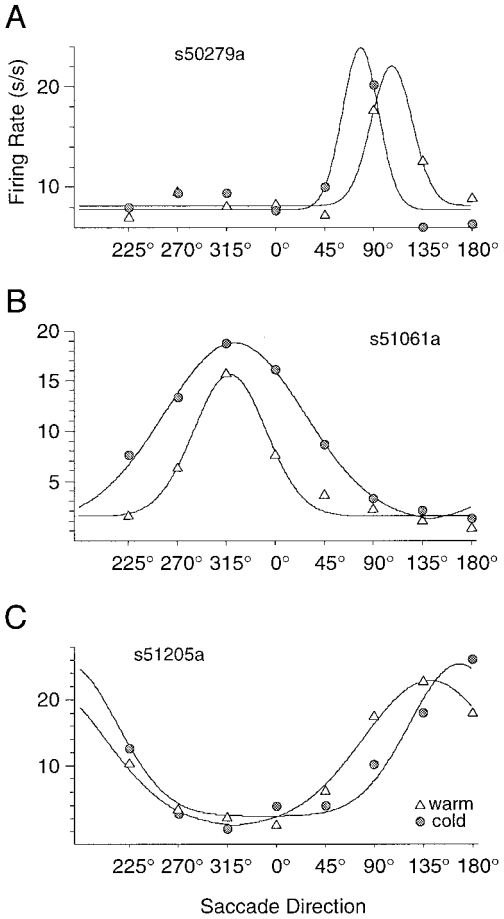

FIG. 13. Examples of changes in the spatial tuning of individual neurons. Gaussian tuning functions fit to mean firing rates observed while the brain was at normal temperature (△) and during cortical cooling ([gcirc]). *A*: saccade period activity of a neuron in parietal area 7ip. Cooling is associated with a clockwise (leftward) shift in the best direction. *B*: saccade period activity of a neuron in prefrontal area 8a. In this instance, the best direction remained constant while the width of tuning changed (broadened). *C*: saccade period activity of a neuron in prefrontal area 8a. A counterclockwise (rightward) shift in the best direction of the neuron occurred during cooling of parietal cortex.

function between parietal and prefrontal cortex, which generate similar patterns of neuronal activity in physiological isolation without requiring or involving the exchange of neuronal signals between them. As this would predict that cooling one cortical area ought to have negligible effect on the other, the present data indicate that a physiological interaction between parietal and prefrontal neurons takes place during ODR performance and that this interaction contributes to the modulation of activity that neurons in both areas exhibit. In this manner, the physiological operations performed by the two cortical areas appear to be linked. It was observed further that the reduction of output that could be assumed to accompany cooling of one of the two cortical areas produced equal effects on neuronal activation during cue, delay, and saccade epochs concurrently recorded in the remaining cortical area (Figs. 9 and 10). This was evidence that the cortical output suppressed by cooling was normally active during each of these ODR task epochs to contribute to the modulation of neuronal activity taking place in the other cortical area during those same times in the ODR trial. Thus the present data favor the hypothesis that neural signals associated with sensory input, working memory operation, and saccade execution in both parietal and prefrontal cortex all participate in cortical output. The heterogeneity of output signals suggested by these data are consistent with the results of Paré and Wurtz (1997), who have combined antidromic activation and unit recording to demonstrate that two physiologically distinct classes of 7ip neuron, one active during the cue period, and another the activity of which extended into the delay and saccade periods of a memory-guided saccade task, both give rise to axons projecting to the superior colliculus.

The present results are in agreement with the data presented by Quintana and colleagues (1989) in their study of the effects of parietal cooling on prefrontal unit activity during delayed match to sample and conditional position discrimination tasks, both of which employed the color of a cue stimulus to direct a delayed arm movement. These authors found that cooling parietal cortex significantly altered the level of activity of some prefrontal neurons in each of the cue, delay, choice, and response epochs comprising these tasks. Further, cooling produced a mixture of increased and decreased levels of activation. Our results extend these by examining the impact of prefrontal inactivation on parietal unit activity and the use of a task employing a visuospatial cue and an oculomotor response to investigate this system. In their study of interactions between prefrontal and inferotemporal cortex, Fuster and colleagues (1985) observed that in either cortical area, remote cortical inactivation had a significant impact on the neuronal activity observed during cue, delay, and choice epochs of the same delayed color match to sample task. The agreement between these data suggests a general pattern of intracortical communication existing between prefrontal cortex and areas providing its input during a variety of working memory-dependent behaviors.

Parietal and prefrontal cooling were equivalent

Parietal and prefrontal cooling were largely equivalent in their impact on neuronal activity. Cooling had a significant impact on cue, delay, and saccade class neurons with comparable frequency irrespective of which cortical area was cooled (Fig. 9). Furthermore suppressive effects were of comparable magnitude (Fig. 10*A*), although saccade responses were enhanced to a larger degree after prefrontal cooling (Fig. 10*B*) than the converse. Thus it did not appear to be the case that the symmetrical patterning of neuronal activity patterns previously described (Chafee and Goldman-Rakic 1998) was achieved through an asymmetrical exchange of signals between parietal and prefrontal neurons. For example, it is possible that activation elicited by the visual stimulus during the cue period originates in parietal cortex and then is transmitted to prefrontal cortex in a strictly feedforward direction. Along similar lines, prefrontal neurons might employ this input to generate locally a neural signal that is sustained throughout the delay period that once initiated drives parietal neurons in a strictly feedback manner. This exchange of different neural signals in feedforward and feedback components of the reciprocal projection between parietal and prefrontal neurons would have the effect of mixing activity patterns between the two populations that were initially unique to one or the other. However, the present data do not support the possibility that activation during any individual period of the ODR task is transmitted in

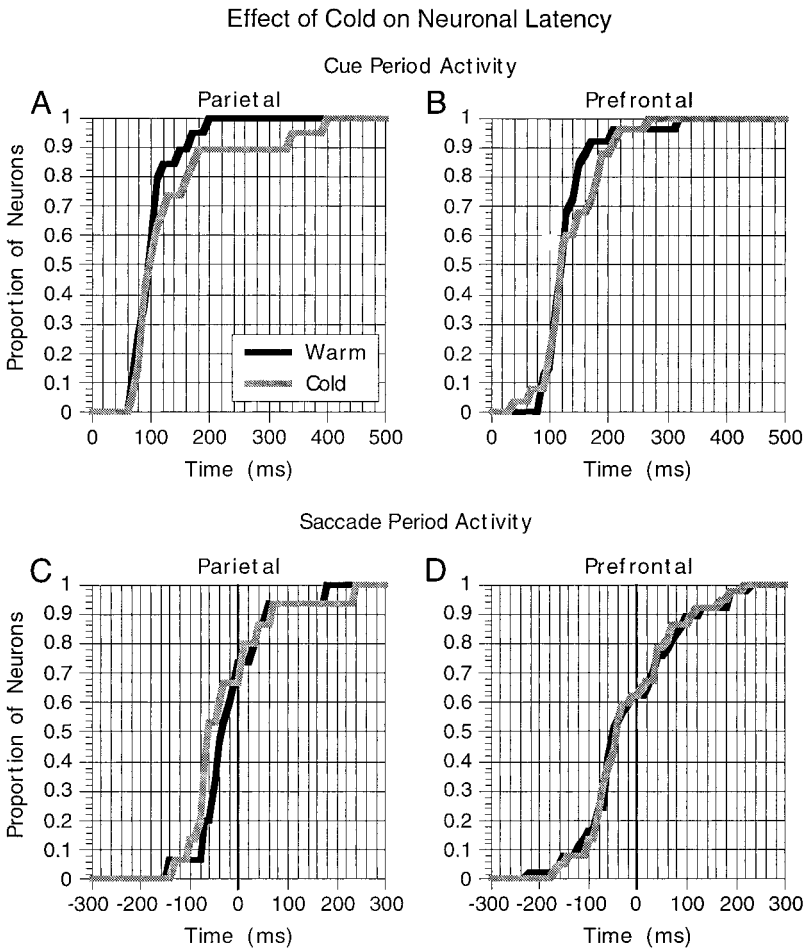

FIG. 14. Effects of cold on neuronal latency. Latency of neuronal activation relative to the onset of the cue (*A* and *B*) and the initiation of the memory-guided saccade (*C* and *D*) were determined for each neuron. Recruitment curves show the cumulative percentage of the population of neurons that have become active at successive time points during cue and saccade periods in parietal (*A* and *C*) and prefrontal (*B* and *D*) cortex. *A* and *B*: activation of parietal and prefrontal neurons during the cue period. Recruitment curves overlap early in the cue period and diverge after ~120 ms with activation on warm trials preceding that on cold trials. Trend was not significant, however. *C* and *D*: activation of parietal and prefrontal neurons during the saccade period. Recruitment curves largely overlap in both parietal (*C*) and prefrontal (*D*) cortex.

only one direction between parietal and prefrontal neurons. Instead, they argue that all neuronal signals in this system are concurrently feedforward and feedback signals and consequently that the input prefrontal cortex provides to parietal neurons conveys the same signals as the input from parietal cortex to prefrontal neurons. This is supported by the symmetry of the effects of cooling parietal and prefrontal cortex on their shared activity. That the suppression of function of prefrontal cortex was able to modify the sustained modulation of neuronal activity during a working memory interval in a distant cortical area (Figs. 6, 9*C*, and 10, *A* and *B*) indicates that the role of prefrontal cortex in working memory may be partly carried out through its output projections to other cortical areas. It is of further interest that prefrontal cooling was effective in altering the response of posterior parietal neurons to the presentation of a visual stimulus in the present experiment. This argues for a prefrontal modulation of even early sensory processing taking place in posterior sensory association cortex, where neurons appear to be driven from two sides in effect, from earlier extrastriate areas on the one hand and prefrontal cortex on the other. Similar feedback influences on neuronal activation evoked by a visual stimulus have been described for V1 neurons, the responses of which can be suppressed by cryoinactivation of V2 (Sandell and Schiller 1982), and also for IT neurons, whose differential activation to the color of a cue stimulus diminishes under conditions of prefrontal inactivation (Fuster et al. 1985). Furthermore, in split-brain monkeys, prefrontal feedback can drive pattern-selective visual activity in inferotemporal neurons that have been otherwise deprived of feedforward visual input from ipsilateral extrastriate cortex (Tomita et al. 1999). Such a dynamic opens a possibility that dysfunction of prefrontal cortex also might impact sensory processing in disease states, contributing to pathology observed in schizophrenia, for example, that is associated with abnormalities in both anatomic and functional characteristics of prefrontal cortex (Goldman-Rakic and Selemon 1997) and also is characterized by sensory hallucinations.

Both enhancement and suppression were observed

In the present experiments, cooling was associated both with enhancement and suppression of the response magnitude observed before cooling, depending on the neuron under study. A similar mixture of enhanced and suppressed unit responses after cryoinactivation has been reported in several studies of corticocortical interaction between striate and extrastriate cortex (Girard et al. 1992; Rodman et al. 1989; Sandell and Schiller 1982), between prefrontal and inferotemporal cortex (Fuster et al. 1985), and between prefrontal and posterior parietal cortex (Quintana et al. 1989). Corticocortical projections target both pyramidal neurons and also GABAergic interneurons within the target area (Somogyi et al. 1998). As such, cooling the neurons that give rise to a corticocortical

projection would be expected to produce a mixture of effects on target pyramidal neurons, a direct suppression of their activity as the level of excitatory input they received was reduced and an indirect augmentation of activity, as excitatory drive to interneurons was reduced and pyramidal neurons in their vicinity were released from inhibition. Although GABAergic interneurons are less numerous than pyramidal cells by ~5 to 1, in the case of basket and chandelier cells, the output of each targets ~300 surrounding pyramidal neurons (Salin and Bullier 1995). Reduced drive to a small number of interneurons could impact a much larger number of pyramidal cells. There is also supporting evidence that activation of corticocortical inputs can produce an exclusively inhibitory influence in some target neurons. Intracellular recording of motor cortical pyramidal neurons demonstrated that in a minority of cases, stimulation of corticocortical inputs from premotor and somatosensory cortex produced inhibitory postsynaptic potentials without a preceding excitatory postsynaptic potential (Ghosh and Porter 1988). In the present data, perhaps the clearest difference between prefrontal and parietal cooling related to the augmentation of saccade period activities during cooling. The degree of augmentation was stronger in this task period when prefrontal cortex was cooled and parietal neurons recorded from than the converse (Fig. 10*B*).

It is also possible that cooling directly enhanced the activity of some neurons within the cooled cortical region and so increased their output. Cooling depolarizes the resting membrane potential and if cooling is slight (5° below normal temperature), higher firing rates result (Adey 1974). Neurons have been observed to discharge repetitively at somewhat colder temperatures (9° below normal temperature) before entering a state of electrical silence (Moseley et al. 1972). Thus neurons cooled to intermediate temperatures may have exhibited an increased level of activity, contributing to the augmentation of neuronal activity we observed in the target cortical region.

Both the enhancing and depressing effects of cooling observed in the present experiments support the view that corticocortical projections within the same hemisphere, perhaps in addition to influencing the temporal structure of spike trains, can and do directly influence the total number of spikes emitted by target neurons during a given behavioral epoch, contributing therefore to changes in average firing rate over time, or rate coding, as this feature of neuronal physiology has been termed (Shadlen and Newsome 1994).

COOLING COMMONLY MODULATED BUT DID NOT BLOCK NEURONAL ACTIVATION. Cooling effects were common in the present results; firing rates of the majority of the current sample of task-related neurons were significantly different at cold temperatures. Some of these significant effects were nonetheless subtle, and the general pattern of activity across the ODR trial typically persisted through cryoinactivation. The effects of cooling were on average ±40% of the activity level in a given task epoch measured before cooling began (Fig. 10). In the monkey visual system, cryoinactivation of area V1 completely silences neurons in areas V2–V4 the receptive fields of which overlap those represented in the inactivated portion of V1 (Salin and Bullier 1995). However, in cases where projections exist to circumnavigate the blocked projection (such as the cat where LGN projections target V2), the effects of cooling V1 are commonly less complete (Salin and Bullier 1995). In the present experiments, two structures in association cortex were examined that share reciprocal projections with 15 cortical structures (Selemon and Goldman-Rakic 1988). Thus the network of input projections that could convey activity potentially relevant to ODR performance into parietal and prefrontal cortex is broadly distributed. Among the cortical projections alone, this network includes inputs from area STP in the upper bank of the superior temporal sulcus (Seltzer and Pandya 1984,1989) and from other extrastriate cortical areas (Barbas and Mesulam 1981; Cavada and Goldman-Rakic 1989; Huerta et al. 1987) as well as from area 7m located on the medial wall of the cerebral hemisphere (Cavada and Goldman-Rakic 1989), all of which are potential conduits for parallel visual input to prefrontal and parietal cortices initiating the chain of events producing delay and ultimately saccade-related neuronal responses within them.

Direct interaction between areas 7ip and 8a

The experimental technique presently employed did not limit inactivation to parietal area 7ip and prefrontal area 8a nor was inactivation of these areas (particularly area 7ip) complete. However, the volumes of cooled cortex included substantial portions of both areas 7ip and 8a (Figs. 3 and 4). Projections between parietal area 7ip and prefrontal area 8a are strong and selective (Andersen et al. 1985a, 1990a; Barbas 1988; Cavada and Goldman-Rakic 1989; Schall et al. 1995). Granting the technological limitations of the cooling method employed, the preferential interconnection of areas 8a and 7ip suggest that changes in neuronal activation we observed in each cortical area were mediated at least in part by changes that cooling imposed on the direct interaction between the two. Thus the cooling effects observed in prefrontal area 8a, for example, were much more likely to be due to partial cooling of area 7ip with which it is directly and reciprocally connected (Cavada and Goldman-Rakic 1989) than to partial cooling of areas surrounding 7ip (such as area 5) that are indirectly or not at all connected to area 8a. However, cooling of some parietal areas, such as areas 7a and DP, were more likely to contribute to the observed effects as these areas both contain neurons that are modulated during ODR performance (Chafee and Goldman-Rakic 1998) and project to prefrontal area 8a (Andersen et al. 1990a). Similarly area 46 in the principal sulcus contains neurons that are driven during ODR performance (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989), and the posterior principal sulcus projects to area 7ip (Cavada and Goldman-Rakic 1989). The present results can be characterized therefore as the effect on the neuronal activity specifically within parietal area 7ip and prefrontal 8a of cooling groups of neighboring areas in each cortical region including but not limited to these two areas.

We estimate, on the basis of the depth of the recorded neurons, the measured temperature-depth relationship (Fig. 3), and a study of the direct effects of cooling in the striate cortex (Girard and Bullier 1989), that cooling suppressed neuronal activation by ≥80% in the majority of neurons in parietal area 7ip and prefrontal area 8a. This represents a substantial if incomplete reduction in output. There is further evidence in a number of systems that the physiological response to cold at this level and beyond is graded and progressive (Gahwiler et al.

1972; Girard and Bullier 1989; Jasper et al. 1970; Moseley et al. 1972). Deeper inactivation of parietal area 7ip or prefrontal area 8a therefore might be expected to produce stronger effects in more neurons but may not be expected to yield substantively different results from those presently obtained. The possibility cannot be excluded at present, however, that an asymmetry in the physiological effects of inactivating areas 7ip and 8a might not emerge if total inactivation of each area was achieved. Finally, changes in neuronal activity we observed may have been secondary to changes in oculomotor behavior that cooling produced. Arguing against this interpretation of the results was the finding that cooling parietal and prefrontal cortex produced largely equivalent effects on neuronal physiology but had differential effects on ODR performance.

The results of the present experiment agree with work in other distributed cortical networks in the visual (Bressler 1995,1996; Payne et al. 1996; Salin and Bullier 1995) and motor systems (Alexander and Crutcher 1990a,b; Ashe and Georgopoulos 1994; Caminiti et al. 1996; Crutcher and Alexander 1990; Johnson et al. 1996) to indicate that patterns of neuronal activity recorded within a single cortical area are likely to reflect concurrent processing in many others. Taken in conjunction with anatomic data indicating the prevalence of projections between cortical areas (Felleman and Van Essen 1991), the present data support a dynamic view in which the patterns of neuronal activity modulation associated with behavioral events are generated by the concerted action of groups of interacting cortical areas. This interaction appears to involve the flux across cortical areas of a group of shared signals exchanged between neurons with similar patterns of activity modulation. The present data favor the inclusion of working memory in such a process through which prefrontal cortex and other cortical areas interact to drive the sustained neuronal discharge associated with the formation and maintenance of internal representations.

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