Dissociation of Spatial-, Object-, and Sound-Coding Neurons in the Mediodorsal Nucleus of the Primate Thalamus

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Tanibuchi, Ikuo, and Patricia S. Goldman-Rakic. Dissociation of spatial-, object-, and sound-coding neurons in the mediodorsal nucleus of the primate thalamus. J Neurophysiol 89: 1067–1077, 2003; 10.1152/jn.00207.2002. The mediodorsal nucleus (MD) is the thalamic gateway to the prefrontal cortex, an area of the brain associated with spatial and object working memory functions. We have recorded single-neuron activities from the MD nucleus in monkeys trained to perform spatial tasks with peripheral visual stimuli and a nonspatial task with foveally presented pictures of objects and faces—tasks identical to those we have previously used to map regional specializations in the dorsal- and ventro-lateral prefrontal cortex, respectively. We found that MD neurons exhibited categorical specificity—either responding selectively to locations in the spatial tasks or preferentially to specific representations of faces and objects in the nonspatial task. Spatially tuned neurons were located in parts of the MD connected with the dorsolateral prefrontal cortex while neurons responding to the identity of stimuli mainly occupied more ventral positions in the nucleus that has its connections with the inferior prefrontal convexity. Neuronal responses to auditory stimuli were also examined, and vocalization sensitive neurons were found in more posterior portions of the MD. We conclude that MD neurons are dissociable by their spatial and nonspatial coding properties in line with their cortical connections and that the principle of information segregation in cortico-cortical pathways extends to the “association” nuclei of the thalamus.

INTRODUCTION

Thalamo-cortical afferents to the prefrontal cortex originate in the mediodorsal nucleus (MD) of the dorsal thalamus. Like the prefrontal cortex, this nucleus expands and differentiates in phylogenetic evolution (Rose and Woolsey 1948; Walker 1940). The MD can be differentiated into subnuclei based on cytoarchitectonic criteria (Olszewski 1952; Walker 1940) and topographically organized projections to distinct prefrontal areas (Akert 1964). In the macaque monkey, the dorsolateral portion of the MD projects to the dorsolateral prefrontal cortex and its ventrolateral portion projects to the inferior convexity of the prefrontal cortex (Akert 1964; Goldman-Rakic and Porro 1985; Kevit and Kuypers 1977; Siwek and Pandya 1991). This nucleus has also been shown to be a key node in the cortico-striato-thalamo-cortical positive feedback network that is compromised in Parkinson’s disease and other basal ganglia disorders (Byne et al. 2000; Eidelberg et al. 2000; Lenz et al.

1999). Recent evidence has implicated the MD as a site of a degenerative process in schizophrenia (Byne et al. 2001; Pakkenberg 1990, 1992; Popken et al. 2000; Young et al. 2000). Anatomical and neurophysiological studies in primates and fMRI studies in humans carried out over the past decade have revealed areas and regions of distinct regional specializations within the prefrontal cortex (e.g., Courtney et al. 1998; Demb et al. 1995; Sweeney et al. 1996). In the rhesus monkey, neurons in the dorsolateral prefrontal cortex (Walker’s areas 46 and 8) have been shown to encode the location of objects in working memory (Boch and Goldberg 1989; Chafee and Gold- man-Rakic 1998; Funahashi and Inoue 2000; Funahashi et al. 1989; Fuster 1973; Fuster and Alexander 1973; Kikuchi-Yo- rioka and Sawaguchi 2000; Kubota and Niki 1971; Thompson and Schall 1999), whereas, in contrast, prefrontal neurons in Brodmann’s areas 12/45 have been shown to respond selectively and robustly to the identity of objects, including pictures of animal and human faces or forms (Freedman et al. 2001; O’Scalaidhe et al. 1997, 1999; Wilson et al. 1993) or to the properties of tactile stimuli (Romo et al. 1999) and most recently to human and animal vocalization (Romanski and Goldman-Rakic 2002). In line with receptive-field mapping of the prefrontal cortex (Mohler et al. 1973; Suzuki and Azuma 1983), the dorsal-ventral specializations in visual memory may be associated with the disposition of visual association afferents representing the peripheral and central portions of the visual fields, respectively (Adams et al. 2000; Barbas and Mesulam 1981; Cavada and Goldman-Rakic 1989; Neal et al. 1990). These regional specializations are in line with the principle of multiple parallel pathways governing the organization of cortico-striato-thalamo-cortical networks (Alexander et al. 1986).

In spite of MD’s close anatomical and functional association with the prefrontal cortex, the exact nature of its contribution to the executive processes carried out in the prefrontal cortex remains obscure. Accordingly, the present study was designed to explore the coding properties of MD neurons and to determine whether they express either or both spatially tuned responses characteristic of dorsolateral prefrontal neurons and preferential responses to faces or objects similar to that found in the inferior prefrontal areas. Based on evidence of broad regional differentiation of the prefrontal areas, we expected that the coding properties of neurons in the dorsal thalamus...
would also be related to their location within the MD and hence to the topography of thalamo-cortical connectivity. Evidence of segregated spatial and nonspatial processing streams within the MD would extend the organizational principle of parallel processing that governs cortico-cortical and cortico-striatal circuits to the “association nuclei” of the dorsal thalamus and would further illuminate the functional organization of the cortico-striato-thalamo-cortical system of the mammalian brain.

**METHODS**

**Subjects**

Two adult rhesus monkeys (Macaca mulatta, male, 9.0–11.0 kg) were trained to perform oculomotor and nonspatial tasks as described in Fig. 1 and in previous publications (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989–1991; O’Scalaidhe et al. 1997, 1999; Romanski and Goldman-Rakic 2002; Wilson et al. 1993). All procedures in the training, surgery, recording, and housing of the monkeys were done in accordance with the Yale University Animal Care and Use Committee and National Institutes of Health Guidelines.

**Surgical procedures**

Prior to surgery, the borders of the MD were identified in MRIs of the monkeys in both coronal and horizontal planes. The surgery for implant of search coils, head bolts, and recording cylinders was conducted under aseptic conditions and pentobarbital anesthesia. The search coils were implanted as described by Judge et al. (1980). Based on the MRI findings, a trephine hole was made in the skull overlying the MD, and a stainless steel chamber for recording was implanted over that opening. Using stereotaxic coordinates, the chamber was tilted laterally by 7° in order that a recording electrode, directed to the medial part of the MD, might not puncture the sagittal sinus. A stainless steel head holder was affixed to the skull with dental acrylic for restraint of the head during recording sessions. The implant was reinforced with stainless steel screws anchored to the skull with dental acrylic.

**Experimental procedures**

Training sessions began approximately 1 mo after surgery. The monkey’s eye movements and position were monitored using a scleral search coil technique (Robinson 1963). An experimental program (Monk) on a PDP-11 computer presented visual stimuli on a 19-in color video monitor, sampled single neuron activity and gaze coordinates, and delivered drops of juice for successful responses. Recording sessions of several hours occurred every other day. After the experimental session, the monkey was returned to its home cage and given full water, food, and fruit. Body weight was regularly monitored.

**Behavioral tasks**

The monkey faced the video monitor in a dimly lit and sound-attenuated room. The two monkeys were trained on an oculomotor delayed-response (ODR) task, a visually guided saccade (VGS) task, a picture fixation (PICT) task, and an auditory fixation (AUD) task. A fixation point (0.5° square; white for the oculomotor tasks and red for the nonspatial tasks) was presented at the center on the video monitor, and the eight peripheral cues (0.5° white square) with 45° angular separation between them were presented at 13° eccentricity from the fixation point in the oculomotor tasks (Fig. 1).

The ODR task was used to test spatial working memory as previously described (Fig. 1) (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989). Each trial was initiated by the monkey fixating on the central target for 0.5 s, whereupon the visual cue was presented at one of the eight peripheral locations (13° eccentricity) for 0.2 s. The cue location was pseudorandomized across trials so that the monkey could not predict the location of the cue on each trial. The animal was required to maintain fixation within an invisible circular window of 3° in diameter centered on the fixation point throughout sequential task epochs: 0.5-s fixation period, 0.2-s cue period, and 3.0-s delay period.

![FIG. 1. Oculomotor delayed-response (ODR), visually guided saccade (VGS), picture fixation (PICT), and auditory fixation (AUD) tasks employed in this study. Top: timing of events in the ODR task. 1: fixation period, 0.5 s; 2: cue presentation, 0.2 s; 3: delay period, 3.0 s; 4: memory-guided saccade. The cue was pseudorandomly presented on each trial at 1 of 8 locations as shown at the bottom right. Top middle: diagram of events in the VGS task. 1: fixation period, 0.5 s; 2: visual-guided saccade. The cue was presented in the same manner as in the ODR task. Bottom middle: diagram of events in the PICT task. 1: fixation period, 0.5 s; 2: stimulus presentation, 1.0 s; 3: poststimulus fixation period, 0.5 s. Bottom: diagram of events in the AUD task. 1: fixation period, 1.0 s; 2: auditory-stimulus presentation, 1.0 s.](http://jn.physiology.org/lookup/doi/10.1152/jn.00974.2002)
The fixation point disappeared at the end of the delay, instructing the monkey to make a saccade to the remembered location within 0.5 s after the disappearance of the fixation target. A saccade within the prescribed 3–6° window encircling the cue was rewarded with a few drops of juice.

In the VGS task (Fig. 1), the monkey was required to look at the fixation point and to maintain fixation for 1.0 s. The fixation point disappeared, and, simultaneously, the visual cue appeared at one of the eight randomly determined peripheral locations for 0.5 s as in the ODR task. In this task, the monkey made a sensory-guided saccade for a juice reward. Cells that exhibited fixation related responses either in this or in the ODR task were excluded from further analysis and are not reported in this study.

The PICT task was designed to map nonspatial functions by identifying neurons that are responsive to the identity or attributes of an object. As shown in Fig. 1, the monkey was required to maintain fixation throughout all task epochs, which included, in sequence, central fixation (0.5 s), pictorial stimulus (1.0 s), and poststimulus fixation (0.5 s). Stimuli consisted of 40 sets of seven colored pictures of faces and other objects as described in O’Scalaidhe et al. (1999). The sequence of pictures within each set was randomly varied.

The AUD task was employed to test auditory-responsive neurons while the monkey maintained fixation throughout a trial. A trial consisted of a 1.0-s fixation period followed by presentation of an auditory stimulus through two small speakers placed to each side of the video monitor at peak intensity of 70–80 dB for 1.0 s. The AUD task consisted of 10 sets of 10 auditory stimuli, made up of whistles, artificial and instrumental sounds, animal and human voices, and so forth as in Romanski and Goldman-Rakic (2002).

Recording procedures

Single-neuron activity was recorded with either tungsten (FHC, 1.2–2.5 MΩ at 1 kHz) or Elgiloy microelectrodes (0.8–1.5 MΩ at 1 kHz). The electrode was advanced by a micromanipulator (Narishige, MO-951) aimed at the MD. We first surveyed the MD with reference to the MRI photographs to determine the location of neurons responding to the oculomotor and sensory tasks. Thereafter, neuronal recording was concentrated in the portions of the MD where responsive neurons were clustered. The on-line computer system sampled neuronal and ocular position signals and stored these data in relation to task events on magnetic media. Data were stored as event buffer files and analog buffer files.

Data analysis

Rasters and histograms of neuronal activity aligned to different task-related events were first examined visually and then statistically analyzed.

ODR and VGS TASKS. Each trial of the ODR task was divided into four epochs (cue, delay, pre, and post). The analysis of cue-related responses was determined over a 0.5-s time segment, which spanned the cue and 0.3 s of the postcue period.

We defined as saccade-related activity any response arising during any time between 0.25 s preceding the initiation of the saccade and 0.5 s after the initiation of the saccade. Saccade-related activity was further classified into presaccadic (pre) and postsaccadic (post) responses; any response starting before and after the initiation of the saccade, respectively. A repeated-measures two-way ANOVA (P < 0.05) performed on the ODR data with task epoch and direction as factors followed by contrasts of firing rates in the four epochs (cue, delay, pre, and post) against firing rates in the 1.0-s intertrial interval (ITI). Firing rates were calculated for the pre- and postsaccadic epochs of the VGS task (0.25 and 0.5 s, respectively) and compared with the ITI in the same way as those of the ODR task. For present purposes, we considered a neuron engaged in spatial processing if it exhibited spatial tuning in any epoch of either the ODR or VGS tasks.

PICT and AUD TASKS. For data analysis purposes, each trial in the PICT and AUD tasks was divided into four time windows: fix, phasic, tonic, and post. In the PICT tasks, the fix period started 0.1 s after the initiation of the fixation target and lasted for 0.4 s. In the AUD task, the fix started 0.5 s after the initiation of the fixation target and lasted for 0.5 s. The other time windows were the same for both tasks: the phasic epoch began at the onset of the pictorial/sound presentation and lasted for 0.2 s. (data not reported here for simplicity.) The tonic period spanned 1.0 s throughout stimulus presentation. The post epoch began at stimulus offset and lasted for 2.0 s. A repeated-measures two-way ANOVA (P < 0.05) was applied to each neuron with stimulus and time window as factors; specific comparisons were made between firing rates in each of the four periods (fix, phasic, tonic, and post) and the 1.0-s ITI. Neurons showing a significant main effect of stimulus or a significant interaction between stimulus and time window were considered selectively responsive. All other responsive neurons were regarded as nonselective (see O’Scalaidhe et al. 1999 for details).

Latencies. Latencies of saccadic responses were determined for the neuron’s preferred target direction, using the method of MacPherson and Aldridge (1979). Summed histograms of unit activity aligned at the initiation of the saccade were smoothed by a Gaussian function with a SD of 15 ms to generate continuous spike density functions (SDFs). The control period was 1 – 2 s before the initiation of saccades, and the mean and SD of the SDF determined during the control period established a 95% confidence interval (Chafee and Goldman-Rakic 1998). The response latency was defined as the midpoint between the first intersection of the corresponding SDFs with the upper (or lower) limit of the confidence interval and the first peak of responses that were sustained for at least 0.1 s beyond the confidence interval. The first intersection for saccadic response started at 0.25 s before saccade initiation. Latency detection in both PICT and AUD tasks was determined similarly using as the control periods the 0.5 s of the fixation periods preceding the onset of visual or sound stimuli, respectively.

Spatial Tuning of Saccadic Response. The spatial selectivity of neurons with task event-related activity was quantitatively analyzed by the Gaussian curve method (Bruce and Goldberg 1985). Tuning curves were obtained by determining the parameters of the Gaussian function that best fit (least χ²) the mean firing rates of these neurons for eight cue directions as described in Chafee and Goldman-Rakic (1998).

Reconstruction of Recording Sites

Anterior-posterior (A-P), medial-lateral (M-L), and dorsal-ventral (D-V) values were recorded for all neurons. For accuracy, the depth of the recording electrodes was measured as follows. At the end of each session, the microdrive assembly, containing the recording electrode in fixed position, was mounted on a cylinder that had been permanently attached to a microscope. This procedure allowed us to accurately measure the depth of the deepest recording site in a session by measuring its distance from a fixed starting point. The difference in depth among the different electrodes used throughout the study was then calculated and used for more exact mapping of recording sites. Stainless steel electrodes were used to make marking sites for the tungsten electrode tracks in the course of the recording session. The electrodes were inserted through the same guide tube, and iron deposits were then made by passing DC current (10–20 μA, 0.5–1.5 min, tip positive). Elgiloy electrodes were kept attached to the microdrive over 7–15 sessions depending on their viability. After an electrode was exhausted, iron deposits were made by employing the same procedure as with stainless electrodes (Fig. 2). After perfusion, the iron deposits were used as landmarks for the reconstruction of recording sites (Fig. 2). On completion of the recordings, one of the monkeys was killed with an overdose of pentobarbital sodium and perfused intracarci-
ally with heparinized saline, followed by buffered 4% formalin with potassium ferrocyanide. The other monkey died prematurely and accidentally, but its brain was saved and postfixed for 6 mo before processing. Both brains were soaked in 0.1 M phosphate buffer containing 30% sucrose buffer at 4°C. The blocks including thalamic recording sites were cut into frontal sections of 40 or 60 μm thickness on a freezing microtome stage. Every other section was stained with neutral red and cresyl violet, respectively. Tissue shrinkage in the two brains was calculated to be 84 and 93%, respectively, on the basis of stereotaxically defined A-P, L-M, and D-V iron deposits. The location of individual units recorded by each electrode was reconstructed from these A-P, L-M, and D-V coordinates and from identification of iron deposits on specific electrode tracks with recorded A-P, L-M, and D-V locations and trajectories of electrode penetrations (Fig. 2). Unmarked electrode tracks and units were interpolated between anatomically recovered tracks. Nomenclature and delineation of the thalamic nuclei followed Olszewski (1952).
TABLE 1. Number of MD, LP, and LD neurons examined by spatial and nonspatial tasks

<table>
<thead>
<tr>
<th>Tasks Examined</th>
<th>MD</th>
<th>LP</th>
<th>LD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODR</td>
<td>204 (34)</td>
<td>43 (3)</td>
<td>18 (3)</td>
<td>265 (40)</td>
</tr>
<tr>
<td>VGS</td>
<td>150 (32)</td>
<td>51 (8)</td>
<td>15 (4)</td>
<td>216 (44)</td>
</tr>
<tr>
<td>ODR + VGS</td>
<td>127 (39)</td>
<td>35 (5)</td>
<td>12 (5)</td>
<td>174 (49)</td>
</tr>
<tr>
<td>ODR or VGS + PICT</td>
<td>115 (16)</td>
<td>40 (6)</td>
<td>3 (0)</td>
<td>158 (22)</td>
</tr>
<tr>
<td>ODR or VGS + PICT + AUD</td>
<td>75 (5)</td>
<td>19 (1)</td>
<td>1 (0)</td>
<td>95 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>227 (75)</td>
<td>59 (16)</td>
<td>21 (6)</td>
<td>307 (97)</td>
</tr>
</tbody>
</table>

MD, mediodorsal; LP and LD, lateral posterior and dorsal, respectively; ODR, oculomotor delayed response; VGS, visually guided saccade; PICT, picture fixation; AUD, auditory fixation. Number in parentheses represents responsive neurons.

RESULTS

Our findings are based on the study of 307 neurons of which 97 were related to one or more tasks, as shown in Table 1. The large number of unresponsive cells reflects our mapping strategy, which was to canvass large areas of the MD and surrounding nuclei to better define the borders of territories containing functionally relevant neuronal activity. Task-relevant neurons were recorded mainly in the left hemisphere primarily in the MD but also in portions of the lateral posterior (LP) and lateral dorsal (LD) nuclei, which border the MD. Although not all neurons were examined in all tasks, each neuron in this report was examined in at least one spatial task (Table 1). Virtually all of the task-related neurons examined in spatial and nonspatial behavioral tasks were recovered in postmortem reconstructions of electrode tracks. Figure 2 presents the reconstructed recording sites in the two monkeys on drawings of cytoarchitectonic divisions of the macaque dorsal thalamus (Olszewski 1952). Recording sites spanned from AP +1.5 to +9.3 mm in front of the interaural line, spanning approximately 7.8 mm and extending the full width of the MD from about 1 to 5 mm lateral to the most medial border of the MD (Fig. 2). The physiological findings are presented below with reference to the anatomical localization of recording sites in the MD and in the adjacent LP and LD nuclei.

Spatially tuned MD neurons

We found that MD neurons (n = 34) exhibited significant (P < 0.05) event-related changes of firing rate in the ODR task similar to those recorded in areas 46 and 8a of the prefrontal cortex. As expected from previous studies of the MD employing the classical manual delayed-response task (Fuster and Alexander 1973; Isseroff et al. 1982), the MD contained all classes of event-related neuronal activities that are present in the prefrontal areas. In our present sample of ODR-responsive neurons, saccade-related neurons were most prominent, as they are in prefrontal areas. Presaccadic-responsive neurons (73%) were more than twice as frequent as postsaccadic ones (27%) and had a mean latency of 70.8 ± 43.2 ms (range 160 to −4 ms), whereas the postsaccadic neurons’ latencies averaged 132.4 ± 97.4 ms (range 24–288 ms).

The striking finding from this study is the degree of stimulus specificity exhibited by MD neurons with task-related responses. The neuron shown in Fig. 3, u11438, responded preferentially to the 45° target in the presaccadic period of the ODR task with a latency of −12 ms but was unresponsive in the VGS task. This neuron also did not respond to any of 21 pictures of objects and faces presented in the PICT task or to any of 20 auditory stimuli presented in the AUD task. Neuron u20388, shown in Fig. 4, exhibited a spatially tuned postsaccadic burst during the VGS task but was unresponsive in the ODR task and likewise unresponsive to any of the nonspatial stimuli presented in the PICT task. These few spatially tuned neurons that did respond in the PICT task were nonselective, i.e., they responded to every PICT stimulus presented (Fig. 5). Overall, not even one of 39 spatially tuned ODR and/or VGS-responsive neurons tested on the PICT task (blue circles in Fig. 2) was preferentially responsive to pictures presented in the latter task. Similarly selective neurons were found in recordings from the LP and LD, indicating that the system for mediating sensory- and/or memory-guided saccades extends to thalamic nuclei with projections to the posterior parietal areas (Asanuma et al. 1985; Jones et al. 1979; Kasdon and Jacobson 1978; Pearson et al. 1978; Schmahmann and Pandya 1990) where neurons also exhibit sensory- and memory-guided spatially tuned activity (Andersen et al. 1985; Chafee and Goldman-Rakic 1998; Gnadt et al. 1988).
FIG. 3. An MD neuron (u11438) with tuned saccade-related activities during the ODR task but lacking responsivity during the VGS, PICT, and AUD tasks. Top: rasters and summed histograms of neuron u11438 with tuned presaccadic activity (but lacking cue and delay activation during the ODR task). This neuron, recorded on the border of the MDMf (Fig. 2, AP +6.3 panel) had an optimal phasic excitatory response with a latency of ~12 ms preceding saccade initiation to the upper right (45°). Top middle, left: rasters and histograms for the preferred direction (45°) aligned at the time of response initiation in the ODR task. Top middle, right: plots show mean firing rates measured during the response period for the 8 different cue directions. The tuning curve is a Gaussian function fit (least $\chi^2$ to the mean firing rates. Mean firing rate for each saccade direction was measured from 200 ms before to 300 ms after initiation of the saccade. Bottom middle, left: this cell was not activated for saccades toward any of the 8 peripheral cue locations in the VGS task. Rasters and histograms show its neuronal activity for the cue presentation at 45° in the VGS task, the direction for which this neuron had an optimal presaccadic response in the ODR task. Bottom middle, right: this neuron was unresponsive in the AUD task. Rasters and histograms show the neuron’s unit activity to 1 of 20 auditory stimuli presented in the AUD task; Bottom: this neuron was unresponsive to any of 21 pictures of objects/faces presented in the PICT task. Rasters and histograms show neuronal responses to a picture of a monkey face (left). The average firing rates of this neuron for 8 of 21 stimuli presented in the PICT task are also shown (right). F, C, D, R, and post fixation, cue, delay, response, and postfixation periods, respectively. Note that in this and in Figs. 4–7, certain images have been adulterated to protect the privacy of individuals from whom permissions were not obtained and/or copyright requirements.

Object/face selective neurons

A novel finding in this study is that PICT stimuli were effective stimuli for a subset (16/115, 14%) of the MD neurons tested with picture stimuli. Sixteen of these neurons significantly changed their firing rate [14 increased, 2 decreased; response latency: 196.9 ± 72.5 (SD) ms; range: 68–296 ms] when the monkeys viewed particular stimuli in the PICT task but were unresponsive during cue, delay, or response periods of either visuospatial task examined. Neuron u20698, shown in Fig. 6, responded only to a picture of a female face and to no other stimuli presented to the monkey. Although this was the most selective neuron recorded in the MD, most other neurons preferentially responded to several objects and faces. Another striking example of a PICT selective neuron is shown in Fig. 7. The preferred stimulus of this neuron, recorded in the LP, was a picture of a bright geometrical object (Fig. 7). This neuron was unresponsive to any event in either the ODR or VGS tasks. None of the six LP neurons that exhibited preferential re-
responses to PICT stimuli were responsive in the oculomotor tasks. Aurally selective neurons

We also tested the responses of a subset of MD neurons to auditory stimuli. Of the 75 neurons that were tested in one or both oculomotor tasks, the PICT task, and the AUD task, only 5 (7%) responded to auditory stimuli. Nonspatial auditory responses are similarly rare in the prefrontal cortex (Romanski and Goldman-Rakic 2002). The neuron shown in Fig. 8 was selectively responsive to seven sounds such as a bird song (top left) and a high-frequency tone (top right) but not to 33 other sounds including a low-frequency tone (middle left). Further, the cell had no significant activations to any of 28 pictures of objects/faces presented in the PICT task (middle right) or to any epoch in the ODR (bottom) and VGS tasks. Although we canvassed a wide area of the MD for auditory responses, all five auditory responsive neurons were located in the posterior portion of the MD (Fig. 2). Further exploration of this part of the thalamus with a more extensive battery of auditory stimuli may reveal more numerous auditory responsive cells and a greater variety of auditory responses.

Correlation of physiology and anatomy

After the termination of the experiments and after histological processing of the brains, the location of recording sites was determined by full reconstructions as described in METHODS. We found that most of the spatially tuned neurons in the MD (blue and green circles in Fig. 2) were located in the lateral half of the MD where the multiform and parvocellular divisions of the nucleus are prominent. Only one of the spatially tuned neurons (1/18) appeared to be located in the magnocellular MD at the border with the MDpc (+6.3 panel in Fig. 2). As shown in Fig. 2, the majority of PICT selective neurons (red triangles in Fig. 2) were also located laterally in the MD, and all but three of them were positioned ventral to the ODR/VGS-responsive neurons. An important caveat is that although we attempted to map a large area of the MD, including its medial magnocellular division, most of our recordings were in the lateral half of the nucleus. It is likely that we have underestimated the degree of domain specificity within the MD and it is also possible that there may be considerable overlap in the domain “maps” suggested by our present results.

FIG. 5. A MD neuron (u20910) with clear but nonselective responses in the PICT task but spatially tuned responses in the ODR and VGS tasks. Top: neuron u20910, recorded in the MDpc (Fig. 2, AP + 5.1 panel), showed optimal activation to cue presentation at the right (0°) and similar tuning in the ODR task. Bottom: this cell responded nonpreferentially to all 84 picture stimuli presented in the PICT task. Rasters and histograms show its neuronal activity to 4 pictures in the PICT task.

FIG. 6. Rasters and histograms of an MD neuron (u20698) documenting its selective response to a picture of a particular female face. Neuron u20698 was identified in the ventrolateral MD of the AP + 5.1 panel in Fig. 2. A: this neuron was selectively responsive only to the picture of 1 of 2 female faces with a response latency of 156 ms (left) and unresponsive to any of 27 pictures, including human and monkey faces and objects (right). B, the average firing rate of the face selective neuron to its preferred stimulus and to a subset of other stimuli presented to this neuron in the PICT task. C: tuning curves of u20698’s activity during the cue, delay, and response epochs of the ODR task. There were no significant activations in any ODR epoch with respect to intertrial activity; nor evidence of preferential response to any of the 8 target locations.
Dissociation of spatial and nonspatial processing coupled with the dorsal-ventral locations of recording sites within the MD provides evidence that the separation of the “what” and “where” visual processing streams that characterize the cortico-cortical distribution of visual information (Ungerleider and Mishkin 1982) can now be extended to the output of the projections of the prefrontal cortex onto the dorsal thalamus. Behavioral deficits in both visuospatial (Isseroff et al. 1982; Schulman 1964) and nonspatial object-based (Aggleton and Mishkin 1983) tasks have been observed after lesions in the MD in monkeys, and cognitive functions have been well documented in humans with MD lesions (e.g., Mair et al. 1979; Squire and Moore 1979; Victor et al. 1971). Segregation of function at the level of the thalamus affirms the principle of parallel processing through the cortico-striato-thalamic loop circuitry of the mammalian forebrain (Alexander et al. 1986).

**FIG. 8.** A: rasters and histograms of a broadly tuned MD neuron (u20271) with preferential responses to auditory stimuli. B: neuron u20271, shown at AP +2.7 in Fig. 2, was recorded in the posterior MD. C: tuning curves of this neuron’s activity during the cue, delay, and response periods of the ODR task. No significant tuning was observed in any ODR period.
Auditory coding in the MD

A small number of MD neurons were also selective for auditory stimuli, i.e., five neurons responded only to specific sounds but not to spatial or visual stimuli. Nor did neurons tested with object and face stimuli respond to aurally presented stimuli. These findings are indicative of separate channels for visually and aurally responsive neurons in the MD, similar to dissociations also observed in the inferior frontal cortex (Romanski and Goldman-Rakic 2002). It is very likely, based on cortical physiology and topography, that neurons responsive to sound localization and sound identification will constitute a further segregation in the MD of information processing within the auditory domain. The inferior prefrontal neurons have also been shown to be sensitive to the temporal order and spectral characteristics of sounds—properties that are fundamental to language processing in humans (Romanski and Goldman-Rakic 2002). It has been proposed that this portion of the inferior convexity region in the nonhuman primate might be homologous to the inferior frontal areas of the human brain, particularly as this region is connected with the auditory association cortex in the superior temporal gyrus (Rauschecker 1998; Romanski et al. 1999a,b). The caudal MD where the auditory-responsive neurons were found in the present study projects to the prefrontal cortex, but the data are not sufficiently detailed to determine whether they project specifically to the inferior regions containing similarly specialized neurons (Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Ray and Price 1993). Nevertheless, the aural responses of MD neurons mirror the auditory specializations of the prefrontal cortex much as the visual and spatially responsive MD neurons mirror the functional properties of the areas to which they project and from which they receive a rich cortico-thalamic innervation.

Source of signals in the MD

A key issue raised by our data is the source of the domain specificity of MD neurons. The primate dorsolateral MD receives its major afferents from the neocortex (Miller 1996; Rouiller et al. 1998; Rouiller and Welker 2000; Schwartz et al. 1991; Siwek and Pandya 1991; Veteran and Pandya 1994), the substantia nigra (Carpenter et al. 1976; Ilinsky et al. 1985) and the superior colliculus (Harting et al. 1980; Lynch et al. 1994). The visuospatial cue-, delay-, and response-related activities of dorsolateral MD neurons in the oculomotor tasks and the feature-specific responses of the cells in the ventrolateral MD may arise entirely or in large part from their respective cortico-thalamic projections, as in the case of antidromically defined cortico-tectal projections recently studied by Sommer and Wurtz (2001). The cortico-thalamic projections arise from both layers V and VI, the former forming giant axonal endings on the proximal dendrites of principal thalamic neurons (Rouiller et al. 1998; Schwartz et al. 1991). Either of these cortico-thalamic origins could be involved in feed-forward transfer of information, particularly sensory information, to the thalamus as discussed and predicted recently by Miller (1996) and Rouiller and Welker (2000). Because our latency measures were quite discrepant for presaccadic and postsaccadic responses, it is also possible that the sources of these signals in the MD are also distinct. Further study of this issue is necessary.

The MD also receives major input from the superior colliculus and the basal ganglia, both of which have a high proportion of saccade-related neurons (Hikosaka and Wurtz 1983; Hikosaka et al. 1989; Munoz and Wurtz 1995; Sommer and Wurtz 2000). In addition, experiments employing ortho- and antidromic stimulation have traced disinhibitory transmission from the dorsolateral prefrontal cortex to the MD via the basal ganglia (Kitano et al. 1998). Similar to findings in the caudate nucleus (Hikosaka et al. 1989) and the superior colliculus (Munoz and Wurtz 1995; Sommer and Wurtz 2000), neurons with presaccadic activities were by far the most common responses recorded in the MD. Further, we were impressed with the robust presaccadic responses observed relative to the sparsity of cue- and/or delay-related neurons. An appealing hypothesis concerning the function of ascending inputs to the thalamus is that they provide feedback to the cortex, through the cortico-striato-thalamic loop circuitry (Alexander et al. 1986), through the tecto-thalamic pathway (Sommer and Wurtz 2000), or through the convergence of both (e.g., Houk 1997, Teuber 1972). Such feedback could serve a role as an efference copy or corollary discharge signal if it arrived at the cortex nearly simultaneously with the issuance, not the execution, of the motor command (Sommer and Wurtz 2002). Neurons in the intermediate layers of the superior colliculus, for example, project both to the MD and to the pontine oculomotor centers, and it would be of interest to learn if these projections are collaterals of the same neurons. The MD sits at the hub of multiple transmission lines, and understanding the dynamic interactions of their messages should illuminate its normal contribution to cognitive operations as well as provide insight into the pathophysiology of disease like schizophrenia in which the working memory and smooth pursuit eye tracking systems of area 46 and 8a are compromised and MD neurons undergo degeneration.

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