European Journal of Neuroscience, Vol. 19, pp. 721–740, 2004

Comparison of learning-related neuronal activity in the dorsal premotor cortex and striatum

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Keywords: basal ganglia, conditional motor learning, frontal cortex, stimulus–response learning, visually guided movement

Abstract

Previous studies have reported learning-related changes in neuronal activity during conditional visuomotor learning, also known as arbitrary sensorimotor mapping, conditional visual discrimination, and symbolic or endogenous mapping. Qualitatively similar observations have been reported for the dorsal premotor cortex, the supplementary eye field, the prefrontal cortex, the hippocampus, the striatum and the globus pallidus. The fact that cells in both the dorsal premotor cortex (PMd) and the basal ganglia show changes in activity during associative learning enables a test of the hypothesis that cortex and basal ganglia function in distributed architectures known as cortical–basal ganglionic modules or 'loops'. We reasoned that if these loops represent functional entities, as proposed, then learning-related changes in activity should occur simultaneously in both the cortical and striatal nodes of a loop. The present results confirmed this prediction; as monkeys learned conditional visuomotor associations, neurons in the premotor cortex and associated parts of the putamen changed their rates at approximately the same time. For the largest number of neurons, the evolution in neural activity occurred in close correspondence to the monkeys' learning curves. As a population, however, learning-related changes in activity continued after the monkeys reached an asymptote in performance.

Introduction

Conditional visuomotor learning (CVML) allows animals to associate any discriminable visual stimulus with any response in a learned motor repertoire. In this form of learning, animals learn by trial and error to associate a stimulus with an action or the target of action, usually based on stimulus dimensions such as colour and shape (Passingham, 1993). Previous neurophysiological studies have related changes in neural activity to this kind of learning in a number of cortical areas, including the dorsal premotor cortex (PMd) (Mitz *et al*., 1991), the supplementary eye field (SEF) (Chen & Wise, 1995a,b), the frontal eye field (FEF) (Chen & Wise, 1995b), the prefrontal cortex (PF) (Asaad *et al*., 1998), and the hippocampus (Cahusac *et al*., 1993; Wirth *et al*., 2003), as well as in subcortical structures such as the striatum (Tremblay *et al*., 1998; Jog *et al*., 1999; Pasupathy & Miller, 2002) and globus pallidus (Inase *et al*., 2001).

Although the mechanisms underlying CVML remain incompletely understood, the fact that neuronal activity patterns evolve over time enables a test of a widely accepted tenant of forebrain organization. According to current thinking, the cerebral cortex and basal ganglia contribute to distributed functional modules called 'loops' (DeLong & Georgopoulos, 1981; Alexander *et al*., 1986; Strick *et al*., 1995). Houk & Wise (1995) called these loops cortical–basal ganglionic modules and suggested that they are one among many kinds of distributed, recurrent modular architectures in the motor system. In cortical–basal ganglionic loops, the cortex sends a nonreciprocated axonal projection to the striatum, which engages the striatal pathways that control the output of the globus pallidus, including its output to thalamocortical neurons, thus closing the loop. Despite the widespread acceptance of this idea, few experiments have been aimed at testing it. The present study compared neuronal discharge rates in PMd and in the striatum as monkeys learned new conditional visuomotor associations, with emphasis on those parts of the putamen that receive inputs from PMd (Takada *et al*., 1998b; McFarland & Haber, 2000). We reasoned that if the concept of cortical–basal ganglionic loops has functional validity, then changes in the PMd and the associated parts of the striatum should occur at the same time. Alternatively, if the basal ganglia functions mainly to mediate habits, then striatal activity changes should occur later than those in PMd or, if the striatum drives appetitive learning, then its activity changes might be predicted to precede those in PMd.

Materials and methods

Subjects and apparatus

Two male rhesus monkeys (*Macaca mulatta*), weighing 8.5 kg and 6.8 kg at the start of recording, served as subjects in this study. They are referred to here as monkey 1 and monkey 2, respectively. All procedures conformed with the *Guide for the Care and Use of Laboratory Animals* (rev. 1996, ISBN 0-309-05377-3), as well as with an animal study proposal approved by the Institutional Animal Care and Use Committee of the National Institute of Mental Health under authority granted by the National Institutes of Health, USA.

The monkeys sat, head fixed, in a primate chair. A video monitor, 30 cm from the monkeys' eyes, was covered by a transparent 25 cm by 17 cm touch screen (C.A.M. Graphics, Amityville, NY) mounted on a

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Received 7 July 2003, revised 2 December 2003, accepted 4 December 2003

doi:10.1111/j.1460-9568.2003.03181.x

4-mm-thick transparent panel. A computer program divided the touch screen's surface area into a 3×3 grid of rectangles, invisible to the monkeys, with each of the nine rectangles measuring 8 cm wide by 5 cm tall. An infrared oculometer in front of the left eye of monkey 1 monitored eye position at 200 samples/s.

Behavioural paradigm

Both monkeys learned arbitrary associations between visual stimuli and reaching movements to one of four target locations. Figure 1 illustrates the spatial pattern of the targets. On each behavioural trial, a centrally positioned instructional stimulus (IS) indicated which one of the four targets on the touch screen would, if contacted by the monkey, produce reinforcement. Each IS consisted of two differently coloured ASCII characters, superimposed, with one ≈5.0 cm and the other ≈3.5 cm high (Gaffan & Harrison, 1988). The touch screen overlaid the monitor such that the IS always appeared in the middle rectangle of the 3×3 grid, and the four response targets corresponded to the four corners of the grid.

Stimuli were selected pseudorandomly, from trial to trial, from a set of eight stimuli. Within any given stimulus set, each stimulus instructed one and only one correct response, and two different stimuli instructed each response. We call this design an 8 : 4 mapping; eight stimuli 'map onto' four responses in equal numbers. The stimulus–response associations for four of the stimuli in the eight-stimulus set were highly familiar to the monkeys (familiar mappings), whereas the associations between the remaining four stimuli and their responses had to be learned through trial and error (novel mappings). For monkey 1, the stimuli used for novel mappings composed two sets of four stimuli that were highly familiar to the animal. Although the stimuli were familiar, the target or movement that they instructed varied from one block of trials to another. For monkey 2, the eight-stimulus sets included two to four novel stimuli, with the exact number varied from block to block to adjust the monkey's learning rate. In sessions with either two or three novel stimuli, additional familiar stimuli (termed fillers) instructed those responses not associated with novel stimuli. This procedure preserved an 8 : 4 mapping without inducing a strong response bias. For both monkeys, novel mappings (including filler stimuli) appeared twice as frequently as familiar mappings.

Monkey 1 began each trial by touching a metal start bar below the touch screen. It had to maintain contact with the bar until a trigger signal (TS) cued the response later in the trial. Touching the metal bar led to the immediate appearance of the four response targets, one in each corner of the screen (see Fig. 1, top). After the monkey had maintained contact for 200 ms, a small white circle (4 mm diameter) appeared in the centre of the video screen. Once the monkey made a saccadic eye movement to fixate this point and maintained fixation for 600 ms, the IS appeared there for 400 ms, termed the IS period. If the monkey broke fixation during the first 150 ms of the IS period, the trial ended. If the monkey broke fixation after this period, the IS disappeared and the trial continued, but such behaviour rarely occurred (see Fig. 4). After the IS period, a grey, 3-cm square replaced the IS and remained on the screen for 0.75–1.75 s, an interval called the instructed-delay period. The disappearance of the grey square served as the TS, after which the monkey could remove its hand from the metal bar and touch one of the four targets. The monkey had a maximum of 1.9 s to initiate a response, up from 1.5 s during training. Once the monkey touched the target and maintained contact for 100 ms, all four target outlines became filled (white). In case of a correct response, after a variable pre-reward period (0.75–1.25 s) a tube delivered ≈0.1 mL of water directly into the monkey's mouth as reinforcement. At the same time, the targets simultaneously disappeared from the screen. After incorrect responses, the targets simultaneously disappeared from the screen after the same variable period, but the response did not produce reinforcement, and, on the next trial, the same IS appeared. This sequence of events (termed a correction trial) continued until the monkey made a correct response. A 2.5-s intertrial interval followed.

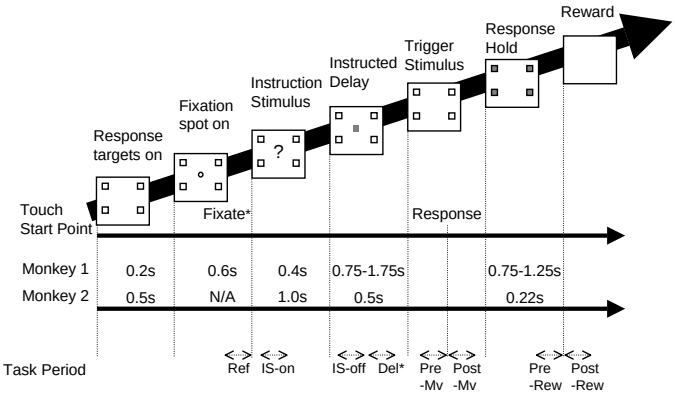

FIG. 1. Behavioural design. Schematics of video screen as each trial progressed. Each larger square represents the video monitor and the small squares depict the four targets. At the centre of the screen, the fixation point, the instruction stimuli (IS) and the trigger stimuli (TS) appear. Beneath these displays, the time line and task periods are designated for each monkey. *Monkey 2 had no fixation requirement and no instructed-delay period. Abbreviations: Del, Delay; IS, Instruction Stimulus; Mv, movement; N/A, not applicable; Ref, reference period; Rew, reward.

The task differed for monkey 2 in several minor respects: there was no fixation requirement; the monkey began each trial by touching a square at the bottom of the touch screen instead of a metal bar; the monkey had to contact that location for 0.5 s prior to IS appearance; the IS appeared for 1.0 s; the neutral grey square appeared for 0.5 s; the monkey had to contact a target for 1.0 s to register a response; and the pre-reward period lasted only 220 ms.

Surgery

Using aseptic techniques and isofluorane anaesthesia (1–3%, to effect), a recording chamber (27 mm × 36 mm) was implanted over the exposed dura mater of the right frontal lobe, along with head restraints. Postoperatively, the animals recovered in an enclosed environment providing constant temperature, humidity, and oxygen partial pressure, under veterinary supervision. Antibiotics and analgesics were administered at the end of surgery and at other times as recommended by the attending veterinarian. After head-restraint implantation, the animals were chaired with the head fixed for increasing periods in accord with the NIH Guidelines for the Use of Restraint Chairs with Nonhuman Primates. Animals were monitored periodically (generally, every half hour) when in head restraint to assure their general well-being.

Magnetic-resonance imaging

Recordings were guided by a coronal and a sagittal series of magnetic resonance (MR) images obtained with an electrode at the depth of the basal ganglia. A 1.5 Tesla whole body scanner (Signa, General Electric Medical Systems, USA) obtained 60 coronal and 60 sagittal MR images, derived from T1-weighted structural MR imaging, at 1-mm and 1.5-mm intervals, respectively.

Recordings

Glass-coated platinum-iridium electrodes (≈0.5–1.0 MΩ, measured at 1 kHz) recorded single-unit potentials in PMd and in the putamen. We also collected a neuronal sample from the caudate nucleus, although its

relatively small size limits the extent of analyses and conclusions for this population. A low-noise preamplifier, with a gain of ten and a frequency response of 10 Hz to 10 kHz, differentially recorded the electrode signals. A multichannel amplifier, which had independently adjustable gains from 0 to 10 000, received the preamplifier outputs, and a multispike detector (Alpha-Omega Engineering, Nazareth, Israel) discriminated single-unit potentials. Typically, during the isolation of single units, the monkeys performed a version of the CVML task with only familiar mappings. Thus, the search strategy caused a potential bias towards isolating cells with activity modulation for this condition, but this search strategy did not vary across recording locations. The potential bias caused by this search strategy could, however, affect the relative frequency of cells selective for familiar vs. novel mappings.

The recording site alternated between the striatum and PMd, with a few days of PMd recording sessions followed by a roughly equal number of basal ganglia sessions. We intentionally limited recordings from tonically active neurons (TANs) in the striatum in the knowledge that they represent only $\approx 5\%$ of the striatal cell population (Aosaki *et al*., 1994).

In monkey 1, a Plexon (Plexon Inc., Dallas, TX) multichannel data-acquisition system (gain, 3000–8000; filtering, 5 kHz−10 Hz) recorded electromyographic (EMG) activity as the monkey performed the task. The sample of tested muscles included triceps, latissimus dorsi, deltoid, extensor digitorum longus, trapezius, flexor carpi radialis, cervical paravertebral, flexor carpi ulnaris, infraspinatus, brachioradialis, extensor carpi radialis, wrist and finger flexors, and sternocleidomastoid muscles. By establishing fixed threshold windows for the EMG data, the relative EMG activity was recorded as a pulse train (pulse-replica recordings). Recording thresholds were set such that there was always some background signal, even during rest.

Data analysis

To evaluate the monkey's learning for any given stimulus, we computed a three-trial moving average of the sequence of correct and incorrect response for each IS. We chose a learning criterion of three-consecutive correct responses because the probability of achieving this level of performance by chance is less than 2% ($4^{-3} = 0.016$) and performance rarely deteriorated dramatically once monkeys reached this criterion. For consistency, we designated the second of those three trials as the specific trial on which the monkey achieved criterion for that IS and designated that trial as normalized trial 0 for the purpose of comparisons with previously published work and the construction of population averages.

For the analysis of response latencies, reaction time (RT) was defined as the time from the TS to the time when the hand broke contact with the metal start bar in monkey 1 or central hold location in monkey 2. The subsequent time taken until the monkey contacted one of the four response targets was defined as the movement time (MT).

We analysed neuronal activity during each trial for eight task periods: a reference period and seven principal task periods. The reference period corresponded to the 500 ms before IS onset; the IS-onset period began 80 ms after the IS onset for a duration of 320 ms; an IS-offset period began 80 ms after offset of the IS for a duration of 170 ms; an instructed-delay period, defined as a 250-ms period ending 250 ms before the TS was given (monkey 1 only); a pre-movement period covered 250 ms prior to breaking screen contact; a movement period covered the 250 ms after breaking screen contact; a pre-reward period covered the 750 ms prior to the delivery of reward; and a post-reward period lasted for 1.0 s after the delivery of reward. Occasionally, we adjusted these time windows as appropriate to the activity of an individual neuron (for seven PMd and five putamen cells, all in monkey 1). Task-related activity (one of the seven principal task periods vs. reference) and directional selectivity (four directions, one for each target) was assessed for each task period by a two-factor analysis of variance (ANOVA, $\alpha = 0.01$). For monkey 2, the number of directions in any given analysis was restricted by the number (two to four) of novel associations the monkey learned in a block of trials.

We then categorized cells according to their activity 'preference' for trials with novel mappings (novel trials) vs. those with familiar ones (familiar trials). Activity for each task period, for novel and familiar trials separately, was compared against reference-period activity (*t*-test, $\alpha = 0.01$), and an additional comparison was made for each task period testing the activity difference between familiar and novel trials. On the basis of these comparisons, task-related cells could fall within one of five categories: familiar only (F), novel only (N), familiar preferred (F > N), novel preferred (F < N), or no preference (F = N).

As in previous studies (Mitz *et al*., 1991; Chen & Wise, 1995a,b), we analysed learning-related activity in each task period and each target location as a separate case. Although activity from different cases within the same neuron cannot be said to be independent from each other, experience has shown that the differences in activity in distinct task periods precludes easy generalization. Thus, analysis by case avoids the assumption that a cell's activity for one task period corresponds to that in another. To evaluate changes in neuronal activity during learning, the change-point test for continuous variables ($\alpha = 0.01$) (Siegel & Castellan, 1988) was applied to novel mappings and, as a control, to familiar mappings, as well. For each case showing a significant change in activity, a cross-correlation analysis measured the relative timing of changes in neuronal activity and changes in performance. We subsequently used the Kolmogorov–Smirnov two-sample test (Siegel & Castellan, 1988) to compare the case-by-case cross-correlation results among neuronal populations. Similar analyses were made on a cell-by-cell basis, in addition to a case-by-case basis.

As described in detail by Siegel & Castellan (1988), the change-point test entails the null hypothesis that no time trend exists in a data series. As applied to the present neuronal data, the null hypothesis holds that no systematic change in neuronal activity occurs over trials. On that assumption, each trial should rank on average near the median. Of course, the ranks must distribute from the highest to lowest activity levels, but if the null hypothesis is true, the cumulative sum of ranks should increase approximately linearly with trial number. The maximal deviation from that expectation signifies, according to this test, the trial on which the change occurs (the change point) and divides the series into all trials up to that point and all subsequent trials. The sampling distribution of the deviation statistic forms the basis for rejecting the null hypothesis (or failing to do so). The significance of a given degree of deviation depends on the number of trials up to and after the change point and is a form of the Kolmogorov–Smirnov test. For behavioural data, the test depends similarly on the maximal deviation from the expected cumulative sum of correct responses as the series of trials progresses.

All novel and familiar trials were subjected to the change-point test, separately, by response direction. For both types of trials, the change-point test was also applied to their reference-period activity. If reference-period activity changed significantly for a given response direction, then all data for that direction were eliminated from the analysis, except for changes of opposite sign. Cases with less than 5 spikes/s throughout learning were also excluded.

For each case of significant learning-related change in activity, a learning-effect index (LEI) was computed by comparing the mean activity for the first three correctly executed trials (A_{early}) to that from

three consecutive trials later during learning (A_{late}), using a contrast ratio:

$$(A_{late} - A_{early})/(A_{late} + A_{early})$$

An LEI of zero reflects no net change in activity, positive values denote increases in activity, whilst negative values indicate decreases in activity. Similar ratios were also computed for reference periods derived from the same trials and stimuli in which cases of significant learning related changes were detected.

Histology

At the completion of neurophysiological data collection, we passed 10 μA of direct, anodal current for 10 s, through the electrodes in order to make electrolytic marking lesions at selected recording sites. Lesions were made at four sites (two striatal, two cortical) in each of six tracks in monkey 1. No lesions were attempted in monkey 2. The animals were later given xylazine (0.02 mg/kg) and ketamine (10–20 mg/kg i.m.) followed by induction of a deep anesthetic state with sodium pentobarbital (60 mg/kg i.v.). Following the complete loss of corneal and cutaneous reflexes, a supplementary dose of sodium pentobarbital was given (30 mg/kg) prior to the perfusion procedure. Both monkeys were perfused through the heart with heparinized physiological saline followed by 10% formol-saline, with five steel pins inserted at known chamber coordinates. The brains were subsequently removed, photographed, and then sectioned at 40 μm on a freezing microtome. A 1 : 3 series of Nissl-stained sections (cresyl violet) was used to plot the locations of recording sites and the estimated track of each penetration by reference to the four recovered electrolytic lesions (for monkey 1) and to the pin holes (for both monkeys). For both monkeys, MR images guided the histological reconstruction.

Results

Behaviour

Both monkeys performed the CVML task with nearly 100% accuracy for familiar visuomotor mappings and quickly learned novel mappings. For comparison, we divided the behavioural data according to whether the neurophysiological recordings come from PMd or from the putamen.

The two monkeys learned novel mapping problems at similar rates, with a problem being defined as learning the correct response to a given IS. For each problem, monkey 1 took an average (± SD) of 9.6 ± 6.3 trials to reach the performance criterion (three consecutive correct responses to a given IS); monkey 2 required 9.1 ± 5.1 trials to do so. For correct trials only, the monkeys took 4.5 ± 2.5 and 3.7 ± 2.0 trials to reach criterion, respectively. The difference for each monkey gives the mean number of errors to criterion: 5.1 and 5.4 trials per problem, respectively, for monkey 1 and monkey 2. The total number of trials to criterion for a set of ISs was the product of the values presented above (9.6 and 9.1 trials to criterion) and the number of concurrent, novel mappings in the set. For monkey 1, this means that it took ≈ 38 trials to learn the novel mappings to criterion, consisting of ≈ 18 correct and ≈ 20 incorrect trials, excluding the interleaved familiar trials. Using the more-sensitive algorithm of Wirth *et al.* (2003) for detecting that learning had occurred, monkey 1 learned in 6.5 ± 4.5 trials, monkey 2 in 7.8 ± 6.3 trials. Figure 2 shows the overall learning curve for monkey 1. The number of total and correct trials to criteria did not differ with respect to recording site (PMd, putamen, and caudate) for monkey 1 (total, $F_{2,270} = 1.66$, n.s.; correct, $F_{2,270} = 1.06$, n.s.) or monkey 2 (yotal, $t_{64} < 1$, n.s.; correct, $t_{64} < 1$, n.s.). Table 1 gives the mean and median trials to criteria as the monkeys learned novel mappings for each recording site.

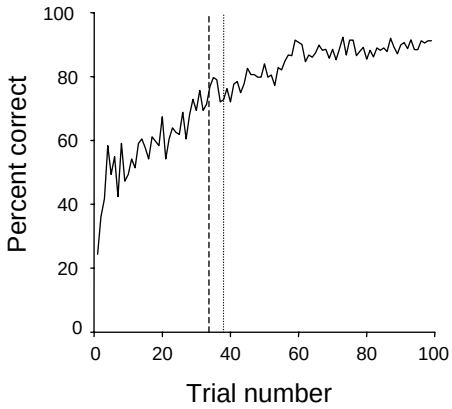

FIG. 2. Learning curve for monkey 1, for concurrent novel mappings. Unlike learning curves in later figures (e.g. Fig. 8D), which illustrate learning only for correct trials and only for one IS at a time, this curve shows the overall improvement in performance as the monkey learns four novel conditional visuomotor mappings. Because problem sets dropped out of the data set shortly after the monkey reaches the performance criterion, an average over last seven trials of a given data set were extrapolated to infinity. The averages are similar to previously published ones (e.g. Wise & Murray, 1999) and show that novel mappings were learned quickly, with an exponential rise having a learning-rate constant of 34 trials (dashed line). The monkey reached criterion, on average, after 38 trials (dotted line).

Figure 3 shows the reaction times (RT) and movement times (MT) for trials with novel mappings, averaged across all recording sessions, normalized with respect to the attainment of criteria (normalized trial 0). Note that neither RT nor MT differed dramatically as a function of where recordings were made and neither showed a strong trend as the monkey learned novel mappings.

Table 2 shows mean RT and MT for three phases of learning, termed early, criterion and late, with all incorrectly performed trials excluded. Early trials comprised the first three trials with novel mappings. Criterion trials include trial '0' (see Materials and methods) and the trials immediately before and after it (trials −1 to +1 in the normalized trial scale). The next three trials (trials 2–4) composed a group of late trials. Trials with familiar mappings were divided likewise, but because early and criterion trials were the same (i.e. the monkey began at nearly perfect performance), Table 2 does not distinguish between them. Both monkeys had faster RTs for familiar than for novel mappings (monkey 1; $F_{1,24} = 79.42$, $P < 0.05$; monkey 2; $F_{1,16} = 38.59$, $P < 0.05$). RT decreased in late trials relative to those at the time the monkey achieved the learning criterion in both monkeys,

TABLE 1. Trials to the learning criteria as the monkeys learned novel conditional visuomotor mappings, by recording site

	Mean		Median	
	All trials	Correct trials	All trials	Correct trials
Monkey 1				
PMd	9.4 ± 6.1	4.4 ± 2.5	8	4
Putamen	10.6 ± 7.1	3.8 ± 2.7	8	4
Caudate	7.8 ± 4.2	3.1 ± 1.8	7	4
Monkey 2				
Putamen	8.5 ± 5.4	2.4 ± 2.0	7	3
Caudate	9.7 ± 4.7	3.0 ± 1.9	7	3

Mean (±SD) and median total trials and correct trials to achieve criterion for each recorded region. Criterion was set as the second of three consecutive correct trials, when performance first reached that level.

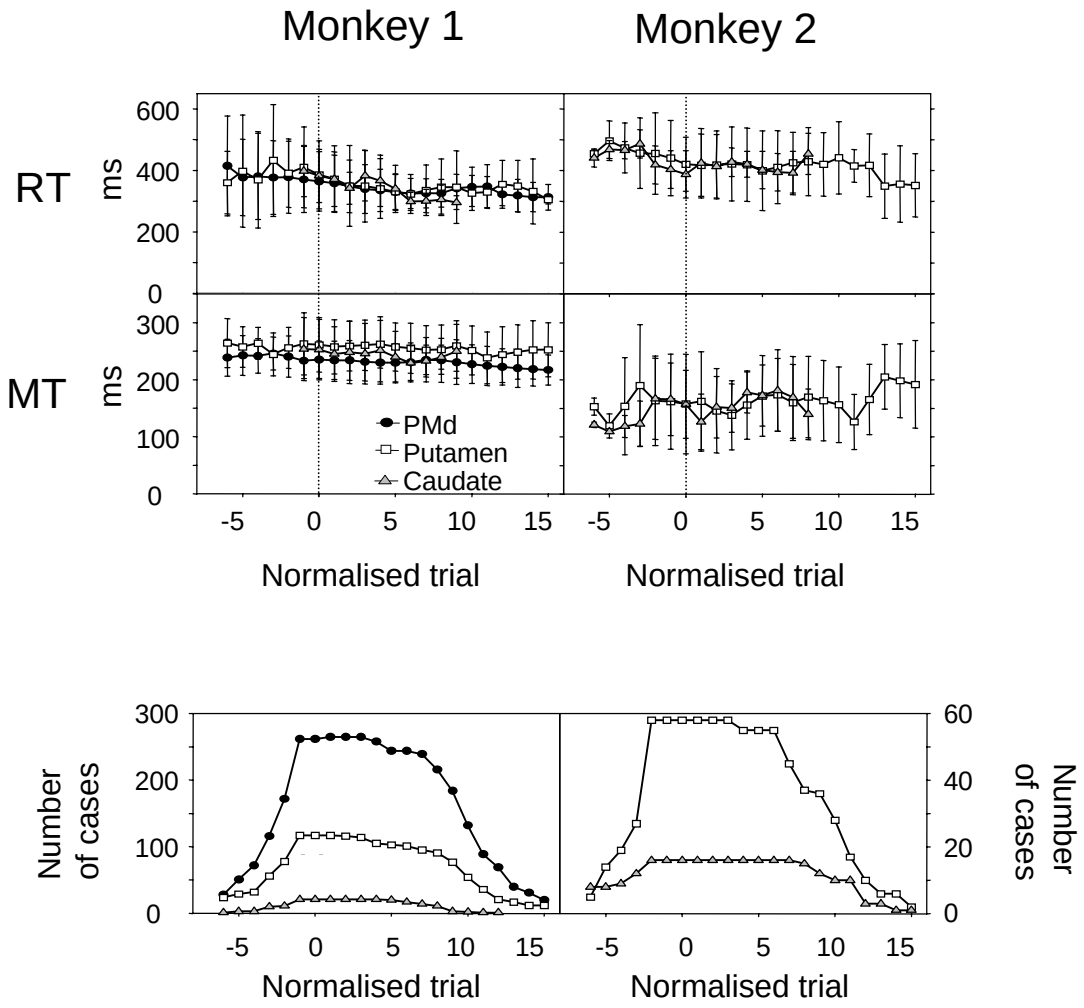

FIG. 3. Reaction time (RT) and movement time (MT), by monkey (mean ± SD), displayed separately for sessions with recordings in PMd, putamen, and caudate. Latencies are aligned on normalized trial 0 (see Materials and methods) and represent a three point average from correct trials only. Bottom, number of cases contributing to each data point in the latency plots for each animal.

although this occurred only for novel mappings in monkey 1 ($F_{1,24} = 6.34$, $P < 0.05$) and only for familiar mappings in monkey 2 ($F_{1,16} = 9.80$, $P < 0.05$). RT also decreased from early to criterion novel trials in monkey 1 ($F_{2,18} = 10.36$, $P < 0.05$) but not in monkey 2 ($F_{2,18} < 1$, n.s.). These effects did not differ significantly as a result of whether the recording site was in PMd, the putamen, or the caudate (monkey 1, $F_{2,24} = 2.51$, n.s.; monkey 2, $F_{1,16} < 1$, n.s.). ANOVA showed that, in monkey 1, RT ($F_{2,24} = 4.07$, $P < 0.05$) and MT ($F_{2,24} = 84.96$, $P < 0.05$) were significantly, if slightly, faster while we recorded from cells in PMd (confirmed by *posthoc* Newman–Keuls analyses).

TABLE 2. Reaction- and movement-times (in msby monkey and trial type

		RT (ms)		MT (ms)	
Trial type	Trial group	Monkey 1	Monkey 2	Monkey 1	Monkey 2
Novel	Early	389 ± 29	425 ± 31	247 ± 11	156 ± 15
	Criterion	365 ± 15	414 ± 13	248 ± 10	150 ± 13
	Late	346 ± 18	415 ± 12	246 ± 12	161 ± 16
Familiar	Early	N/A	N/A	N/A	N/A
	Criterion	337 ± 11	395 ± 28	246 ± 16	160 ± 24
	Late	327 ± 10	357 ± 20	254 ± 14	175 ± 18

Data (±SEM) are given separately for the first three trials with a novel IS, trials at the time of reaching criterion (early, normalized trials −1 to +1) and a group of subsequent trials (late, normalized trials +2 to +4). Similar data are also given for familiar IS; the near-perfect performance of monkeys with familiar IS means that 'early' trials are typically also the first three trials.

Oculomotor data was obtained for monkey 1. Inspection of the data revealed that the monkey typically fixated the IS as required, and although the monkey initially broke fixation after the IS disappeared, it typically fixated the neutral grey square prior to the end of the delay period. Following the TS, the monkey typically made a saccade to the intended target immediately prior to making the reaching movement. Thus, oculomotor behaviour for task periods such as the IS-on, pre-movement, and movement periods was reasonably consistent. Examination of 16 randomly selected sessions (eight for PMd and eight for putamen recordings) revealed no obvious differences in oculomotor behaviour for different recording sites. Figure 4 shows representative oculomotor records for familiar and novel trials.

EMG data were also obtained from monkey 1 from 15 muscles or muscle groups. While many of the recordings showed activity related to the task, and to reaching movements specifically, there were few instances of muscle activity changing during the course of learning (15

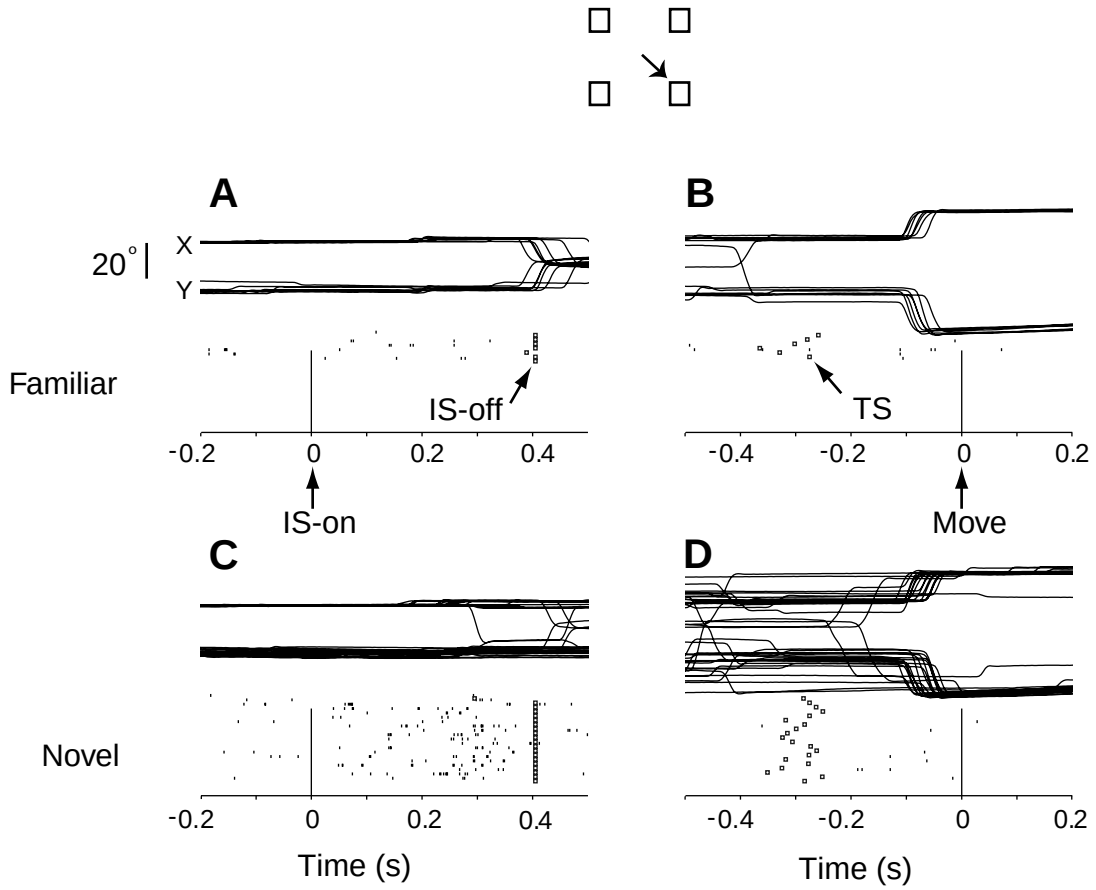

FIG. 4. Oculomotor behaviour for familiar trials (A and B) and novel trials (C and D) for the data displayed in Fig. 7A–D. Data from correct trials only; response to bottom, right target, as depicted at the top of the figure. (A and C) Eye position aligned on IS onset, for horizontal (X) and vertical (Y) dimensions. The monkey fixated a point in the middle of the screen prior to stimulus onset for 600 ms and continued to fixate the IS when it appeared in place of the fixation point. There was no fixation requirement following IS offset. (B and D) Eye position aligned on the onset of the reaching movement (Move) shows that the monkey had more variable oculomotor behaviour preceding the TS, but typically made a saccade to the target immediately prior to the reaching movement.

cases statistically, 3.6% of the sample with $\alpha = 0.01$), the majority of which ($n = 10$) were in the pre-movement and movement periods.

Recording locations

Figure 5 shows the reconstructed recording sites. Virtually all of the cortical sample appears to be located in PMd, between the superior precentral sulcus and the superior limb of the arcuate sulcus, within ± 4 mm of the frontal plane containing the posterior limit of the arcuate sulcus. Recorded putamen cells were generally located in the middle part of the putamen along its rostrocaudal axis and, in monkey 1, were concentrated in the dorsomedial aspect of the putamen. Putamen cells in monkey 2 were somewhat more caudal and more ventrolateral, on average, than those in monkey 1. Caudate cells were generally recorded from the head and body of the caudate, and not from the tail.

Neuronal database

We recorded from 120 PMd cells (all in monkey 1), 120 cells in the putamen (75 in monkey 1), and 44 cells in the caudate (22 cells in monkey 1). ANOVA revealed significant task relations for neuronal activity in all seven principal task periods, as shown in Table 3. Tests on the percentage of task-related cells revealed no significant differences between PMd and putamen ($\chi_1^2 = 3.04$, n.s.). Because of the small size of the caudate sample, this statistical test excluded those data.

Figure 6 shows several examples of task-related activity in both the PMd and putamen. Neurons at both recording sites showed task-related modulation during the IS-on (Fig. 4A and G); IS off and instructed-delay (Fig. 4B and H); pre-movement (Fig. 4C and I); movement (Fig. 4D and J); pre-reward (Fig. 4E and K); post-reward (Fig. 4F and L) periods.

Learning-related changes in activity

Cases of learning-related activity were defined as signed changes in neural activity in a given task period (and not seen in the corresponding reference period) as detected by the change-point test for continuous variables ($\alpha = 0.01$). Tables 4 and 5 give the percentage and number of learning related changes in each task period. Cases that showed statistically significant changes were divided into those increasing and those decreasing as a function of learning, roughly corresponding to changes termed learning-dependent and learning-selective in previous reports (Chen & Wise, 1995a).

Figure 7 depicts two separate cells in PMd that showed learning-related changes in discharge modulation. Figure 7A–D illustrates an example of a learning-related increase in activity, during the IS-on period, from one PMd neuron in its preferred direction (down and to the right). As noted above, the phrase familiar trials refers to trials requiring the monkeys to respond according to familiar mappings; the term novel trials refers to trials involving novel mappings. During

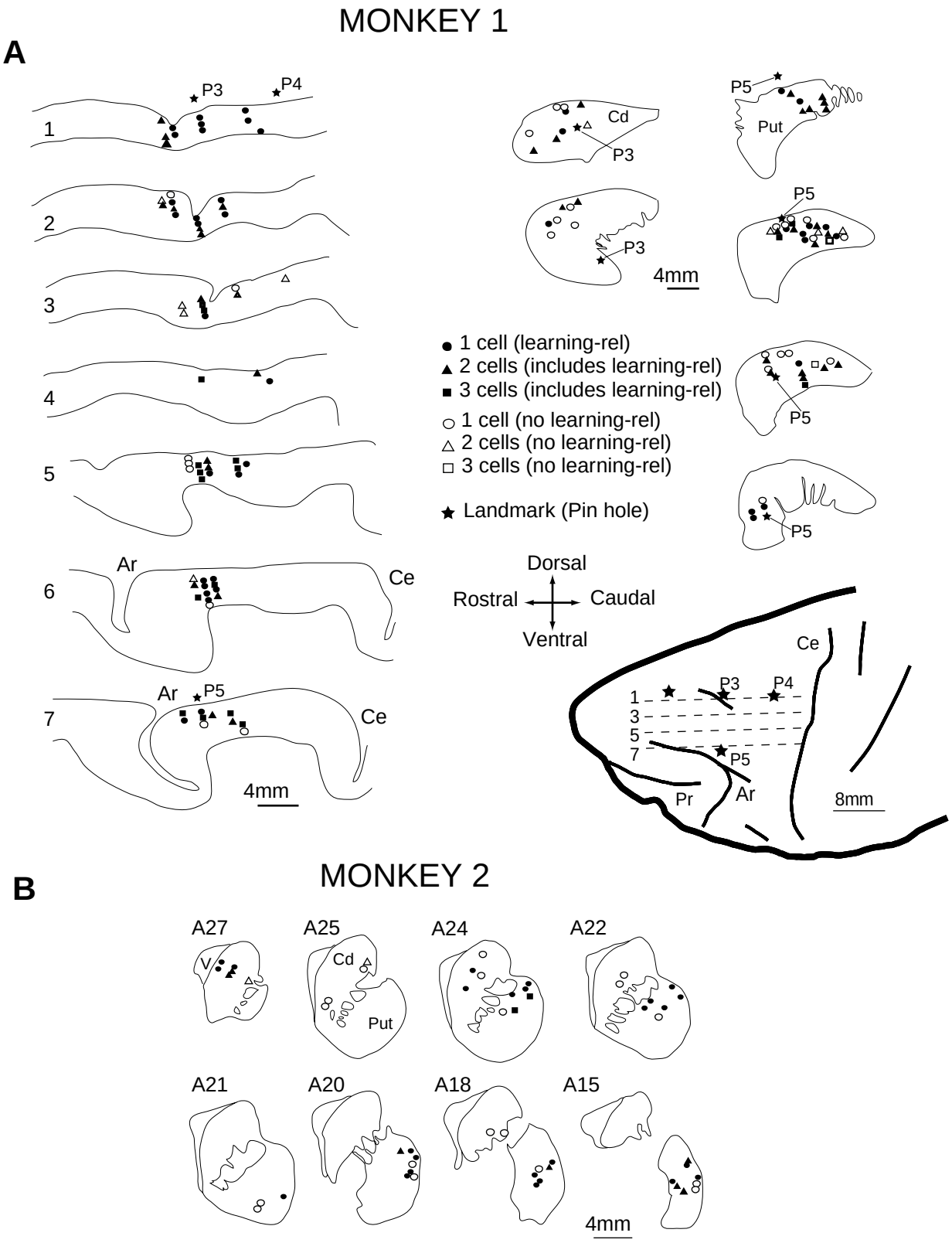

FIG. 5. Histological reconstruction. (A) Estimated location of cells in PMd and striatum in monkey 1. The dashed horizontal lines on the dorsal view of the left hemisphere (bottom right) correspond to oblique parasagittal sections 1, 3, 5 and 7 on the left. Reconstruction is relative to the pin holes (P3–5) as marked in 1 and 7 (stars), as well as to electrolytic lesions and MR images (not shown). Cortex and putamen sections are at 1 mm intervals; the caudate sections are 2 mm apart. Lower sections are lateral to upper ones; the most medial putamen section is 3 mm lateral to the most lateral caudate section. The filled symbols represent the location and number of cells showing learning-related activity, the unfilled symbols indicate the location of cells without such activity. (B) Estimated location of cells in the striatum in monkey 2. The coronal sections are labelled to indicate the distance anterior (A) from the interaural line (mm). Abbreviations: Ar, arcuate sulcus; Cd, caudate; Ce, central sulcus; Pr, principal sulcus; Put, putamen; V, lateral ventricle.

TABLE 3. Percentage of task-related cells, by task period, both monkeys combined (correct trials only, ANOVA on each of the seven principal task periods vs. reference-period activity for four directions)

Recording site	Effect	IS-on	IS-off	Delay[a]	Pre-Move	Move	Pre-Reward	Post-Reward	Total Cells
PMd	Main	40.8	25.8	29.2	33.3	35.0	35.8	44.2	120
	Directional	8.3	14.2	9.2	20.8	20.8	20.0	10.8	
Putamen	Main	21.7	21.7	28.0	23.3	24.2	28.3	39.2	120
	Directional	2.5	2.5	1.3	11.7	12.5	10.8	9.2	
Caudate	Main	15.9	18.2	0.0	15.9	20.5	25.0	36.4	44
	Directional	4.5	4.5	0.0	4.5	4.5	4.5	6.8	

Main effect indicates activity is greater than baseline for all directions taken together, a directional effect signifies an effect of the location of the correct response target, i.e. its direction from the starting hand location ($\alpha = 0.01$). Abbreviations: delay, instructed-delay period; move, movement period; IS, instruction stimulus. [a]monkey 1 only.

familiar trials that required a response to the bottom, right target, the cell demonstrated a low level of activity throughout the trial (Fig. 7A). When the monkey was required to make the same movement in novel trials (Fig. 7B), the cell initially (for the first four trials on which that IS was presented) showed a low level of activity. However, as learning progressed, the cell began to show significant modulation during the IS-on period. Figure 7C and D shows the average activity in this task-period (marked by the arrows above the histogram) for familiar (Fig. 7C) and novel (Fig. 7D) trials (black lines), together with activity during the reference period on the same trials (grey lines) and the performance of the monkey (unfilled circles), all smoothed with the same three-point moving average. These figures show only correctly executed trials. Accordingly, although the IS differs for familiar and novel trials, both the IS and the movement are the same for all illustrated trials within each display (e.g. Fig. 7D). Together, these findings show that the cell's activity cannot simply reflect the IS or the monkey's response. Further, the stability of activity in the reference period shows that the learning-related activity could not be accounted for in terms of unstable cell isolation or any interaction of the neuron with the electrode.

Figure 7E–H illustrates the activity of a second PMd cell, one that shows learning-related changes in activity during the post-reward period. This cell was active during, and immediately prior to, the onset of the IS, but its discharge rate after the reward is of most interest here. The cell showed heightened modulation immediately after the delivery of reward, most notably for early trials requiring the learning of novel mappings. As the monkey's performance improved, i.e. as the monkey learned the novel mapping, the post-reward activity decreased (Fig. 7H), eventually to the level seen for familiar trials requiring the same response. This pattern of activity resembles the reward-prediction error signal described for dopamine neurons and in some striatal cells by Schultz and colleagues (Hollerman & Schultz, 1998; Hollerman *et al*., 1998; Tremblay *et al*., 1998; Waelti *et al*., 2001).

Figure 8 depicts two putamen cells that also demonstrated learning-related changes in activity. The top four panels (Fig. 8A–D) illustrate an example of a learning-related increase in activity, during the IS-on period. Note the overall resemblance to the PMd cell shown in Fig. 7A–D. This cell shows very low firing rates during familiar trials that required a response to be made to the top right target (Fig. 8A) and shows similarly little activation during the first four novel trials involving a similar movement (Fig. 8B). However, as learning progressed the cell showed significant modulation during the IS-on period. Figure 8E–H illustrates an example of a learning-related decrease in activity in the putamen, for the pre-reward period.

Figure 9 shows the learning-related activity of two caudate cells. Figure 9A–D illustrates an example of a learning-related increase during the IS-on period; much like the PMd (Fig. 7A–D) and putamen (Fig. 8A–D) cells shown previously. Figure 9E–H illustrate learning-related decreases during the IS-on period for another caudate cell.

Significant learning-related changes in activity were observed in 88 PMd (all in monkey 1), 74 putamen (47 in monkey 1), and 19 caudate cells (9 in monkey 1). As shown in Table 4, these made up 73%, 62%, and 43% (uncorrected) of the sampled neurons in the three recording sites, respectively. Neurons sometimes showed learning effects for more than one task period and for more than one response direction, yielding a total of 390 cases of significant changes in activity in PMd, 245 (162 in monkey 1) in the putamen, and 55 (27 in monkey 1) in the caudate. Tables 4 and 5 show how these cases of learning-related changes in activity were distributed across task periods. Chi-square tests showed no significant differences by task period or recording site. The majority of cells in all recording areas demonstrated directionally selective activity. For 52% of learning cases in the cortex, a change was seen only for one response direction and not for the other in a given task period. Similar values were obtained for cases in the putamen (62% monkey 1, 74% monkey 2) and the caudate (70% monkey 1, 57% monkey 2). Comparing across task periods, there was a significant tendency for a degree of correspondence in the response directions showing learning-related changes in activity. For each task period in which a significant learning-related activity change was observed for one and only one response direction, we computed a directional consistency statistic based on a comparison of observed data with the same data shuffled randomly by direction. Only cells that showed stability in the reference period for all four directions were analysed. As expected, shuffling the direction assigned to each case of learning-related activity change reduced the directional consistency statistic to chance levels ($23 \pm 25\%$, SD). The observed directional consistency was significantly higher ($41 \pm 35\%$; Kruskal–Wallis test, d.f. $= 1,373$, $\chi^2 = 26.8$, $P << 0.001$), which demonstrates that the response directions associated with learning-related activity changes were not randomly distributed.

Comparison of PMd and putamen populations

For cases showing significant learning-related changes in activity by the change-point test, population averages were constructed, as in previous reports (Mitz *et al*., 1991; Chen & Wise, 1995a). Cases with significant increases were analysed separately from those with significant decreases. For each task period passing the change-point test, a cross-correlation analysis assessed the degree to which changes in performance lagged or preceded changes in neural activity. Figure 10 shows the distribution of these peak correlation coefficients, and the lead and lags at which they occurred. Analyses of these lags using the Kolmogorov-Smirnov two-sample test ($\alpha = 0.01$) revealed no significant difference between cases showing increases and decreases, for any task period, for any recording site, or for either monkey. Accord-

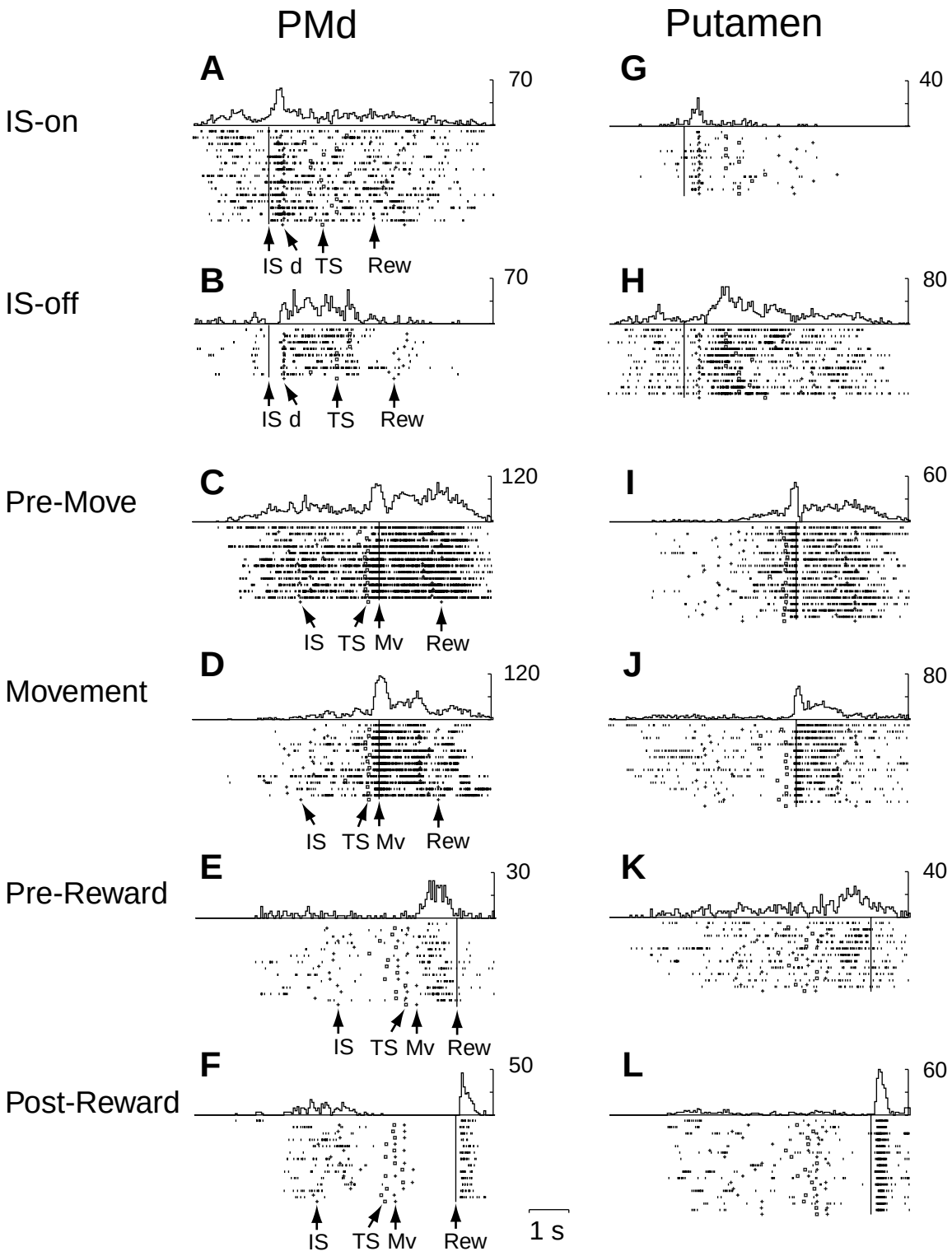

FIG. 6. Examples of task-related activity in PMd and putamen. Activity patterns of 12 different neurons, six from PMd (left) and six from the putamen (right). Correct trials only. Each raster line shows activity during one trial, with each tick mark representing the time of occurrence of an action potential. Panels A, B, G and H are aligned on stimulus onset; panels C, D, I and J are aligned on movement onset; and panels E, F, K and L are aligned on reward delivery. Abbreviations: IS, instruction stimulus; d, instruction stimulus offset (which begins the instructed-delay period); TS, trigger stimulus; Mv, movement onset; Rew, reward delivery. Activity scales in spikes per s.

ingly, all of these data sets are combined in the grand averages illustrated in Figs 11 and 12. For these population averages, activity in each case was averaged across three trials (equally weighted) and normalized with respect to the maximum averaged firing rate. Note that these averages combine the activity from several task-periods during a trial. We also constructed averages for each task period and, although they appear noisier due to the smaller data sets, these averages closely resemble the grand means presented here. On average

TABLE 4. Percentage of cells that showed learning-related changes, both monkeys combined

	IS-on	IS-off	Delay	Pre-Move	Post-Move	Pre-Reward	Post-Reward	Any
PMd	32	33	33	38	29	38	38	73
Putamen	17	25	20	29	20	27	29	62
Caudate	14	16	5	20	14	11	18	43

TABLE 5. Number of learning-related cases, both monkeys combined, as detected by the change-point test for continuous variables ($\alpha = 0.01$)

	Novel mappings			Familiar mappings		
	PMd	Putamen	Caudate	PMd	Putamen	Caudate
IS-on	53	21	6	18	8	0
IS-off	51	35	9	11	9	0
Delay[a]	46	30	4	7	8	0
Pre-Move	58	42	10	5	15	0
Post-Move	47	32	7	15	12	1
Pre-Reward	63	42	7	9	6	1
Post-Reward	72	43	12	13	11	1
Totals	480	480[a]	176[a]	480	480[a]	176[*]

[*]Because there was no delay period for monkey 2, the number of comparisons for that task period was 300 for the putamen and 88 for the caudate.

(±SEM), changes in PMd modulation lagged changes in performance by 1.5 ± 0.2 trials; in the putamen they did so by 1.8 ± 0.2; and in caudate the lag was 1.5 ± 0.4. There was no significant differences in the distribution of lags for PMd and the putamen as revealed by the Kolmogorov–Smirnov test ($D_{360,207} = 0.09$, n.s.). The caudate did not differ from either the putamen or PMd populations, but we note the small number of caudate cells sampled. Additional analysis confirmed that these changes in population activity did not reflect cell instability, as indicated either for familiar mappings or in reference-period activity (Figs 11 and 12; ANOVA, $\alpha = 0.01$).

Figures 13 and 14 illustrate the size of these learning effects. For each task period showing significant learning-related activity, we computed a learning-effect index. As a benchmark for comparison, index values of ±0.33 indicate a doubling or halving of discharge rate during learning (dashed lines in Fig. 13). Figure 13 shows how this index evolved over the course of learning for the population of PMd and putamen cells. Note the stable index value near 0 for the reference period. Figure 14 shows the distribution of the index for normalized trials 4–6 in greater detail. Analysis of the effects shown in Fig. 14 revealed that the learning-effect index for the task-period activity significantly differed from those for reference activity, both for cases that showed increases ($F_{1,201} = 20.98$; $P < 0.01$) and decreases ($F_{1,316} = 68.40$; $P < 0.01$) during learning. No difference was observed based on recording sites (increases, $F_{1,201} < 1$; n.s.; decreases, $F_{1,316} < 1$; n.s.). Similar results were seen for analyses of ratios derived from normalized trials 7–9 and 10–12.

We also performed two more restricted analyses on the data from monkey 1. Neuroanatomical evidence indicates that the forelimb representation of PMd projects to the dorsomedial part of the putamen, within 2–3 mm of the boundary with the internal capsule, extending to the striatal bridges within the internal capsule and perhaps to the most ventrolateral aspect of the caudate nucleus at the same frontal level (Takada *et al*., 1998b; McFarland & Haber, 2000). Accordingly, we compared neurophysiological data for the PMd cells in monkey 1 to the 24 cells (43 cases) that fell within the most medial part of the putamen (within 2–3 mm of the internal capsule) in the same monkey. Nearly all of these cells were located in the dorsomedial aspect of the putamen (Fig. 5A). For this subset of neurons, cross-correlation analysis showed that learning-related changes in activity in the dorsomedial putamen lagged changes in performance by 1.0 ± 0.4 trials. This result did not differ from the lag demonstrated by the PMd cases ($D_{360,43} = 0.10$, n.s.). In a separate population analysis, data from periods of uncertain fixation were eliminated from the analysis. After removing data from the IS-off and instructed-delay period, the comparison between PMd changes (1.3 ± 0.3 trials) and putamen (1.5 ± 0.3 trials) did not differ from the other task periods or from each other ($D_{270,103} = 0.09$, n.s.).

Finally, we categorized cells according to their preference for novel or familiar trials, using the data from monkey 1. Although the neuronal search strategy introduced a bias toward cells with activity during familiar trials, the PMd and putamen samples contained significantly more cells with a preference for novel trials than for familiar trials (Fig. 15, $\chi_1^2 = 40.3$, $P < 0.05$).

Discussion

The current study compared learning-related changes in activity in PMd and the putamen, part of which receives inputs from PMd (Künzle, 1978; Takada *et al*., 1998b; McFarland & Haber, 2000). We reasoned that if the anatomical concept of cortical–basal ganglionic loops has functional validity, then changes in the cortex and the associated parts of the striatum should occur concurrently. The loop hypothesis of telencephalic organization, although well known and reasonably well accepted, has rarely been subjected to experimental test. The observations of similar patterns of task-related activity in neocortex and the parts of the striatum to which they project has been noted often in the past. For instance cells in the head of the caudate (Rolls *et al*., 1983) resemble those in ventral prefrontal cortex (Thorpe *et al*., 1983), the stimulus-selective properties of caudal striatal cells (Caan *et al*., 1984; Brown *et al*., 1995) resemble those of inferotemporal areas (Gross, 1992), and the reinforcement-related properties of ventral striatal cells (Williams *et al*., 1993) may reflect striatal afferents from limbic regions. However, such similarities between striatal and cortical activity is only weakly suggestive of a loop organization; they could result from many causes. If neocortex and its targets in the striatum genuinely function as integrated, recurrent neural networks, as has been proposed (DeLong & Georgopoulos, 1981; Alexander & DeLong, 1985; Alexander *et al*., 1991; see also Houk & Wise, 1995; Beiser & Houk, 1998; Hikosaka, 1998), then activity in both regions should change contemporaneously during learning.

In accord with the loop hypothesis, we found no significant differences in the timing, across trials, of activity changes for PMd and putamen. (The caudate nucleus also showed learning-related activity changes at approximately the same time.) For both increasing and decreasing learning-related activity, the population averages showed only small changes in activity, if any, until approximately the time that learning reached asymptotic levels. Then these populations commenced a steady rise or fall in activity over the course of 10–15 trials for each IS ($\approx$40–60 trials overall, incorrect and familiar trials excluded).

This finding has some relevance to the concept of consolidation. In general, memory appears to progress from a short-lived, fragile form to a long-lasting, more stable one. According to current thinking, neurons store information in two ways: sustained, recurrent activity levels for short periods of retention and changes in synaptic weights for long periods (e.g. O'Reilly *et al*., 2002). The changes in activity observed in PMd or striatal neurons were not likely to reflect information stored in recurrent circuits because the activity rates typically reset to baseline levels during the intertrial interval. Instead, learning-related changes in

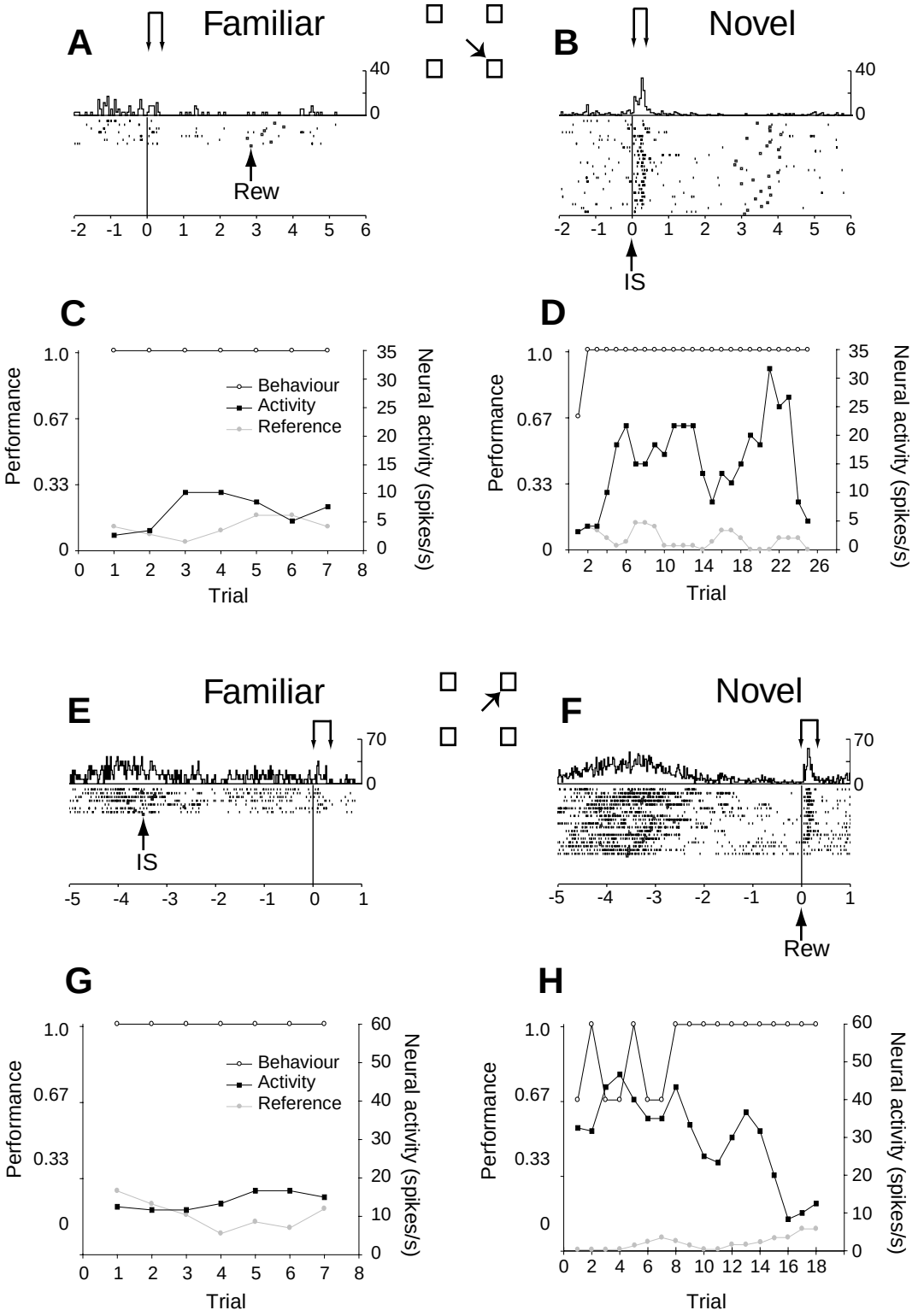

FIG. 7. Learning-related activity from two cells in PMd. One cell demonstrates learning-related increases in activity (A–D) and the other cell shows learning-related decreases (E–H). Data from correct trials only. (A) Perievent histogram and raster display, aligned on stimulus onset, for the lower, right target; familiar trials. (B) Same as in A, for novel trials. (C and D) Three-point moving averages for the data above each graph, for the task period depicted by the arrows above the histograms (filled square), for activity in the reference period (grey circle) and for behaviour (proportion correct responses of the three trials in the moving average, unfilled circle). Note that because only correct trials are included in these averages, the learning appears to be faster than in Fig. 2, although the monkey did learn this mapping relatively rapidly. E–H, shows data from a second PMd cell in the format of A–D, except for the filled squares in G and H show activity for the post-reward period and for the upper, right target. Because this cell shows significant pre-IS, anticipatory activity, post-movement data is used for reference activity. Abbreviations: IS, instruction stimulus; Rew, reward.

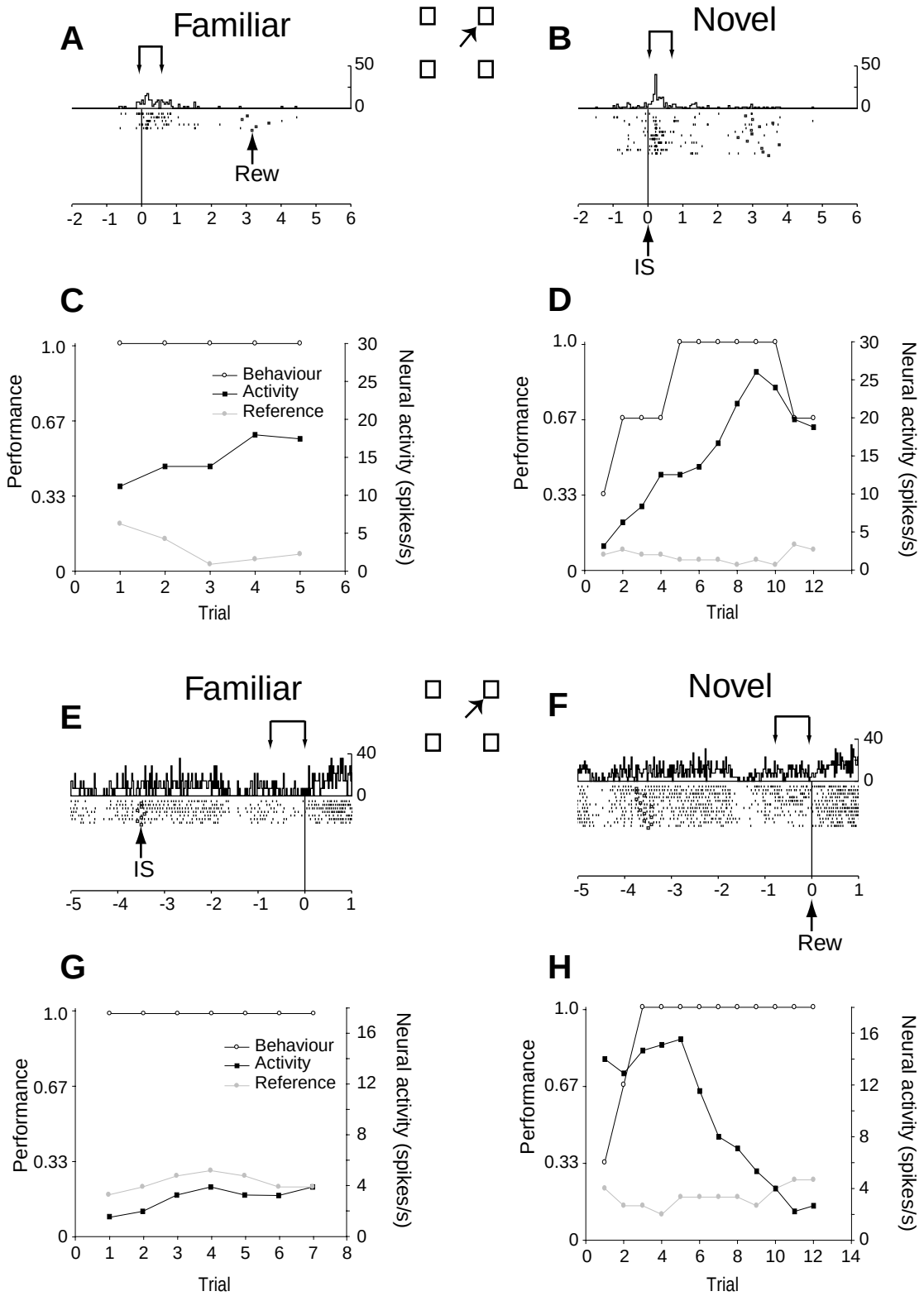

FIG. 8. Learning-related activity from two cells in the putamen in the format of Fig. 7. One cell demonstrates learning related increases in activity (A–D) and the other cell shows learning related decreases in activity (E–H).

activity probably reflected the strength of synapses upon the cells we studied. We cannot comment on how long those changes lasted, because we typically monitored cells for less than an hour. But the finding that changes continued to occur after the monkeys reached a behavioural plateau (Figs 11A and B, and 12A and B) suggests that the synaptic weights continued to adjust, which could have played a role in stabilizing the information stored in the synaptic weight matrix of the relevant neural networks.

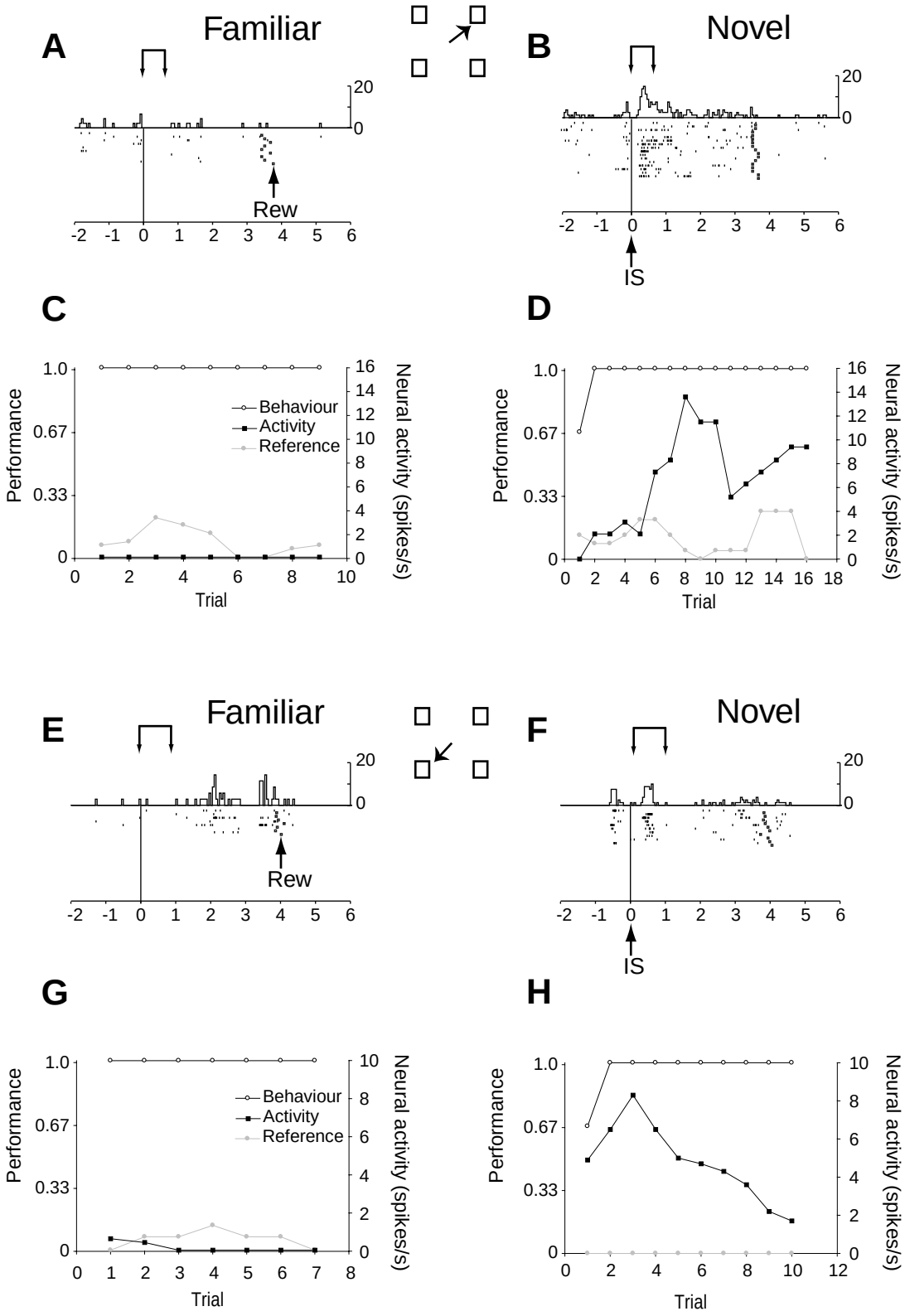

FIG. 9. Learning-related activity from two cells in the caudate nucleus in the format of Fig. 7. One cell demonstrates learning related increases in activity (A–D) and the other cell shows learning related decreases in activity (E–H).

Interpretational problems

In considering changes in PMd and putamen activity, it is important to consider factors other than associative learning. For example, in monkey 1, reaction time (RT) was slightly faster for PMd recordings than for the striatum. This small difference may have reflected the fact that although recording sessions between PMd and striatum were usually intermixed, on occasion recording began in PMd and pro-

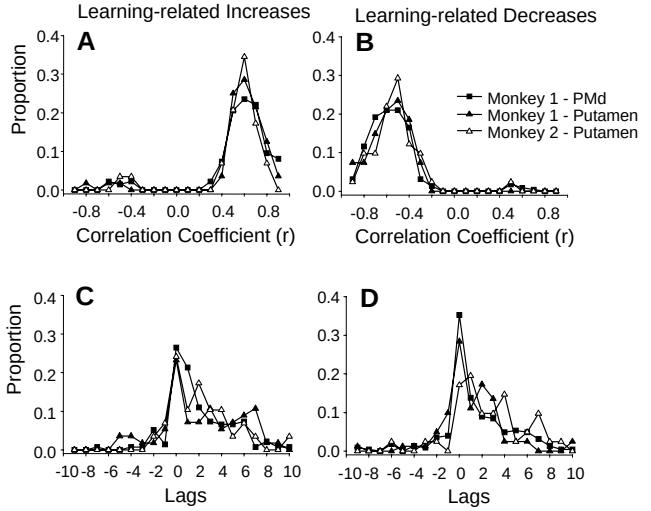

FIG. 10. Distribution of peak correlation-coefficients (A and B) and distribution of lags for peak correlations (C and D). A positive lag means that the activity change followed the learning curve by the designated number of trials. (A and C) Data for learning-related increases in activity. (B and D) Data for learning-related decreases in activity.

gressed to the striatum later in the session. However, these differences were subtle, as shown by Fig. 3, and unrelated to learning rates. Monkey 1 also showed slightly faster RTs after achieving criterion performance vs. later trials (Table 2). Whilst pre-movement activity may correlate with RT (Lee & Assad, 2003), previous studies have ruled out this account of learning-related activity (Mitz *et al*., 1991; Chen & Wise, 1995a). Neurons in PMd (Crutcher & Alexander, 1990; Fu *et al*., 1993; Wise *et al*., 1997; Crammond & Kalaska, 2000; Gomez *et al*., 2000; Messier & Kalaska, 2000; Cisek *et al*., 2003) and its targets in the putamen (Crutcher & DeLong, 1984; Crutcher & Alexander, 1990; Turner & Anderson, 1997; Ueda & Kimura, 2003) encode movement direction and amplitude, but neither these kinematic parameters nor EMG activity varied substantially during CVML. The small and infrequent differences in EMG activity during learning provide an unlikely account for the neurophysiological results.

As for factors such as oculomotor behaviour and attention, the task required the monkeys to attend to the centre of the screen for knowledge of both where and when to respond. Attention may have varied in some subtle way, but the stimulus remained highly salient from the beginning to the end of the learning session. There was also a fixation requirement during stimulus presentation for monkey 1. That monkey had relatively stable gaze at the centre of the screen at the time of both the IS and TS (Fig. 4). Moreover, although the monkeys did show increased oculomotor activity during the delay period for novel trials, there was no evidence for any differences in eye movements for PMd and striatal recordings. Furthermore, removal from the analyses of the periods of inconsistent gaze did not affect the timing of learning-related activity changes relative to behaviour. Similarly, changes in neural activity were unlikely to reflect changes in response to any particular dimensions of the visual stimulus. Monkey 1 performed the task using only familiar stimuli, some of which changed their response mappings daily and some of which did not. For correctly executed responses, the same response followed the same stimulus early vs. late in learning, yet the activity significantly changed in cells classed as learning related. It could not reflect simply the features of the stimulus or the motor response.

It is possible that learning-related changes in neural activity reflected changes in the internal state of the monkey, such as reward expectancy or motivation. Such accounts can be discounted for the majority of neurons, in which learning-related changes were apparent for only one of the four targets, as such nonspecific factors would not be directionally specific. Nevertheless, although they cannot account for learning-related activity changes, nonspecific factors such as reward expectancy contribute to neural activity in both PMd and in the striatum (Fiorillo *et al*., 2003).

An account of learning-related activity in terms of stimulus sensitization or habituation is also unlikely, as previous work has ruled out both mechanisms (Mitz *et al*., 1991; Chen & Wise, 1995a). In the present study, the use of highly familiar stimuli for novel mappings in monkey 1 argues further against these possibilities.

The lack of change in reference-period activity and its rarity in familiar-trial activity (Table 5) argues against the idea that the results reflect a change in the cell isolation or irritation artefacts. Furthermore, the fact that the response directions associated with learning-related activity changes were significantly nonrandom indicates some consistency across the trial. When learning-related activity occurs for one response direction in a given task period, that neuron has significantly greater likelihood of showing learning-related activity changes for that same response in other task periods. Artefactual learning-related changes should be randomly distributed with respect to response direction.

Functional implications for conditional visuomotor learning

The mechanisms of CVML are of particular interest because this form of behaviour allows individuals to learn a wide variety of goal-directed actions guided by arbitrary associations among motor responses and sensory cues. The behavioural flexibility that these mechanisms afford may underlie the symbolic guidance of actions, including social communication (Murray *et al*., 2002).

The current study showed that cells in both the PMd and the striatum demonstrate changes in firing rates that accompanied CVML. This finding confirms previous reports for both regions (Mitz *et al*., 1991; Tremblay *et al*., 1998). The timing of neuronal activity changes with respect to behaviour were similar to those found in PMd by Mitz *et al*. (1991), and in SEF by Chen & Wise (1995a,b).

There is also evidence from recordings in rats that the striatum plays a role in the acquisition and performance of stimulus–response associations. Jog *et al*. (1999) reported that the percentage of task-related cells in dorsolateral striatum increased as rats gradually learned a two-choice auditory stimulus-response task. Data from individual cells recorded from multiple sessions revealed similar findings. Their task was a conditional motor learning task, and differs from CVML only in the sensory modality of the IS. Although the authors interpreted their results in terms of 'habits', it seems unlikely, based on the relatively small number of trials the rats experienced, that their rats performed according to the formal definition of a habit from animal learning theory (Balleine & Dickinson, 1998). Carelli *et al*., 1997), in contrast, recorded from cells in dorsolateral striatum while rats learned a single association between a tone and a lever press. They reported that, as rats became proficient at the task over the course of hundreds of trials (perhaps instigating a habit), the extent of activity related to the conditioned response decreased with learning. Thus, one might be tempted to conclude that, in rats, activity in the dorsal striatum increases during appetitively driven decisions (as in Jog *et al*., 1999), but that it decreases as the rat forms a habit (as in Carelli *et al*., 1997). However, much more work will be needed to substantiate such a claim. The present data give no support to the idea that dorsal striatum functions exclusively in habits (McDonald & White, 1993).

Regarding the preference for novel over familiar trials mentioned above, we observed this property both for the putamen and PMd. This

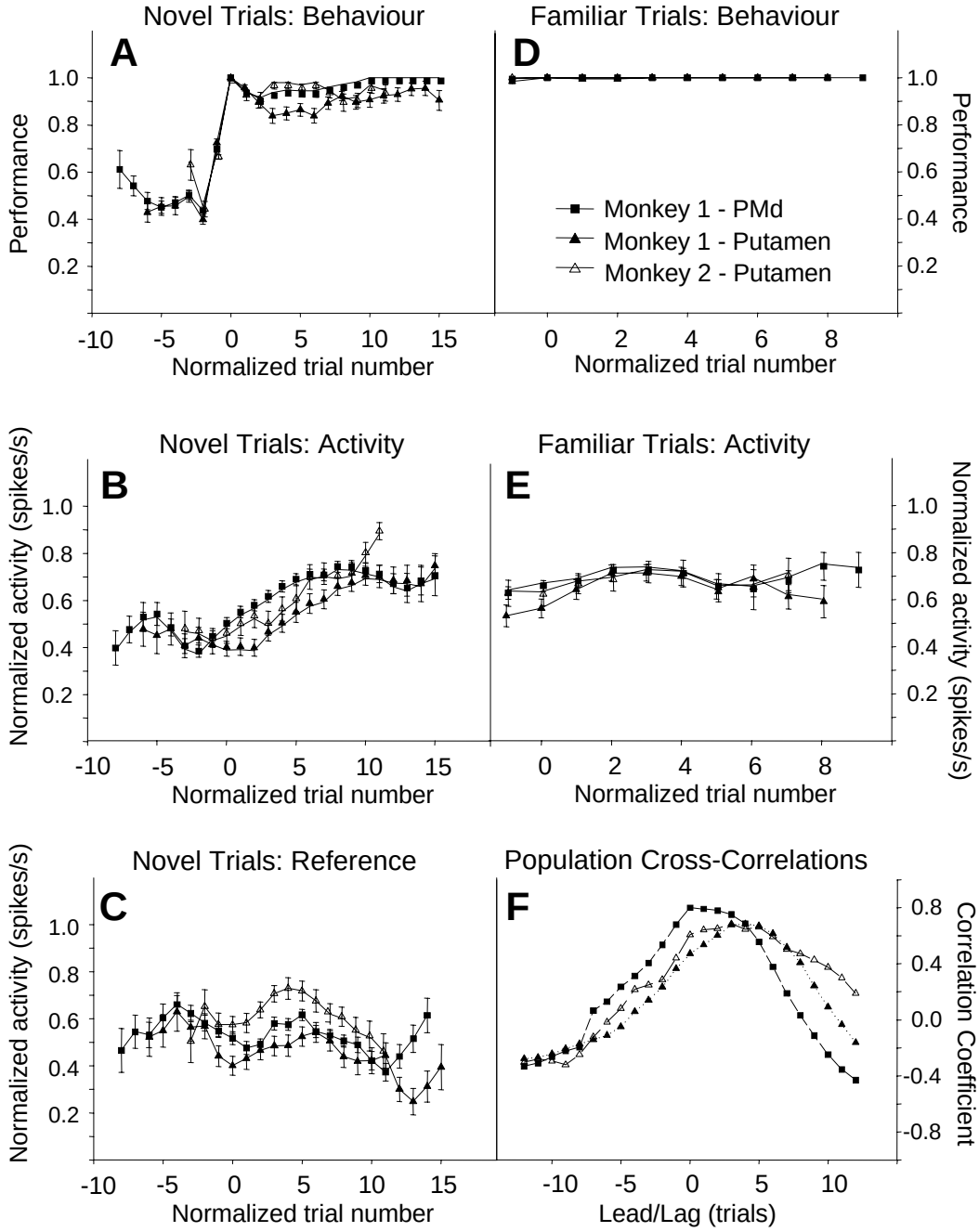

FIG. 11. Population averages for cases showing learning-related increases in activity. Data shown separately for monkey 1 (filled symbols) and monkey 2 (unfilled symbols), and for PMd (filled squares) and putamen (triangles). Correct trials only. A–E show three-point, moving averages (± SEM). (A) Performance accuracy for novel trials, averaged over all cases of learning-related increases in activity for each recording site. Figure 3 (bottom) shows the number of cases contributing to each data point. (B) Neuronal activity for all cases with learning-related increases in activity on novel trials, by recording site and monkey. Data are normalized relative to the maximum firing rate observed for each case (see Materials and methods). Note that the data for the second monkey (unfilled triangles) covers a smaller range of trials, reflecting the smaller number of associations the monkey was required to learn in a given problem set. (C) Activity in the reference period for all cases shown in B. (D) Performance accuracy for the familiar trials having the same target as in A. (E) Neuronal activity for the familiar trials shown in D. For each case, data comes from the same task period that contributed to the learning-related increases in B. (F) Population cross-correlations of the changes in performance plotted in A and the changes in neuronal firing plotted in B. Note that positive leads denote changes in behavioural performance occurring prior to changes in neural activity, whilst negative lags denote changes in behavioural performance occurring after changes in neural activity.

result occurred notwithstanding the sampling bias toward cells with activity on familiar trials. These findings resemble those of Chen & Wise (1995b) for eye-movement-related activity in the SEF. They found a preponderance of preferences for novel stimuli and mappings, although both preferences were observed. The present results also concur with those of Tremblay *et al*. (1998), who reported similar numbers of neurons that demonstrate either an increase or decrease in neuronal activity in novel trials vs. familiar ones.

The reports of learning-related changes in neural activity in premotor cortex (including SEF) (Mitz *et al*., 1991; Chen & Wise, 1995a,b), prefrontal cortex (Asaad *et al*., 1998), the basal ganglia (Tremblay *et al*., 1998; Inase *et al*., 2001), and the hippocampus

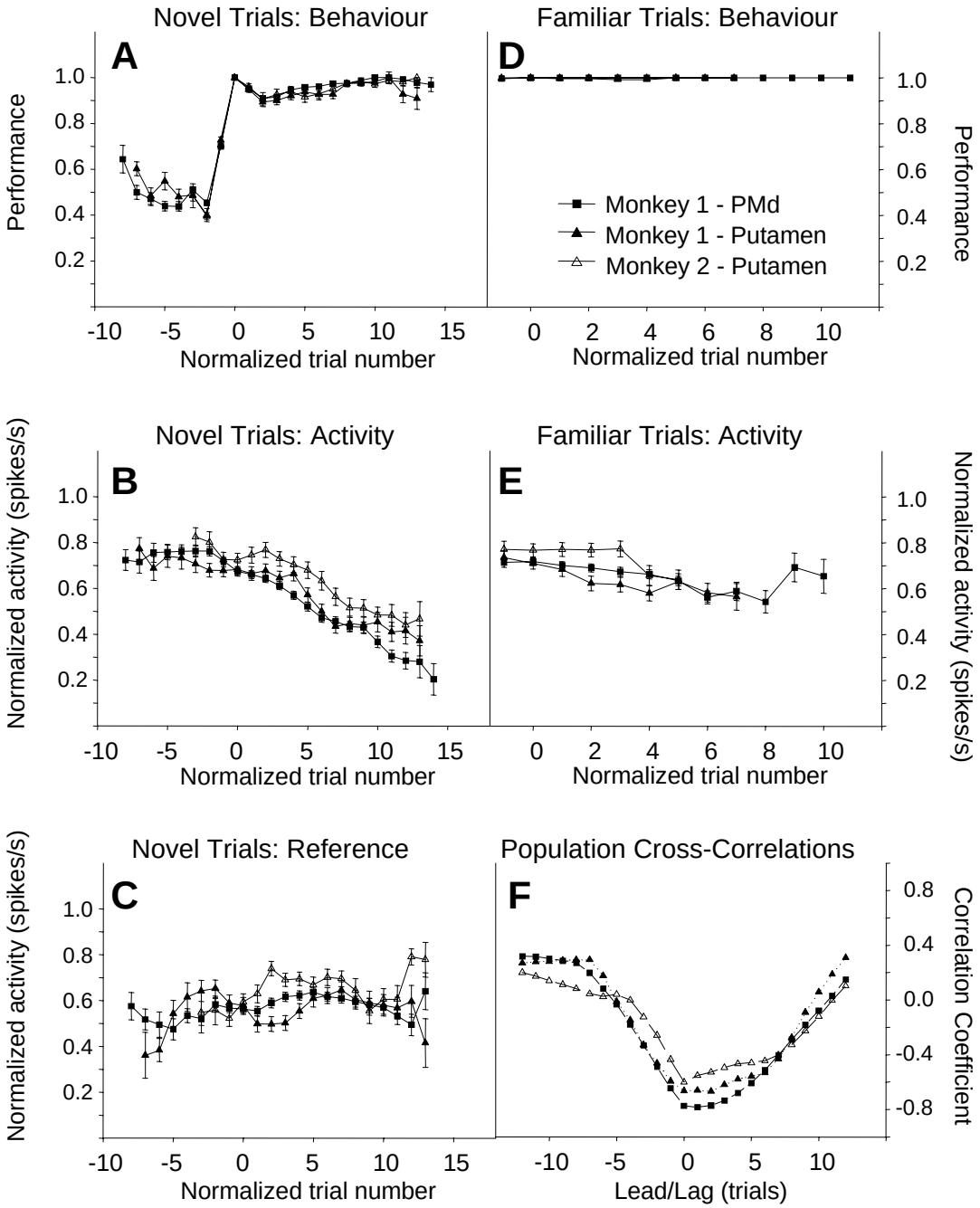

FIG. 12. Population data for cases showing learning-related decreases in activity in the format of Fig. 11.

(Cahusac *et al*., 1993; Wirth *et al*., 2003) largely parallel the results of neuropsychological studies in monkeys. These studies demonstrate the necessary neural substrates for normal performance or acquisition of CVML includes PMd (Halsband & Passingham, 1985; Petrides, 1985), the orbital and ventral aspects of the prefrontal cortex and its interaction with inferotemporal cortex (Gaffan & Harrison, 1988; Eacott & Gaffan, 1992; Wang *et al*., 2000; Bussey *et al*., 2001, 2002), the basal ganglia in conjunction either with thalamus (Canavan *et al*., 1989) or PMd (Nixon *et al*., 2002), and the hippocampal system (Rupniak & Gaffan, 1987; Murray & Wise, 1996; Brasted *et al*., 2002, 2003). In contrast, lesion studies have found no evidence for parietal involvement in CVML (Rushworth *et al*., 1997; Pisella *et al*., 2000), whilst the discrimination of response–reward contingencies, which could conceivably assist CVML acquisition, have recently been attributed to the cingulate cortex (Hadland *et al*., 2003).

The neuroimaging literature also supports a role for cortex and basal ganglia in CVML (Paus *et al*., 1993; Deiber *et al*., 1997; Toni & Passingham, 1999), including increased striatal involvement as learning progresses (Toni *et al*., 2001a). Imaging studies have, in general, failed to detect accompanying blood-flow changes in PMd during learning, or they have found only small changes (Deiber *et al*., 1991; Paus *et al*., 1993; Deiber *et al*., 1997; Toni & Passingham, 1999; Toni *et al*., 2001a). By contrast, many imaging studies provide evidence for a role of PMd in performing according to either familiar mappings (Sweeney *et al*., 1996; Grafton *et al*., 1998; Toni *et al*., 2001b). Such inconsistency in neuroimaging findings may arise for any number of

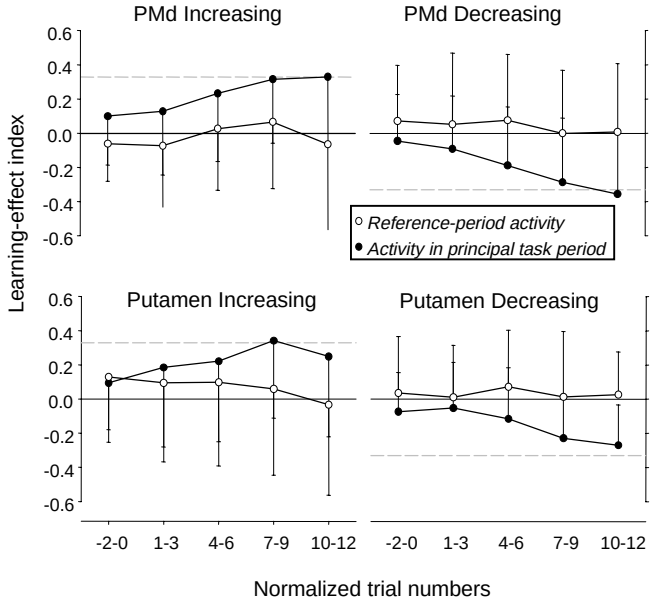

FIG. 13. Learning-effect index (LEI) as a function of normalized trial number. Mean and (SD) LEI in PMd (A and C) and putamen (B and D), for cases showing learning-related increases (A and B) and decreases (C and D) in activity (filled circles). The LEI measures the activity change from the first three correct trials to the three correct trials corresponding to the normalized trial numbers shown on the *x*-axis. An index of ±0.33 (dashed lines) indicates a doubling (A and B) or halving (C and D) of discharge rate. Note that the evolution of the LEI does not occur in the corresponding reference-period activity (unfilled circles).

reasons, discussed elsewhere (Brasted & Wise, 2004). For example, the combination of learning-related decreases and increases in PMd, as shown in the current study and elsewhere (Mitz *et al*., 1991; Chen & Wise, 1995a), makes it difficult to predict a particular neuroimaging result.

Nevertheless, a recent analysis of 'effective connectivity' has led to a contention that corticostriatal interactions strengthen during CVML

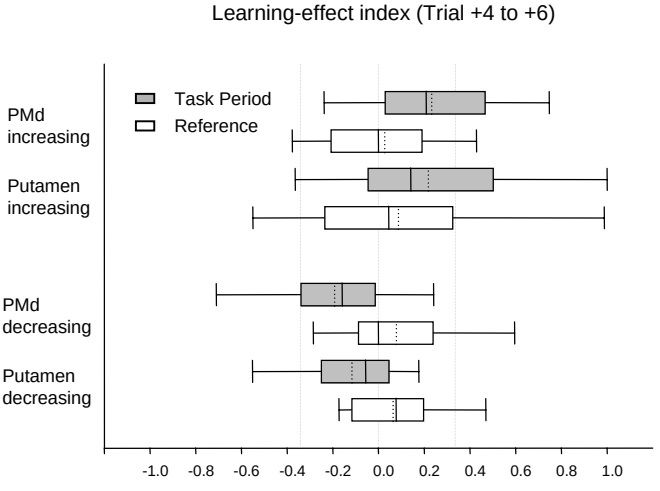

FIG. 14. Learning-effect index vs. reference. LEI for the first three correct trials vs. normalized trials +4 to +6. Box plots show the mean (dotted lines) and median (solid line) LEI, together with the 25- and 75-percentile values (borders of box) and the 10- and 90-percentile values (whiskers). The activity from task periods showing learning-related changes in activity (grey boxes) significantly differs from the activity change in reference-period activity (white boxes).

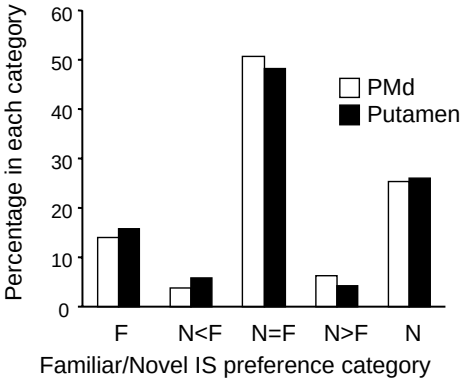

FIG. 15. Proportion of cells in PMd and putamen, for monkey 1, classified according to their preference for novel (N) or familiar (F) trials. N, significant difference from reference-period in novel trials, only; F, significant difference from reference-period activity in familiar trials only. N < F, N > F, significant difference between familiar and novel trials, as well as from reference-period activity in both. N = F, significant task-related activity relative to reference-period activity, but no significant difference between novel and familiar trials.

(Toni *et al*., 2002). The analytical methods of these investigators suggested that, as learning progressed, variation in the BOLD signal in the medial temporal and inferior frontal areas became increasingly correlated with that seen in the striatum. In addition, changes in the BOLD signal in the striatum became increasingly correlated with those subsequently seen in the premotor cortex. These analyses led the authors to infer that CVML depends on increased activity in corticostriatal pathways, an inference that is not inconsistent with the time course of cortical and striatal activity reported in the current study. However, the conclusions of Toni *et al*. (2002) depend on a degree of corticostriatal convergence that has not been conclusively demonstrated with neuroanatomical methods. An alternative means for interaction is through direct corticocortical projections. The importance of interaction between ventral prefrontal and inferotemporal cortex has been established for CVML (Eacott & Gaffan, 1992; Bussey *et al*., 2002). It is interesting to note that although the most severe deficits in CVML follow dorsal premotor and ventral prefrontal lesions – and neuroimaging results point to those areas, as well (Toni *et al*., 2001a; Eliassen *et al*., 2003) – evidence of strong direct corticocortical connectivity between these two regions remains elusive (Lu *et al*., 1994; Ghosh & Gattera, 1995; Stephan *et al*., 2000; Wang *et al*., 2002). An additional mechanism for the integration of segregated basal ganglia-thalamocortical circuits could involve striato-pallido-thalamocortical projections (Toni *et al*., 2002) or interaction via the claustrum (Tanné-Gariepy *et al*., 2002).

Striatal recording sites in relation to PMd–basal ganglia anatomy

PMd both sends corticostriatal projections and receives inputs from pallidothalamocortical projections (Alexander *et al*., 1986; Alexander & Crutcher, 1990; Parent & Hazrati, 1995; Sakai *et al*., 1996; Rouiller *et al*., 1999; Middleton & Strick, 2000), and it projects predominantly to dorsomedial aspects of the middle rostrocaudal levels of the putamen (Künzle, 1978; Takada *et al*., 1998b; McFarland & Haber, 2000), near the projections from forelimb representation in other nonprimary motor areas such as the supplementary motor area (SMA) (Strick *et al*., 1995; Inase *et al*., 1996; Takada *et al*., 1998a), the pre-SMA (Inase *et al*., 1999) and the ventral premotor cortex (PMv) (Takada *et al*., 1998b). The forelimb representation in primary motor cortex (M1) innervates more lateral regions within the putamen (Künzle, 1975; Flaherty & Graybiel, 1993; Parthasarathy & Graybiel, 1997; Takada *et al*., 1998a,b). In the current study, the cortical cells studied

were located in PMd domain of the putamen, principally its forelimb area (Kurata *et al*., 1985; Matelli *et al*., 1991; Godschalk *et al*., 1995; Raos *et al*., 2003). However, no independent confirmation of the motor or mechanoreceptive fields was attempted in the present study. Some putamen cells were located in more lateral areas which receive projections from hand and arm representations of M1, and some striatal cells were located more medially, in the parts of the caudate nucleus that probably receive input from areas 8 and 9.

Functional implications for cortex–basal ganglia interactions

A variety of theories have relied on the idea that striatal connectivity is well suited to detecting complex contextual input patterns and evidence that it uses such context for the prediction of reinforcement (Houk *et al*., 1995; Schultz, 1998; Suri & Schultz, 1999; Bar-Gad *et al*., 2000; Suri *et al*., 2001). On this view, the striatum detects the context for a learned action, estimates a predicted outcome, and provides this information to the cortex as well as to targets in the brainstem (Houk & Wise, 1995; Mink, 1996; Bar-Gad *et al*., 2000; Bar-Gad & Bergman, 2001; Gurney *et al*., 2001). Consistent with this idea, the results of the current study demonstrate that as monkeys learn the context for a given response, related areas of the putamen and PMd exhibit changes in activity, and so with a similar time course. Of further relevance is the finding that learning-related activity occurred as often during pre-reward and post-reward periods – after the associative response had been selected and executed – as during the earlier periods in which the responses were selected. This finding suggests a requirement for cells in both PMd and putamen to monitor the outcome of a context-based response choice. Neurons in the prefrontal cortex, SEF, and the anterior cingulate cortex appear to monitor the consequences of learned actions (Stuphorn *et al*., 2000; Hollerman *et al*., 2000; Ito *et al*., 2003), and it is likely that neurons in PMd and the putamen participate in similar processes. A recent review by Schultz *et al*. (2003) also notes the general similarity and simultaneity of changes in the striatum and associated parts of frontal cortex in the context of learning. The findings reported here therefore accord with the idea that related areas of cortex and the striatum play a role in context recognition and the contextual addressing of motor skills.

Note added in proof

Readers are referred to a recent study by Hadj-Bouziane & Boussaoud (2003).

Acknowledgements

We thank Mr Jim Fellows for assistance with behavioural training, Dr Andrew R. Mitz for technical and engineering support, and Mr Ethan Buch for assistance with data analysis. This research was supported by the Division of Intramural Research Programs of the National Institute of Mental Health.

Abbreviations

CVML, conditional visuomotor learning; EMG, electromyographic activity; F, familiar trials, i.e. trials with familiar visuomotor mappings; IS, instruction stimulus; LEI, learning-effect index; MR, magnetic resonance (brain imaging); MT, movement time; N, novel trials, i.e. trials with novel visuomotor mappings; PMd, dorsal premotor cortex; RT, reaction time; SEF, supplementary eye field; TS, trigger stimulus.

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