Temporary Inactivation in the Primate Motor Thalamus During Visually Triggered and Internally Generated Limb Movements

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van Donkelaar, P., J. F. Stein, R. E. Passingham, and R. C. Miall. Temporary inactivation in the primate motor thalamus during visually triggered and internally generated limb movements. *J. Neurophysiol.* 83: 2780–2790, 2000. To better understand the contribution of cerebellar- and basal ganglia-receiving areas of the thalamus [ventral posterolateral nucleus, pars oralis (VPLo), area X, ventral lateral nucleus, pars oralis (VLo), or ventral anterior nucleus, pars parvicellularis (VApc)] to movements based on external versus internal cues, we temporarily inactivated these individual nuclei in two monkeys trained to make visually triggered (VT) and internally generated (IG) limb movements. Infusions of lignocaine centered within VPLo caused hemiplegia during which movements of the contralateral arm rarely were performed in either task for a short period of time (~5–30 min). When VT responses were produced, they had prolonged reaction times and movement times and a higher incidence of trajectory abnormalities compared with responses produced during the preinfusion baseline period. In contrast, those IG responses that were produced remained relatively normal. Infusions centered within area X never caused hemiplegia. The only deficits observed were an increase in reaction time and movement amplitude variability and a higher incidence of trajectory abnormalities during VT trials. Every other aspect of both the VT and IG movements remained unchanged. Infusions centered within VLo reduced the number of movements attempted during each block of trials. This did not appear to be due to hemiplegia, however, as voluntary movements easily could be elicited outside of the trained tasks. The other main deficit resulting from inactivation of VLo was an increased reaction time in the VT task. Finally, infusions centered within VApc caused IG movements to become slower and smaller in amplitude, whereas VT movements remained unchanged. Control infusions with saline did not cause any consistent deficits. This pattern of results implies that VPLo and VLo play a role in the production of movements in general regardless of the context under which they are performed. They also suggest that VPLo contributes more specifically to the execution of movements that are visually triggered and guided, whereas area X contributes specifically to the initiation of such movements. In contrast, VApc appears to play a role in the execution of movements based on internal cues. These results are consistent with the hypothesis that specific subcircuits within the cerebello- and basal ganglio-thalamo-cortical systems preferentially contribute to movements based on external versus internal cues.

INTRODUCTION

The cerebellum and basal ganglia appear to make different contributions to the control of movement. In particular, the cerebellum has been implicated in triggering and guiding movements based on external sensory cues (Jueptner et al. 1996; Mushiake and Strick 1993; Stein and Glickstein 1992). Individuals with lesions to the cerebellum have a great deal of difficulty producing movements under visual guidance (Beppu et al. 1987; van Donkelaar and Lee 1994). However, these difficulties are reduced when the external cues are removed and/or the movements are self-generated. In contrast, the basal ganglia have been implicated in the selection, inhibition, and sequencing of movements (Boecker et al. 1998; Brotchie et al. 1991; Jueptner et al. 1997; Kermadi and Joseph 1995; Mink 1996). Moreover, there is some evidence that these processes are directed preferentially at movements that are memorized or internally generated (Hikosaka and Wurtz 1985; Mushiake and Strick 1995). This is supported by the fact that individuals with Parkinson's disease display deficits in producing internally generated or remembered movements that are reduced when external cues are provided (e.g., Crawford et al. 1989; Morris et al. 1996; Oliveira et al. 1997).

The projections from the cerebellum and basal ganglia are anatomically segregated at the level of the thalamus (Rouiller et al. 1994; Sakai et al. 1996). Cerebellar dentate nucleus outputs terminate in the oral portion of the ventral posterolateral nucleus (VPLo) and area X, whereas outputs from the internal segment of the globus pallidus (GPi) terminate in the oral portion of the ventral lateral nucleus (VLo) and the parvocellular portion of the ventral anterior nucleus (VApc). We recently have demonstrated that the functional specificity described in the preceding text is restricted to specific portions of the cerebellar- and basal ganglia-receiving parts of the primate motor thalamus (van Donkelaar et al. 1999a). In particular, the majority of cells in area X become preferentially active during movements triggered and guided by the appearance of visual targets, whereas the majority of cells in VApc become preferentially active during movements based on internal cues. In contrast to this relatively high degree of functional specificity, cells in VPLo and VLo do not display as clear a preference for movements based on external versus internal cues. These results are consistent with the hypothesis that different anatomically segregated portions of the motor thalamus are involved to varying degrees in the control of visually triggered versus internally generated movements.

In the present experiments, we attempted to confirm this hypothesis by infusing lignocaine into sites centered within each of these separate thalamic nuclei in monkeys trained to make simple reaching movements based on external versus internal cues. We predicted that the behavioral deficits observed would be a function of the movement task being per-

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formed and the degree of functional specificity observed within each nucleus. A preliminary version of these results has appeared in abstract form (van Donkelaar et al. 1997).

METHODS

Animals and apparatus

Experiments were conducted on two male rhesus macaque monkeys (*Macaca mulatta*), weighing between 4.8 and 5.2 kg, and cared for in accord with American Physiological Society guidelines. The monkeys were trained to perform reaching movements in a two-dimensional workspace with the right hand using a manipulandum that allowed multijoint responses. Two precision potentiometers measured the anterior-posterior and medial-lateral position of the manipulandum. The manipulandum itself was positioned underneath an angled semisilvered mirror and was made visible with diffuse illumination of the homogeneous background. The monkeys faced the mirror and viewed targets that could be projected from an overhead computer screen. They received liquid rewards for making movements starting with the manipulandum just in front of the torso and ending with the arm almost fully extended ~15 cm away.

Behavioral tasks

The two behavioral tasks that were used have been described in detail previously (van Donkelaar et al. 1999a). Briefly, in both tasks the monkey began each trial holding the manipulandum at the start position ~5 cm in front of its torso. In the visually triggered task (VT), a target then appeared after a variable length of time (2–3 s), and the monkey reached for it with the manipulandum to obtain the reward. The reward zone was actually larger (2 × 4 cm) than the target itself (1 cm^2), and the target was centered within this area. During most (80%) trials, the target appeared at the center of the screen directly in front of the monkey, whereas during the remainder (20%), the target appeared 5 cm to the left or right of center. These latter trials kept the monkey from producing stereotyped movements to the central target. In the internally generated task (IG), no target appeared, and the monkey was rewarded for making a spontaneous movement to a virtual target zone located 15 cm away. The reward or target zone was 4 cm deep and covered the entire width of the workspace. The only other requirement was that the monkey had to wait ≥3 s between each movement. Thus in the VT task, the target provided an external cue about when and where to reach—it triggered and guided the response. By contrast, in IG trials the movements were self-initiated and guided to a remembered target location. In both tasks, the monkey was rewarded after the manipulandum was held in the reward zone for 200 ms after which the monkey was allowed to return to the start position. The two tasks were presented in alternating blocks of trials each lasting 2.5 min long.

Surgical procedures

After initial training, each monkey was anesthetized [ketamine hydrochloride (10 mg/kg im) and alphaxalone/alphadolone acetate (5 mg/kg iv)], and a vertical recording chamber (18 mm ID) was implanted stereotaxically over the left thalamus under aseptic conditions. In addition, two small stainless steel tubes for stabilizing the head were horizontally positioned in front of and behind the chamber and cemented to the skull using dental acrylic. During the surgery, ventriculographs were taken in the frontal and sagittal planes to help determine the location of the thalamus with respect to the recording chamber. Postoperative analgesics and antibiotics were given as required.

Injection procedures

Lignocaine (5%) dissolved in sterile physiological saline was injected into different thalamic nuclei from which arm movement related activity had previously been recorded (van Donkelaar et al. 1999a). A stainless steel cannula (0.3 mm OD) was lowered into the thalamus through a guide tube via a hydraulic microdrive. Injections were delivered through the cannula at a rate of 2 μl/min for a duration of 2–5 min; in the majority of the sessions, 4 μl was infused. In addition, control injections in which saline alone was administered also were performed in the second monkey.

Data analysis

We compared the movements performed in each task before, during, and after the injections. The movement parameters that were measured included the following: the number of movements successfully completed during each 2.5-min block; the reaction time in the VT task defined as the time required to initiate the movement after the appearance of the target (no latency measure was possible in the IG task and latencies <100 and >800 ms in the VT task were excluded from subsequent analysis); the movement time defined as the period from movement onset to offset; peak velocity; and the magnitude and trial-to-trial variability of movement amplitude in the anterior-posterior plane. Movement amplitude was defined as the difference in the start and stop positions demarcated by a velocity threshold (0.5 cm/s). In addition, because the reward zone covered a 4 cm extent in the anterior-posterior plane, it was possible for the monkey to generate a movement that varied quite substantially in this dimension yet still resulted in a reward being delivered. Thus systematic differences in the magnitude or variability of movement amplitude could be measured within the context of otherwise successful performance of the tasks. Moreover, it may be possible for the animal to receive a reward simply by slowing down in the reward zone without actually stopping. However, neither monkey employed this strategy. Finally, as mentioned in the preceding text, latency measures were not possible in the IG task. However, because the IG movements were timed (i.e., the animal had to wait ≥3 s after arriving at the starting position), in theory it may have been possible to compare the start position hold times pre- and postinfusion to gain insight into the effects of inactivation on movement initiation in this task. Unfortunately, the start position hold times were quite variable even during preinfusion trials, making comparisons before and after infusion difficult at best. Changes in all of these measurements relative to the time of lignocaine injection were assessed using analyses of variance (ANOVA) with post hoc Tukey's tests.

Histological procedures and identification of thalamic nuclei

During the final sessions electrolytic marker lesions were made at selected sites in the thalamus by passing DC current (20 μA, 30 s) through a microelectrode. At the end of the experiments, a lethal dose of pentobarbital sodium was administered, and the monkey subsequently was perfused transcardially with saline, followed by 10% buffered Formalin. The brain was removed and fixed, frozen, and sectioned in the sagittal plane at 50 μm. Every fifth section was stained with cresyl-violet and mounted.

The thalamus was parcellated according to the nomenclature and cytoarchitectonic criteria of Olszewski (1952) and Matelli and colleagues (1989). The borders demarcating VPLo, area X, VLo, and VApc as well as the electrolytic marking lesions were identified for each histological section (see van Donkelaar et al. 1999a for a complete description of this process). The infusion sites were reconstructed based on their microdrive coordinates relative to those from the marker lesions. In addition, lateral and coronal X-rays taken after each experiment with the cannula in place were compared with the ventriculographs obtained during surgery to confirm the mediolateral and anteroposterior position of the cannula with respect to the motor thalamus. Also results from single unit recording sessions in the same monkeys (van Donkelaar et al. 1999a) allowed us to identify the dorsoventral and posteriolateral borders of the motor thalamus based

on the high-frequency discharge characteristic of the reticular nucleus and the somatosensory responses characteristic of the caudal portion of the ventral posterolateral nucleus (VPLc), respectively. Finally we used microstimulation to help confirm the location of VPLo/VLc (van Donkelaar et al. 1999a); it previously has been shown that the threshold for electrical stimulation of movement rises dramatically as one moves rostrally from VPLo/VLc to VLo and VApc (Buford et al. 1996; Miall et al. 1998; Vitek et al. 1996).

RESULTS

A total of 20 infusions of lignocaine were made at four different sites in each monkey. In addition, single control injections of saline were made at the same four sites in the second monkey. The injection sites as well as the volumes of affected tissue in each case based on the estimates of Martin (1991) are shown in the sagittal histological reconstructions in Fig. 1. Although the infusions were clearly centered in the goal nucleus in each case, the lignocaine very likely spread to surrounding nuclei. If this spread was extensive, however, one would predict that the functional consequences of the infusions should be similar across the different experimental sessions. The fact that the observed deficits varied quite systematically across sessions (see following text) suggests that the individual infusions mainly influenced processing in their target nuclei.

Monkey 1 was able to complete a minimum of five blocks of each type of task within each session (i.e., 1 preinfusion and 4 postinfusion blocks). *Monkey 2* completed a minimum of four blocks of each type of task within each session. In most of the graphs, the data from each monkey are treated separately. For the statistical analyses, two-way ANOVAs were completed for each monkey using trial blocks (4 or 5 levels) and sessions (2 or 3 levels) as the repeated measures unless stated otherwise. The pattern of results, however, was very similar for each animal.

VPLo infusions

In four of the five sessions in which infusions centered within VPLo were made, hemiplegia became apparent and lasted for 5–30 min. During this time, the monkey was unable to move the arm contralateral to the site of infusion in either the VT or IG tasks. Moreover when tested outside of the experimental tasks, the arm was limp, and the monkey could not be induced to move it. The effects of the hemiplegia were quantified by measuring the number of trials that were completed during each 2.5-min block of trials. As can be seen in Fig. 2, this value decreased substantially during the postinfusion period in both tasks. Repeated-measures ANOVAs (RM ANOVAs) were performed on the data from each monkey. In both cases, a significant main effect of trial block was obtained [*Monkey 1*: $F(4,20) = 3.25$, $P < 0.0374$; *monkey 2*: $F(3,8) = 5.84$, $P < 0.0205$]. Post hoc Tukey's tests revealed that each monkey completed significantly fewer trials during *blocks 3* and *4* compared with the other blocks. In *monkey 1* there was also a significant main effect for task type [$F(1,20) = 11.95$, $P < 0.003$], indicating that fewer trials were completed overall in the IG task relative to the VT task (Fig. 2*A*). Importantly, there were no interaction effects. This implies that the influence of lignocaine infusion into VPLo was similar in terms of the number of trials completed in both tasks. Saline injections never resulted in hemiplegia.

Further analysis of the movements themselves showed that they differed in the two tasks. Figure 3, *A* and *B*, shows typical pre- and postinfusion trials in the VT and IG tasks, respectively. The graphs display movements along the anterior-posterior axis plotted against time and are aligned on movement onset. Whereas the IG movements remained essentially unaffected after the infusion of VPLo in terms of their gross kinematic characteristics (Fig. 3*B*), the VT movements were clearly abnormal (Fig. 3*A*). In particular, there was a marked increase in variability in the arm trajectory occurring in the latter half of the movement as the hand approached the target.

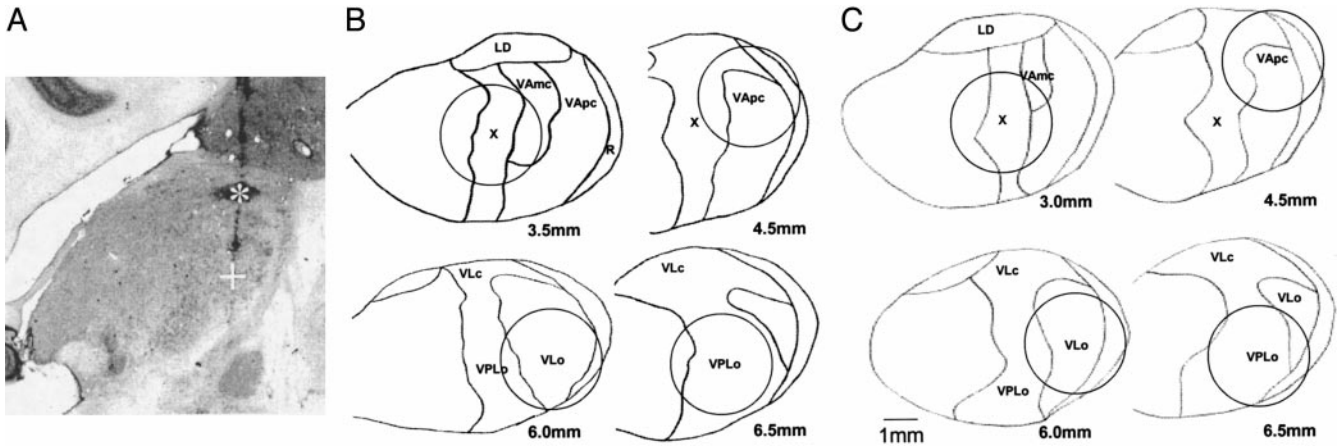

FIG. 1. *A*: photomicrograph from *monkey 2* showing marker lesion (*) and path of infusion cannula (dark vertical track) into ventral posterolateral nucleus, pars oralis (VPLo, +). The photomicrograph is reconstructed in *C*, *bottom right*. Figures in *B* and *C* are sagittal sections showing the histologically reconstructed estimates of the location and extent of inactivated tissue after infusion with lignocaine in *monkey 1* (*B*) and *monkey 2* (*C*). The radius of the circle in each case is 2 mm and is based on the estimates of Martin (1991). It is apparent in each section that the area of inactivation included surrounding thalamic nuclei; however, the majority of affected tissue was centered in the target nuclei. Numbers in the *bottom right corner* of each section represent the distance from the midline. LD, lateral dorsal nucleus; R, reticular thalamic nucleus; VAmc, ventral anterior nucleus, pars magnocellularis; VApc, ventral anterior nucleus, pars parvicellularis; VLc, ventral lateral nucleus, pars caudalis; VLo, ventral lateral nucleus, pars oralis; X, area X.

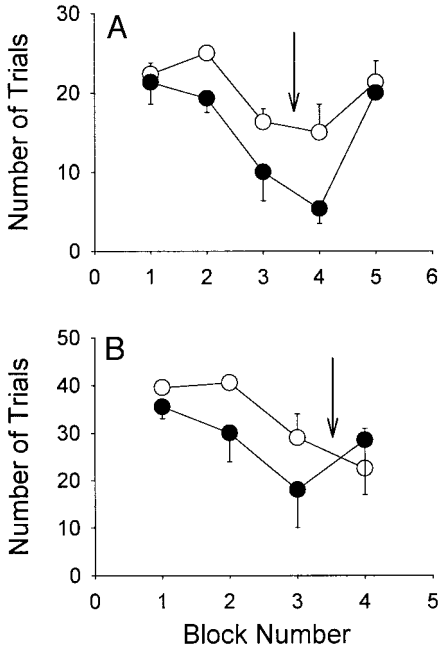

FIG. 2. Average number of trials produced during each 2.5-min block of trials for the visually trigggered (VT) task (○) and the internally generated (IG) task (●) in *monkey 1* (*A*) and *monkey 2* (*B*) after inactivation of VPLo. The first block of trials represent the preinfusion baseline and the remainder represent postinfusion blocks. In both cases, there was a significant reduction in the number of trials produced after the infusion. ↓, period of time during which the animal was unable to move the arm. This varied from session to session from 5 to 30 min. Error bars, 1 SE.

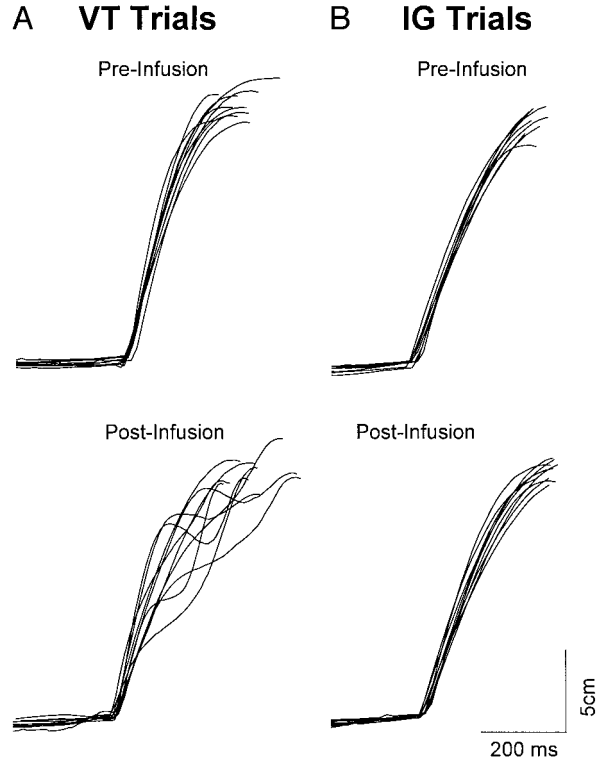

FIG. 3. Hand trajectories along the anterior-posterior axis plotted against time from typical pre- and postinfusion trials in the VT (*A*) and IG (*B*) tasks in *monkey 1* during sessions in which VPLo was inactivated. After the infusion, there was a high incidence of trajectory abnormalities in the VT task. This characteristic was not present in IG trials produced around the same time after the infusion.

IG movements generated immediately before or after a block of abnormal VT movements rarely displayed such characteristics. Previous research has demonstrated similar reductions in hand movement variability in cerebellar patients during responses produced with reduced visual cues or in a self-generated manner (Beppu et al. 1987; Morrice et al. 1990; van Donkelaar and Lee 1994). The frequency with which these abnormalities occurred during all postinfusion blocks of VT trials is plotted for each thalamic nucleus that was inactivated in Fig. 4. For this analysis, an abnormality was considered to be present if its absolute velocity was ≥10% of the peak velocity of the main movement and its duration was >50 ms. A RM ANOVA using thalamic nucleus and each monkey as factors revealed a significant main effect of nucleus [$F(3,56) = 17.22$, $P < 0.001$]. Post hoc Tukey's tests demonstrated that this effect was due to differences in the incidence of trajectory abnormalities after infusions centered within VPLo compared with the other three nuclei as well as a difference between area X compared with VLo and VApc. This pattern of results was similar across both animals. Moreover infusions of saline into these nuclei did not result in any trajectory abnormalities. Thus the ability to smoothly guide the hand to the target became compromised after inactivation of cerebellar-receiving nuclei, and within these nuclei it was much more common after infusions centered within VPLo than area X.

We also looked at several other parameters of movement performance in each task after the VPLo infusions. Figure 5, *A–D*, plots the changes in reaction time and movement time for each monkey. RM ANOVAs demonstrated that there was a significant increase in reaction time (Fig. 5, *A* and *B*) in the VT task in both monkeys [*monkey 1*: $F(4,10) = 4.09$, $P < 0.0322$; *monkey 2*: $F(3,4) = 26.46$, $P < 0.004$]. Post hoc Tukey's tests revealed that this was due to significantly longer reaction times in *trial blocks 3* and *4* in both monkeys. Thus after the appearance of the target, the monkeys took significantly longer to initiate their response when VPLo was inactivated. Analysis of the movement time results (Fig. 5, *C* and *D*) demonstrated significant interaction effects between trial block and task type for both monkeys [*monkey 1*: $F(4,20) = 4.88$, $P < 0.008$; *monkey 2*: $F(3,8) = 4.57$, $P < 0.038$]. Post hoc Tukey's tests revealed that this was due to longer movement times in *trial*

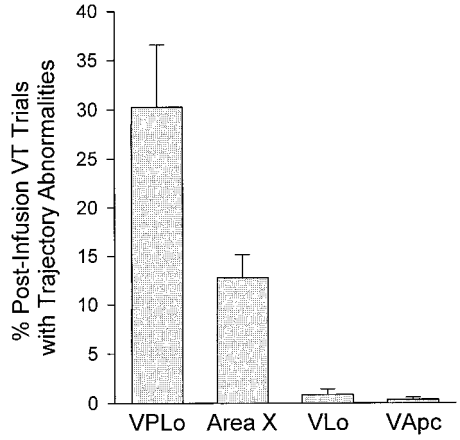

FIG. 4. Average percentage of postinfusion VT trials that contained trajectory abnormalities as the hand approached the target for each of the thalamic nuclei that were inactivated. This average represents the mean across all relevant trial blocks for both monkeys. Error bars, 1 SE.

blocks 3 and *4* in the VT task in *monkey 1* and *trial blocks 2–4* in the VT task in *monkey 2*. Thus after infusions centered within VPLo, the time required to complete the VT movements after they were initiated increased, whereas the IG movement times remained relatively invariant. By contrast, saline infusions did not cause any significant changes in either reaction time or movement time. The longer movement times in the postinfusion VT trials were not the result of lower peak velocities. Rather the presence of trajectory abnormalities during most of these trials appeared to be the cause. Comparison of the postinfusion VT trails with and without such abnormalities showed that the movement times were significantly longer in the former than the latter (*t*-test, $P < 0.05$). Thus the increase in movement time during the postinfusion VT trials appeared to be the result of variations in the trajectory of the hand as it approached the target rather than smaller initial agonist impulses as reflected in reduced peak velocities. This implies that VPLo normally contributes to visual-feedback based adjustments to movement trajectories.

Area X infusions

In contrast to what was observed after VPLo inactivation, infusions centered within area X never caused hemiplegia: the number of trials produced during each postinfusion block did not differ significantly from the number produced during the preinfusion period. However, as mentioned in the preceding text, there was an increase in the incidence of trajectory abnormalities in the VT task although it did not occur as frequently as that after inactivation of VPLo (see Fig. 4). Figure 6 displays the other main effects observed after infusion of area X. Figure 6, *top*, shows typical trajectories along the anterior-posterior axis plotted against time and aligned on target onset for a series of pre- and postinfusion trials in the VT task. Clearly, the reaction time was greater in the postinfusion trials.

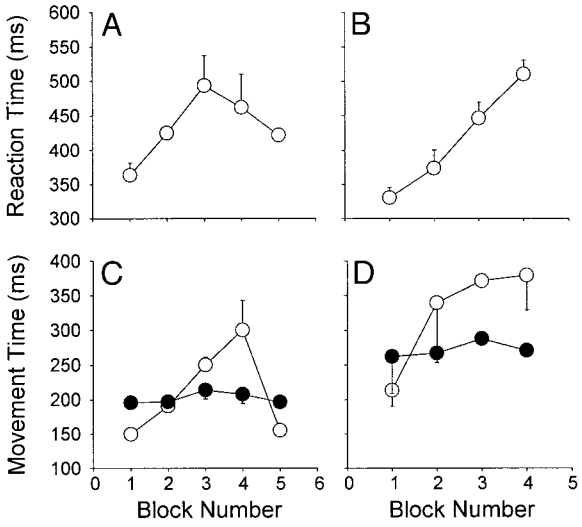

FIG. 5. Mean reaction time in the VT task for *monkey 1* (*A*) and *monkey 2* (*B*) during VPLo inactivations. *Trial block 1* represents the preinfusion baseline and the remainder represent postinfusion trials blocks. In both animals there was an increase in reaction time during the postinfusion period. Mean movement time in the VT (○) and IG (●) tasks for *monkey 1* (*C*) and *monkey 2* (*D*) during VPLo inactivations. After the preinfusion baseline (*trial block 1*), there was a significant increase in movement time in the VT task only in both animals. Error bars, 1 SE.

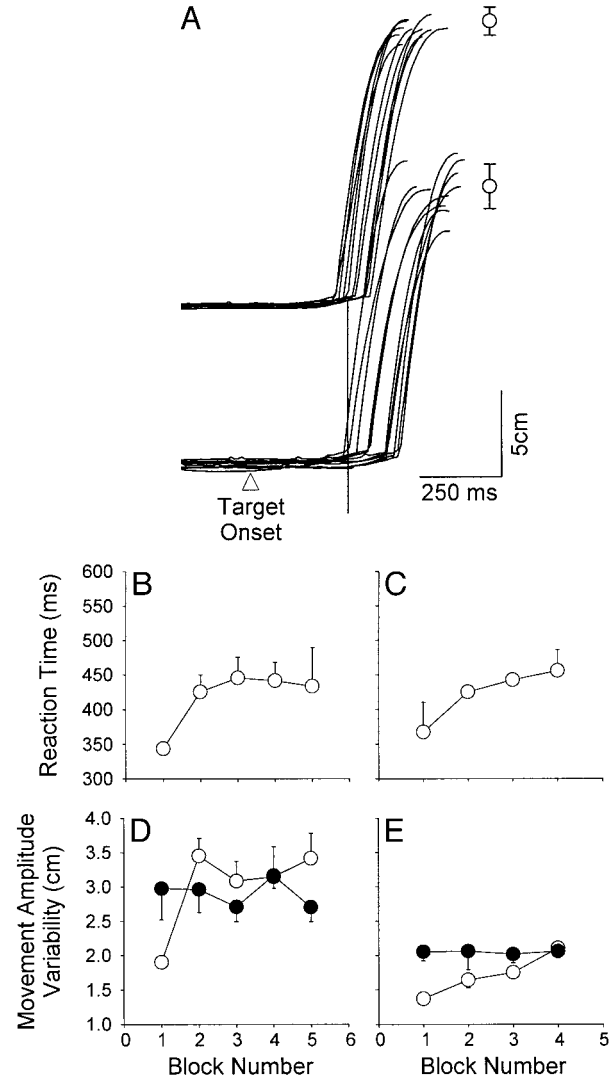

FIG. 6. Hand trajectories along the anterior-posterior axis plotted against time from typical pre- (*top*) and postinfusion (*bottom*) VT trials in *monkey 2* (*A*) during sessions in which area X was inactivated. Traces are aligned on the appearance of the target (open triangle). The vertical line represents the mean reaction time for the preinfusion trials and demonstrates that most of the postinfusion trials had longer reaction times. The open circle and error bars represent the mean ± SE of the movement amplitudes in both sets of trials. Clearly, the variability is greater in the postinfusion trials. Averages for reaction time in the VT task in *monkey 1* (*B*) and *monkey 2* (*C*). In both animals there was a significant increase in reaction time during the postinfusion trials (*block number* ≥*2*). Averages for movement amplitude variability in the VT (open circles) and IG (filled circles) tasks for *monkey 1* (*D*) and *monkey 2* (*E*). Compared with the preinfusion trials (*block number 1*) there was a significant increase in movement amplitude variability in the postinfusion VT trials but not the IG trials for both animals. Error bars, 1 SE.

RM ANOVAs demonstrated that there was a significant increase in reaction time (Fig. 6, *B* and *C*) in the VT task in both monkeys [*monkey 1*: $F(4,10) = 7.13$, $P < 0.0055$; *monkey 2*: $F(3,4) = 5.11$, $P < 0.012$]. Post hoc Tukey's tests showed that this effect was due to significantly longer reactions times in *trial blocks 2–5* in *monkey 1* and in *trials blocks 2–4* in *monkey 2*. In addition to the effect on reaction time, the amplitude of the movements became more variable after the infusion. This change in movement amplitude variability appeared to be limited to the VT task. RM ANOVAs revealed significant interactions on the standard deviation of movement amplitude

between trial block and task type for both monkeys [*monkey 1*: $F(4,20) = 3.33$, $P < 0.03$; *monkey 2*: $F(3,8) = 5.55$, $P < 0.023$]. Post hoc Tukey's tests showed that these interactions were due to the movement amplitude variability being significantly greater in *trial block 5* than in *trial block 1* of the VT task in *monkey 1* and significantly greater in all the trial blocks of the IG task and in *trial block 4* of the VT task than in *trial block 1* of the VT task for *monkey 2*. Thus the variability of the movements in the VT task increased after infusion of area X to reach levels similar to or higher than that observed in the IG task. The other variables that we measured (movement time; peak velocity) did not change in either task after area X inactivation, nor were any of the measured variables significantly affected by injections of saline.

VLo infusions

Infusions centered within VLo caused a reduction in the number of trials completed during the postinfusion period. Figure 7, *A* and *B*, shows this for both tasks after infusion of VLo with evidence of subsequent recovery in *monkey 1* (Fig. 7*A*). RM ANOVAs demonstrated a significant main effect for trial block in both monkeys [*monkey 1*: $F(4,20) = 2.93$, $P < 0.0431$; *monkey 2*: $F(3,8) = 55.42$, $P < 0.0001$]. Post hoc Tukey's tests revealed that fewer trials were completed in block 3 compared with all other blocks in *monkey 1*. In *monkey 2*, fewer trials were completed in *blocks 2–4* than in *block 1* and in *blocks 3* and *4* than in *block 2*. In addition to the effect across trial blocks, there was also a significant effect of task type in both monkeys [*monkey 1*: $F(1,20) = 5.39$, $P < 0.031$; *monkey 2*: $F(1,8) = 22.56$, $P < 0.001$]. In each case more trials were completed in the VT task than in the IG task. There was not, however, a significant interaction between trial block and task type. This indicates that the infusions of VLo had a similar effect across trial blocks on both the VT and IG tasks.

Interestingly, rather than being less successful at accurately completing each trial, the monkey simply made fewer attempts during each block of trials. Outside of the task context the posture of the arm appeared normal and brisk limb movement responses could be elicited for food rewards. Furthermore the movement times, peak velocities, and amplitudes of those experimental task responses that were produced did not change after the infusion. The only other change resulting from infusions centered within VLo was a significant increase in reaction time during the VT task (Fig. 7, *C* and *D*). RM ANOVAs demonstrated that this was true for both monkeys [*monkey 1*: $F(4,10) = 4.77$, $P < 0.021$; *monkey 2*: $F(3,4) = 15.15$, $P < 0.012$]. Post hoc Tukey's tests revealed that this was due to the reaction time in *trial blocks 3–5* being significantly longer than in *trial block 1* in *monkey 1*, and the reaction time in *trial block 4* being significantly longer than in *trial blocks 1* and *2* in *monkey 2*. Thus the ability to react quickly to the appearance of a visual target is impaired after infusions centered within VLo. Saline infusions did not cause any significant changes in the measured variables.

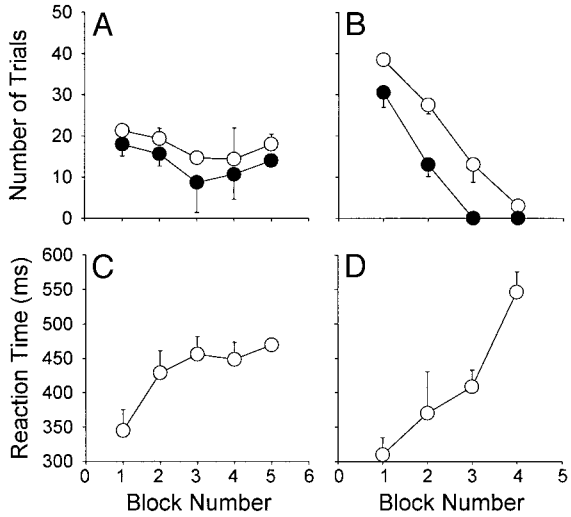

FIG. 7. Average number of trials produced during each 2.5-min block of trials for the VT task (○) and the IG task (●) in *monkey 1* (*A*) and *monkey 2* (*B*) after inactivation of VLo. In both types of tasks, there was a significant reduction after the infusion (*block number* ≥*2*). Average reaction time in the VT task in *monkey 1* (*C*) and *monkey 2* (*D*) in sessions in which VLo was inactivated. In both animals, there was a significant increase in reaction time after the preinfusion baseline (*block number 1*). Error bars, 1 SE.

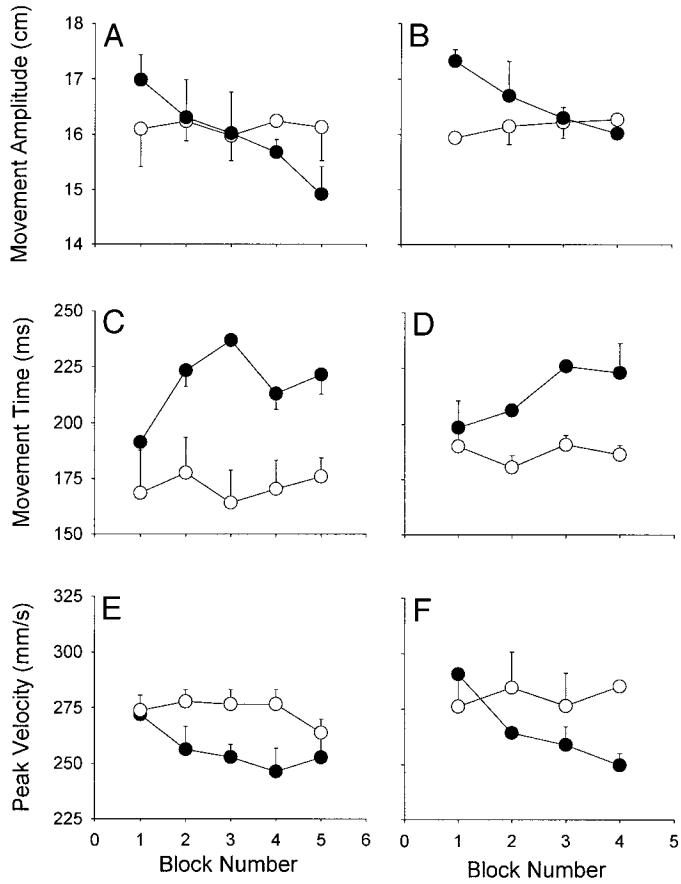

FIG. 8. Averages for movement amplitude in the VT (○) and IG (●) tasks for *monkey 1* (*A*) and *monkey 2* (*B*). After infusion of VApc, there is a significant reduction in movement amplitude in the IG task only (*block number* ≥*2*). Average movement time in the VT (○) and IG (●) in *monkey 1* (*C*) and *monkey 2* (*D*). After inactivation of VApc, there was a significant increase in movement time in the IG task only. Average peak velocity in the VT (○) and IG (●) in *monkey 1* (*E*) and *monkey 2* (*F*). After VApc inactivation, there was a significant decrease in peak velocity in the IG task only. Error bars, 1 SE.

VApc infusions

After infusions within VApc there was a marked reduction in the amplitude of the IG movements (Fig. 8, *A* and *B*). RM

ANOVAs revealed significant interactions between trial block and task type for movement amplitude in both monkeys [*monkey 1*: $F(4,20) = 3.00$, $P < 0.043$; *monkey 2*: $F(3,8) = 4.30$, $P < 0.044$]. Post hoc Tukey's tests demonstrated that this was due to movement amplitude being significantly smaller in *trial blocks 4* and *5* than in *trial block 1* in the IG task in *monkey 1* and in *trial block 4* than in *trial block 1* in the IG task in *monkey 2*. In other words, the IG movements became smaller in amplitude after infusions centered within VApc, whereas the VT movements remained relatively constant. Despite the fact that the IG movements were smaller in magnitude, they actually took longer to complete than the VT movements (Fig. 8, *C* and *D*). RM ANOVAs demonstrated significant interactions between trial block and task type for movement time in both monkeys [*monkey 1*: $F(4,20) = 3.11$, $P < 0.038$; *monkey 2*: $F(3,8) = 5.03$, $P < 0.03$]. Post hoc Tukey's tests showed that this was due to the movement times being significantly slower in *trial blocks 2–5* than in *trial block 1* of the IG task and also slower than all the trial blocks in the VT task in *monkey 1*. In *monkey 2* the movement times were significantly slower in *trial blocks 3* and *4* of the IG task than *trial block 1* of the IG task and slower than *trial blocks 1* and *2* of the VT task. Finally, analysis of the peak velocities showed that the increased movement times in the IG task were due to smaller peak velocities (Fig. 8, *E* and *F*). RM ANOVAs revealed significant interactions between trial block and task type for this variable in both monkeys [*monkey 1*: $F(4,20) = 2.89$, $P < 0.048$; *monkey 2*: $F(3,8) = 4.63$, $P < 0.037$]. Post hoc Tukey's tests showed that in *monkey 1* this was due to peak velocities being significantly higher during *trial block 1* than the rest of the trial blocks in the IG task. In *monkey 2*, the peak velocity in the first trial block of the IG task was significantly higher than that in the third and fourth blocks. This reduction in peak velocity is consistent with a smaller initial agonist burst under these conditions. Thus after infusions centered within VApc, IG movements became smaller in magnitude, were completed more slowly, and had reduced peak velocities compared with the VT movements. The other measures that were examined (number of trials, reaction time in the VT task, and movement amplitude variability) did not display any significant changes after infusion of VApc nor were any significant effects observed after saline infusions.

DISCUSSION

The goal of the present investigation was to examine how inactivation of different nuclei in the cerebellar- and basal ganglia-receiving territories of the motor thalamus affected the initiation and execution of movements based on internal versus external cues. Recall that in the VT task the target triggered and guided the response and the target position was varied (although the target appeared at the center of the display most often); by contrast, in the IG task the movements were self-initiated and directed to a remembered target location that did not vary. Thus the different task-dependent effects that were observed after infusions centered within each nucleus can be inferred to be due to the specific contributions that each nucleus makes to these processes. Before we discuss the deficits observed in this study, it is important to examine the way in which lignocaine has its effect.

Specificity and spread of lignocaine

Lignocaine is a local anesthetic that blocks the conduction of action potentials in the targeted neural tissue. It does not differentiate between cell bodies and axons in its effects and therefore may interrupt the activity in fiber tracts passing nearby the site of infusion. In the case of the motor thalamus, these would include the anterior portion of the internal capsule and the mammillothalamic tract. The internal capsule carries fibers of the corticospinal tract. As such, if it is inactivated the animal should become hemiplegic. This is certainly what occurred after infusion of lignocaine into VPLo. However, none of the other infusion sites resulted in such an effect; even when infusions were centered within VLo, which like VPLo is located on the lateral edge of the thalamus adjacent to the internal capsule, hemiplegia never occurred. Thus it is difficult to reconcile this functional dissociation with a potential common effect on corticospinal tract fibers within the internal capsule. The mammillothalamic tract carries memory-related signals from the mammillary body to different portions of the ventral thalamus. Because the task we used was overlearned by the animals, it was unlikely to have involved a substantial memory component. Thus even if the mammillothalamic tract was inactivated by infusion of lignocaine into the target thalamic nuclei, it would be of little functional consequence for the task being performed.

A second concern with respect to the infusions was the potential for spread of the lignocaine from the target nucleus into surrounding nuclei within the thalamus. On the basis of the results of Martin (1991), we estimated the extent of spread to be ~4 mm. Our reconstructed infusions sites were between 5 and 8 mm apart and a minimum of 2.5 mm from any nuclear border. Thus the lignocaine almost certainly spread into thalamic nuclei that were not targeted by the infusions and also may not have inactivated the entirety of each targeted nucleus. Two points give us confidence in making functional distinctions between thalamic nuclei based on the current inactivation results. First, there is a certain degree of somatotopy especially within VPLo and VLo. In particular, an "onion-like" layering exists with face being surrounded by upper limb, which in turn is surrounded by lower limb as one moves in a mediolateral direction (Vitek et al. 1996). Thus if there was spread of lignocaine across the lateral borders of area X and VApc, the most likely cells within VPLo and VLo, respectively, to be affected would have been those representing the face. Because facial movements associated with ingesting the liquid reward were common to the tasks being performed, it is difficult to reconcile the functional distinctions that were observed after infusions of the medial and lateral thalamic nuclei with this potential common effect. Second, although the lignocaine may have spread ≤4 mm from the injection site, the functional consequences appeared to be much more restricted. An example of this is related to the hemiplegia observed after infusions centered within VPLo. On some occasions, only the arm was affected. Because the arm and leg representations are separated by 1–2 mm within VPLo (Vitek et al. 1994), this suggests that the spatial-temporal resolution of the functional effects can be quite high despite the relatively large absolute volume of affected tissue.

Functional consequences of lignocaine infusion

We have shown previously that the activity of cells in each of these nuclei varies in a systematic manner depending on the movement context (van Donkelaar et al. 1999a). From these results we have hypothesized that *specific subcircuits* within the cerebello- and basal ganglio-thalamo-cortical systems contribute in varying degrees to the control of VT versus IG movements. The results from the present investigation are generally consistent with these findings. After infusions centered within area X, the monkeys appeared to have difficulty integrating the visuospatial information provided by the target into appropriate and consistent motor responses in the VT but not the IG task. Thus only movements that were triggered and guided by a visual target were influenced by infusion of area X, whereas movements based on an internal cue remained largely unaffected. In contrast to this functional specificity for VT movements in area X, infusions centered within VApc produced deficits restricted to IG movements. In particular, after such infusions, the IG but not the VT movements were smaller in amplitude and slower than those produced prior to the infusion. Taken together, these results are consistent with our recording results showing that area X cells contribute preferentially to VT movements and VApc cells preferentially contribute to IG movements (van Donkelaar et al. 1999a).

The relatively high degree of functional specificity for movements based on internal versus external cues observed in area X and VApc was much less apparent in VPLo and VLo. When VPLo was infused with lignocaine the most obvious behavioral deficit was temporary hemiplegia on the contralateral side of the body. Before and after these hemiplegic episodes, the ability of the monkey to control the limb and accurately perform both tasks was greatly compromised. Thus in a very general sense infusions centered within VPLo reduce the ability to perform movements regardless of the behavioral context. When the movement trajectories were examined in detail, however, it became apparent that deficits existed in the VT but not the IG responses. Thus although VPLo appeared to contribute in a general way to the ability to generate movements, it also appeared to play a more specific role in the initiation and execution of movements based on visual cues. The presence of these deficits is consistent with several previous human clinical studies showing cerebellar symptoms in patients with thalamic damage (Fukuhara et al. 1994; Louis et al. 1996; von Cramon 1981). These results are also consistent with our recording results (van Donkelaar et al. 1999a). Although we found that most VPLo cells did not differentiate between the VT and IG tasks, there was also a large subset of cells (~30%) that fired exclusively during movements made in response to the appearance of the visual target. By contrast, very few VPLo cells were found to fire exclusively to the IG task.

When infusions were made into VLo, there was also a significant reduction in the number of trials that were executed successfully in both tasks. This did not appear to be related to any hemiplegia, however. In fact, relatively normal limb movements could be elicited outside the experimental task, and those movements that were generated within the tasks had movement times and amplitudes that did not differ significantly from preinfusion responses. Only reaction times in the VT task were increased significantly after VLo inactivation, implying that VLo normally contributes to the initiation of movements made to visual targets. This result is generally consistent with the findings from our recording experiment (van Donkelaar et al. 1999a). As in VPLo, we found a large proportion of cells in VLo that did not differentiate between the VT and IG tasks. It is quite possible that these cells contribute to the initiation of both types of movements but that because of the nature of our tasks and measurements, the latency deficits after inactivation become apparent only during VT movements. A more difficult finding to explain is the reduction in the number of completed trials without any other obvious motor deficits. One possible explanation is that VLo normally contributes to the "motivation" required to perform the tasks. Indeed, we have found that a large proportion of cells in the basal ganglia-receiving territories of the primate thalamus possess what appears to be reward-contingent activity (van Donkelaar et al. 1999b). When such cells are inactivated, the monkey may have trouble linking the performance of the task with reward delivery, and the number of attempts made would very likely be reduced as a consequence. In what follows, we discuss how these results can be interpreted in light of previous functional and neuroanatomic studies within the cerebello- and basal ganglio-thalamo-cortical systems.

Cerebellum and the visual control of movement

There is a large body of evidence that is consistent with the hypothesis that the cerebellum contributes in a significant way to the visual (or more generally sensory) control of movement. Subjects with cerebellar damage have a great deal of difficulty performing reaching movements under visual guidance (e.g., Beppu et al. 1987; Brown et al. 1993). When visual information concerning the position of the hand or the target (or both) is removed, cerebellar subjects perform much more consistently (e.g., Beppu et al. 1987; van Donkelaar and Lee 1994). Functional imaging studies demonstrate significant cerebellar activation during visually guided limb movements (e.g., Inoue et al. 1998; Jueptner et al. 1996). Finally, neuronal recording studies have shown that cells within the cerebellar cortex and deep nuclei become active prior to visually guided arm movements (e.g., Fortier et al. 1989; Marple-Horvat and Stein 1987).

Mushiake and Strick (1993) showed that this specificity for visually guided movements is restricted at the level of cerebellar dentate to particular portions of this nucleus. They demonstrated that dentate cells coding preferentially for visually guided movements tend to be located in the caudal portion of this deep nucleus, whereas cells that do not differentiate between visually guided and remembered movements are located more rostrally. The former part of the dentate projects mainly to area X, whereas the latter projects to VPLo (Strick et al. 1993). Thus the functional specificity observed at the level of the dentate for the cues used to trigger and guide movement is preserved in the cerebellar-receiving areas of the primate thalamus (van Donkelaar et al. 1999a). As discussed in the preceding text, the results from the present investigation are largely consistent with these findings. On the basis of these combined results, one would predict that infusions made in the caudal dentate should result in analogous deficits to those observed after area X inactivation, whereas rostral dentate infusions should lead to deficits similar to those observed after VPLo inactivation. Unfortunately, although there have been

numerous cerebellar deep nuclei inactivation studies, none have addressed this question directly.

Basal ganglia and IG movement

Just as the cerebellum has been implicated in the control of VT movements, it also has been suggested that the basal ganglia contributes in a significant way to the control of IG movements. However, unlike the clear evidence supporting the role of the cerebellum in visually guided action, studies that have examined the contribution of the basal ganglia to IG movements have produced less convincing results. Two studies with largely similar results are most pertinent to the discussion of the present findings. Mink and Thach (1991) and Inase and coworkers (1996a) both inactivated portions of the main output structure of the basal ganglia, the internal segment of the globus pallidus (GPi) in monkeys trained to perform limb movements based on external versus internal cues. In both cases, the main deficit that was observed was a flexor drift in the contralateral arm. More importantly, in both studies there was no evidence that the movements based on internal cues were more adversely effected by the inactivation than movements based on external cues. Instead these researchers suggested that the basal ganglia were involved in maintaining appropriate balances between flexors and extensors to allow a particular movement to occur regardless of the context (Mink 1996). How can the results from the present study be reconciled with those from Mink and Thach (1991) and Inase et al. (1996a)? First, we did not find any evidence of flexor drift after either VLo or VApc inactivation. This is relatively simple to explain: in our set-up the handle was blocked mechanically from moving beyond the start position in the direction of elbow flexion, whereas in both the Mink and Thach (1991) and Inase et al. (1996a) studies the handle had to be held at a central starting position with appropriate levels of elbow flexor and extensor activation. Thus although it is likely that flexor drift could occur after VLo or VApc infusion, it may not have been observed in the present study simply because of the nature of the experimental set-up. A second more difficult discrepancy to explain is the fact that we found a clear functional distinction between movements based on external versus internal cues when VApc was inactivated, whereas Mink and Thach (1991) and Inase and coworkers (1996a) did not when they inactivated GPi, which provides the main input to VApc.

The key to reconciling these divergent results may be in the *locations* at which GPi was inactivated relative to its pattern of connectivity to VLo and VApc. Mink and Thach (1991) and Inase et al. (1996a) inactivated the mid- to ventral half of the GPi. This part of the GPi projects to the middle portion of VLo. By contrast the more dorsal part of the GPi projects mainly to lateral and rostral aspects of VLo and VApc (DeVito and Anderson 1982). Moreover, Mushiake and Strick (1995) have demonstrated that the majority of cells in the dorsal GPi display a preference for movements based on internal cues, whereas most GPi cells located more ventrally do not differentiate between movements based on external or internal cues. Thus a functionally distinct subcircuit from the dorsal GPi to VLo and VApc appears to process information related to movements based on internal cues. The finding from the present investigation that infusions centered within VApc result in deficits in the amplitude and velocity of internally generated movements is consistent with this hypothesis. Indeed previous recording studies have shown that arm-related neuronal activity in the globus pallidus is modulated by movement amplitude and velocity (e.g., Georgopoulos et al. 1983; Turner and Anderson 1997). Moreover, individuals with Parkinson's disease tend to make hypometric and bradykinetic movements that are ameliorated by providing visual cues (Jackson et al. 1995; Morris et al. 1996; Oliveira et al. 1997). Finally, imaging studies have demonstrated that the cerebello-thalamo-cortical pathways are overactive in Parkinson's patients during externally initiated movements and thus appear to compensate for the deficits observed during IG tasks (Rascol et al. 1997; Samuel et al. 1997). Taken together, the present results imply that the bradykinetic and hypometric movements observed in Parkinson's disease result from malfunctioning in the pallido-thalamic subcircuit projecting through VApc.

Thalamocortical projections

Recent neuroanatomic studies have demonstrated that there is considerable overlap in the cortical projections from the cerebellar- and pallidal-receiving portions of the thalamus (e.g., Holsapple et al. 1991; Hoover and Strick 1993, 1999; Inase and Tanji 1995; Inase et al. 1996b; Matelli and Luppino 1996; Matelli et al. 1989). This implies that more than one cortical area may contribute to movements based on internal versus external cues and/or to the behavioral measures disrupted by our infusions. Indeed studies that have examined this issue typically have found that the degree of functional specialization within different cortical areas is relative rather than absolute (e.g., Mushiake et al. 1991). Be that as it may, we nevertheless found a pattern of deficits after thalamic inactivation that is largely consistent with this relative degree of cortical specialization and the underlying thalamocortical projection patterns. Because this reconfirms the results from our previous recording study (van Donkelaar et al. 1999a) and a detailed discussion of the functional subcircuits arising from the basal ganglia and cerebellum can be found in that paper, we will not delve into this issue any further here. One point does warrant further discussion, however. In particular, of the deficits observed in the present study, the most striking was the hemiplegia after infusions centered within VPLo. This certainly is not too surprising given the strong projection from VPLo to the primary motor cortex (MI). However, VLo also sends a strong projection to MI and infusions centered on this nucleus never resulted in hemiplegia. How can this discrepancy be accounted for? Neuroanatomic studies have demonstrated that VPLo sends projections to the deep cortical layers in MI where microstimulation elicits movements at low thresholds (Asanuma and Rosen 1972). By contrast, VLo sends projections to more superficial layers in MI (Nakano et al. 1992). Thus VPLo appears to have more direct access to corticospinal neurons. This idea is supported by the finding that movements can be elicited at low thresholds after microstimulation in VPLo but not in VLo (Buford et al. 1996; Miall et al. 1998; Vitek et al. 1996). Thus the more direct route by which VPLo projects to corticospinal neurons may account for the fact that temporary hemiplegia was observed most consistently after infusions centered within this area of the thalamus.

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