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Visuomotor adaptation during inactivation of the dentate nucleus

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RECENT experiments have suggested that the process of visuomotor adaptation depends on how a visual distortion is introduced. The cerebellum is thought to be involved in adapting to rapidly introduced visual distortions; however its role in adapting to a gradually introduced distortion is unknown. We tested adaptation to a sudden or a gradual introduction of a visual distortion, during reversible inactivation of a monkey's dentate nucleus. There was significant adaptation in both of these tasks without any lignocaine infusion and during saline infusions. However after inactivation the ability to adapt to either visual distortion was slightly impaired. This dysfunction was significant when the visuomotor distortion was introduced over several trials, suggesting that the cerebellum has a differential contribution to visual adaptation depending on the type of visuo-motor disturbance encountered. *NeuroReport* **10:1029–1034 © 1999 Lippincott Williams & Wilkins.**

Key words: Arm movements; Cerebellum; Monkey; Visuo-motor adaptation

Introduction

Classically, the cerebellum has been regarded as having a critical role to play in motor learning [1]. As this remains fundamental to many of the contemporary ideas regarding its role in movement control, the importance of the cerebellum in motor learning has attracted intense experimental interest [2]. Many studies have involved reaching movements during which a disparity is introduced between the actual and perceived hand position. Patients with cerebellar atrophy show little or no motor adaptation while wearing reversing prisms, and temporary inactivation of specific areas of the cerebellar hemispheres has a similar detrimental effect on adaptation [3–5]. These studies involved introducing a visual distortion between the actual and perceived hand position in a single trial. However it has been known for some time that visuomotor adaptation can occur in a variety of paradigms [6]. Recently, these ideas have received further support by examining the after-effects of a novel visuomotor distortion that was implemented in two different ways [7]. A visuomotor distortion was introduced either in a single trial (step adaptation) or over the course of several trials (ramp adaptation). Both forms of adaptation showed sizeable after-effects, a crucial sign of motor system involvement in skill acquisition [3]. However the size of after-effect was greater in ramp adaptation implying an important behavioural difference between these types of adaptation [7].

If the cerebellum is the biological substrate of motor adaptation then disrupting its function should impair all forms of adaptation regardless of the sensorimotor signals driving adaptation. However if there is a disparity between the effect of cerebellar dysfunction on step and ramp adaptation it suggests that the role of the cerebellum in motor adaptation is more ambiguous than suggested by many contemporary theories.

Materials and Methods

A male monkey (*Macaca mulatta*) was trained to reach out and grasp a manipulandum situated beneath a silvered mirror which prevented any direct viewing of arm movements (Fig. 1a). Manipulandum position was represented by a cursor, which along with a target box was projected into the plane of the manipulandum. At the start of each trial the target was a centrally located starting box. In the standard condition the position of the cursor on the silvered mirror was congruent with the manipulandum position. Consequently a movement of the manipulandum in a particular direction brought about a corresponding movement of the cursor. This condition required the cursor to be placed within the starting box for 1.2 s, after which one of two laterally placed target boxes appeared. By moving the manipulandum the monkey was able to capture the target with the cursor. During the arm movement only the target box was projected onto the mirror. The cursor (representing the manipulandum position) only became visible once the movement

was completed. If the target was captured within a time limit of 2.0 s and held for 1.2 s the monkey was rewarded with fruit juice.

Adaptation tasks: The relationship between manipulandum and cursor position was altered in two different adaptation tasks. The position of the cursor was rotated by 15° around the central starting box. This resulted in an offset of ~20 mm, from the final target position (Fig. 1b).

In the step adaptation task the 15° discrepancy was introduced in a single trial while in the ramp adaptation task it was introduced over the course of 15 trials, 1° per trial.

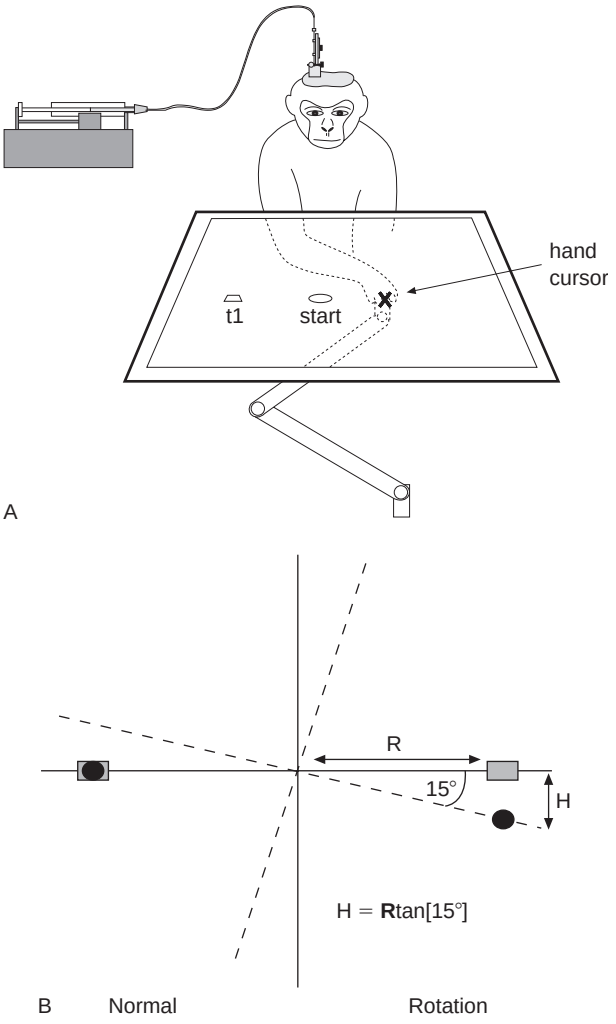

FIG. 1. (**a**) Experimental set-up showing the monkey moving a manipulandum, beneath a silvered mirror while lignocaine was infused into the dentate nucleus. During the movement only the target box was projected onto the mirror, the cursor only become visible once the movement was completed. (**b**) The effect of rotation on cursor position. Under normal conditions the position of the hand (box) and cursor position (circle) were congruent (left-hand side). A disparity between cursor and hand position was produced when a rotation of 15° was added. The perceived effect of this was a function of the distance from the centre of the rotational, which in this case was the starting box. With the target box 70 mm away an offset of ~20 mm in the y-axis between actual and perceived hand position was generated.

Ramp adaptation was introduced at the start of a 150 s exposure block while step adaptation was introduced randomly after the performance of 10–17 movements. Because these adaptation paradigms were so different and because ramp adaptation is by definition gradual, comparison was based upon the effects of removing the visual distortion. Moreover it is generally agreed that this is the most appropriate way to examine the effects of adaptation as it ameliorates the confounding influence of non-motor processes such as cognition in the adaptation process [3]. This period of post-adaptation was carried out in a 150 s time block where the distortion was removed at random after the completion of 10–17 movements performed with the full 15° of distortion. At least 12 consecutive trials had to be completed after the removal of the distortion for the data to be included in the analysis. These trials were known as the de-adaptation phase.

Surgical procedures: Once fully trained the monkey underwent standard aseptic surgical procedures (under Saffan (0.2 mg/kg) anaesthesia to place a stainless steel chamber over the stereotaxic coordinates posterior 9.8 mm and lateral 6.8 mm (right dentate nucleus) from ear bar zero.

Infusion protocol: In each session, the dura was anaesthetized with 5% topical lignocaine and an infusion cannula (outside diameter 0.3 mm) inserted and directed to the ipsilateral (right-hand side) dentate nucleus. Lignocaine was infused to induce a reversible inactivation (5% in saline at a rate of 2 μl/min for 2 min). Post-infusion arm movements were carefully observed for 2 mins, for signs of cerebellar dysfunction. Infusions were stopped once these signs became apparent or when additional infusions made the total volume up to 12 μl. The monkey then started the behavioural task. Once the session was completed radiographs were used to confirm the cannula position.

Kinematic analysis: The x and y co-ordinates of cursor and hand position were recorded at 70 Hz during arm movements. Positional error was calculated as the difference, in y coordinates, between the final cursor position and the target. This was used as a measure of error because both adaptation tasks required an alteration of the animal's trajectory in the y-axis (Fig. 1b). Performance errors were then averaged across trials to generate post-adaptation curves. A statistical comparison of three trials before and after-removal of the visual distortion was used to assess the size of the post-adaptation after-effect [8]. An ANOVA was used to compare the performance errors made with and without infusion follow-

ing removal of the distortion the so-called de-adaptation period.

Results

Lignocaine infusion: Lignocaine infusion produced poorly organized and uncoordinated movements that typically became noticeable within 3–6 min after the onset of infusion and lasted for about 30–40 min, which was often longer than the monkey was prepared to work when making dysmetric movements. Consequently it was not possible to compare the monkey's movements before and after infusions on the same day. Nevertheless, movements observed on subsequent days appeared normal.

The precise nature of the lignocaine effect was dependent upon the position of the infusion cannula. Infusing lignocaine in a relatively small area (sites I, II and III, giving a total of 18 post-adaptation blocks in each condition, Table 1) produced dysmetria and uncoordinated arm movements. These sites were, therefore, used to investigate the effects of dentate nucleus inactivation upon both types of adaptation. Another two sites (sites IV and V, giving a total of 11 post-adaptation blocks in each condition, Table 1) were also inactivated with lignocaine; the most noticeable effect was a difficulty in controlling tongue and facial movements. In neither area were eye movements noticeably effected.

Effects upon post-adaptation sessions without infusion: Both post-step and post-ramp adaptation curves were constructed from 20 post-adaptation blocks (Fig. 2). Both showed a prominent after-effect with a significant difference in performance error between three trials before and after removal of the distortion (step: $p < 0.05$, ANOVA ($F_{1,236} = 6.82$); ramp: $p < 0.05$, ANOVA; $F_{1,236} = 7.02$). By the end of the experimental block of step post-adaptation, baseline conditions had been re-acquired as there was no significant difference between the first two and the last two trials ($p > 0.05$, ANOVA; $F_{1,156} = 1.4$). However there was a significant difference between these trials for ramp post-adaptation ($p < 0.05$, ANOVA; $F_{1,156} = 2.9$).

Effects of lignocaine upon post-adaptation: In the step condition, post-adaptation after-effect was evi-

Table 1. Repeated lignocaine infusions were made in five sites (I–V) with the same infusion volume being used on each occasion. Despite the larger volumes of lignocaine infused into sites IV and V these never resulted in abnormalities of arm movements. Smaller volumes of lignocaine infused into sites I–III consistently gave uncoordinated and tremulous reaching movements. Five saline infusions (each of 10 μl) never showed any effect on arm movements.

Site	Stereotaxic coordinates		Lignocaine infusions		Saline infusions Number (all 10 μl)
	Anterior (mm)	Lateral (mm)	Number	Volume (μl)	
I	−8.8	6.0	7	4	1
II	−8.8	7.5	5	8	2
III	−8.3	6.0	6	4	2
IV	−9.8	6.0	8	12	–
V	−8.8	5.5	3	12	–

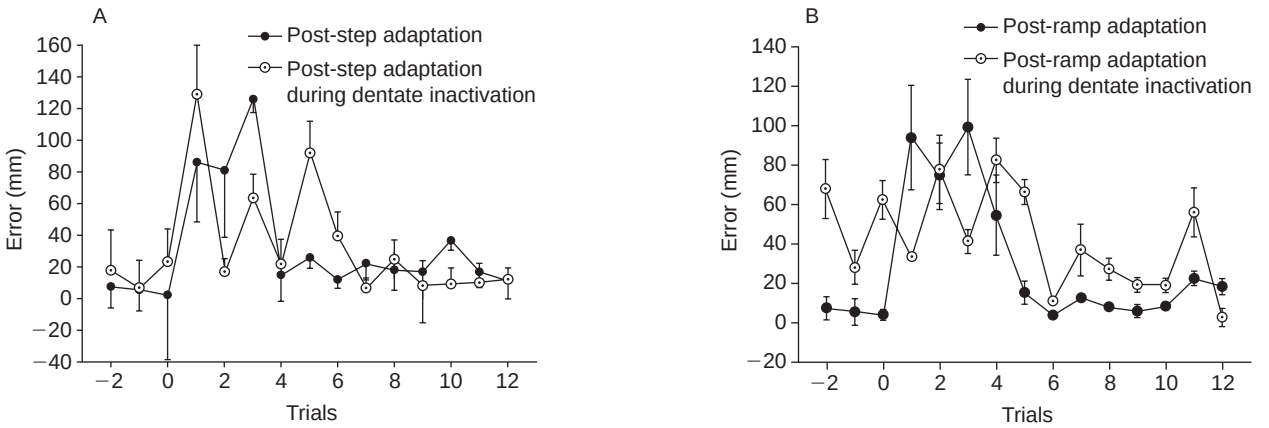

FIG. 2. (**a**) Errors made during post-step adaptation with and without lignocaine infusion into sites I–III of the dentate nucleus. Trial zero shows when the distortion was removed. In both cases there was clear evidence of a post-adaptation after-effect which did not differ significantly across the conditions. Nor was there a significant difference between the performance errors made in either condition. (**b**) Errors made during post-ramp adaptation with and without lignocaine infusion into sites I–III of the dentate nucleus. Without infusion there was clear evidence of a post-adaptation after-affect, demonstrated by a significant difference between the three trials before and three trials after the distortion was removed. However following lignocaine infusion into the dentate nucleus, errors at the end of the adaptation period were high and no after-effect could be demonstrated, suggesting that lignocaine infusion prevented motor adaptation.

dent as a significant rise in performance error observed when the distortion was removed ($p < 0.05$, ANOVA; $F_{1,106} = 4.05$; Fig. 2). Nevertheless baseline conditions were soon re-acquired, and there was no significant difference between errors made in the first and the last two trials across all the blocks ($p > 0.05$, ANOVA; $F_{1,70} = 1.12$). Moreover, there was no significant difference between the performance errors made during de-adaptation with or without infusion ($p > 0.05$, ANOVA; $F_{1,454} = 1.58$). These observations are consistent with adaptation having occurred despite inactivation of the dentate nucleus, with the implication that the role of the dentate nucleus in step adaptation is relatively minor.

The ramp condition showed a quite different pattern. Performance errors were significantly raised across all those experiments in which lignocaine had been infused into the dentate nucleus ($p < 0.05$, ANOVA; $F_{1,454} = 4.28$). This was also reflected in the lack of a statistical difference between the three trials immediately preceding and the three trials following the removal of the visual distortion, so there was no evidence of a post-adaptation after-effect ($p > 0.05$, ANOVA; $F_{1,106} = 1.44$; Fig. 2). This implies that motor adaptation did not occur during the ramp condition when lignocaine was infused into the dentate nucleus; this is consistent with the relatively large performance errors in the trials before the visual distortion was removed. Nevertheless a decrease in performance error did occur on return to standard conditions (between the 5th and 6th trials), suggesting that there was no need to re-adapt to standard conditions because of the limited initial adaptation to the novel condition. However, the performance errors did not return completely to pre-adaptation levels, as there was a significant difference between the last two trials of post-ramp adaptation performed with and without infusion ($p < 0.05$, ANOVA; $F_{1,70} = 4.20$).

Effects of saline infusions: Infusion of saline (10 µl), once into site I and twice into both sites II and III, did not effect step or ramp post-adaptation (Table 1). Both continued to show a significant post-adaptation after-effect (step: $p < 0.05$, ANOVA; $F_{1,56} = 4.68$. ramp: $p < 0.05$, ANOVA; $F_{1,56} = 5.08$) and the performance errors made across the trials for each condition were not significantly different from when no infusion had been made into the dentate nucleus (step: ANOVA; $F_{1,596} = 1.58$. ramp: $p > 0.05$, ANOVA; $F_{1,596} = 1.65$).

Effect of infusion site: As mentioned above, lignocaine infusions into two sites (IV and V) that were slightly posterior and lateral to sites I, II and III had little effect upon arm movements. This was in accord with their lack of effect upon either adaptation condition. In both conditions, there was a significant post-adaptation after-effect (step: $p < 0.05$, ANOVA; $F_{1,128} = 4.58$. ramp: $p < 0.05$, ANOVA; $F_{1,128} = 4.78$) and performance errors during de-adaptation were not significantly raised compared with trials in which no infusion was made into the dentate (step: $p > 0.05$, ANOVA; $F_{1,740} = 1.43$. ramp: $p > 0.05$, ANOVA; $F_{1,740} = 1.2$). This was despite the higher volumes of lignocaine which were consistently infused into these two sites (Table 1).

Histology: The axial sections show a zone of chronic scarring restricted to the medio-lateral position of the dentate which did not extend into its more posterior aspects (Fig. 3). Perhaps more importantly, the interpositus nucleus showed relatively little sign of having been damaged.

Discussion

The role of the cerebellum in visuomotor adaptation was examined in two tasks: step adaptation, when a novel visuomotor disturbance (15° rotation) was introduced in a single trial, and ramp adaptation when the distortion was introduced over 15 trials at a constant rate (1°/trial).

In the control conditions, successful adaptation occurred irrespective of how the novel visuomotor

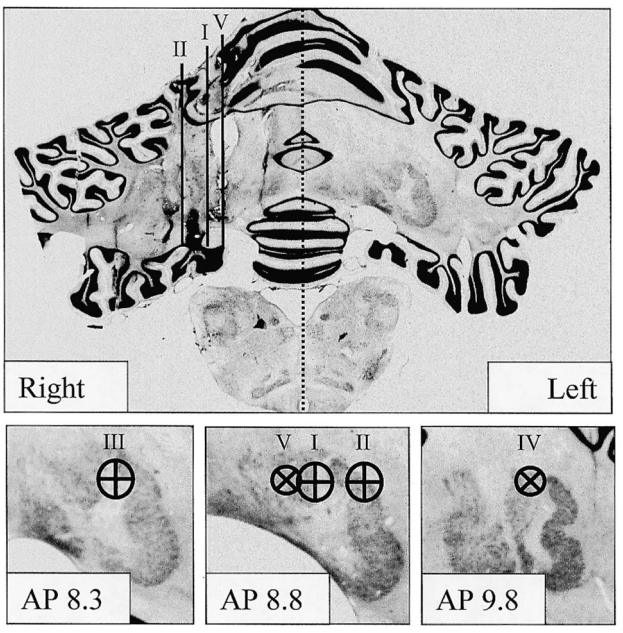

FIG. 3. The large box contains a complete axial cerebellar section taken at ~8.8 mm posterior from ear bar zero showing the infusion tracts associated with sites I, II and V (Table 1). The lower three diagrams show each of the antero-posterior planes in which infusions were placed; for display purposes these have been projected onto the intact contralateral (left) dentate nucleus.

rotation was introduced. The pattern of errors made during post-adaptation showed an increase in performance error followed by a steady decrease over several trials. This post-adaptation performance is indicative of the motor system's involvement in adaptation, as opposed to such changes being due to cognitive or motivational processing [3].

Dentate nucleus inactivation led to significant increases in the amplitude of performance errors in ramp de-adaptation; moreover an after-effect was absent. Generally the infusions had relatively minor effects upon motor performance. This was intentional, because it was necessary to minimize the motor deficits so that the monkey would continue to work. Nevertheless the impairments observed were specifically due to the effects of lignocaine because saline infusions into the same sites failed to bring about substantial changes in movements or in de-adaptation, nor did they obliterate the after-effect. The most effective sites for inducing uncoordinated movements were in the dorsal areas of the dentate nucleus and nearby areas of white matter. Nearby sites (IV and V) within this zone were ineffective at disrupting reaching movements. Despite relatively large volumes of lignocaine being infused the only obvious impairment following infusions into these sites was a difficulty in controlling movements of the mouth (Table 1). In contrast, infusions into the medial and mid-anterior regions of the dorsal aspect of the dentate (sites I, II and III) consistently resulted in disorganized limb movements.

Despite this apparent specificity we cannot be certain that regions other than the dentate nucleus, for example the interpositus nucleus and the adjacent cerebellar cortex, were not effected by the lignocaine. However, if the interpositus nucleus had been influenced to a significant degree then changes in the arm movements commensurate with inactivation of the nucleus, for example a reduced ability to grasp the manipulandum, would have been anticipated [9]. Consequently it seems the lignocaine infusions had a specific and reasonably circumscribed effect consistent with earlier results [10–12].

These observations implicate the lateral cerebellum in playing a critical role in ramp adaptation, while it plays a less fundamental role in step adaptation. Consequently the neuronal circuits within the cerebellum may not have a general adaptive function but instead a more specific role to play in adaptation. This interpretation is inconsistent with contemporary theories, which form a dichotomy between those that adhere to the cerebellum having a role to play in adaptation and those that are firmly opposed to such a suggestion [13–16]. Nevertheless, some recent experimental work is in accord with the suggestion that different circuits within the motor system have distinct roles to play in adaptation.

Previous studies have shown that the anatomical circuits involved in acquiring a movement sequence have been found to depend greatly upon whether or not the sequence is explicitly or implicitly presented [17,18]. An analogous distinction may be present for visuomotor adaptation with step (an explicit perturbation) and ramp (an implicit perturbation) adaptation relying upon different neuronal circuits. This anatomical segregation is likely to reflect changes in the importance of particular areas of the motor system as learning proceeds. In the initial stages of visuomotor adaptation when a substantial discrepancy between actual and perceived hand position is introduced (analogous to the step adaptation paradigm used here) then areas other than the ipsilateral cerebellum seem to be involved in adaptation. Functional imaging studies have shown that in the initial stages of adaptation the dorsal lateral prefrontal cortex and associated structures are involved in motor adaptation [19]. Moreover, when the possible influence of error correction is accounted for then the intraparietal cortex showed significant changes in blood flow [20]. In an independent study, as visuomotor adaptation proceeded there was a concomitant fall in blood flow bilaterally to the cerebellar cortex while blood flow to the ipsilateral dentate nucleus remained significantly elevated [21]. Therefore, as with our ramp adaptation, while the magnitude of performance error was low, the dentate nucleus still appeared critical to motor adaptation.

The lateral cerebellum is, therefore, critical for adapting to subtle changes in the environment which ordinarily might include compensating for a gradual change in limb dynamics, for example during growth. These physical changes are likely to persist for some time and so require a stable learning substrate. This may be reflected by the behavioural observation that ramp adaptation shows a larger and more sustained after-effect than step adaptation [7]. In contrast, extracerebellar areas for instance the intraparietal and dorsolateral prefrontal cortices may be responsible for compensating to rapid but perhaps transient changes in the visuomotor environment.

Conclusion

Step and ramp adaptation are two distinct processes, which can be distinguished physiologically by their dependence upon the lateral cerebellum. Ramp adaptation was exclusively prevented by inactivation of the dentate nucleus while step adaptation was spared. That such a specific relationship is present implies that the role of the cerebellum in motor

adaptation is more ambiguous than suggested by contemporary theories.

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