Abstract  There is growing evidence that the cerebellum is involved in the implicit learning of movement sequences. On the serial reaction time (RT) task patients with cerebellar lesions fail to demonstrate normal decreases in RT and we have shown a similar effect in monkeys with bilateral cerebellar lesions. However, it is not clear if this impairment is unique to sequence learning or whether the cerebellum is also involved in the learning of discrete responses to predictable visual targets. We investigated this possibility in another group of monkeys with bilateral lesions of the cerebellum centred on the lateral nuclei. Three animals were pre-operatively trained to make rapid manual responses to a single target appearing on a touch-sensitive VDU screen. In one condition, a target could appear at any of three possible locations (spatially unpredictable). In a second condition the target always appeared in the same place (spatially predictable). A third condition was similar to the second except that the onset of the target was temporally predictable whereas in the previous conditions this parameter was randomized. Following the lesions, the RT savings earned on the conditions in which the cues were predictable were abolished. This was despite a lack of significant increase in movement times. The results imply that the animals were either failing to predict the spatial location or time of presentation of the target, or that they were unable to use their prediction to improve their reaction times. The function of the cerebellum in motor sequence learning may therefore be part of a more general operation in learning to prepare responses to predictable sensory events.

Keywords  Cerebellum · Basal ganglia · Sensory prediction · Reaction-time task · Primates

Introduction  Motor learning involves learning both the organization and timing of movements. In its initial phase, motor learning is predominantly influenced by sensory inputs. Exploitation of these inputs relies on an ability to extract information concerning their predictability, both in the spatial and temporal domains. Visuomotor sequence-learning tasks provide a well-studied example of this process whereby, with practice, subjects learn to respond to the appearance of repeating patterns of visual cues with improved accuracy and speed. Such learning may proceed with or without awareness of the ongoing improvements in performance (Nissen and Bullemer 1987; Grafton et al. 1995; Rauch et al. 1995).

The network of structures that subserve human forms of motor learning has gradually been revealed by a rapidly growing number of functional neuroimaging studies (Seitz and Roland 1992; Jenkins et al. 1994; Grafton et al. 1995; Flament et al. 1996; Shadmehr and Holcomb 1997; Toni et al. 1998). They include parts of the prefrontal, premotor, motor and parietal cortices and subcortical areas such as the cerebellum and basal ganglia. The limitation of these studies is that they have done little to reveal what precisely each of these structures contributes to the learning process. We have investigated the specific role of the cerebellum in visuomotor sequence learning by making bilateral lesions centred on the dentate nuclei of monkeys trained to perform such a task.

In an earlier report (Nixon and Passingham 2000), we observed that monkeys with cerebellar lesions were impaired on a serial reaction-time (SRT) task. The impairment was specific to the latter phase of learning and supports similar claims made for patients with cerebellar lesions (Doyon et al. 1997, 1998). In the present study, we test the hypothesis that these impairments are not confined to sequence learning, but reflect a more general deficit in making use of cues with predictive value. We therefore tested the ability of the monkeys to make discrete responses on the basis of cues predicting either the timing or direction of movement.
Monkeys were trained on a choice reaction-time task requiring rapid manual responses to visual targets appearing on a video screen. The performance of the animals was assessed before and after surgery by measuring their reaction times (RTs) and movement times (MTs) to both predictable and unpredictable targets. This study has been published previously in abstract form (Nixon and Passingham 1998b).

Materials and methods

Subjects

The study used three adolescent, male cynomolgus monkeys (Macaca fascicularis) identified in this report as NEW, HAL, and MOR. The animals had previously served as a control group in a related study (Nixon and Passingham 2000). They had a considerable history of automated behavioural testing and did not require further adaptation.

The monkeys were housed and tested in accordance with the Principles of laboratory animal care (NIH publication No. 86–23, revised 1985) and the UK Home Office guidelines for the use of laboratory animals.

Apparatus and preoperative training

The animals sat in a dimly lit room facing a large (50-cm screen) VDU onto which computer-generated stimuli could be presented. The VDU screen was pressure sensitive and could send touch coordinates with a spatial resolution of less than 2 mm and a temporal resolution of ±2.5 ms. A semi-opaque push-button (22-mm diameter) was placed centrally, 10 cm in front of the VDU. The cage in which the animals sat was large enough to allow freedom of movement for the monkey but at the same time restrict his access to the apparatus. This was achieved by placing a transparent Perspex panel between the cage and the push button. A small aperture, large enough for the monkey to pass his whole arm through, was placed on the right hand side of the panel. This configuration enforced use of the right arm for the execution of all responses throughout testing and prevented bimanual strategies. A hole to the left of the panel provided access to a food box, which was opened at the end of the session. The experiment was controlled entirely by microcomputer and custom hardware, with a timing accuracy of ±1 ms.

At the start of each trial, the lens of the push-button was illuminated by a 1.2-W bulb contained within its casing. This signal indicated to the animal that the trial had started and that the button could now be depressed. The monkeys were required to reach, with their right arm, through the hole in the Perspex panel and to depress the push-button for a random period of time (400–2,200 ms, “hold” period). When sufficiently depressed, the button provided a tactile click to indicate that its switch had been actuated. This feedback was simultaneously enhanced by extinguishing the source of illumination and at the same time presenting three large circles (90-mm diameter) on the VDU screen. These circles were placed in the same locations as three of the targets used in the SRT task described previously (Nixon and Passingham 2000), that is, two oriented vertically above the push-button, and one equidistant between them on the righthand side of the screen. The circles indicated the possible positions at which target stimuli could appear and the end of the hold period. The targets were filled circles (40-mm diameter) and only one target could appear in a single trial. The objective for the monkey was, on the appearance of a target, to release the push-button and touch the target as quickly as possible. A touch anywhere within the outer circle in which the target appeared was considered a correct response. Touch feedback was enhanced by the immediate removal of the target stimulus accompanied by a brief audible tone. Correct trials were rewarded with the delivery of a flavoured diet pellet into a receptacle below the VDU. After an inter-trial interval of 5 s, the push-button was re-lit and the monkey had to respond with the push-button to initiate the next trial. RTs were measured from the appearance of the target to the release of the button, and MTs were measured from the release of the button to the touch of the target. All RT and MT readings were saved to disk for later analysis.

Preoperative training for this task lasted approximately 1 month. The monkeys were already highly trained at making rapid, simultaneous movements and so pretraining consisted mainly of encouraging them to depress and hold the push-button for the maximum required duration (2,200 ms). When their reaching movements were smooth and accurate, the monkeys were encouraged to make rapid responses by slowly reducing the target duration from 3,000 ms to 500 ms in steps of 500 ms per session. Late touches were rewarded if they occurred not more than 500 ms after extinction of the target stimulus. Touches to non-target zones or within the spaces between the circles were considered to be erroneous and resulted in the trial being repeated.

Preoperative testing consisted of a total of 18 sessions, each of 150 correctly performed trials. The first six sessions comprised trials where both target location and onset were unpredictable (“baseline” condition). The target could appear at any time between 400 and 2,200 ms after the push-button had been depressed at any of three locations. The following six sessions comprised trials where target location, but not onset, were constant and therefore predictable. Each of the three possible target locations was used for two separate, non-consecutive sessions. The final six sessions comprised trials where target onset was fixed at 1,300 ms, but its location was again randomized. The median RTs for the random and constant target parameters were then compared to provide a measure of the extent to which the animals benefited from the predictability of either target location or onset time.

Postoperative retesting

After surgery, the animals were allowed a 3-week recovery period, after which they were retested on another task which required a maximum of a further 3 weeks. They were then retested on the present task after first assessing their ability to perform the task in the required manner. This assessment was carried out over a single session of 150 trials, and particular attention was paid to the number of premature push-button releases and target misses made by each animal. When they were able to perform the task satisfactorily, the monkeys’ response times were assessed over 18 sessions (6 sessions for each of the three task conditions) presented in the same order as for the pre-operative testing.

Surgery and histology

The three animals in this study all received bilateral lesions of the lateral cerebellar nuclei, centred on the dentate (lateral) nuclei. This site was chosen because it is known to be the principal source of the cerebello-thalamo-cortical pathway that projects to areas to be involved in motor sequence learning (Middleton and Strick 1997). The lesions were made using multiple micro-injections of the excitotoxin kainic acid, using stereotaxic procedures described by Nixon and Passingham (1999, 2000). The right and left cerebellar hemispheres were lesioned, in that order, on separate occasions approximately 1 week apart. At time of surgery, the animals were in excellent health and weighed between 4.5 and 5.8 kg.

At the completion of the experiment, the animals were killed, the brains removed and then cut and stained to enable analysis of the lesions. The procedures for the perfusions and histological processing were identical to those described by Nixon and Passingham (1999, 2000), with the exception that two additional sections (per millimetre) were collected and slide-mounted so as to enable a more precise reconstruction of the lesions.

The lesions for all three monkeys are shown in Fig. 1. In NEW and MOR the dentate lesions were complete in both hemispheres,