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Inactivation of the superior cerebellar peduncle blocks expression but not acquisition of the rabbit's classically conditioned eye-blink response

(learning/memory/cerebellum)

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ABSTRACT **The localization of sites of memory formation within the mammalian brain has proven to be a formidable task even for simple forms of learning and memory. Recent studies have demonstrated that reversibly inactivating a localized region of cerebellum, including the dorsal anterior interpositus nucleus, completely prevents acquisition of the conditioned eye-blink response with no effect upon subsequent learning without inactivation. This result indicates that the memory trace for this type of learning is located either (*i*) within this inactivated region of cerebellum or (*ii*) within some structure(s) efferent from the cerebellum to which output from the interpositus nucleus ultimately projects. To distinguish between these possibilities, two groups of rabbits were conditioned (by using two conditioning stimuli) while the output fibers of the interpositus (the superior cerebellar peduncle) were reversibly blocked with microinjections of the sodium channel blocker tetrodotoxin. Rabbits performed no conditioned responses during this inactivation training. However, training after inactivation revealed that the rabbits (trained with either conditioned stimulus) had fully learned the response during the previous inactivation training. Cerebellar output, therefore, does not appear to be essential for acquisition of the learned response. This result, coupled with the fact that inactivation of the appropriate region of cerebellum completely prevents learning, provides compelling evidence supporting the hypothesis that the essential memory trace for the classically conditioned eye-blink response is localized within the cerebellum.**

Identification of the site or sites of memory formation and storage within the brain for any particular type of memory is an essential prerequisite for elucidating the cellular or subcellular mechanisms as well as the network level properties that mediate the acquisition, retrieval, and expression of that particular memory. Although much progress toward identifying potential sites of memory formation and storage has been achieved, definitive localization of a particular memory locus within the mammalian brain has remained frustratingly elusive. A major obstacle impeding this localization of memory traces is the necessity of first identifying the neural-anatomical circuitry essential for acquisition and expression of a particular learned response. For at least one form of learned behavior—aversive, classically conditioned discrete skeletal movements, specifically, the classically conditioned eye-blink response—the neural circuitry essential for acquisition and expression of the learned response has largely been identified (for review, see ref. 1). In brief, the results of lesion, recording, and stimulation studies indicate that the conditioned stimulus (CS) pathway includes sensory relay nuclei, the pontine nuclei, and mossy fiber projections, via the middle cerebellar peduncle, to the cerebellum (2–4); that the unconditioned stimulus (US) pathway includes somatosensory relay nuclei, the inferior olive, and its climbing fiber projections, via the inferior cerebellar peduncle, to the cerebellum (5, 6); and that the conditioned response (CR) pathway includes the cerebellum, its projections via the superior cerebellar peduncle (SCP) from the interpositus nucleus to the red nucleus and red nucleus projections to premotor and motor nuclei (7–15).

Reversibly inactivating a critical region of cerebellum encompassing the dorsal aspects of the anterior interpositus nucleus and overlying regions of cerebellar cortex during eye-blink conditioning with local cooling (16), microinjection of the γ-aminobutyric acid agonist muscimol (17), or infusion of the sodium channel blocker lidocaine (18) completely prevents acquisition of the learned response with no effect upon the ability to acquire the CR in subsequent training without inactivation and with no effect upon the ability to perform the unconditioned response (UR). In marked contrast, inactivation of the contralateral red nucleus, a major efferent target of the cerebellar interpositus nucleus that is essential for performance of the CR (see above), prevents expression but not acquisition of the CR (17, 19). Infusions of lidocaine into white matter just ventral to the interpositus, which would presumably inactivate cerebellar output fibers, also prevent expression but not acquisition of the learned response (18). Inactivation of the motor nuclei (accessory abducens and facial) and surrounding regions of reticular formation, which mediate performance of the CR and the UR, prevents expression of both the CR and UR but has no effect on the ability to learn the CR (20, 21). Collectively, these results argue that the critical locus of memory formation and storage for the eye-blink CR is localized to a region of cerebellum encompassing the dorsal aspects of the anterior interpositus and regions of overlying cortex, because inactivation of this region of cerebellum completely prevents learning from occurring while inactivation of structures downstream from the cerebellum in the essential eye-blink circuit does not prevent acquisition of the CR but does prevent expression.

It is well established that output fibers of the interpositus nucleus project, via the superior cerebellar peduncle, to several regions within the brain other than the red nucleus, including, but not limited to the thalamus, inferior olive, pontine nuclei, and the nucleus reticularis tegmenti pontis (22). Thus, it remains possible that one or more of the efferent targets of the cerebellum might be the locus of the memory trace for the eye-blink CR. If the memory trace were normally formed or stored within one or more of these sites efferent from the cerebellum, then the total abolition of both acquisition and expression of the eye-blink CR after appropriate lesions of the

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Abbreviations: CR, conditioned response; CS, conditioned stimulus; LRN, lateral reticular nucleus; SCP, superior cerebellar peduncle; TTX, tetrodotoxin; UR, unconditioned response; US, unconditioned stimulus.

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cerebellum must be caused by disruption of essential cerebellar input to these targets and not disruption of the memory trace itself. Although the infusions of lidocaine into the white matter just ventral to the interpositus nucleus that block CR expression but not acquisition (ref. 18 and see above) argue against an extracerebellar locus of memory, the present study was designed to test this possibility directly.

If the memory trace for the eye-blink CR is, indeed, formed in some structure(s) efferent from the cerebellum, then inactivation of the SCP (which would block the output of the interpositus) should prevent learning from occurring, just as inactivation of the interpositus nucleus itself does. If, on the other hand, the memory trace is formed within the cerebellum, inactivation of the SCP should not block acquisition of the CR but should prevent its expression. To distinguish between these two possibilities, we trained rabbits while their ipsilateral SCP was temporarily inactivated by microinjections of the sodium channel blocker tetrodotoxin (TTX) into the SCP. TTX reversibly blocks propagation of action potentials along axons by temporarily blocking voltage-gated sodium channels (23) and is commonly used to created discrete reversible lesions within the central nervous system but has not previously been used to inactivate regions of the essential eye-blink circuit during conditioning. We then tested the animals without inactivation to determine whether any learning had occurred during the previous inactivation training. We report here that inactivation of the SCP does not prevent acquisition of the CR but does block its expression, a result that would appear to rule out the possibility that the essential memory trace for the eye-blink CR is formed in some structure(s) efferent from the cerebellum.

To further extend this result, a separate group of animals was trained with electrical microstimulation of the lateral reticular nucleus (LRN) as the CS. Stimulation of the LRN, which projects heavily to the ipsilateral interpositus nucleus as mossy fibers in the inferior cerebellar peduncle (22, 24), has been shown (25) to serve as an effective CS, and lesions of the interpositus completely abolish the CR learned to this LRN stimulation CS (25, 26). As described below, the effects of SCP inactivation on conditioning with an LRN stimulation CS were identical to those using an auditory CS: no effect upon the ability to acquire the CR but complete blockage of CR expression.

METHODS

Twenty-three New Zealand albino rabbits (*Oryctolgus cuniculus*, weight 2.4–2.9 kg) were implanted with chronic stainless steel guide cannulae (0.6 mm o.d.) fitted with an internal stainless steel stylet extending 1.5 mm beyond the base of the cannulae. Stylet tips were aimed at the ipsilateral (left) superior cerebellar peduncle where the fiber bundle just exits the cerebellum; coordinates (dependent upon weight) were 3.5–4.0 mm anterior, 14.5–15.0 mm ventral, and 2.5 mm lateral of the λ skull suture with λ positioned 1.5 mm ventral to the bregma suture. Seven of these rabbits were also implanted with bipolar electrical stimulating electrodes (stainless steel, epoxylite-coated, 150-μm exposed tip) aimed at the ipsilateral LRN (electrodes oriented in the rostral–caudal plane, 1 mm apart, center coordinate: 1 mm anterior, 2.5 mm lateral, and 21 mm ventral from λ). Cannulae and electrodes were held in place with dental acrylic anchored to the skull with three stainless steel skull screws. A small receptacle designed to hold a minitorque potentiometer was also attached to the skull. A 1-mm loop of surgical suture was attached to the apex of the left nictitating membrane. All animals received a 7-day post-surgical recovery and, on day 8, a 1-h adaptation session in which they were restrained and placed in the behavioral recording apparatus but were presented with no stimuli. Behavioral training began the following day.

Behavioral training was composed of 11 daily conditioning sessions in which a CS was paired with a coterminating corneal airpuff US (100 ms, 2.1 N/cm^2). In one group (n = 10), the CS was an auditory white noise (350 ms, 87 decibels) presented binaurally through small ear phones placed in the rabbits' ears. In the second group (n = 7), the CS was electrical microstimulation of the LRN (350 ms, 200 Hz, 50 μA, 0.1-ms pulses). Each session consisted of 100 trials: 80 paired trials with 10 CS alone and 10 air-puff alone test trials evenly distributed throughout the session. Intertrial intervals ranged between 20 and 40 s (mean, 30 s). During all sessions, a CR was defined as any extension of the nictitating membrane $\geq$0.5 mm after CS onset but preceding US onset. On CS-alone trials, a CR was any extension of the nictitating membrane ($\geq$0.5 mm) occurring within 750 ms after CS onset.

Prior to the start of each of the first six training sessions, each rabbit received an infusion of TTX into the SCP (2.0 pmol in 90 nl of physiological saline). No infusions were administered prior to sessions 7–9. All animals received a 2-day rest between sessions 6 and 7 to ensured no lingering effects of infusion. A separate group of controls (n = 6) were infused with TTX prior to each of the first six sessions and placed in the restrainer and conditioning chamber but were not presented with any stimuli. These animals received a 2-day rest after session 6 and were then trained (without any infusion) on sessions 7–9 with the auditory white noise CS. Prior to session 10, all rabbits were infused with TTX and then trained, as in the previous sessions. Finally, 1 h prior to session 11, all rabbits were infused with muscimol (5.0 nmol in 500 nl of saline) to assess the effects of this drug on the previously learned response. All infusions consisted of removal of the internal stylet, insertion of an inner infusion cannula (which extended 1.5 mm below the base of the outer guide cannula), infusion of the drug at 0.3 μl/min, removal of the infusion cannula 2 min after the infusion, and reinsertion of the stylet.

After all training, animals were sacrificed with an overdose of sodium pentobarbital and perfused through the aorta with physiological saline and a 10% (vol/vol) formalin solution. Anodal current (70 μA, 7 s) was passed through each of the LRN stimulation electrodes. Brains were removed and stored in formalin until sectioned on a cryostat. The sections were stained with cresyl violet and Prussian blue, after which the positions of the cannulae tips and LRN electrode tips were determined.

Data were analyzed with analysis of variance followed by Newman–Keuls post hoc analysis of significant ($P < 0.05$) main effects.

RESULTS

Four rabbits trained with the white noise CS and two trained with the LRN stimulation as CS performed a significant number of CRs during the infusion phase of training (sessions 1–6), each reaching at least 80% CRs during at least one of these sessions. Infusion of TTX into the SCP prior to session 10 had no effect on performance of the previously learned response. Histological analysis of the cannulae locations for these animals revealed placements outside of the SCP (see Fig. 2*A*). Based upon these criteria, it was concluded that the infusions of TTX prior to sessions 1–6 were not effectively blocking the SCP; thus, these animals were excluded from further study. One rabbit trained with LRN stimulation as the CS never learned the CR during any of the 11 sessions (mean percentage of CRs on any session never exceeded 14%). This animal was also excluded.

In all remaining rabbits, TTX infusions prior to sessions 1–6 completely prevented any expression of CRs whether animals were trained with a white noise CS (n = 6) or LRN stimulation (n = 4) as CS (Fig. 1*A*). On session 7, the first session without infusion, these animals performed the CR at asymptotic levels

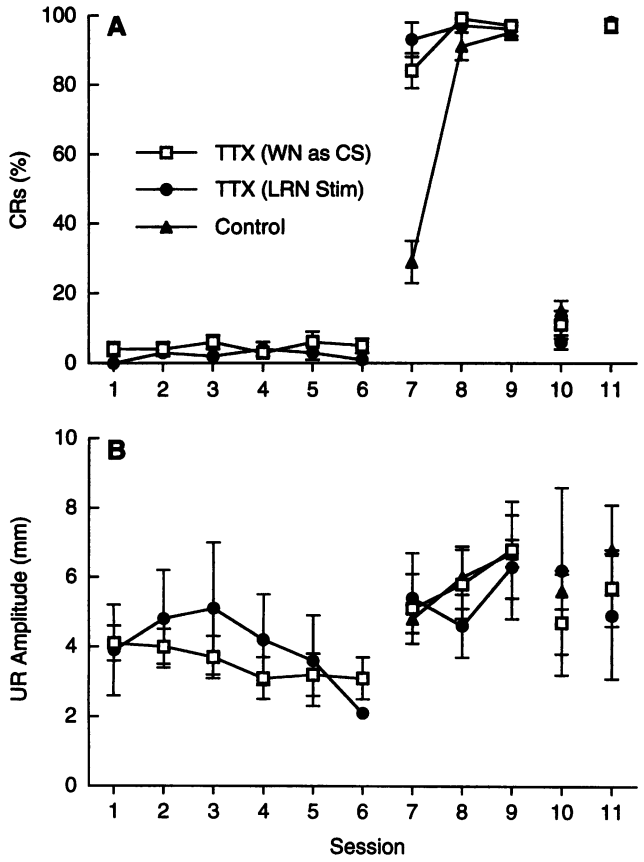

FIG. 1. (*A*) Percent CRs (mean ± SEM) for all conditioning sessions from all animals with effective cannulae placements. TTX was infused into the SCP of each animal prior to sessions 1–6 and session 10. No infusions were administered prior to sessions 7–9. Muscimol was infused prior to session 11. Animals trained with an auditory white noise as CS (open squares, $n = 6$) or with electrical microstimulation of the LRN as CS (solid circles, $n = 4$) performed no significant number of CRs during the first six infusion sessions. On session 7, the first session without infusion, these animals performed the CR at asymptotic levels from the start of training; they had fully learned the CR during the previous six inactivation sessions. Controls (solid triangles, $n = 6$) were infused with TTX and restrained but presented with no stimuli during sessions 1–6. These animals performed significantly fewer CRs on session 7, their first conditioning session with the auditory CS, and subsequently learned the CR on following sessions. TTX infusions prior to session 10 completely abolished the previously acquired CR in all rabbits. Infusion of muscimol prior to session 11 had no effect upon the CR in any rabbit. (*B*) UR amplitude (mean ± SEM) on airpuff-alone test trials. TTX infusions prior to sessions 1–6 resulted in UR amplitudes significantly lower than URs on sessions 7–9 in which no infusions were administered. Infusion of TTX prior to session 10 or muscimol prior to session 11 had no significant effect upon UR amplitudes compared with UR amplitudes on session 9 in which no infusions were administered. Symbols are as in *A*.

from the start of training. They had fully learned the CR during the previous six infusion sessions despite having performed no CRs during those sessions. Controls, which had been restrained and infused with TTX but presented with no stimuli during sessions 1–6, performed significantly ($P < 0.0002$) fewer CRs on session 7 (their first conditioning session) and subsequently learned the CR over the following two sessions. The mean number of trials to reach a learning criterion (TTC) of eight CRs in nine consecutive trials for the animals infused with TTX and trained with the auditory CS or with the LRN stimulation CS was significantly ($P < 0.0001$) lower than controls during session 7 [(TTC mean ± SEM); auditory CS, 13 ± 3; LRN stimulation, 7 ± 4; controls, 78 ± 7]. TTX infusions prior to session 10 completely abolished the previously acquired CR in all rabbits. Infusion of muscimol (which would inactivate cell bodies and dendrites but not fibers of passage) into the SCP and surrounding regions prior to session 11 had no effect at all on performance of the CR in any rabbit. TTX infusions into the SCP caused behavioral effects in some but not all rabbits. The most common effect was the inability to stand stably and/or an observable tremor in gait when walking. These effects varied in severity among rabbits and, in all cases, disappeared 2–3 h after infusion. Thus, blocking cerebellar output via the SCP, which would block projections to all brain regions including the red nucleus, had no effect upon rabbits' ability to acquire the learned response with an auditory or with a brainstem stimulation CS.

UR amplitudes (measured on airpuff alone trials) during infusion sessions 1–6 were lower ($P < 0.02$) than UR amplitudes measured during noninfusion sessions 7–9 for both the auditory and LRN stimulation groups (Fig. 1*B*). However, there were no significant differences between UR amplitudes measured on session 9 (no infusion) and session 10 (TTX infusion), although the CRs were completely abolished during session 10.

Placements of all cannula tips are shown in Fig. 2*A*. Effective placements were located either within or just adjacent to the SCP. Cannulae placements further than ≈0.75 mm from the SCP did not affect animals' ability to learn or perform the CR after TTX infusions. Fig. 2*B* shows the histology from one rabbit (trained with the auditory CS) with an effective cannula placement in the SCP. LRN electrode tips for rabbits with effective SCP cannulae were located as follows: two pairs were located within or just bordering the LRN; in one rabbit, the posterior electrode was in the rostral–lateral–ventral border of the LRN while the anterior electrode was located ≈1 mm rostral to the LRN; and the final pair was located in the reticular formation 0.75–1 mm dorsal and medial to the rostral aspects of the LRN.

DISCUSSION

To date, numerous studies from several laboratories (1, 27, 28) using a variety of techniques in different species have consistently reported a similar finding: appropriate lesions of the cerebellum, either temporary or permanent, completely prevent acquisition and expression of the classically conditioned eye-blink response. This effect of cerebellar lesion on the eye-blink CR may be explained in one of two ways: (*i*) lesions of the cerebellum disrupt an essential memory trace that is localized within the cerebellum or (*ii*) cerebellar lesions disrupt essential cerebellar output that ultimately projects to the site of memory formation and storage. The present results appear to rule out the second possibility. Inactivation of the superior cerebellar peduncle with microinjections of the sodium channel blocker TTX, a manipulation that would block essential cerebellar output, did not prevent acquisition of the CR with either an auditory or brainstem stimulation CS but did block CR expression. This result is in agreement with Nordholm *et al.* (18) who found that infusion of lidocaine over three training sessions into the white matter ventral to the interpositus nucleus, which would inactivate cerebellar output fibers, blocked expression but not acquisition of the CR to a tone CS.

It is unlikely that the effects of TTX infusion were a result of diffusion of drug into regions adjacent to the SCP, for instance the parabrachial nuclei, vestibular nuclei, nuclei of the lateral lemniscus, or the supratrigeminal region, and not the result of direct inactivation of the SCP itself. (*i*) Effective cannula placements were located within or adjacent to the SCP. (*ii*) If cannulae were placed more than ≈0.75 mm from the SCP, TTX infusions had no effect upon acquisition or expression of the CR, suggesting that the effective radial spread of the TTX infusion was <0.75 mm, a result consistent

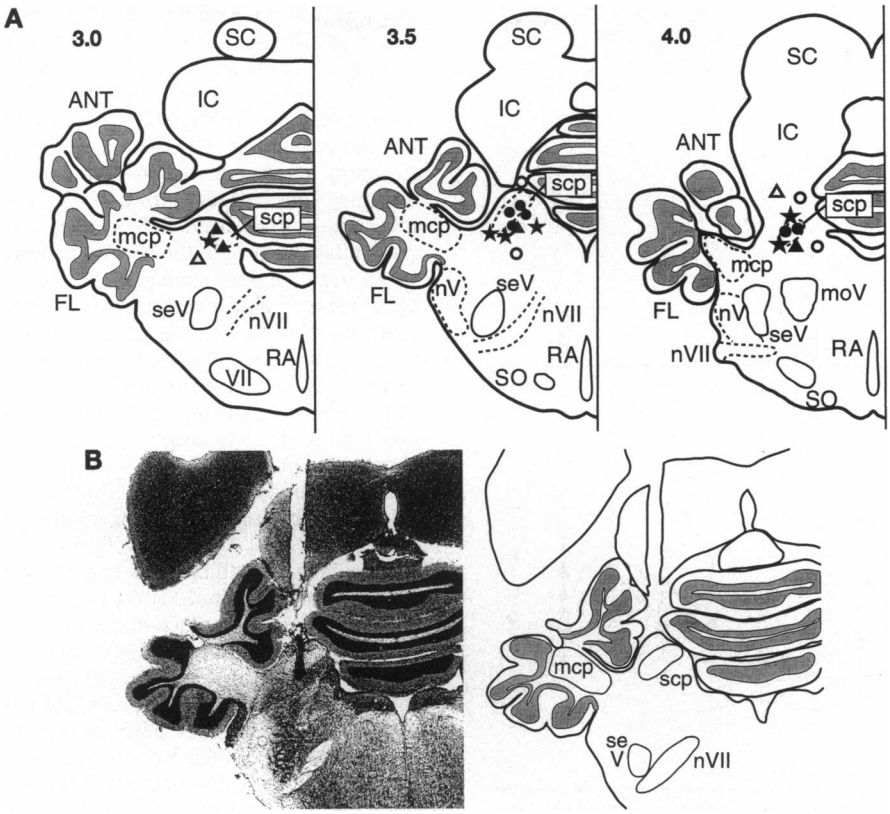

FIG. 2. (*A*) Locations of cannulae tips for all rabbits. Solid circles, auditory CS, effective placements; open circles, auditory CS, ineffective placements; solid triangles, LRN stimulation CS, effective placements; open triangles, LRN stimulation CS, ineffective placements; solid stars, controls. Effective placements are located within or just adjacent to the SCP. Cannulae placements greater than about 0.75 mm from the SCP did not prevent acquisition or expression of the CR. Numerals above each section represent distance (mm) rostral to the λ skull suture. (*B*) Photomicrograph and outline drawing of a coronal section showing effective cannula placement in the SCP. This animal was trained with the auditory CS. ANT, anterior lobe; FL, flocculus; IC, inferior colliculus; mcp, middle cerebellar peduncle; moV, motor trigeminal; nV, Vth nerve; nVII, VIIth nerve; RA, raphe nucleus; SC, superior colliculus; scp, superior cerebellar peduncle; seV, sensory trigeminal; SO, superior olive; VII, facial nucleus.

with reports of others (29). Finally, infusion of the γ-aminobutyric acid agonist muscimol (which would inactivate dendrites and somata but not fibers of passage) had no effect upon the CR even at a dose substantially larger than doses necessary to abolish the CR if infused into the interpositus nucleus, the red nucleus, or the motor nuclei.

Currently, there is some debate in the literature concerning the effects of cerebellar lesions on the UR in well-trained rabbits (7, 30, 31). Recent results (7, 32), however, rule out the possibility that a performance deficit alone (31, 33), were it to exist, could account for the total abolition of CRs after appropriate cerebellar lesions. Clark and Lavond and coworkers (16, 19) used reversible cooling to inactivate the anterior interpositus or magnocellular red nucleus during acquisition (cooling of either structure completely prevented performance of the CR in trained animals). Cooling of the interpositus completely prevented learning of the CR and had no effect at all on performance of the UR (measured on US alone trials). In striking contrast, cooling of the red nucleus did not prevent learning but did markedly impair performance of the UR. The effects of TTX infusions on the UR amplitudes described in the present study provide further evidence against the performance deficit argument. SCP inactivation with TTX prior to sessions 1–6 resulted in a decrease in UR amplitude compared with UR amplitudes without inactivation (sessions 7–9), yet the animals were able to learn the CR. TTX infusions prior to session 10 completely abolished the CR during that session without any significant effect upon the UR, a result consistent with permanent lesions of the SCP (8).

The results of the present study and the numerous reversible lesion studies described above (16–21) contradict the report of Welsh and Harvey (34) in which lidocaine was infused into the region of the interpositus nucleus during transfer training from a light to a tone CS. However, the present results are in complete accord with an ever growing body of literature that indicates that the cerebellum is critically involved in a number of different learned tasks. For instance, lesion, recording, and stimulation studies indicate that specific regions of the flocculus are critically involved in vestibulocular reflex adaptation (for review, see ref. 35). Thach and associates (for review, see ref. 36), utilizing recording and lesioning techniques, have implicated localized regions of cerebellum in primates as critically involved in adaptation of hand–eye coordination. Cerebellar vermis appears to be essentially involved in acquisition and expression of aversive, Pavlovian conditioned bradycardia in rabbit since lesions of this structure prevent acquisition and abolish retention of CRs without affecting unconditioned heart rate responses and electrophysiological recordings reveal learning-related changes in neuronal activity (37). The lateral cerebellar hemispheres appear to be critically involved in an instrumental avoidance bar pressing task (38). Finally, there is growing evidence that, within humans, the cerebellum is involved in complex cognitive tasks (for review for instance, see ref. 39).

The mandatory CR pathway for the eye-blink CR has been identified: interpositus nucleus, its output projections, via superior cerebellar peduncle, to the contralateral magnocellular red nucleus, and the descending rubral projections to the ipsilateral motor nuclei. In brief, neurons in the critical region

of the interpositus, where unilateral lesions completely and permanently abolish acquisition, retention, and relearning of the ipsilateral CR with no effect on the UR, develop a learning-induced increase in discharge frequency that forms an amplitude–time course model of the behavioral CR that precedes and predicts the occurrence and form of the CR both within trials and over the trials of training (7, 9, 10, 40). Microstimulation of the critical interpositus region elicits eye blinks in untrained animals and lesions of the SCP abolish this stimulation-elicited response and CRs learned to peripheral CSs; the CR circuit is hard-wired from interpositus to behavior (8, 9, 41). Unit recordings from the critical region of the red nucleus (in the magnocellular division) develop the same learning-induced model of the CR as do neurons in the interpositus, and very small lesions in this region of the red nucleus also abolish the CR with no effect on the UR (12, 13, 19, 42). In trained animals, lidocaine or cold-probe inactivation of the interpositus abolishes both the behavioral CR and the learning-induced neuronal model in the red nucleus; inactivation of the red nucleus abolishes the behavioral CR but has no effect on the learning-induced neuronal model in the interpositus (16, 19, 42). Reversible lesions of the interpositus nucleus, which completely prevent acquisition of the CR, demonstrate that the memory trace must be formed at or beyond the cerebellar site of inactivation (16–18). The results of the present study and previous work (18) indicate that the memory trace is not formed in some site beyond the cerebellum. Based on these results, we conclude that the memory trace for eye-blink conditioning must be localized to the ipsilateral lateral cerebellum. Our findings strongly support the hypothesis that the memory traces for learned movements are formed and stored in the cerebellum (36, 43–46).

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