

Concomitant Classical Conditioning of the Rabbit Nictitating Membrane and Eyelid Responses: Correlations and Implications

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MCCORMICK, D. A., D. G. LAVOND AND R. F. THOMPSON. *Concomitant classical conditioning of the rabbit nictitating membrane and eyelid responses: Correlations and implications*. *PHYSIOL. BEHAV.* **28**(5) 769-775, 1982.— Simultaneous recordings of muscle unit activity from the muscles of the left and right eyelids (*M. obicularis oculi*) and recordings of the movement of the left nictitating membrane (NM) were taken during classical conditioning in the rabbit using a tone CS paired with an airpuff UCS to the left cornea. The unconditioned eyelid responses were found to be bilateral. The conditioned eyelid responses were also bilateral in most animals. Both the conditioned and unconditioned eyelid responses were larger on the left side. The conditioned responses of the left and right eyelids and the left NM were found to increase in magnitude and decrease in latency from the onset of the CS over training trials in almost the exactly same manner (correlations as high as .99). Behaviorally, the three responses could occur independently, suggesting that the cranial nuclei which control them (left abducens/accessory abducens, left facial nucleus, right facial nucleus) are not strongly coupled. Thus, for the learned response, it is suggested that the three nuclei are controlled by a common central system. This finding has implications for the nature of the engram—the essential neuronal circuitry encoding the learned response.

Nictitating membrane Classical conditioning Eyelid responses

EYELID or nictitating membrane (NM) conditioning is perhaps the most widely used paradigm for the study of basic properties of classical conditioning of striated muscle responses [2, 8, 10, 30, 33, 35]. In past studies, a variety of conditioned stimuli (e.g., tone, light, shock) have been used in conjunction with a variety of unconditioned stimuli (e.g., corneal airpuff, periorbital shock, glabella tap) [27, 33, 35]. A combination of an auditory CS paired with a corneal airpuff UCS in the rabbit has proved extremely useful for analysis of the neuronal basis of associative learning, due in part to the facts that the rabbit is docile and that an airpuff UCS permits an artifact-free recording of neuronal data during the UCS period in training [33].

In past studies, the conditioned and unconditioned responses have almost always been referred to as a single response in isolation, e.g., NM extension, eyelid closure, or change of heart rate, even though it is known that under the same conditioning procedures all three of these responses may be conditioned [7, 10, 30, 31]. It is not yet clear exactly what is being conditioned in these paradigms and if more than one response is conditioned, how independent the different components of the conditioned response, e.g., NM

and eyelid responses, are. For example, the acquisition rates of the conditioned eyelid and NM responses seem to be similar, although there are no reports of the two being measured simultaneously [10,30]. If a number of responses are being conditioned, the degree of relationship among these responses will have important implications for the nature of the engram—the essential neuronal plasticity that codes the learned response.

In current work in our laboratory, we have recorded neuronal unit activity throughout the brainstem in the well trained rabbit [20]. A number of neural structures respond in association with the conditioned response including the facial nucleus, third nucleus, abducens and accessory abducens nuclei, fifth motor and sensory nuclei, and the cerebellum and its related structures. These recordings suggested that a number of responses were being conditioned, although the only response measured was that of NM extension [4, 13, 20]. The present study was done to delineate more exactly the conditioned and unconditioned responses which develop in the rabbit during classical conditioning of the NM response, and more specifically to determine the relationship in the acquisition rates of the NM and eyelid responses.

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METHOD

Surgery

Eight rabbits were used. They were anesthetized with a mixture of fluothane gas (2–3%) and oxygen. A headstage through which wires from the recording electrodes could be connected to the amplifiers each day was fastened to the animal's head with dental acrylic onto skull screws. A small loop of silk thread was sutured into the left nictitating membrane (NM). All animals were allowed five days to recover before training commenced.

Training Procedure

After recovery, the animals were placed in a Plexiglas restrainer within a sound isolation chamber and allowed to adapt for two hours. A headgear containing the airpuff outlet nozzle, first stage FET amplifiers and a minitorque potentiometer was attached to the animal's headstage during adaptation and behavioral training. The left eyelids were held open by eyeclips and the movement of the NM was monitored through the use of a minitorque potentiometer attached by a thread to the suture in the animal's NM.

Throughout training the conditioned stimulus (CS) was a 350 millisecond, 1 kilohertz tone at 85 dB SPL, and the unconditioned stimulus was a 100 millisecond corneal airpuff to the left eye which measured 210 g/cm² (3 psi) pressure at the source and delivered via a hose with an internal diameter of 5 mm. The outlet nozzle had an internal diameter of 3 mm and was placed 5 mm from the animal's eye. Care was taken to insure that the UCS synchronizing pulse used in computer analysis was coincident with the arrival of the airpuff at the cornea of the animal's eye. The interstimulus interval was set at 250 milliseconds.

The animals were trained in daily sessions of 13 blocks of 9 trials each in which the first trial of each block was a tone-alone test trial. The intertrial interval was pseudorandom and had a mean of 60 seconds. A conditioned response was defined as movement of the NM 0.5 mm or greater within the 250 milliseconds after the onset of the CS. Criterion performance was set at eight conditioned responses in any nine consecutive trials. All animals were trained one additional session after the session in which this criterion was met.

Data Collection and Analysis

Microelectrodes with approximately 50 μ m of exposed tip were inserted into the muscles of the left and right eyelids (*M. obicularis oculi*) prior to each session of training. The multiple muscle unit (MMU) activity from these electrodes was amplified by battery powered solid state FET amplifiers and recorded on magnetic tape. The movement of the NM was recorded simultaneously as a potential change across the minitorque potentiometer. Synchronizing pulses were also recorded which denoted the onset of each trial as well as the onset of the CS and of the UCS.

During analysis, the MMU records were band pass filtered at one kilohertz to five kilohertz at a roll off of 48 dB per octave to filter out slow wave activity and movement artifacts. This technique resulted in good quality MMU records (see Fig. 1). The activity of the MMUs were analyzed by passing the filtered signal through a pulse height discriminator set at 2.5 \times the noise level. The data was collected in three millisecond time bins for the entire 750 milliseconds of each trial. Each trial was broken into three

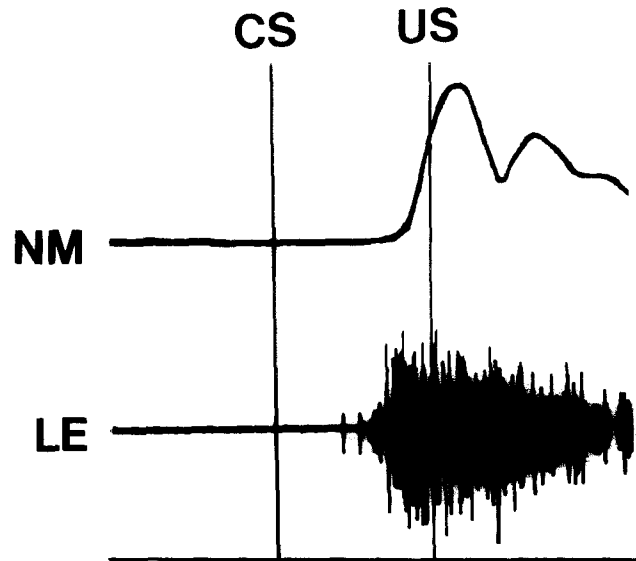


FIG. 1. Typical multiple muscle unit (MMU) record taken from the muscle of the left upper eyelid (*M. obicularis oculi*) of a well trained animal. The upper trace is the movement of the left NM with up being extension across the eyeball. The first vertical line represents the onset of the CS while the second vertical line represents the onset of the UCS.

periods: the Pre-CS period (the 250 milliseconds prior to CS onset), the CS period (the 250 milliseconds after the onset of the CS), and the UCS period (the 250 milliseconds after the onset of the UCS).

Since muscle units have no spontaneous firing rate other than that corresponding to spontaneous movements, the standard method for analyzing the unit activity as Z scores based upon spontaneous Pre-CS activity could not be utilized [33]. Instead we adopted a measurement of the conditioned response as the precent asymptotic response, defined by dividing the magnitude of the response of each tone-alone trial by the asymptotic response magnitude for that animal and multiplying by 100. The asymptotic response magnitude for the NM was estimated as the average area in millimeter-milliseconds under the curve described by the movement of the NM on the last six tone-alone trials of paired conditioning (see Fig. 2). For the eyelid MMU response, the asymptotic conditioned response was estimated as the average number of action potentials in the CS and UCS periods above baseline on the last six tone-alone trials of paired training.

The latency to onset of the NM and eyelid responses during conditioning was measured for the average histogram of each block by measuring the distance from the onset of the CS sync pulse to the onset of the response and then converting to milliseconds (see Fig. 4). This method gave a measurement of onset latency with an accuracy of \pm five milliseconds. The onset latencies of the unconditioned responses were more accurately measured from the raw records by displaying each response at a high gain and sweep speed on a storage oscilloscope.

RESULTS

All eight animals had simultaneous recordings of the

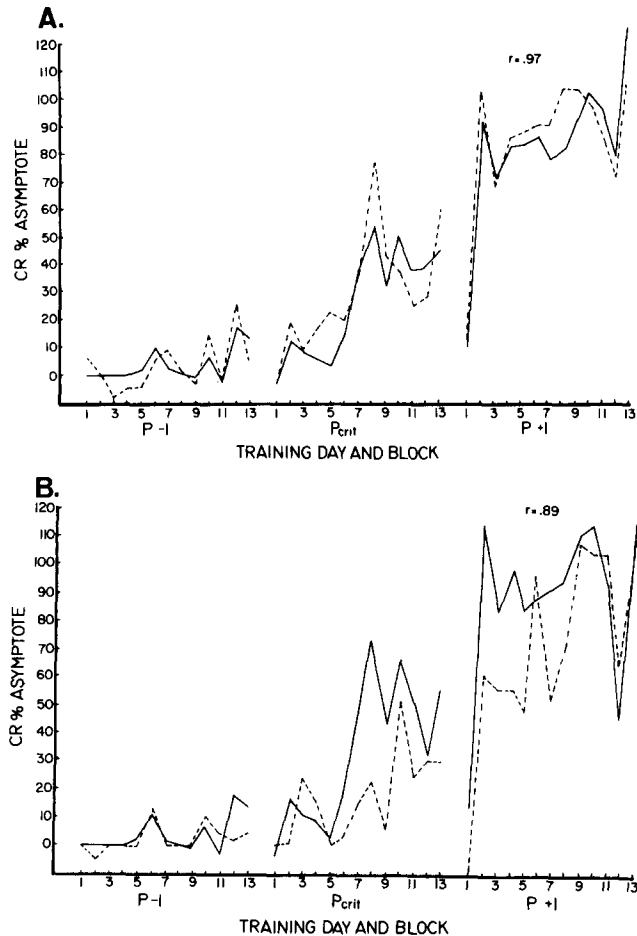


FIG. 2. Conditioning rates of the left NM and the left and right eyelids. Graph A. represents the conditioning rate of the left eyelids and left NM. The solid line represents the left NM while the dashed line represents the left eyelids. CR % Asymptote is found by dividing the response on the tone-alone trials for that block by the average response on the tone-alone trials on the last day of paired training and multiplying by 100. Pcrit is the day on which the animals reached criterion performance of eight conditioned responses on any nine consecutive trials. P -1 is the training day prior to Pcrit and P +1 is the training day after Pcrit. Graph B. represents the conditioning rate of the right eyelids and left NM for the six animals which showed bilateral conditioned responses. The solid line represents the left NM and the dashed line represents the right eyelids.

movement of the left nictitating membrane (NM) and MMU activity of the left eyelids throughout behavioral training. Seven of the animals also had simultaneous recordings of MMU activity from the right eyelids.

Unconditioned responses were found to be bilateral in all seven animals. The magnitude of the unconditioned response was estimated as the number of action potentials rising above the comparator level during the UCS period for the first block of paired trials on the first day of paired training. For the left eyelids this response was found to be 80.9 ± 31.7 (mean \pm standard deviation) action potentials. The response in the right eyelids was found to be significantly smaller (6.3 ± 3.6 action potentials $t(12) = 5.8, p < 0.001$). The latency to onset of the unconditioned left eyelid response was found to be 7.3 ± 0.73 milliseconds from the time of the arrival of

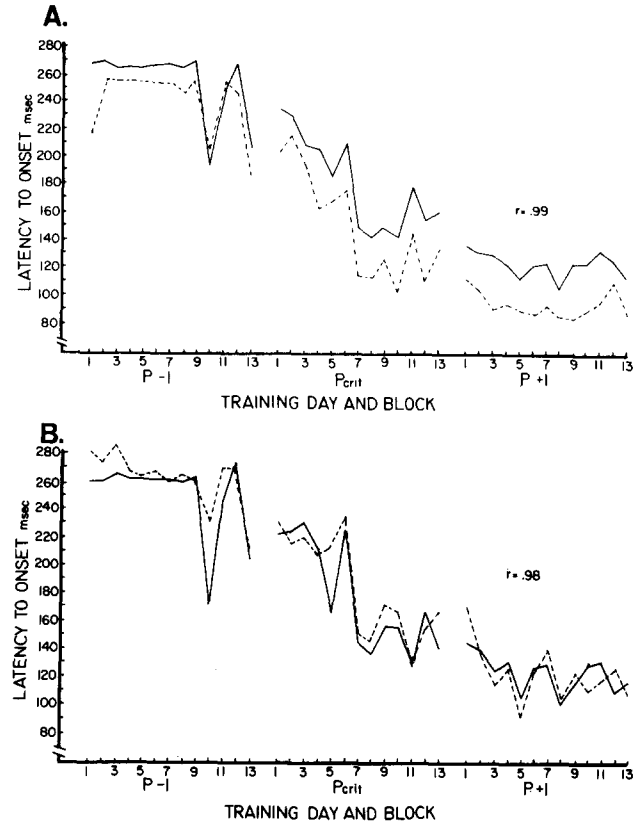


FIG. 3. Latency to onset of the behavioral responses from the onset of the tone in milliseconds. Graph A. represents the latencies found for the left eyelids and left NM of all eight animals. The solid line represents the latencies for the left NM while the dashed line represents the latencies for the left eyelids. Graph B. represents the latencies for the right eyelids and left NM for the six animals which showed bilateral conditioning. The solid line represents the latencies of the NM while the dashed line represents the latencies of the right eyelids. P -1, Pcrit, and P +1 are as in Fig. 2.

the airpuff at the cornea of the eye. The latency of the left NM response was found to be 22.4 ± 5.0 milliseconds. The latency of the right eyelid response was found to be 23.5 ± 6.9 milliseconds. However, many of the right eyelid responses also possessed a smaller, shorter latency response (latency 10.7 ± 3.1 milliseconds).

Figure 2 illustrates the acquisition rate of the eyelid and NM responses. Both the left and right eyelids conditioned at a rate which closely paralleled the conditioning of the left NM (correlations equal .97 and .89, respectively). Thus the magnitude of all three conditioned responses increased during acquisition in very close relation to one another, with the highest correlation occurring between the left eyelid and the left NM.

Figure 3 illustrates the latency to onset of the eyelid and NM responses during conditioning. The decrease in latency of the left and right eyelid responses occurred at a rate which is highly correlated with that found for the NM response (.99 and .98, respectively). On the last day of paired training (P +1), the onset of the left eyelid conditioned responses preceded the onset of the left NM responses by 29.5 ± 8.2 milliseconds, whereas the conditioned responses of the right eyelids were seen to precede the NM responses by an aver-

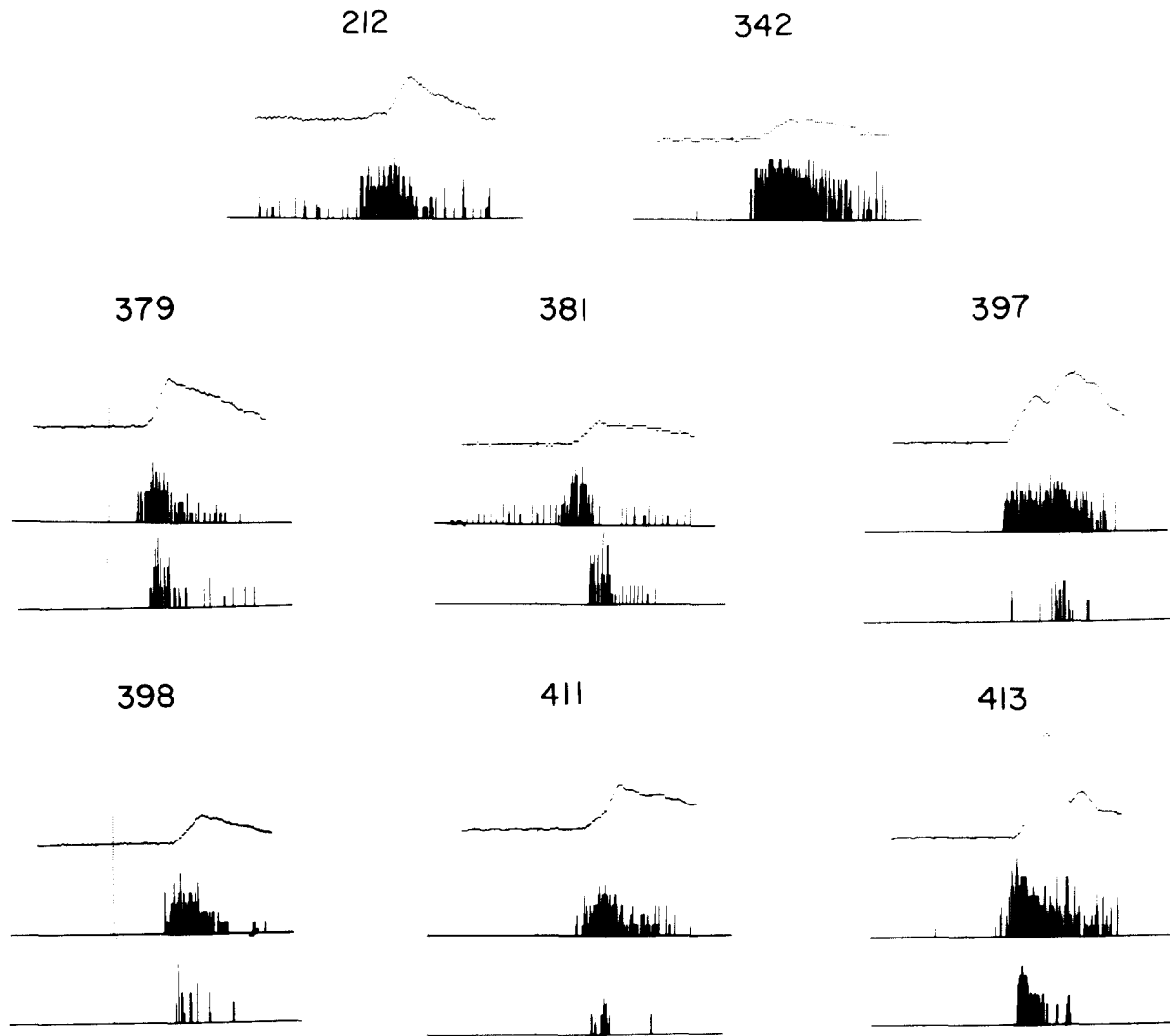


FIG. 4. Typical conditioned responses of the left NM and eyelids and the right eyelids occurring on the tone-alone trials of the last day of paired training. The upper trace in each set represents NM movement with up being extension across the eyeball. The middle trace is a histogram representing the response of the left eyelids while the bottom trace is a histogram representing the response of the right eyelids. The vertical line represents the onset of the tone. Each bar of the histograms is 3 milliseconds in duration. Animal 212 had no data recorded from the right eyelids, while animal 342 did, but showed very few bilateral CRs.

age of only 1.2 ± 12.7 milliseconds. Thus the latency to onset of the conditioned responses of the left and right eyelids were found to decrease at almost exactly the same rate as did the latency to onset of the left NM. Furthermore the left eyelids came to precede the left NM by approximately 29.5 milliseconds.

Figure 4 illustrates representative responses seen in the left and right eyelids and left NM on the tone-alone trails of the last day of paired training. The responses of the left eyelids are seen to precede the left NM and right eyelid responses by varying latencies. The right eyelid responses vary in magnitude and are smaller than the left eyelid responses. The average asymptotic response of the left eyelid was 149.8 ± 77.0 action potentials, while the average asymptotic response of the right eyelid was 41.0 ± 29.0 action potentials (27.6% of left eyelid response). These differences were significantly different, $t(12) = 3.5$, $p < 0.01$.

During conditioning, spontaneous blinks of the left NM were seen to be nearly always accompanied by spontaneous blinks of the left eyelids. However, numerous occasions were found in which movements of the left or right eyelids were not accompanied by corresponding movements of the left NM (see Fig. 5). This and the fact that one animal did not show conditioning of the right eyelids indicates that the three responses can operate independently of each other, even though they condition at almost exactly the same rate. Indeed, a full size blink of either eyelid could be elicited without movement of the contralateral eyelid by touching the cornea with a cotton swab.

After behavioral training was completed, three of the eight animals were given an additional day of training, during which preliminary recordings were taken from various muscles of the face and body. The animals exhibited conditioned contractions of much of the superficial facial musculature,

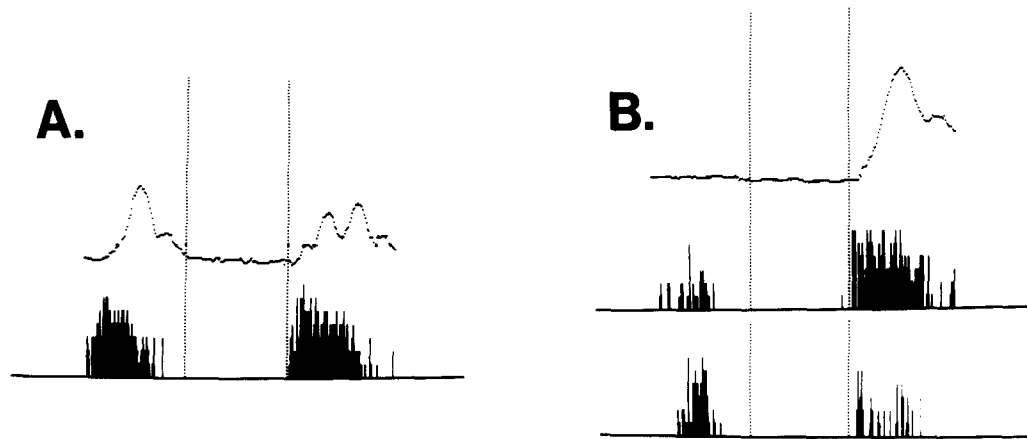


FIG. 5. Part A represents spontaneous blinks of the left NM and left eyelids in the Pre-CS period. The first vertical line represents the onset of the tone while the second vertical line represents the onset of the airpuff. Part B represents a spontaneous blink of the left and right eyelids without accompanying movement of the left NM. The upper trace in each set represents the movement of the NM while the histogram just beneath this represents the response of the left eyelids. In Part B the lower histogram represents the response seen in the right eyelids. Each bar of the histograms is 3 milliseconds in duration.

including the nasal musculature, which responded in a manner related to an increased respiration rate in response to the CS. One of the animals showed conditioned head movements (away from where the airpuff would have originated) involving the neck musculature. No jaw or bodily movements showed conditioned responding, although movements of the head (involving the neck musculature) and occasionally the body, jaw and mouth regions were seen in response to the UCS. Through informal observations of an additional ten animals we have found that an animal's responses to the CS and UCS may differ widely, from one extreme of completely unilateral eyelid and NM conditioning only, to the other extreme of bilateral conditioned responses involving much of the facial and neck musculature, with the average animal reacting much as the animals detailed above. Thus the average conditioned response trained under the conditions used in this study may be described best as a largely unilateral synchronous facial "flinch" centering about closure of the eyelids and extension of the NM, usually with some bilateral components.

DISCUSSION

The mean latency to onset of the unconditioned left NM response in the present experiments is 22.4 ± 5.0 msec. This value agrees well with the assumption of a relatively direct reflex pathway. Stimulation of the abducens nerve produces NM extension with an onset latency of 16.7 ± 2.0 milliseconds—the time required for nerve conduction, initiation of muscle contractions that produce eyeball retraction and the consequent passive extension of the NM [4]. In agreement with this value, the onset of firing of neurons in the abducens nucleus precedes the onset of the NM movement by 16–18 msec [4]. Corneal stimulation produces activation of the fifth sensory nucleus in about 3 msec [5,15]. This leaves approximately 1 to 3 msec for transmission from the fifth sensory nucleus to the accessory abducens/abducens nuclei, a range consistent with either a direct connection or a dysynaptic pathway relaying through one set of interneurons (e.g., in the reticular formation) [3]. A recent investigation using periocular shock as the UCS has found that the

latency of the UCR is a negative exponential function of stimulus current with an asymptote of 17 milliseconds [23]. Disterhoft *et al.* [9] have also reported a latency of 17.5 milliseconds when using an airpuff measuring 5 psi at the source (which is considerably stronger than the 3 psi used in the present study).

The mean latency to onset of the unconditioned left eyelid muscle unit response is 7.3 ± 0.73 msec, consistent with a previous report of 7.5 ± 0.5 msec for cat [15]. It has been suggested that this shortest latency pathway is direct from the fifth sensory nucleus to the facial nucleus and does not involve an interneuron, at least in the cat [15]. The right eyelid response typically had a much longer latency (23.5 ± 6.9 msec), implying a polysynaptic pathway. However smaller, short latency responses (10.7 ± 3.1 msec) were often present suggesting a relatively direct pathway from left fifth sensory nucleus to right facial nucleus. The unconditioned eyelid response is bilateral as might be expected given that the fifth sensory nucleus has a small contralateral projection [1]. This is consistent with the report by Disterhoft *et al.* [9] that the unconditioned NM response is bilateral.

The recordings from various muscles of well trained rabbits in the present study have shown that the conditioned response is best described as a synchronous facial "flinch" centered about closure of the eyelids and extension of the NM, usually with some bilateral components. The muscles involved in the conditioned response varied considerably between animals but in all cases included the ipsilateral eyelid and NM responses. The time courses of these responses both within trials and over the trials of training were extremely similar. This stands in marked contrast to conditioned heart rate deceleration to periorbital or pinna shock in the rabbit, which has been shown to occur in as few as ten trials [27,31]. However, over the trials of training this conditioned heart rate deceleration decays and eventually becomes accelerative with a time course that appears closely related to the acquisition of the somatic conditioned responses [27].

The most important result of the present experiment is the extremely high correlations between the conditioned left NM

and left and right eyelid responses over the course of learning, both in terms of amplitude and latency (see Figs. 2 and 3). The most obvious possible explanation—that the motor nuclei are directly and very tightly coupled—can be ruled out. The two eyelids can easily be made to respond independently of each other (see Results). Although there is a possible anatomical substrate for coordinated activity of the left facial and accessory abducens/abducens nuclei [6, 12, 16, 34] the left eyelid can respond independently of the left NM, i.e., spontaneous responses. Axons from the accessory abducens/abducens nuclei are reported not to give off collaterals before they exit the brain [11,12]. Consistent with this, electrical stimulation of the abducens nucleus produces eyeball retraction and NM extension but no movement of the eyelid [4,28].

The extremely close correspondence between the conditioned left eyelid and NM responses and the right eyelid response has strong implications for the locus of the essential neuronal plasticity that codes learning in this paradigm. Either this plasticity develops in the motor nuclei or elsewhere. If it develops in the motor nuclei it must develop relatively independently in each, given that they are not all tightly coupled. Such independently developing plasticity could not possibly produce the virtually perfect covariance of the learned responses, particularly in terms of latency (see Fig. 3). Therefore, the plasticity must develop elsewhere. There are again two possibilities—either it develops in some part of the reflex pathways or elsewhere.

A number of lines of evidence argue strongly against the plasticity developing in neurons of the reflex pathways. For example, morphine selectively and completely abolishes the conditioned response but has no effect at all on the reflex response to corneal airpuff [18]. Spreading depression induced in the contralateral motor cortex has a similar effect [21], as do lesions in several locations in the brain [8, 17, 19]. Furthermore, scopolamine has been found to retard the rate of acquisition of the conditioned response without affecting the amplitude of the unconditioned response [14,24].

There is a relatively direct pathway between the auditory system and at least the seventh cranial nucleus that mediates the startle or alpha eyelid response to a sudden or loud sound. This may or may not involve a part of the trigeminal reflex pathway. In the cat, the onset of the unconditioned alpha response of eyelid muscle unit activity to a click stimulus has a latency of approximately 20 msec [35]. The mean onset latency of conditioned eyelid muscle unit activity under the conditions of our experiment is 80 msec and the minimum

latency shown consistently by any animal is 58 msec. This long latency of the conditioned response could not be accounted for if the essential neuronal plasticity is localized to the "alpha response" pathway, at least not in terms of the time courses of known synaptic processes.

In sum, the virtually perfect correspondence between the learned NM and eyelid responses and their relatively long latencies would seem to argue strongly that the essential neuronal plasticity coding the learned response must involve brain system structures other than the motoneurons, reflex pathways and alpha response pathways. In particular, the present data strongly suggest essential involvement of a central system that acts synchronously on all the motor nuclei involved in generation of the several components of the conditioned response. Higher brain structures such as the hippocampus and cerebral cortex have been shown to play important roles in NM and eyelid conditioning [2, 21, 33, 36]. However, animals with all brain tissue above the level of the midbrain or thalamus are capable of learning the standard delay conditioned NM and eyelid responses ([22, 25, 26, 29, 32], D. Enser, personal communication, 1976). In recent work we have found that the ipsilateral cerebellum is essential for the conditioned response. Ablation of the ipsilateral lateral cerebellum or electrolytic destruction of portions of the dentate and interpositus nuclei and surrounding fibers causes selective, complete and permanent abolition of the conditioned NM and eyelid responses but has no effect on the unconditioned reflex responses [19].

We suggest that the common central system containing the essential neuronal plasticity that codes the learned response is localized to the cerebellum and related structures. As learning develops, this cerebellar system comes to exert precisely timed excitatory influence over all the motor nuclei involved in the conditioned response. Our lesion studies suggest that the essential memory trace for the eye being trained develops entirely in the ipsilateral cerebellar system. However, there is a variable degree of coordinated plasticity established in the contralateral cerebellar system, which may mediate to some extent conditioned responding in the opposite eye [19].

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