

# Cerebellar Cortical Degeneration Disrupts Discrimination Learning But Not Delay or Trace Classical Eyeblink Conditioning

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The authors investigated classical eyeblink conditioning in a relatively rare patient, B.R., with extensive cerebellar cortical atrophy and marked sparing of the dentate nucleus. Patient B.R.'s ability to acquire and extinguish simple associations (delay and trace conditioning tasks) as well as her ability to acquire more complex associations (temporal and simple discrimination tasks) were examined. There are 2 primary findings from this study. First, B.R. showed normal acquisition and extinction in delay and trace conditioning. Second, she demonstrated a complete inability to learn associative discriminations, even in the case of a simple 2-tone discrimination within the context of a delay paradigm. The latter finding was unexpected because of the sparing of her deep cerebellar nuclei. These data suggest that the cerebellar cortex, or pathways traversing cerebellar cortex, play an important role in classical eyeblink discrimination learning.

Lesion studies in both animals and humans have confirmed that the associative learning of conditioned responses (CRs) in eyeblink conditioning is dependent on the lateral cerebellar cortex, the lateral interpositus–medial dentate nuclear region, and the superior cerebellar peduncle (McCormick & Thompson, 1984). In general, electrophysiological studies have corroborated these lesion studies in rabbits (Clark, McCormick, Lavond, & Thompson, 1984; McCormick et al., 1981; McCormick, Lavond, & Thompson, 1983; R. F. Thompson, 1991).

The above findings from animal studies have been extended to case studies with human neurological patients. For example, Lye, O'Boyle, Ramsden, and Schady (1988) reported that an individual with a unilateral lesion in the right

cerebellar hemisphere produced significantly fewer CRs when the conditioned stimulus (CS) was presented to the ipsilateral eye as compared to the contralateral eye in a delay conditioning task. Similarly, Solomon, Stowe, and Pendlebury (1989) reported that a patient with a history of cerebrovascular accidents that damaged cerebellar circuitry showed very little if any CR acquisition (6 CRs) over 100 trials.

Impairments in conditioning performance have also been reported in larger studies of patients with cerebellar atrophy. Topka, Valls-Sole, Massaquoi, and Hallett (1993) examined delay eyeblink conditioning in two groups of cerebellar patients: five patients with pure cerebellar cortical atrophy and seven patients with additional brainstem atrophy. The ability to acquire eyeblink responses was impaired but not absent in both patient groups as compared to normal individuals. Topka et al. assumed that the deep cerebellar nuclei were spared in both patient groups, therefore they argued that lesions involving the cerebellar cortex or the inferior olive and climbing fiber pathways are sufficient to cause impairments in classical conditioning. In addition, McGlinchey-Berroth et al. (1995) demonstrated that patients with amnesia caused by Korsakoff's syndrome and recovered chronic alcoholics display impaired conditioning in a delay paradigm. Korsakoff patients did not exhibit any increase in production of CRs above baseline levels across learning trials. Learning in the recovered alcoholic participants was not abolished but was impaired compared to normal individuals. McGlinchey-Berroth et al. (1995) attributed the impairment in both groups to chronic cerebellar deterioration resulting from years of alcohol abuse.

Two neuropsychological studies have looked at the distribution of neurological damage in individual patients to

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examine the relative roles of the cerebellar cortex and deep nuclei. Daum and her colleagues (Daum et al., 1993) examined delay classical conditioning in seven patients: four with bilateral cerebellar lesions due to idiopathic cerebellar ataxia with atrophy restricted to the cerebellum (the extent of cerebellar atrophy was not specified) and three with unilateral damage caused by either stroke or resection (location of the lesions within the cerebellum varied, with one patient's lesion sparing the deep nuclei). As a group, the cerebellar patients were severely impaired in delay eyeblink conditioning. Two patients did, however, show some conditioning. It is important that the one patient with noted spared deep nuclei demonstrated some acquisition of CRs. Daum et al. concluded that it is probable that the acquisition demonstrated by these two patients was mediated by undamaged critical areas of the cerebellum.

Woodruff-Pak, Papka, and Ivry (1996) also investigated delay eyeblink conditioning in 14 cerebellar patients that included a mixed group of 7 unilateral and 7 bilateral patients. Lesion sites were primarily limited to cerebellar cortex, with some lesions extending to deep nuclei, specifically the interpositus nucleus. Both the bilateral and unilateral patients were significantly impaired in CR production (unilateral patients were impaired only on the ipsilateral side). The relationship between topography of cerebellar lesion and classical conditioning was also considered. Woodruff-Pak et al. (1996) reported that one unilateral patient whose lesion site was described as extremely lateral in the right superior hemisphere, thus sparing the deep nuclei, conditioned normally in both eyes. In a second unilateral patient, whose lesion site included the globose nucleus, conditioning was abolished in the ipsilateral eye. Finally, 2 additional unilateral patients demonstrated impaired conditioning in the ipsilateral eye; however, they were able to produce some CRs. The authors attributed the CR production to sparing of the globose nucleus and concluded that if the globose nucleus is spared, and the lesion is limited to the cerebellar cortex, then CR acquisition is impaired but not abolished.

A recent imaging study conducted by Logan and Grafton (1995) further supports the notion that the deep cerebellar nuclei play a critical role in eyeblink conditioning in humans. Using positron emission tomography, the investigators found significant activation in the inferior cerebellar cortex and deep cerebellar nuclei of humans performing the eyeblink delay conditioning task. Blaxton et al. (1996) also reported increased activity in the deep nuclear regions during delay conditioning.

In the present study we report on the performance of a relatively rare patient with marked idiopathic cerebellar degeneration. As shown in Figure 1, B.R. has extensive cerebellar cortical atrophy with marked sparing of the dentate nucleus. Given the clear radiological evidence of severe cerebellar cortical atrophy that does not extend to the deep nuclei, we made hypotheses regarding her performance in several eyeblink conditioning paradigms.

First we examined B.R.'s ability to acquire and extinguish CRs in a series of delay (Experiment 1) and trace conditioning (Experiment 2) tasks. The preponderance of

evidence suggested that B.R. would show some acquisition in delay and trace conditioning, but whether her acquisition would be impaired relative to normal participants in both tasks was in question. Specifically, given the distribution of atrophy, we predicted that B.R. would show acquisition in the delay task. It was unclear, however, whether her acquisition would be impaired relative to normal participants. Findings from rabbits suggested that her performance would be normal (Clark et al., 1984; Lavond, Hembree, & Thompson, 1985; Lavond, Lincoln, McCormick, & Thompson, 1984; McCormick et al., 1981; L. T. Thompson, 1990; Yeo, Hardiman, & Glickstein, 1985), whereas human studies suggested that her level of acquisition could be below normal (Daum et al., 1993; Woodruff-Pak et al., 1996). The trace conditioning task varies from the delay task in one crucial manner: the CS and the unconditioned stimulus (US) are temporally separated. The underlying neural substrates that are essential for normal performance and retention in this task include the deep cerebellar nuclei (R. F. Thompson, 1991; Woodruff-Pak, Lavond, & Thompson, 1985) and the hippocampus (McGlinchey-Berroth, Carrillo, Gabrieli, Brawn, & Disterhoft, 1997; Moyer, Deyo, & Disterhoft, 1990; Solomon, Vander Schaaf, Norbe, Weisz, & Thompson, 1986; however, see Woodruff-Pak, 1993). Neither of these structures appeared to be compromised in B.R.; we therefore predicted that she would demonstrate acquisition in this task. However, it was again unclear if B.R.'s acquisition would be normal or impaired relative to normal participants.

Second, we examined B.R.'s ability to learn a temporal discrimination task (Experiment 3). A number of studies have indicated that the cerebellar cortex is critical in learning the timing aspects of classical conditioning (e.g., Ivry & Keele, 1989; Perrett, Ruiz, & Mauk, 1993). Using the paradigm developed by Mauk and Ruiz (1992), we predicted that B.R. would acquire CRs (albeit perhaps at an impaired level) to each of the two CS tones but would be impaired in eliciting differentially timed CRs. The nature of this timing deficit was expected to be revealed as an inability to alter the onset or peak latency of CRs to match the two US onset latencies. To anticipate the results, our predictions were not borne out: B.R. did not show any conditioning for either of the two CSs. This experiment was, therefore, followed by a simple discrimination learning task (Experiment 4) to determine if it was the temporal processing demands that caused B.R.'s poor performance in Experiment 3 or if it was the need to learn a discrimination that produced the impairment. Indeed, we found that the latter was true, as in Experiment 4 B.R. was also completely unable to learn a simple discrimination. A final trace conditioning task (Experiment 5) confirmed that B.R.'s performance in the discrimination tasks was not related to an advancement in her disease.

## General Method

B.R. was tested on a number of different classical eyeblink conditioning paradigms. The methods and procedures common to these paradigms are described next; specific procedures for each task are described in separate sections.

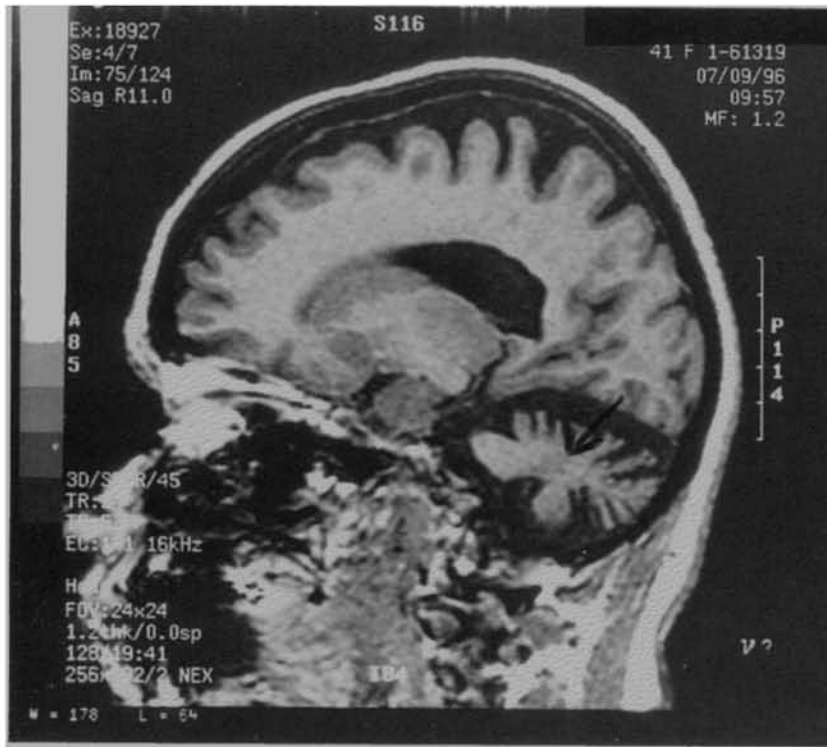
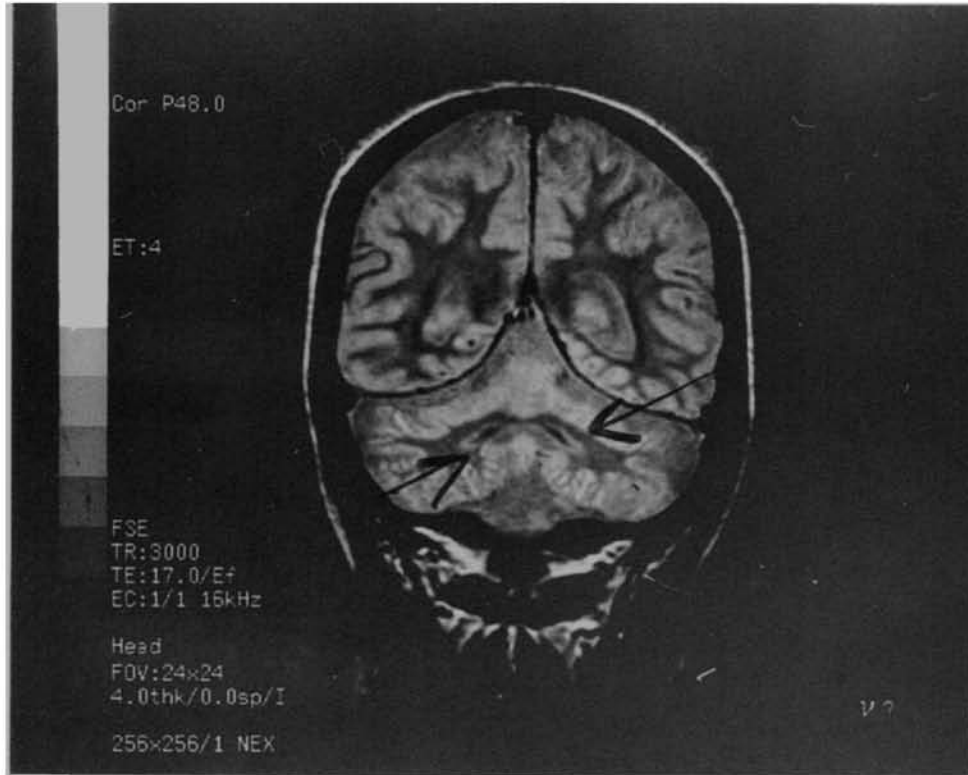


Figure 1. Coronal (top) and sagittal (bottom) slices of B.R.'s magnetic resonance imaging scan showing extensive cerebellar cortical atrophy and intact deep cerebellar nuclei.

## Participants

**Patient description.** B.R., a 42-year-old, right handed, high school educated, single, White woman, developed initial symptoms suggestive of cerebellar dysfunction in 1993 at which time she was diagnosed with marked idiopathic cerebellar degeneration. Her symptoms included slurred speech, lightheadedness, and balance difficulties. Neurological exam results at that time indicated dysarthria and soft cerebellar signs, including asymmetric lateral gaze nystagmus and mild dysmetria. Repeated magnetic resonance imaging (MRI) scans (1993–1996) demonstrated marked, diffuse atrophy of the cerebellum, sparing of the pons and medulla, and mild cerebral atrophy with no focal lesions. Visual, somatosensory, and brainstem-evoked potentials were normal. Past medical history was negative, with no family history of gait disorder or neurodegenerative disease. Otoneurology evaluation results concluded unquestionable degenerative disorder, with mild dysarthria, left horizontal and down-beating nystagmus, ataxia, vertigo, and vestibular dysfunction. Given occasional acute decrements in her clinical course, the form of the degeneration was viewed as rare type.

**Normal control participants.** We compared the performance of B.R. with that of a group of normal control participants deemed to have no neurological impairments. Normal control participants for each experiment were matched as closely as possible to B.R. for age and education (delay conditioning: mean age = 47 years [ $SE = 9.86$ ], mean education = 15.0 years [ $SE = 0.75$ ]; trace conditioning: mean age = 44 [ $SE = 5.57$ ], mean education = 15.8 [ $SE = 0.80$ ]; temporal discrimination learning: mean age = 44 [ $SE = 2.94$ ], mean education = 14.8 [ $SE = 0.97$ ]; discrimination delay conditioning: mean age = 44 [ $SE = 5.79$ ], mean education = 15.4 [ $SE = 0.87$ ]). Although the normal control group was not identical in each experiment, all normal control participants were trained in each successive eyeblink task to ensure equality of carryover and training effects in both the control participants and B.R.

## Neuropsychological Testing

The control participants were screened to ensure they were free of any history of neurological illness or disease, diabetes, hypertension, and other vascular diseases that may affect cognitive function. As such, it was assumed that their mental abilities were not compromised, and therefore they did not receive the neuropsychological battery. B.R.'s neuropsychological status was evaluated with a number of standardized tests.

**General cognition.** The Wechsler Adult Intelligence Scale—Revised (based on age-scaled scores; Wechsler, 1981) revealed that B.R.'s intellectual abilities were low average overall (Full Scale IQ = 83). In particular, her verbal abilities were low average (Verbal IQ = 88), and her visual-spatial abilities were average (Picture Completion, Block Design) to low average (Picture Arrangement, Object Assembly), with the exception of Digit Symbol performance (age equivalent: 5th percentile), which requires quick information processing and motor speed.

**Attention and speed of information processing.** The Wechsler Memory Scale—Revised (Wechsler, 1987) revealed that B.R.'s attentional capacity ranged from low average to average (Attention/Concentration Index). Forward digit span was 5–6 digits (22nd percentile) and digits backward was 3–4 (53rd percentile). Auditory vigilance was impaired, however, for both simple targets (odd numbers) and complex targets (two consecutive odd numbers). Mild distractibility was also noted. Visual scanning and attention (Letter Cancellation) were slow but accurate given extra time. Mental control was good (counting from 1 to 20: 16 s, 0

errors; reciting alphabet; 9 s, 0 errors), but performance on complex tasks requiring greater divided attention and concentration showed mild difficulties (e.g., adding serial 3s resulted in multiple errors because of loss of set).

## Apparatus and Stimuli

The eyeblink conditioning apparatus used in all of the experiments conducted with B.R. was a modified version of that designed for eyeblink conditioning in rabbits (Akase, Thompson, & Disterhoft, 1994; L. T. Thompson, Moyer, Akase, & Disterhoft, 1994), and it has been used in our previous studies with human participants (e.g., Carrillo, Thompson, Gabrieli, & Disterhoft, 1997; Gabrieli et al., 1995; McGlinchey-Berroth et al., 1997).

The CS, an 85-dB tone (either 1000 or 5000 Hz), was delivered binaurally over earphones. The US was a 100-ms corneal airpuff delivered to the right eye of sufficient magnitude to cause a reliable 3-V unconditioned response (UR; approximately 3 psi). Eyeblink movements were monitored with an infrared diode/phototransistor aimed at the right eye. This device monitors and amplifies light reflectance from the cornea in a 0- to 5-V DC range, which was then digitized and stored by a microcomputer. Eyeblink amplitude is an inverse function of the amount of reflected light contacting the phototransistor aimed at the cornea. The detector was adjusted so that the baseline setting when the eye was open was near 1 V and the highest amplitude when the eye was fully closed was less than 5 V. An eyeblink was classified as a CR if (a) the eyeblink occurred during the CS-US interstimulus interval (ISI) and (b) the blink was 4 SD greater than the mean baseline response amplitude during the period immediately before the presentation of the CS. Eyeblinks that occurred less than 200 ms after tone onset were recorded as alpha responses and not considered a CR (Gormezano, 1966). On each trial there was a 750-ms baseline recording period prior to the onset of the CS. This period allowed us to assess spontaneous blink rates. The intertrial interval averaged 10 s but varied randomly from 8 s to 12 s.

Participants were seated in an upright armchair and fitted with the eyeblink apparatus in a sound-attenuated room. After participants provided informed consent, the experimenter read the following instructions:

Please make yourself comfortable. You will experience different stimuli from time to time including a tone and a mild puff of air to your right eye. If you feel like blinking, please do so; just relax and let your natural reflexes take over.

The experimenter was seated in the same room, out of the direct view of the participants, so that questions could be answered as they arose. During the delay and trace conditioning studies, Patient B.R. and normal control participants viewed a silent movie (Charlie Chaplin's *Goldrush*) to reduce boredom. For the remaining tasks the movie was not shown, as it has been found to interfere with conditioning in more challenging paradigms (Carrillo, Gabrieli, & Disterhoft, 1996).

After each testing session participants were questioned about their awareness of the task demands. Specifically, participants were asked the following series of open-ended questions: (a) What did you think was going on in the experiment? (b) Did you think there was a relationship between the tone and the airpuff? (c) Did you feel like blinking to one tone more than another (if there were two CSs)? (d) Did you notice anything different happening during various parts of the experiment?

Experiment 1: Delay Conditioning

Procedure

Training included 60 conditioning trials followed by 30 extinction trials. Each conditioning trial consisted of the 850-ms tone overlapped by a 100-ms coterminating corneal airpuff. During extinction, the tone (CS) was presented alone (see Figure 2).

Results and Discussion

We calculated confidence intervals for the percentage of conditioning trials in which control participants produced a CR. The normal 95% confidence interval ranged from 68 to 81. As can be seen in Table 1, the percentage of trials in which B.R. produced a CR (71.67) fell within this interval during conditioning. The learning curves for B.R. and normal control participants are presented in Figures 2 and 3. B.R. showed a normal acquisition curve, reaching normal performance by Block 2. Normal controls acquired the CR rapidly, reaching 80% CRs by Block 3. The mean number of trials that occurred before the normal participants produced the first CR was 3.2 ( $SD = 1.6$ ). B.R. exhibited her first CR at Trial 7. As shown in Figure 3, the normal participants learned at a faster rate than Patient B.R. did. These results are similar to that of Solomon and his colleagues (Solomon, Pomerleau, Bennett, James, & Morse, 1989), who examined the acquisition of CRs over the human life span and also found rapid learning curves in participants between the ages of 18 and 49. Participants who fell within this age range obtained a mean of 62% CRs after

the first 10 trials of learning. Woodruff-Pak and Thompson (1988) found similar results in their younger participants trained on delay conditioning (learning progressed from 40% to 80% CRs over the first 72 trials). Therefore, rapid rates of learning were expected in the age group we examined (the mean age of the normal control participants was in the mid-40s; Patient B.R. was 42 years old). These results suggest that cerebellar atrophy limited to the cerebellar cortex did not interfere with acquisition in delay eyeblink conditioning. Thus, it appears that B.R.'s deep nuclei were sufficient to support normal delay eyeblink conditioning. It appears from these data that B.R. is intact in the delay conditioning task.

B.R. produced only 1 alpha response during conditioning trials. Normal participants produced 2.0 ( $SE = 1.53$ ) alpha responses during conditioning trials.

In addition to her normal acquisition, B.R. also displayed intact extinction. The mean percentage of trials during extinction in which B.R. produced a CR was 13. This performance was similar to that of the normal control participants, whose mean percentage of extinction trials with a CR was 21. The reduction in the percentage of CRs for the normal participants from conditioning trials to extinction trials was significant,  $t(4) = 4.78, p < .01$ .

On the basis of the awareness inquiry, we learned that B.R. was aware of the two stimuli occurring during training (tone and puff) but was largely unaware of a relation between the two. She reported that the experiment was "similar to the MRI with the beeps." When directly asked about the relation between the CS and the US, she responded, "No relation, really," and denied a relation on further questioning. However, after the awareness questioning was completed, B.R. made a vague comment to the experimenter indicating some awareness of the temporal relationship that she was unable to state explicitly ("Noise then I knew. . . I was getting ready because I noticed it stung my eye."). Therefore B.R. had some awareness of the relations but was not as explicitly aware as the normal participants.

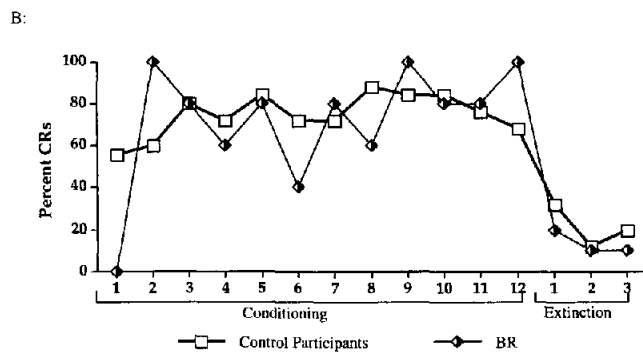
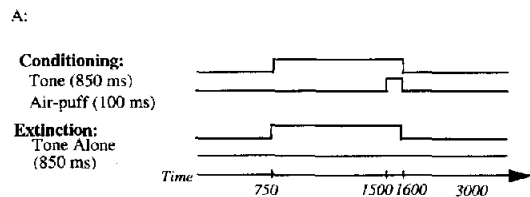


Figure 2. A: The time course illustrates a paired conditioned stimulus (CS)-unconditioned stimulus conditioning trial in the delay conditioning task and unpaired CS alone, extinction trial. B: Learning curve and time course for delay conditioning. The x-axis represents trial blocks consisting of five trials each; the y-axis represents the mean percentage of conditioned responses. CR = conditioned response; BR = Patient B.R.

Experiment 2: Trace Conditioning (Right and Left Eyes)

Procedure

Sixty conditioning trials were presented using a 100-ms, 1000-Hz, 85-dB tone as the CS and a 100-ms, 3-psi corneal airpuff as the US. The CS and US were separated by a 500-ms silent trace period. Thirty extinction trials followed conditioning (see Figure 4). The same procedure was replicated with the CS and US presented to the left eye to ensure no lateralization effect. The trace conditioning session followed the previous training in the delay conditioning task by approximately 3 weeks.

Results and Discussion

As in Experiment 1, we calculated the 95% confidence interval for the percentage of trials in which control participants produced a CR. This interval was found to range from 54 to 74. As can be seen in Table 2, the percentages of trials in which B.R. produced a CR in both her right and left

Table 1  
Means and Standard Errors of CRs, CR Onset and Peak Latency, CR Amplitude, and UR Amplitude for Patient B.R. and Normal Control (NC) Participants During Delay Conditioning

Participant	% CRs	CR onset latency (ms)	CR peak latency (ms)	CR amplitude (mV)	UR amplitude (mV)
B.R.	71.67	398.10	465.18	4,203.72	3,389.52
NC					
<i>M</i>	74.67	382.50	594.84	2,193.78	2,490.19
<i>SE</i>	3.32	61.86	80.24	416.45	496.37
<i>CI</i>	68–81	116–649	250–940	1,038–3,350	1,112–3,868

Note. CR = conditioned response; UR = unconditioned response; CI = confidence interval.

eyes (71.67 and 61.67, respectively) fell within this normal interval during conditioning. As the learning curves presented in Figures 3 and 4 indicate, acquisition was very rapid and occurred within the first block of trials. It is clear from these data that B.R. is intact in the trace conditioning task and that her performance does not differ as a function of which eye receives the US. Similar to the findings of Woodruff-Pak et al. (1985), these results suggest that cerebellar atrophy that is limited to the cerebellar cortex and does not extend into the deep nuclei does not interfere with acquisition in trace eyeblink conditioning.

Also, as shown in Table 2, B.R.'s response-onset latency, CR peak latency, and UR amplitude fell within the normal range with both the right and left eyes. A possible impair-

ment was found in the CR amplitude measure. B.R.'s mean CR amplitude fell below the normal confidence interval for the right eye and was just within the lower limit of the normal interval for the left eye. This may reflect a subtle deficit that was not apparent in the delay task (in fact, recall that her CR amplitude was greater than normal in delay conditioning). Perhaps the increased temporal processing demands of the trace task were sufficient to reveal this slight impairment.

Again both B.R. and the control participants demonstrated rapid rates of learning in the trace conditioning task. As shown in Figure 3, the mean number of trials that occurred before the normal participants produced the first CR was 2.4 ( $SD = 1.3$ ). B.R. exhibited her first CR at Trial 3. It is important to keep in mind that B.R. and the normal control participants had been previously trained in delay conditioning; thus, a transfer of learning from the delay task to the trace task was expected. Given this transfer of learning, it was not surprising that acquisition was faster in the trace paradigm reported above than when trace conditioning is administered alone.

B.R. did not produce any alpha responses during conditioning on the right eye and only 1 alpha response during conditioning on the left eye. Normal participants produced 5.8 ( $SE = 2.3$ ) alpha responses during conditioning trials. This finding is consistent with the relatively low number of alpha responses observed in delay conditioning.

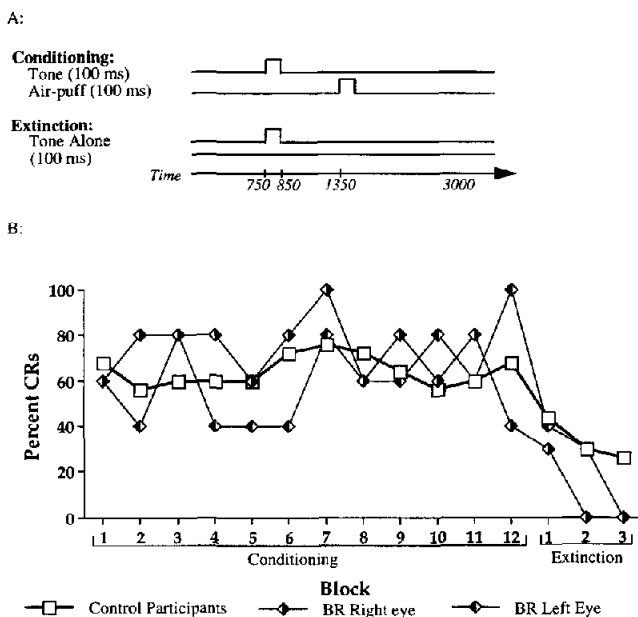


Figure 3. A: The time course illustrates a paired conditioned stimulus (CS)–unconditioned stimulus conditioning trial in the trace conditioning task and unpaired CS alone, extinction trial. B: Learning curve and time course for trace conditioning. The x-axis represents trial blocks consisting of five trials each; the y-axis represents the mean percentage of conditioned responses. CR = conditioned response; BR = Patient B.R.

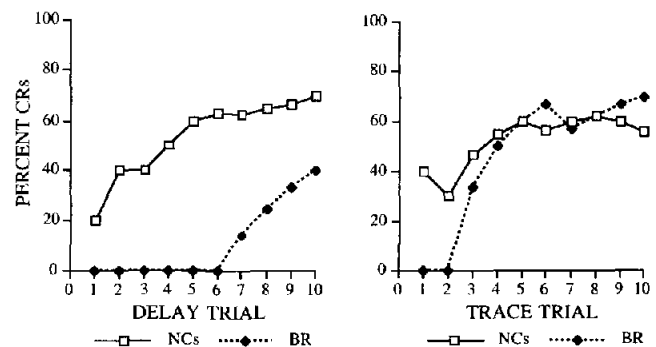


Figure 4. Mean percentage of conditioned responses (CRs) over the first two blocks of 10 conditioning trials in the normal control participants (NCs) and Patient B.R. (BR) in the delay and trace conditioning tasks.

Table 2  
*Means and Standard Errors of CRs, CR Onset and Peak Latency, CR Amplitude, and UR Amplitude for Patient B.R. and Normal Control (NC) Participants During Trace Conditioning (Right and Left Eyes)*

Participant	% CRs	CR onset latency (ms)	CR peak latency (ms)	CR amplitude (mV)	UR amplitude (mV)
B.R.					
Right eye	71.67	378.41	508.81	2,271.40	3,022.89
Left eye	61.67	393.28	465.80	2,410.21	3,436.56
NC					
<i>M</i>	64.33	395.72	541.13	2,972.92	3,141.01
<i>SE</i>	3.6	42.1	23.4	179.7	175.1
<i>CI</i>	54-74	279-513	476-606	2,401-3,545	2,584-3,698

*Note.* CR = conditioned response; UR = unconditioned response; CI = confidence interval.

B.R. also displayed intact extinction. The mean percentages of trials in which B.R. produced a CR were 10 with the left eye and 23 with the right eye. This performance was similar to that of the normal control participants, whose mean percentage of trials with a CR was 33. The reduction in the percentage of CRs for the normal participants from conditioning trials to extinction trials was significant,  $t(4) = 2.98, p < .05$ .

When asked a series of questions pertaining to awareness after the training session, B.R. indicated that she had been aware of the two stimuli occurring during training (tone and puff) and was also aware of a relation between the two. She reported that the "beep" was a "warning" but could not articulate the specific temporal relation between the two stimuli. Therefore B.R. again had some awareness of the relationship but was not as explicitly aware as the normal participants.

### Experiment 3: Temporal Discrimination Learning

#### *Procedure*

Two different tone CSs were used to signal two different ISIs before the onset of the US. Ninety conditioning trials consisting of two randomly ordered trial types were presented: In Type 1, a 1000-Hz tone was presented for 350 ms prior to the onset of a 100-ms airpuff. In Type 2, a 5000-Hz tone was presented for 750 ms prior to the onset of a 100-ms airpuff. Both tones coterminated with the airpuff. Thirty extinction trials (15 of each trial type) followed (see Figure 5). B.R. was tested on a total of 180 conditioning trials (run in two sessions spaced 2 weeks apart) in an attempt to maximize the likelihood that she would learn the discrimination. The temporal discrimination paradigm was run approximately 8 months after the trace conditioning study.

#### *Results and Discussion*

We calculated confidence intervals for the percentage of trials in which control participants produced a CR in both the 350-ms and the 750-ms delay conditions. The normal 95% confidence interval on trials with a 350-ms delay ranged from 34 to 72, and on trials with a delay of 750 ms the confidence interval was 56 to 96. Learning curves for both B.R. and the normal participants are shown in Figure 5. As presented in Table 3, the percentages of trials in which

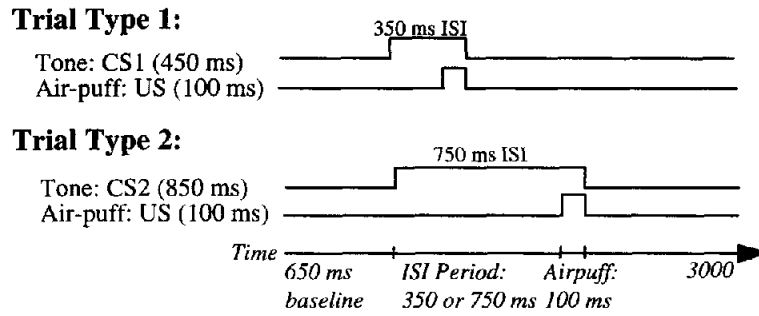
B.R. produced a CR in both training sessions in the 350-ms delay condition (8.89 and 6.67, respectively) and the 750-ms delay condition (17.78 and 22.22) fell far below the normal confidence interval during conditioning. It was clear from these data that B.R. was impaired in acquisition in this temporal discrimination task.

These results suggest that cerebellar atrophy limited to the cerebellar cortex and not extending into the deep nuclei interfered with temporal discrimination learning, as B.R. did not acquire CRs normally to either of the individual pairings of the two CS tones. Unfortunately, because of her poor performance we were unable to assess our primary hypothesis. Even after 180 conditioning trials B.R. did not produce reliable CRs. Response onset latency, CR peak latency, and UR amplitude are shown in Table 3. For B.R., however, these measures are unreliable because they were calculated from a small percentage of trials in which a CR occurred. Normal control participants, on the other hand, showed a significant shift in both CR onset latency,  $t(4) = 3.11, p < .05$ , and CR peak latency,  $t(5) = 8.32, p < .01$ , between the two tones. The shift in CR peak latency from the short-latency condition (350 ms) to the longer latency condition (750 ms) in the normal control participants was considerable (236-ms shift, from 320 to 556 ms).

The normal control participants produced a mean of 2.8 alpha responses ( $SE = 0.92$ ) during 350-ms delay trials and 1.6 alpha responses ( $SE = 0.75$ ) during 750-ms delay trials. During her first training session, B.R. produced 3.0 alpha responses during the 350-ms delay trials and 2.0 alphas during the 750-ms delay trials. B.R. produced 1.0 (350-ms delay) and 3.0 (750-ms delay) alpha responses during the second training session.

The normal control participants' mean percentages of trials with a CR during extinction were 19 on 350-ms delay trials and 23 on 750-ms delay trials. The reduction in the percentage of CRs for the normal participants from conditioning trials to extinction trials was significant,  $t(4) = 2.47, p < .07$ , and  $t(4) = 4.73, p < .01$ . B.R. produced a CR in 7.0% (Session 1) and 0.0% (Session 2) of the trials during extinction following the 350-ms ISI condition and in 27.0% (Session 1) and 7.0% (Session 2) of the trials following the 750-ms ISI condition. Thus, B.R. did not demonstrate any

A:



B:

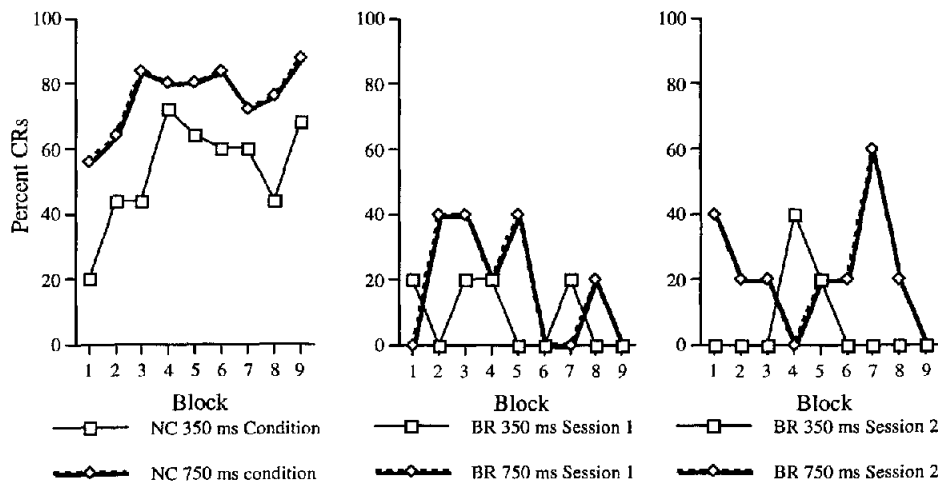


Figure 5. A: The time course illustrates the two trial types in the temporal discrimination task. Trial Type 1 is a paired conditioned stimulus (CS)–unconditioned stimulus (US) conditioning trial with an interstimulus interval (ISI) of 350 ms, and Trial Type 2 is a paired CS–US with an ISI of 750 ms. B: Learning curve and time course for temporal discrimination conditioning. The x-axis represents trial blocks consisting of five trials each; the y-axis represents the mean percentage of conditioned responses (CRs). NC = normal control participants; BR = Patient B.R.

conditioning to the two CSs and produced a similar percentage of CRs during conditioning and extinction trials.

It was uncertain from the above results what aspect(s) of the experimental demands was causing B.R.'s impairment. The task was a complex one, as it involved both learning a discrimination and associating that discrimination with differently timed responses. An impairment in either of these elements of the task could have produced the severe impairment that was observed. In the next experiment we attempted to identify the nature of B.R.'s impairment by removing the temporal processing demands. Therefore B.R.'s ability to learn a simple discrimination was examined.

Experiment 4: Discrimination Delay Conditioning

Procedure

On a reinforced trial, a tone (CS+) was followed by an airpuff (US). On a nonreinforced trial, a second tone (CS–) was

presented alone. The CS+ was a 1000-Hz tone, and the CS– was a 5000-Hz tone. We used a delay paradigm similar to the one described above: The 100-ms US (airpuff) followed the CS+ (tone) after 750 ms on reinforced trials, and both stimuli terminated simultaneously. Patient B.R. received two consecutive sessions each consisting of 60 acquisition trials (30 CS+ and 30 CS–; see Figure 6). The discrimination delay conditioning task was run in one session approximately 2 weeks after the temporal discrimination task.

Results and Discussion

As seen in Table 4, we calculated confidence intervals for the percentages of trials in which the normal control participants produced a CR to both the reinforced CS (CS+, or Tone 1) and the nonreinforced CS (CS–, or Tone 2) CS conditions. The normal 95% confidence interval on reinforced trials ranged from 39 to 89, and on nonreinforced trials the confidence interval was 0–55. Normal individuals produced a mean percentage of CRs

Table 3  
*Means and Standard Errors of CRs, CR Onset and Peak Latency, CR Amplitude, and UR Amplitude for Patient B.R. and Normal Control (NC) Participants During Temporal Discrimination Learning*

Participant	% CRs	CR onset latency (ms)	CR peak latency (ms)	CR amplitude (mV)	UR amplitude (mV)
B.R.: Session 1					
350-ms ISI	8.89	260.50 <sup>a</sup>	383.25 <sup>a</sup>	3,779.12 <sup>a</sup>	2,821.92 <sup>a</sup>
750-ms ISI	17.78	465.30 <sup>a</sup>	574.70 <sup>a</sup>	3,203.53 <sup>a</sup>	3,091.41 <sup>a</sup>
B.R.: Session 2					
350-ms ISI	6.67	281.25 <sup>a</sup>	300.50 <sup>a</sup>	1,957.41 <sup>a</sup>	2,323.82 <sup>a</sup>
750-ms ISI	22.22	453.52 <sup>a</sup>	495.33 <sup>a</sup>	2,905.10 <sup>a</sup>	2,125.32 <sup>a</sup>
NC: 305-ms ISI					
<i>M</i>	52.89	250.62	320.43	2,553.76	2,467.40
<i>SE</i>	6.90	19.62	10.12	210.04	147.76
CI	34–72	196–305	292–349	1,971–3,137	2,057–2,878
NC: 750-ms ISI					
<i>M</i>	76.00	302.59	555.80	2,981.83	2,360.05
<i>SE</i>	7.15	27.94	29.24	288.90	143.63
CI	56–96	225–380	475–637	2,180–3,784	1,961–2,759

Note. CR = conditioned response; UR = unconditioned response; ISI = interstimulus interval; CI = confidence interval.

<sup>a</sup> Calculated with a small percentage of CRs.

in 64% of CS+ trials and 25% of CS- trials. The difference between the percentages of CRs the normal participants produced during reinforced and nonreinforced trials was significant,  $t(4) = 4.19, p < .05$ . In Figure 6 the learning curves for B.R. and the normal participants are presented.

As displayed in Table 4, the percentages of trials in which B.R. produced a CR in both training sessions on CS+ trials (6.67 and 23.33, respectively) fell far below the normal confidence interval during CS+ conditioning. B.R. did not display normal acquisition of the CS+–US association. In addition, she produced a CR in 6.66% and 13.33% of CS- trials. Thus, her performance across reinforced versus nonreinforced trials is equivalent, demonstrating no evidence of ability to learn the two-tone discrimination (see Figure 6). It is clear from these data that B.R. is impaired on the simple discrimination task. B.R.'s response onset latency, CR peak latency, and UR amplitude are shown in Table 4; however, because these measures were calculated from a small percentage of trials in which a CR occurred they are not indicative of discrimination learning in B.R.

The normal control participants produced a mean of 9.0 alpha responses ( $SE = 4.00$ ) during discrimination learning trials. During her first training on the discrimination task, B.R. did not produce any alpha responses, and she produced 2.0 during the second 60 discrimination trials.

The above results suggest that the experimental demands involved in discrimination learning were the underlying cause of B.R.'s impairment in the temporal discrimination task (Experiment 3). Taken together, both findings indicate a role for the cerebellar cortex in eyeblink discrimination learning.

## Experiment 5: Trace Conditioning (Right Eye)

### Procedure

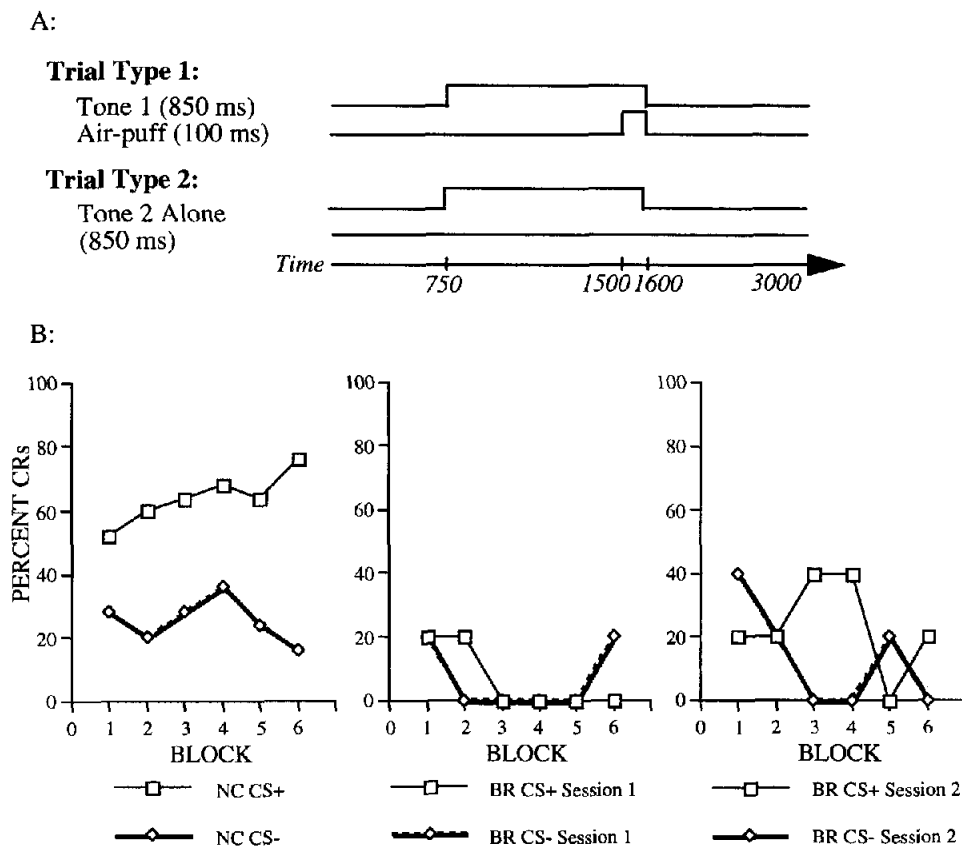
We administered trace conditioning following the identical procedure described in Experiment 2 above. B.R.'s performance was compared with that of the normal control participants described in Experiment 2 as well.

### Results and Discussion

The normal 95% confidence interval ranged from 54 to 74 (see Table 2, Experiment 2). The percentage of trials in which B.R. produced a CR during conditioning (60.00%) again fell within this interval. It is clear from these data that B.R. was intact in this trace conditioning task and that advancing deterioration in clinical course was likely not responsible for her impaired performance in the temporal or simple two-tone discrimination learning paradigms. B.R.'s response onset latency (429.76 ms), CR peak latency (482.79 ms), and UR amplitude (3399.06 mV) all fell within the normal range. A possible impairment that was found in the CR amplitude measure during the initial testing session was replicated as, again, B.R.'s mean CR amplitude (2365.01 mV) fell below the normal confidence interval. B.R. displayed intact extinction. The mean percentage of trials in which B.R. produced a CR was 10.

## General Discussion

Cerebellar cortical atrophy caused a profound impairment in discrimination learning in Patient B.R. This impairment was found in the context of normal acquisition and extinction in delay and trace eyeblink conditioning. The inability to learn even simple discriminative responses was not expected a priori. Recall that we predicted only an impairment



*Figure 6.* A: Time course of the two trial types in the simple discrimination task. Trial Type 1 is a paired conditioned stimulus (CS)–unconditioned stimulus conditioning trial, and Trial Type 2 is a nonreinforced trial in which the CS is presented alone. B: Learning curve and time course for simple discrimination conditioning. The x-axis represents trial blocks consisting of five trials each; the y-axis represents the mean percentage of conditioned responses (CRs). NC = normal control participants; BR = Patient B.R.

in the timing aspects of temporal discrimination learning. The underlying rationale for this prediction was twofold. First, we predicted the timing impairment because B.R.'s cerebellar cortex was severely atrophied, and this region has been shown to be important in the expression of learned temporal discriminations (Perrett et al., 1993). Second, we did not predict a discrimination impairment because there is no indication in the classical conditioning literature to date that cerebellar lesions are associated with impaired discrimination.

The cerebellum has historically been regarded as a structure important for the coordination of motor movements. Clinical observations have shown that patients with cerebellar degeneration demonstrated deficits in coordination of extremity and voluntary movement, gait, posture, equilibrium, and speech (for a review, see Schmahmann, 1997). Experimental ablation work supported these clinical observations and suggested that the cerebellum was specifically not involved in functions such as sensation, perception, attention, learning, memory, mood, and language (Schmahmann, 1997). These findings appeared to rule out any cerebellar involvement in cognition.

More recent empirical work, however, challenges these findings and indicates that the cerebellum's role is not limited to purely motor functions but rather is involved in a range of higher order cognitive functions (for reviews, see Houk, Buckingham, & Barto, 1996; Parkins, 1997; Thach, 1996). For example, Thompson and his colleagues have done extensive work documenting the essential role of the cerebellum in all forms of classical eyeblink conditioning in rabbits (McCormick et al., 1981; L. T. Thompson, 1986, 1990). In addition, neuropsychological studies with humans conducted by Ivry and his colleagues have indicated that the cerebellum is critical for the normal operation of an internal timing mechanism (Ivry & Diener, 1991; Ivry & Keele, 1989; Ivry, Keele, & Diener, 1988). Also, Kim, Ugurbil, and Stick (1994) found that bilateral activation of the dentate nuclei was three to four times greater when participants attempted to solve a pegboard puzzle compared to activation during simple movements of pegs. Cerebellar involvement has also been documented during language generation tasks (Fiez, Petersen, Cheney, & Raichle, 1992; Raichle et al., 1994), imagined movement (Decety, Sjoeholm, Ryding,

Table 4  
Discrimination Delay Training

Participant	% CRs	CR onset latency (ms)	CR amplitude (mV)	UR amplitude (mV)
Patient B.R.:				
Discrimination				
Initial 60 trials				
Tone 1	6.67	506.50 <sup>a</sup>	2,591.80 <sup>a</sup>	2,385.10 <sup>a</sup>
Tone 2	6.67	441.00 <sup>a</sup>	3,601.16 <sup>a</sup>	1,416.31 <sup>a</sup>
Subsequent 60 trials				
Tone 1	23.33	444.60 <sup>a</sup>	3,557.42 <sup>a</sup>	2,793.50 <sup>a</sup>
Tone 2	13.33	432.50 <sup>a</sup>	3,625.85 <sup>a</sup>	2,208.96 <sup>a</sup>
NC: Discrimination (60 trials)				
Tone 1				
<i>M</i>	64.00	427.71	2,294.07	3,002.88
<i>SE</i>	9.15	25.82	211.46	196.75
<i>CI</i>	39–89	350–508	1,610–2,909	2,397–3,576
Tone 2				
<i>M</i>	25.00	471.16 <sup>a</sup>	1,943.79 <sup>a</sup>	1,169.53 <sup>a</sup>
<i>SE</i>	10.83	35.67	220.05	314.87
<i>CI</i>	0–55	392–585	1,468–2,752	586–2,361

Note. CR = conditioned response; UR = unconditioned response; NC = normal control participants; CI = confidence interval.

<sup>a</sup> Calculated with a small percentage of CRs.

& Stenberg, 1990; Ryding, Decety, Sjoeholm, & Stenberg, 1993), and sequencing (Fiez et al., 1992; Inhoff, Diener, Rafal, & Ivry, 1989).

In this context it is important to consider the existence of prominent projections between the cerebellum and the prefrontal cortex (Leiner & Leiner, 1997; Middleton & Stick, 1994) that may underlie the cerebellum's role in higher order cognitive function. For example, Blaxton et al. (1996) found enhanced blood flow to the frontal cortex during the first block of conditioning trials in a classical eyeblink conditioning study. The enhanced activity subsided as the eyeblink CR was acquired. These findings suggest that the neural connections between the prefrontal cortex and cerebellum may form a functional system involving the frontal lobes and the cerebellum that supports cognitive function and may be specifically important for learning in a classical conditioning paradigm.

There are also several reports suggesting a specific role of the cerebellum in discrimination learning using cognitive paradigms. For example, Parkins (1997) presented evidence to support the idea that the cerebellum is involved in "low-level" or "holistic" discriminations (compared to high-level or abstract discrimination performed by the cerebrum). Also, in a series of functional MRI studies it was found that dentate activation was greatly enhanced when sensory discriminations were required compared to when subjects received only passive stimulation (Gao et al., 1996; Parsons, Bower, Gao, & Xiong, 1997).

The present study extends these findings into the realm of classical discrimination learning. B.R. was clearly unable to acquire differential responding both in the case of a simple two-tone discrimination task and in a more complex temporal discrimination task. It is important to point out that B.R.'s performance in the temporal discrimination task was

not predicted on the basis of the findings from the rabbit study by Perrett, Ruiz, and Mauk (1993). However, it may be critically important that the rabbits in Perrett et al.'s study first learned the temporal discrimination (i.e., their CRs were appropriately timed as a function of the CSs) and then received aspiration lesions of the cerebellar cortex. Following the cerebellar lesions to the anterior lobe structures, both CSs elicited similarly timed CRs that peaked at very short latencies. Perrett et al. concluded that whereas the cerebellar nuclei may support the basic expression of responses, the "cerebellar cortex may mediate the temporal discriminations that are necessary for the learned timing of conditioned responses" (p. 1708; see also Mauk & Donegan, 1997). Patient B.R.'s cortical atrophy was extensive and included anterior lobe damage (see Figure 1). B.R.'s performance differed from the rabbits in Perrett et al.'s study in that B.R. did not demonstrate CR acquisition. The findings from the present study suggest that the cerebellar cortex not only might mediate the expression of learned temporal discriminations but may also underlie discrimination learning per se. Our data suggest that had the cerebellar cortical lesions in Perrett et al.'s study been done prior to temporal discrimination training the rabbits might not have shown even the inappropriately timed CRs. The short-latency CRs were presumably stored elsewhere than in the anterior lobe of the cerebellum.

It is necessary to also consider the underlying factors involved in B.R.'s normal acquisition in delay and trace conditioning. The current findings diverge from those of past studies examining delay eyeblink conditioning in that B.R. performed normally on both of these tasks. In contrast, a number of other studies using the delay paradigm have reported either elimination or an impairment in the performance of individuals with cerebellar lesions or atrophy

(Daum et al., 1993; Lye et al., 1988; McGlinchey-Berroth et al., 1995; Solomon et al., 1989; Topka et al., 1993; Woodruff-Pak et al., 1996). What can account for the differences in findings in these studies? The obvious candidate is the precise topography of damage within the cerebellum. Unfortunately, a number of factors have heretofore prevented a clear analysis of this issue. For example, there are some patients reported in the literature who have not had imaging studies and, for those who have, radiological reports typically cite only "general cerebellar atrophy." Consequently, many researchers are forced to speculate on the distribution of damage on the basis of the performance of their patients. For example, Daum et al. (1993) reported that their MRI findings were of insufficient resolution to allow a detailed analysis, but in the case of two patients who displayed some acquisition speculated that "cerebellar damage in patients 4 and 7 did not involve the areas that are critical for the mediation of classical conditioning" (p. 754). Similarly to patient B.R., the critical areas supporting delay and trace learning may be the deep nuclear regions.

An exception, however, is the study by Woodruff-Pak et al. (1996), who do appear to have clear radiological studies. They reported on three patients with specific reference to either sparing or damage to the deep nuclei. One patient (Patient 4) had a unilateral left cerebellar aneurysm including the deep nuclear region. Conditioning in the ipsilateral eye was eliminated and in the contralesional eye was only 28%. A second unilateral patient (Patient 2) had an infarct that was just superior to the deep nuclear region. This patient produced 12% CRs in the ipsilateral eye and 74% in the contralesional eye. A final patient (Patient 14) had a small right cerebellar infarct that was lateral in the superior hemisphere. This patient performed at normal levels: 75% ipsilateral and 69% contralesional. At first glance, these findings appear contradictory but may be understood on the basis of individual differences in neuropathology. In Patient 4 a bilateral deficit was observed following a unilateral aneurysm. It is possible, however, that the aneurysm was large enough to cause a mass effect that impaired performance bilaterally. Patient 2 follows the expected pattern based on an ipsilateral impairment. Patient 14, whose deep nuclei were clearly spared, performed normally in both eyes. This one patient, therefore, is the only other patient, in addition to B.R., reported in the literature who has cerebellar damage that spares the deep nuclei and conditions at normal levels in the delay conditioning task. It is notable, however, that Patient 14's lesion was very small and located in the superior right hemisphere. Thus, it is unclear from this patient whether it was the particular lesion site or simply the small size of the lesion that allowed for normal performance. In contrast, B.R.'s cortical atrophy was very extensive, thus providing greater confidence that conditioning was most likely supported by intact deep cerebellar nuclei.

The possible contribution of a voluntary component in B.R.'s CRs should also be considered. However, a number of factors suggest that this was not a primary mediator in her intact performance on delay and trace conditioning tasks. For example, recall that, in delay and trace conditioning,

B.R.'s acquisition was actually slower than the normal participants' acquisition. Also, B.R. was not aware of the relationship between stimuli in the delay conditioning task, and her awareness was not as explicit as the normal participants' was in the trace conditioning task. In addition, it is unclear why voluntary responding would have contributed to the conditioning performance in delay and trace tasks but not in the temporal and simple discrimination tasks. If voluntary responding was a contributing factor, one would have expected to see it in all of these tasks, not just in the delay and trace conditioning tasks. We suggest that B.R.'s responses instead appear to be primarily mediated by intact cerebellar deep nuclei circuitry. However, a role of voluntary responding in the production of CRs remains plausible and should be addressed in future studies.

A final issue is the finding that the amplitude of B.R.'s CRs varied as a function of task. In particular, significantly higher amplitudes were found in the delay conditioning task, whereas lower amplitudes (significant in the right) were found in the trace conditioning task. One possible explanation for this finding involves the increase in temporal demands in the trace conditioning task. However, Yeo and Hardiman (1992) reported depressed amplitudes of CRs in their delay conditioning task after cerebellar cortical lesions in rabbits. The locus of these alterations was likely the cerebellar cortex, as others have suggested that it may participate in the modulation of CRs. Specifically, on the basis of findings from a discrimination reversal task in rabbits, Gould and Steinmetz (1994) suggested that the cerebellar cortex plays a greater role in general response modulation than does the interpositus nucleus by determining features of responding such as response timing or response amplitude. Precisely why we found enhanced CR amplitude during delay conditioning but reduced CR amplitude during trace conditioning, while Yeo and Hardiman found decreased CRs during delay, is not clear and is a subject for future study.

The findings from this study suggest that (a) bilateral cerebellar cortical atrophy disrupts discrimination learning in classical eyeblink conditioning, (b) atrophy limited to the cerebellar cortex (that does not extend into the deep nuclei) does not appear to impair simple associative learning in the delay and trace conditioning tasks, and (c) the cerebellar cortex appears to be involved in modulating the amplitude of CRs. These findings provide support for the notion that the cerebellum plays an important role in human cognitive function. However, there are limitations to our study that must be addressed in future research. First, our findings are based on the extensive study of only one patient, and replication in a larger group study is clearly warranted. A related second issue is our direct comparisons between Patient B.R. and the other cases in the literature, which include a mixture of patients with discrete lesions and patients with more diffuse atrophy. It is unclear at this time whether differences in pathophysiology produce functionally important differences in performance in classical eyeblink conditioning. Larger sample sizes and group studies are necessary to assess this important issue. Last, the possible contribution of a functional system involving the fron-

tal lobes and the cerebellum in discrimination learning could not be adequately addressed in this study. Radiological evidence demonstrated that B.R.'s generalized cerebral atrophy included the frontal lobes. Future studies should aim at examining learning in additional cerebellar patients (with clearly delineated distributions of damage), further defining the role of specific regions within the cerebellum in cognition and, finally, examining the nature of the interactions between the cerebellum and other regions of the brain (i.e., hippocampus and temporal lobes, prefrontal and association cortices). Findings from such studies would facilitate the formation of hypotheses regarding the precise role of the cerebellum in learning and cognition.

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