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Functional anatomy of human eyeblink conditioning determined with regional cerebral glucose metabolism and positron-emission tomography

(classical conditioning/cerebellum/hippocampus/basal ganglia/2-deoxyglucose)

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ABSTRACT **Relative cerebral glucose metabolism was examined with positron-emission tomography (PET) as a measure of neuronal activation during performance of the classically conditioned eyeblink response in 12 young adult subjects. Each subject received three sessions: (*i*) a control session with PET scan in which unpaired presentations of the tone conditioned stimulus and corneal airpuff unconditioned stimulus were administered, (*ii*) a paired training session to allow associative learning to occur, and (*iii*) a paired test session with PET scan. Brain regions exhibiting learning-related activation were identified as those areas that showed significant differences in glucose metabolism between the unpaired control condition and well-trained state in the 9 subjects who met the learning criterion. Areas showing significant activation included bilateral sites in the inferior cerebellar cortex/deep nuclei, anterior cerebellar vermis, contralateral cerebellar cortex and pontine tegmentum, ipsilateral inferior thalamus/red nucleus, ipsilateral hippocampal formation, ipsilateral lateral temporal cortex, and bilateral ventral striatum. Among all subjects, including those who did not meet the learning criterion, metabolic changes in ipsilateral cerebellar nuclei, bilateral cerebellar cortex, anterior vermis, contralateral pontine tegmentum, ipsilateral hippocampal formation, and bilateral striatum correlated with degree of learning. The localization to cerebellum and its associated brainstem circuitry is consistent with neurobiological studies in the rabbit model of eyeblink classical conditioning and neuropsychological studies in brain-damaged humans. In addition, these data support a role for the hippocampus in conditioning and suggest that the ventral striatum may also be involved.**

Eyeblink conditioning is a basic form of associative learning that has been studied extensively in humans since the 1930s. Animal models of this form of conditioning have demonstrated close behavioral parallels with human conditioning, lending support to the hypothesis that the learning shares common neurobiological substrates in humans and other mammals (1). Eyeblink conditioning is well-suited for neurobiological analyses because the use of appropriate unpaired control procedures can help distinguish between areas of the brain that are responding to the sensory stimuli or the motor response and those that are selectively activated under paired learning conditions. This feature makes the paradigm an ideal candidate for neurobiological analysis in humans using positron-emission tomography (PET) to identify regions of the brain that are specifically activated under paired training conditions relative to unpaired control procedures.

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Although eyeblink conditioning is a seemingly simple form of learning, under normal conditions it appears to involve the interaction of diverse brain systems. Neurobiological studies (conducted primarily in rabbits) have identified the cerebellum and its brainstem connections as essential components of the eyeblink conditioning circuit (see ref. 2 for review), with conditioned stimulus (CS) and unconditioned stimulus (US) information hypothesized to converge in cerebellar cortex and interpositus nucleus (3).

Though not essential for acquisition and retention, some forebrain areas, such as the hippocampus, also show learning-related changes in neural activity and may play a modulatory role in learning (4–6). In addition, lesions of the hippocampus, which do not interfere with acquisition of simple delay conditioning, do interfere with context conditioning and markedly impair learning in more complex paradigms (7–10). Other forebrain areas, including basal ganglia, neocortex, and septal nuclei, have been less extensively studied but may also play a role in eyeblink conditioning (11–16).

Human lesion studies are consistent with what is known about the organization of eyeblink conditioning in the rabbit brain. Several studies (17–21) have found that individuals with cerebellar damage show impaired eyeblink conditioning largely in the absence of motor deficits interfering with performance of unconditioned eyeblinks. Studies of medial temporal lobectomy patients have found that such subjects are able to learn the simple delay conditioned response (CR) but are impaired with some complex conditioning paradigms (22, 23).

In the present study we sought to determine whether cerebellar and hippocampal brain areas known to be involved in rabbit eyeblink conditioning are also active during human eyeblink conditioning. In addition, we were interested in determining what other regions of the brain might be specifically activated by the conditioning. PET imaging was used to examine the functional anatomy of human eyeblink conditioning. Relative cerebral glucose metabolism (relCMRglc) was examined using 2-[^{18}F]fluorodeoxyglucose (FDG) as a measure of local neuronal activity under an unpaired control condition and a paired training condition after the subjects had learned the CR. Differences between the two scans were calculated to identify regions with learning-related changes of brain activity. In an exploratory analysis, areas whose change in metabolic activity was significantly correlated with degree of learning were also identified.

METHODS

Subjects. Twelve normal volunteers recruited through campus newspaper advertisements completed all phases of the experiment. Exclusionary criteria included a history of neu-

Abbreviations: relCMRglc, relative cerebral metabolic rate for glucose; PET, positron-emission tomography; FDG, 2-[^{18}F]fluorodeoxyglucose; CS, conditioned stimulus; US, unconditioned stimulus; rCBF, regional cerebral blood flow; CR, conditioned response.

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rologic or psychiatric disorders, recent drug use, or pregnancy. The subjects ranged in age from 18 to 27 yr (mean ± SD, 23 ± 4 yr), were all right-handed, and included five males and seven females. All subjects gave informed consent in accordance with the University of Southern California Institutional Review Board.

Eyeblink Conditioning. Subjects were seated in a chair in the PET scanning room and fit with a lightweight adjustable plastic headgear that held an airpuff nozzle and a noninvasive infrared light-emitting diode and detector assembly for measuring closure of the right eyelid. A 1-kHz, 85-decibel sound pressure level tone of 600 ms duration delivered through speakers placed on either side of the subject's head served as the CS. The US was a 100-ms puff of medical grade air to the right cornea, measuring 5 psi (1 psi = 6.89 kPa) at the source (with the apparatus used, this intensity reliably elicited blinks but was not reported to be noxious). Delivery of the stimuli and on-line collection of digitized eyeblink data were performed by an IBM personal computer and custom interface (24). Blinks of 0.5 mm or greater were scored as responses. CRs were those responses occurring between 150 ms after tone onset and US onset (25). Similarly, on unpaired trials, responses occurring between 150 and 500 ms after tone onset were scored as pseudoCRs. Trials with responses occurring in the 250 ms preceding or the 25 ms following CS onset were scored as bad trials and excluded from analysis.

On the first day of training, stimuli were given in a random unpaired manner as a control condition to rule out nonassociative effects of stimulus exposure and motor performance on relCMRglc. Eight blocks of 19 trials each (10 tone alone and 9 airpuff alone) were given in a fixed pseudorandom sequence at an average intertrial interval of 14 s (range, 0–28 s). Delivery of stimuli was paused prior to the last 6 blocks during preparation of the subject's arm for i.v. injection of 7.5 mCi of FDG (1 Ci = 37 GBq). Stimuli were resumed simultaneous with FDG injection and continued for 6 blocks (30 min) through the FDG uptake period. Following the final 30 min of training, subjects were placed in the PET scanner for 30 min of image acquisition (see below).

On the second day of the experiment (1–6 days later), subjects were given 1 hr of paired training to allow learning of the CR. The third experimental day (occurring within 2–7 days of the first experimental day) was the paired test session. The protocol was identical to day 1, except that paired tone–airpuff presentations were administered. On both paired training days, 10–12 blocks of 10 trials each were administered (1 tone alone and 9 paired trials; interstimulus interval, 500 ms) at an average intertrial interval of 28 s (range, 23–33 s). FDG (7.5 mCi) was injected prior to the last 6 blocks of training on day 3. Thus, during the FDG uptake period on the paired and unpaired days, subjects received the same number of tone and airpuff presentations in the same time period, but with no CS–US contingency on the unpaired day.

Throughout all phases of the experiment the subjects viewed a silent videotape of cartoons to help keep them awake and alert (26). No subject saw the same video segment twice, and subjects did not all see the video segments in the same order. Subjects were told that they would feel mild puffs of air to their eyes and hear occasional tones and were instructed to relax and let their natural reactions take over as they watched the videotape.

PET Imaging. Following behavioral data collection, the subjects were placed on the tomograph bed and positioned in the Siemens/CTI 953/A-16 PET scanner so that the tomographic plane of section was parallel to the canthomeatal line. Head immobilization was achieved with a custom-built Plexiglas device (27). After a 2-min image to check head position, counts were acquired for 30 min for final image reconstruction. Geometric attenuation correction was performed. The PET scanner collects 31 contiguous planes of data that are 3.375 mm thick, with nominal in-plane resolution of 5 mm and transaxial resolution of 4 mm full width at half-maximum.

Image Analysis. Metabolic images were aligned within subjects using an automated registration algorithm (28). Images from each subject were then transformed into the stereotaxic coordinate space of Talairach and Tournoux (29) using an automated affine transformation of 12 parameters (30, 31). After coregistration of all images to the Talairach coordinate space, the field of view for which data were available in all subjects extended from approximately +10 to −60 mm relative to the anterior–posterior commissural axis. Data from each individual were rescaled using pairwise global normalization between the two scans. Previous studies of metabolic imaging have shown that although intrasubject global metabolism can vary on the order of 10% from day to day, regional day-to-day differences are negligible after accounting for this global change (32). Metabolic values were not weighted as a function of time after FDG administration. Images were smoothed to a final image resolution of 18 mm full width at half-maximum. After smoothing, the number of gray matter resolving elements was ≈50 (33).

Learning-related changes of relCMRglc were determined using paired t tests on a pixel-by-pixel basis comparing the paired scan with the unpaired scan for all subjects who met a learning criterion of 50% CRs ($n = 9$). Pixels with a significance beyond the statistical threshold of $P < 0.01$ (two-tailed) were displayed in pseudocolor onto an anatomic reference atlas of 15 normal magnetic resonance images aligned in the Talairach space using the same registration technique (31). The maximum within each site was visually identified, and coordinates were determined with respect to the anterior commissure at the midline. In addition, pixel-by-pixel Pearson product–moment correlation coefficients were calculated correlating percentage change in relCMRglc between the paired and unpaired day with the behavioral difference in responding to the tone on the paired vs. unpaired day. Pixels with significance beyond a threshold of $P < 0.05$ were displayed in pseudocolor on the reference atlas. All subjects, including those who did not meet the behavioral criterion of 50% CRs, were included in this analysis.

RESULTS

Behavior. Three of the subjects did not reach a learning criterion of at least 50% CRs during the uptake period on the paired day and were excluded from the paired t test analysis. Behavioral responses of the remaining nine subjects to the tone during the 6 blocks of trials administered during the tracer uptake period on the unpaired and paired days are shown in Fig. 1. The frequency of bad trials, which can be taken as an approximation of spontaneous blink rate, is also depicted. No difference was seen between bad trial frequency and responding to the tone on the unpaired day. Responding to the tone on the paired day was significantly greater than responding on the unpaired day [$t(8) = 11.6$, $P < 0.00001$].

Data for the three subjects who did not reach the learning criterion are presented in Fig. 1*B*. No significant difference was found between their responding on the paired and unpaired days, confirming the absence of significant conditioning in those subjects. Although there were no obvious differences between the subjects who did and did not condition well, boredom, the relatively stressful scanning environment, or prior exposure to even random unpaired stimuli might have contributed to poor conditioning.

Learning-Related Changes. Table 1 depicts the sites and coordinates of brain areas that were significantly more active on the paired day than on the unpaired day. No areas were identified that were significantly less active on the paired day. As shown in Fig. 2, areas of significant activation include several sites in the cerebellum bilaterally, a location on the border of the ipsilateral midbrain and inferior thalamus, and the ipsilateral hippocampal formation. Bilateral activation was

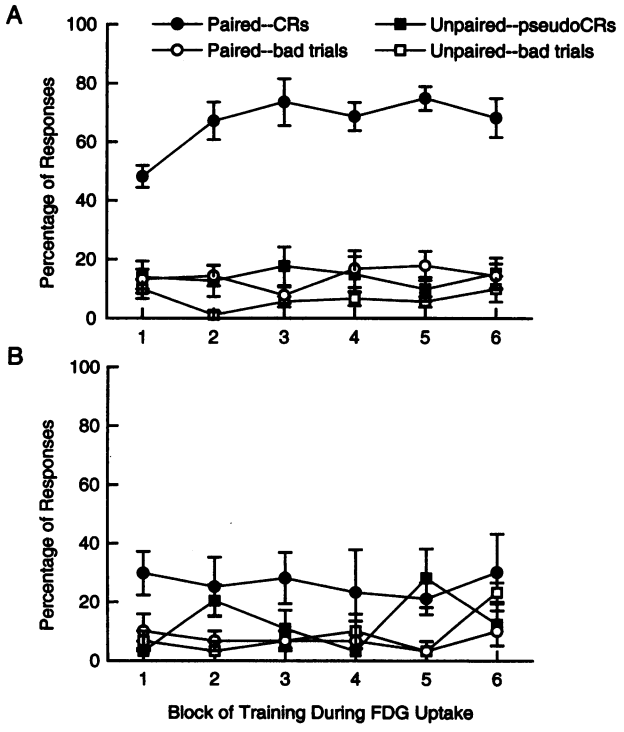

FIG. 1. Percentage responding to the tone (closed symbols) during the FDG uptake period on the unpaired and paired training days. Open symbols show bad trial frequency, an approximation of spontaneous blink rate. Circles, responses on the paired day; squares, responses on the unpaired day. Data are presented as mean ± SE. (*A*) Response rates for the nine subjects who met the learning criterion. (*B*) Response rates for the three subjects who did not meet the learning criterion.

seen in the ventral striatum. Cortical sites included the right middle temporal gyrus and left occipitotemporal fissure.

Correlations with Learning. Because of constraints on the amount of radiation individual subjects could receive, only two PET scans could be obtained from each subject. Thus, it is possible that changes in activation seen between the 2 days were unrelated to learning, *per se*, but might be related to nonspecific aspects of the training protocol, such as adaptation to the testing situation or alterations in attention or anxiety. Therefore, in an exploratory analysis, we took advantage of the rather large range of conditioning performance exhibited by our entire group of 12 subjects by performing pixel-by-pixel

FIG. 2. Functional localization of human eyeblink conditioning (paired vs. unpaired scan comparison). Metabolic changes with a significance of $P < 0.01$ are shown in white, superimposed on an anatomic magnetic resonance imaging atlas of normal subjects fit into the same stereotaxic space as the PET images. The left side of each image is the subject's right (ipsilateral to the trained eye). (*Upper Left*) Midsagittal section showing significant areas in the anterior cerebellar vermis, inferior thalamus/red nucleus, and ventral striatum. (*Lower Left*) Transverse section at −12 mm relative to the anterior–posterior commissural axis showing the right middle temporal gyrus, right hippocampal formation, anterior cerebellar vermis, and left cerebellar cortex sites. Coronal sections are at −53, −40, −27, and 13 mm relative to the anterior commissure. Areas of significant change include the right inferior cerebellum (−53), anterior cerebellar vermis (−53), right middle temporal gyrus (−53), left cerebellar cortex and left deep nuclei/pontine tegmentum (−40), right hippocampal formation (−27), right inferior thalamus/red nucleus (−27), and bilateral ventral striatum (13).

Pearson product–moment correlations of relative percentage changes in relCMRglc with the increase in responses to the tone on the paired vs. the unpaired day. Table 2 and Fig. 3 depict regions in which significant correlations were found. Areas that were significantly positively correlated with degree of learning included bilateral cerebellar sites, including the ipsilateral deep nuclei and cerebellar cortex, ipsilateral midbrain, bilateral ventral striatum, and contralateral occipitotemporal fissure. In addition, metabolic activity of the ipsilateral hippocampal formation was weakly correlated ($r = 0.58$, $P = 0.047$) with degree of learning. Areas that were significantly negatively correlated included sites in the contralateral occipitotemporal fissure, superior and middle temporal gyri, and ipsilateral posterior inferior cerebellum.

DISCUSSION

These data support an important role for the cerebellum in classical conditioning of the human eyeblink response. Re-

Table 1. Brain regions showing significant increases in activity in the paired vs. unpaired scan comparison

Brain region	Talairach coordinate, mm			*t*	*P*
	x	*y*	*z*		
Cerebellar site					
Right inferior cerebellum	−16	−47	−36	4.08	0.005
Anterior cerebellar vermis	−2	−53	−4	4.68	0.005
Left cerebellar cortex	23	−41	−12	5.97	0.0005
Left cerebellar deep nuclei or pontine tegmentum	6	−40	−20	5.40	0.001
Left inferior cerebellum	23	−48	−32	3.86	0.005
Other brain areas					
Right inferior thalamus/red nucleus	−8	−17	0	5.04	0.001
Right hippocampal formation	−30	−10	−10	3.94	0.005
Right ventral striatum	−9	14	−6	5.60	0.0005
Left ventral striatum	17	12	−6	5.21	0.001
Right middle temporal gyrus	−55	−1	−14	3.93	0.005
Left occipitotemporal fissure	39	−32	−6	4.40	0.005

Only the subjects who met a learning criterion of 50% CRs ($n = 9$) are included.

gions of the cerebellum, including the deep nuclei and cortex bilaterally, were significantly more active in the trained state compared to the unpaired control condition. More importantly, the relative change in metabolic activity in several cerebellar sites, including the ipsilateral deep nuclei and cerebellar cortex, correlated significantly with the increase in behavioral responses to the tone in the paired condition relative to the unpaired condition, suggesting that these changes are specifically related to learning, rather than to nonspecific aspects of the experimental protocol. These data are consistent with human lesion studies that have demonstrated impaired conditioning in patients with cerebellar damage (17–21) and with stimulation, recording, and lesion studies in the rabbit that suggest an essential role for the ipsilateral cerebellum in eyeblink conditioning (34–37). Whether the changes in metabolic activity represent long-term depression, long-term potentiation, or some other mechanism of plasticity cannot be determined, because metabolic imaging measures primarily changes of local synaptic activity from both excitatory and inhibitory connections (38). What is clear from these PET data, however, is that there is some overall change of synaptic activity related to learning in these cerebellar areas.

Increased metabolic activity was also seen in the cerebellum contralateral to the trained eye, despite the ipsilateral relationship of the cerebellum to the body. Similarly, the inferior thalamus/red nucleus ipsilateral to the trained eye (and hence opposite to the expected side) showed increased activity in the paired condition. It is possible that such activation is related to the bilateral CRs that occur to some degree in rabbits and to a much larger degree in humans (unpublished observations); activation in the contralateral cerebellum has also been observed in recording studies in rabbit cerebellum during eyeblink conditioning, suggesting that some degree of plasticity may occur in the contralateral cerebellum even when the US is applied unilaterally (39). In addition, changes of activity correlated with learning were seen in anterior regions of cerebellar cortex, which may be particularly important for adaptive timing of CRs (40, 41).

An important role for the hippocampus was also confirmed by the finding that the ipsilateral hippocampal formation was significantly more active in the trained state compared to the unpaired control condition, consistent with numerous studies in the rabbit (4, 7). In addition, activation of a smaller region of the ipsilateral hippocampal formation was weakly correlated ($r = 0.58$, $P = 0.047$) with degree of learning. These data suggest that even in the simple delay classical conditioning paradigm, there is the opportunity for interaction with the declarative memory system.

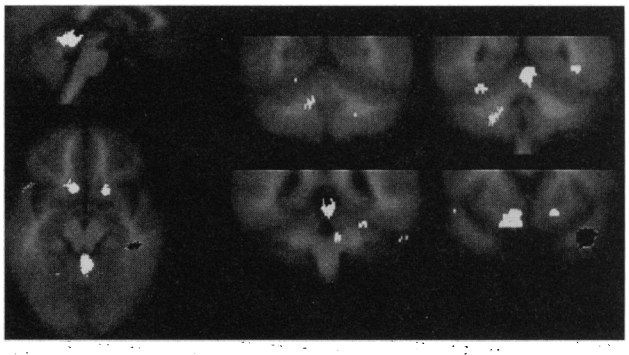

FIG. 3. Correlation of metabolic changes with performance. Areas whose relative metabolic change is significantly ($P < 0.05$) positively correlated with learning performance are displayed in white; negative correlations are displayed in black. The left side of each image is the subject's right. (*Upper Left*) Midsagittal section showing positive correlation in anterior cerebellar vermis. (*Lower Left*) Transverse section at −6 mm relative to the anterior–posterior commissural axis showing positive correlations in the ventral striatum bilaterally, anterior cerebellar vermis, and right cerebellar cortex, and negative correlations in the left occipitotemporal fissure. Coronal sections are at −59, −53, −41, and 13 mm relative to the anterior commissure. Positively correlated regions include the right cerebellar deep nuclei and cerebellar cortex (−59 and −53), left inferior cerebellum/deep nuclei (−59), anterior cerebellar vermis (−53 and −41), left occipitotemporal fissure (−53), left pontine tegmentum and cerebellar cortex (−41), and bilateral ventral striatum (13). Negative correlations include the left superior/middle temporal gyri (13).

One of the most striking results was the activation in the ventral striatum bilaterally, which was significantly correlated with learning. Although some lesion and recording studies in the rabbit have suggested striatal involvement in eyeblink conditioning (14, 15), the nature of that involvement has not been clarified and may be a fruitful area for investigation in rabbits and humans. However, the striatum has been implicated as critical for other procedural learning tasks in humans and other animals (42–45). Spatial resolution was insufficient to determine whether the areas of significant correlation included the basal forebrain region as well as the ventral striatum. Involvement of cholinergic basal forebrain areas would be consistent with neuromodulatory effects on conditioning (12, 46).

Areas of learning-related changes in activity in the ipsilateral striatum and cerebellar cortex were similar to those

Table 2. Brain regions showing significant correlation with learning

Brain region	Talairach coordinate, mm			*r*	*P*
	x	*y*	*z*		
Positive correlation					
Right cerebellar deep nuclei	−14	−59	−22	0.63	0.03
Right cerebellar cortex	−30	−53	−12	0.63	0.03
Inferior right cerebellar cortex	−22	−53	−32	0.60	0.04
Anterior cerebellar vermis	0	−47	−2	0.82	0.001
Left cerebellar cortex	25	−44	−14	0.60	0.04
Left inferior cerebellum/deep nuclei	15	−62	−30	0.59	0.04
Left pontine tegmentum	6	−41	−22	0.63	0.03
Right midbrain	−9	−30	0	0.63	0.03
Right gyrus rectus/ventral striatum	−12	11	−10	0.78	0.003
Left ventral striatum	17	12	−6	0.78	0.003
Left occipitotemporal fissure	36	−54	2	0.67	0.02
Negative correlation					
Left superior/middle temporal gyri	41	14	−22	−0.73	0.007
Right posterior inferior cerebellum	−18	−85	−32	−0.64	0.03
Left occipitotemporal fissure	40	−32	−6	−0.64	0.03

All subjects, including those that did not meet a learning criterion of 50% CRs ($n = 12$), are included.

reported in two recent PET studies of human eyeblink conditioning (47, 48) in which regional cerebral blood flow (rCBF) was measured during acquisition. However, the direction of change was different in the studies: glucose metabolism increased in the two areas with paired training, whereas rCBF increased in the striatum in one study and decreased in the other, and blood flow decreased in the cerebellar cortex in both rCBF studies. Additional studies are clearly required to better interpret the functional significance of increased vs. decreased blood flow or metabolic activity with learning. However, some additional differences between the studies that may be relevant include the duty cycle or stimulus density [≈2 or 3 blinks per scan in the Molchan *et al.* (47) study vs. 60 blinks per scan in the current study] and the fact that both rCBF studies included scanning over early periods of acquisition, whereas our study scanned after subjects had received much more training. Thus, experimental differences could be related to differences of tracers or training protocols or differences between acquisition and retention of conditioned responses.

Neocortical areas showing increased metabolic activity with learning were identified in the temporal lobes and occipitotemporal region, which also contained sites of negative correlation with learning. The functional contribution of these brain regions to the task remains unknown, however. Neocortical sites that have been implicated in the other PET studies include primary auditory cortex and posterior cingulate cortex (47) and bilateral prefrontal cortex (48). Thus, it is also important to note that conditioning-related changes in metabolic activity may be present in brain structures above the level of mid-thalamus, which were outside the field of view of our study.

One possibility to consider in interpretation of these PET data is that in addition to acquisition of the eyeblink response, significant autonomic conditioning may also have occurred during the experiment. Although a 500-ms interstimulus interval is not optimal for autonomic conditioning, Durkin *et al.* (49) have shown that significant heart rate conditioning does occur using stimuli and timing parameters similar to those employed in the current experiment. Thus, it is possible that some of the areas that were significantly activated on the paired day relative to the unpaired day represent synaptic activity related to autonomic rather than somatomotor conditioning. Although autonomic responses were not measured in the current study, in future studies it would be instructive to examine correlations of changes in metabolic activity with performance on both types of conditioning tasks to further delineate the commonalities and differences in their neurobiological substrates.

In summary, the current study provides functional localization data from normal subjects, which, together with human lesion data and with results obtained from animal studies, provide convergent evidence of involvement of cerebellar and hippocampal systems in basic associative learning of the classically conditioned eyeblink response. In addition, involvement of the ventral striatum is also suggested by the current data and may be an important area for research in both humans and rabbits.

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