Double Dissociation of Conditioning and Declarative Knowledge Relative to the Amygdala and Hippocampus in Humans

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Science, New Series, Vol. 269, No. 5227 (Aug. 25, 1995), 1115-1118.

Stable URL:
http://links.jstor.org/sici?sici=0036-8075%2819950825%293%3A269%3A5227%3C1115%3ADDOCAD%3E2.0.CO%3B2-I

Science is currently published by American Association for the Advancement of Science.

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5. Blocks were spaced at least 1 km apart. Within each block, we surveyed checkerboard grids of 20-by-20 points with 30.5-m spacing and used these grids for snowshoe hare live trapping. Two experimental areas were provided with supplemental food (commercial rabbit chow, 16% protein) year round. In the summer of 1987, we built one electric fence around 1 km^2 to exclude mammalian predators, and over the following year we covered 10 ha with monofilament to reduce avian predation. The monofilament was never effective in preventing avian predation inside the electric fences, and consequently we did not rely on it as a part of the treatment. In the summer of 1988, we built a second electric fence around 1 km^2 to use for the combined predator reduction–food addition treatment. We modified the design of the electric fences in 1988 to make them more effective, and since then they have worked effectively to prevent mammalian predators from entering the area. The fences are permeable to snowshoe hares. We could not replicate either the predator reduction or the predator reduction–food addition treatment because of maintenance costs and the difficulty of maintaining electric fences in the Yukon winter with −45°C temperatures. The fences had to be checked every day during winter. From 1976 to 1985, we trapped hares in six areas within the main study region and found that their population trajectories were very similar (*3*). We thus have no reason to suspect strong area effects on the unreplicated predator reduction plots.
6. We used three control areas but were not able to trap hares in all of them every year. We have more detailed data on hares from control area 1. The three control areas had quite different histories during the increase phase from 1986 to 1988. Control area 3 reached its greatest hare density in 1988 and remained at a plateau until 1990. Control area 2 reached its peak density in 1990, and control area 1 reached its peak in 1989. By the late peak in 1990 and during the decline phase, the control areas were much more similar to each other in hare densities.
7. The electric fence was 10-stranded, 2.2 m in height, and carried 8600 V. Snow tracking of mammalian predators meeting the fence illustrated its effectiveness. We excluded mammalian predators virtually continuously from January 1989 onward. Our attempts to use monofilament fishing line as a deterrent to birds of prey was largely ineffective because ice formation and snow accumulation on the lines in winter caused them to break or collapse to the ground. We used monofilament on 10 ha of the predator exclosure but did not attempt to use it on the combination treatment area. The predator exclosures thus were mammalian predator exclosures and were still subject to avian predation.
8. We fertilized two 1-km^2 blocks of forest with commercial fertilizer. In May 1987, we used ammonium nitrate at 25 g/m^2. In May 1988, we switched to NPK fertilizer and used 17.5 g of N/m^2, 5 g of P/m^2, and 2.5 g of K/m^2. In 1989, we used half this amount, and in the years 1990 to 1994 we used the full amount as in 1988. The fertilizer was spread aerially and we did ground checks to make sure it was uniformly spread. We do not present the data here to show the plant growth responses, but all elements of the flora responded dramatically to the added nutrients (C. J. Krebs *et al.*, unpublished data).
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6 March 1995; accepted 20 June 1995

Double Dissociation of Conditioning and Declarative Knowledge Relative to the Amygdala and Hippocampus in Humans

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A patient with selective bilateral damage to the amygdala did not acquire conditioned autonomic responses to visual or auditory stimuli but did acquire the declarative facts about which visual or auditory stimuli were paired with the unconditioned stimulus. By contrast, a patient with selective bilateral damage to the hippocampus failed to acquire the facts but did acquire the conditioning. Finally, a patient with bilateral damage to both amygdala and hippocampal formation acquired neither the conditioning nor the facts. These findings demonstrate a double dissociation of conditioning and declarative knowledge relative to the human amygdala and hippocampus.

Studies in animals have established that the amygdala is critical for emotional conditioning (*1*), whereas several human and nonhuman primate studies have established that the hippocampus and surrounding regions are necessary for establishing declarative knowledge (*2*). Because of the rarity of patients with selective bilateral damage restricted to either the amygdala or hippocampus, the exact roles of these structures in emotional and declarative learning have not been established clearly for humans (*3*). Here, we report the relative contributions of the amygdala and hippocampus to emotional conditioning and to the establishment of declarative knowledge in humans. We studied three people with distinct brain lesions: SM046 had bilateral destruction of the amygdala, but bilaterally intact hippocampi; WC1606 had bilateral hippocampal damage, but bilaterally intact amygdalae; and RH1951 had bilateral damage to both hippocampus and amygdala (*4*) (Table 1 and Fig. 1). Four normal participants of comparable age and education served as controls.

Two conditioning experiments were carried out. The first, a visual-auditory conditioning experiment, used monochrome slides as the conditioned stimuli (CS) and a startlingly loud sound (a boat horn delivered at 100 dB) as the unconditioned stimulus (US). The second, an auditory-auditory conditioning experiment, used computer-generated tones as the CS (the US was the same as in the visual-auditory experiment). In both experiments, the skin conductance response (SCR) was the dependent measure of autonomic response (*5*). Each conditioning experiment was performed three times in SM046 and twice in WC1606 and

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RH1951. For each participant one visual-auditory and one auditory-auditory conditioning experiment were carried out on the same day, separated by 1 to 2 hours. Conditioning experiments were repeated on the following day (or days), about 24 hours after the first set of experiments. The order of visual-auditory (slide-sound) and auditory-auditory (tone-sound) conditioning was counterbalanced across the conditioning experiments (6).

The conditioning protocol consisted of three phases. In the habituation phase, slides of four different colors (green, blue, yellow, and red) were presented repeatedly to the participant (6 to 12 times) in an irregular order, until the SCRs to these slides approached zero (<0.05 μS). In the conditioning phase, 26 slides of the same four colors were presented in an irregular order. Six of the slides were blue and were followed immediately by a startling sound (US) of 1-s duration. There were six further presentations of a blue slide not followed by the US. Thus, only the blue slides served as the CS. The remainder of the slides (non-CS) were 14 red, green, or yellow slides never paired with the US (7). Finally, in the extinction

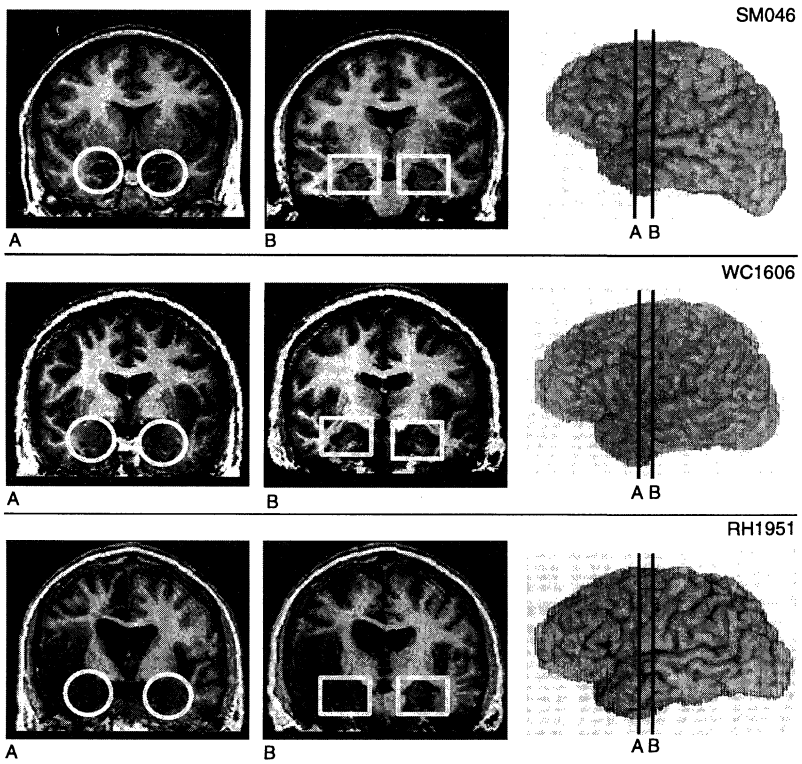

Fig. 1. Neuroanatomical findings in the three experimental participants. (**A**) and (**B**) show coronal sections through the amygdala and hippocampus, respectively, taken from the three-dimensional reconstruction of each participant's brain. The reconstruction was based on magnetic resonance data and obtained with Brainvox (*17*). The region of the amygdala is highlighted by white circles and the region of the hippocampus by white rectangles. SM046 has extensive bilateral damage to the amygdala, but not to the hippocampus. Detailed anatomical analyses of her magnetic resonance imaging (MRI) scans are presented in (*13*). The damage begins in the rostral portion of the amygdala and extends throughout the caudal portion. Damage to the left amygdala is somewhat more extensive than damage to the right amygdala, but considering the connectivity and pathology of the amygdala, it is reasonable to conclude that both are severely dysfunctional as a result of the damage (*13*). The most anterior sector of the entorhinal cortex shows some damage, but there is no indication that this makes any contribution to her memory profile. No other areas of damage are detected. Specifically, the hippocampus is intact bilaterally. WC1606 has bilateral damage to the hippocampus proper, but not to the amygdala. We base this conclusion on several lines of evidence: (i) The mechanism of injury (ischemia-anoxia), which is known to produce damage to CA1 neurons in the hippocampus (*3*); (ii) the neuropsychological outcome (a declarative learning defect); and (iii) a comparison of the hippocampal volumes of WC1606 to those of two age-matched controls [one with brain damage (a stroke in the occipital lobe) and one without] with the use of chronic neuroanatomical data—that is, neuroimaging (MR) data collected several years after the onset of the lesion. The results of this analysis indicated that the left and right hippocampi of WC1606 are reduced by about 33% each, relative to the two control subjects. A similar analysis was conducted on the amygdala volumes of WC1606 and the controls. The results indicated that there is no reduction in the volumes of WC1606's amygdalae. In short, the circumstances of his injury, and the neuroimaging and neuropsychological evidence, are suggestive of hippocampal, but not amygdala, damage. RH1951 has extensive bilateral damage to the amygdala, hippocampus proper, and surrounding cortices. The amygdalae and entorhinal cortices are destroyed bilaterally. The hippocampus is destroyed on the right and severely damaged on the left.

Table 1. Demographic and neuropsychological data for experimental participants. Underlined scores are defective.

Characteristic	Participant		
	SM046	WC1606	RH1951
Sex	Female	Male	Male
Age (years)	30	47	42
Handedness	Right	Right	Right
Years of education	12	12	16
Verbal IQ*	86	83	110
Performance IQ*	90	80	116
General memory index†	89	71	75
Delayed memory index†	88	52	53
Speech	Normal	Normal	Normal

*From the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (*16*). †From the Wechsler Memory Scale–Revised (WMS-R) (*16*).

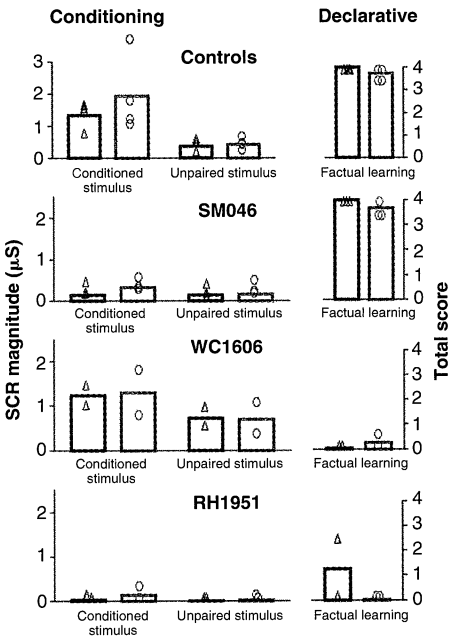

Fig. 2. Magnitudes of SCRs and total factual learning scores (*8*) from the visual-auditory (blue) and auditory-auditory (red) conditioning experiments, from normal controls ($n = 4$), SM046 (three trials), WC1606 (two trials), and RH1951 (two trials). Each triangle or circle on the graph represents data from one participant (in the case of controls) or one trial (in the case of patients). Each bar represents the mean magnitude or score from all participants or trials. [Each circle or triangle on the graph represents the mean magnitude of SCRs from six presentations of the conditioned stimuli (blue slides or tones not followed by the US), 14 presentations of unpaired stimuli, or the total factual learning score from the conditioning experiment.]

phase, the participant was exposed to 6 to 12 repeated presentations of the CS (blue slide) without the US, and without any other colors, until the SCR activity returned to the level seen during habituation (<0.05 μS). The auditory-auditory conditioning experiment was identical to the one just described, except that four computer-generated tones were used in place of the color slides. Five minutes after completion of the conditioning experiment, the participant was asked to answer the following questions, using an oral question-and-answer format: (i) How many different colors did you see? (ii) Tell me the names of those colors. (iii) How many different colors were followed by the horn? (iv) Tell me the name (or names) of the color (or colors) that were followed by the horn (8).

Bilateral damage to the amygdala entirely blocked the ability of SM046 to acquire conditioned SCRs to the CS but did not preclude the acquisition of facts about which stimuli (CS) were followed by the US. Specifically, during the conditioning phase of the experiments SM046 failed to generate SCRs to the CSs in both the visual and auditory experiments but was able to provide accurate and complete factual information regarding which stimuli had been followed by the US. The opposite result was obtained with participant WC1606. His bilateral hippocampal damage did not interfere with his ability to acquire conditioned SCRs but blocked his ability to acquire new facts. During the conditioning phase, WC1606 generated normal SCRs to the CSs in both the visual and auditory experiments. However, he could not provide factual information about the nature of the CS-US pairings; for example, he was never able to report that it had been the blue slide that had been paired with the boat horn. In participant RH1951, combined bilateral hippocampal and amygdala damage halted both the acquisition of conditioned SCRs and new facts. In the conditioning phases of the experiments, RH1951 never evidenced SCRs to the CSs and could not report factual information about which stimuli had been paired with a US or other details about the nature of the conditioning experiments (Figs. 2 and 3).

It is important to note that our results cannot be explained on the basis of a defect in electrodermal response in these participants. All three showed normal SCRs whenever the US was presented together with the CS (Fig. 4). This is consistent with the notion that the amygdala is not necessary for the generation of electrodermal activity per se (*9*, *10*) but that it is indeed essential for the coupling of sensory stimuli with affect—that is, the establishment of sensory-affective associations (*11*). Also, the fact that the results from the visual-auditory conditioning did not differ from those of the auditory-auditory conditioning rules out any major difference in the association of a CS and a US of different sensory modalities (intermodal associations) versus a CS and a US of the same sensory modality (intramodal associations) (Figs. 2 and 3).

The neuroanatomical connectivity of the amygdala enables it to associate converging inputs from various exteroceptive sensory modalities with the comprehensive changes in somatic state that define an emotional response (*12*). We suggest that the amygdala is indispensable for emotional conditioning and for the coupling of exteroceptive sensory information with interoceptive information concerning somatic states (emotion and affect) (*13*, *14*). On the other hand, the hippocampus, and the medial temporal lobe memory system of which it is a part, are essential for the learning of relations among various exteroceptive sensory stimuli. Our findings are consistent with previous studies in animals, which suggested that the amygdala is essential for the association of contextual (complex) or discrete (simple) cues with affect, whereas the hippocampus is critical for learning the relations among contextual cues (*15*). Our findings, however, demonstrate this double dissociation between emotional and declar-

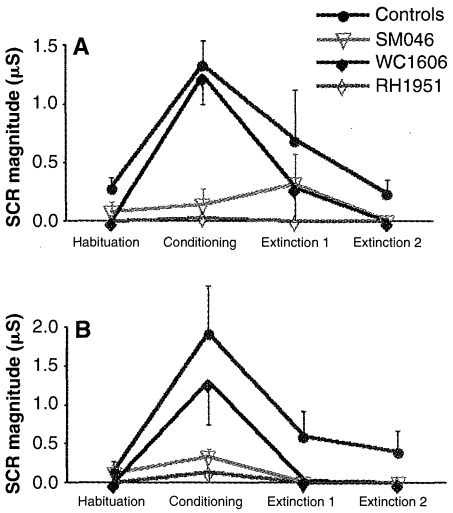

Fig. 3. Magnitudes of SCRs in the conditioning phase as compared to the SCRs in the habituation and extinction phases. Each point on the visual-auditory conditioning (**A**) and auditory-auditory conditioning (**B**) plots represents the mean ± SEM of the magnitudes of SCRs generated by controls, SM046, WC1606, and RH1951 during each phase of the conditioning experiment. Each habituation score represents the mean (from $n = 4$ controls, three trials for SM046, two trials for WC1606, and two trials for RH1951) of the mean magnitude of SCRs generated in response to the last three slides or sounds preceding conditioning. Each conditioning score represents the mean of the mean magnitude of SCRs generated in response to six presentations of the CS (not followed by the US). Each extinction 1 score represents the mean of the mean magnitude of SCRs generated in response to the first three repeated presentations of the CS during extinction. Each extinction 2 score represents the mean of the mean magnitude of SCRs in response to the last three repeated presentations of the CS.

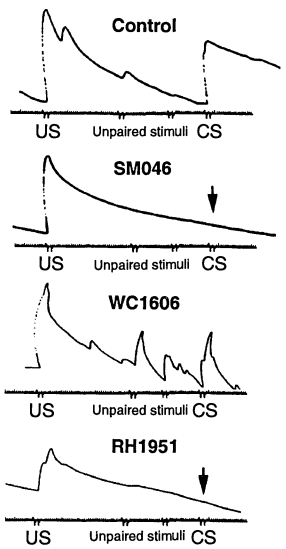

Fig. 4. Sample copies from the original polygraph records of one control, SM046, WC1606, and RH1951. All samples are presented with the same magnitude scale (microsiemens) on the *y* axis and the same time scale (seconds) on the *x* axis (*6*). Each sample depicts a continuous record of electrodermal activity across the same series of slides (trials) in the conditioning phase of visual-auditory conditioning. The US corresponds to the blue slide followed by the US on the 13th trial of the conditioning phase. Unpaired stimuli correspond to the yellow and red slides on the 14th and 15th trials. CS corresponds to the blue slide not followed by the US on the 16th trial [see (*7*) for slide sequence]. Note the complete absence of conditioned SCRs (black arrows) in SM046 and RH1951, but the preserved SCRs to the US itself. Indeed, the mean SCR magnitudes in response to the six blue slides followed by the US in the three participants were 2.4 μS (SM046), 2.6 μS (WC1606), and 1.5 μS (RH1951). These values are well within the normal range, relative to controls in our study [SCR magnitudes from the six blue-US slides were 2.0 μS (control 1) and 2.4 μS (control 2)]. Both controls and patient WC1606 initially produced SCRs to the unpaired slides or tones. However, after two to three CS-US pairings, the SCRs produced by controls to the unpaired stimuli subsided, whereas those produced by patient WC1606 did not, although the magnitudes of his SCRs to the CS were higher than those to the unpaired stimuli as shown here. Together, the combined results from SM046, WC1606, and RH1951 suggest that the amygdala is necessary for the acquisition of the conditioned SCR. However, the hippocampus is important for learning the discrimination between paired and unpaired stimuli. The observation that hippocampal damage interfered with WC1606's ability to respond differentially, at low magnitude, to a stimulus that initially was responded to at high magnitude is reminiscent of previous work in rabbits, in which hippocampal damage disrupted discrimination reversal conditioning of the rabbit nictitating membrane response (*18*). Hippocampal damage selectively disrupted the animals' ability to respond differentially, at a low rate, to a stimulus previously responded to at a high rate.

ative learning in humans and thus offer insight on how the ensuing and different forms of knowledge may come together in the human brain.

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4. Participant SM046 has bilateral amygdala damage because of Urbach-Wiethe disease. Detailed information pertaining to her neuropsychological profile, her neuroanatomical status, and facts about her daily life (especially with regard to impairments in emotional reactivity) is published [R. Adolphs, D. Tranel, H. Damasio, A. Damasio, *Nature* **372**, 669 (1994); R. Adolphs, D. Tranel, H. Damasio, A. R. Damasio, *J. Neurosci.*, in press]. In brief, she has low average intellect and normal anterograde declarative memory, as measured by conventional procedures (Table 1). Although the exact point at which SM046 acquired her amygdala damage is not clear, the literature on Urbach-Wiethe disease and reports of SM046's childhood suggest that the neurological symptoms resulting from the disease were progressively acquired throughout late childhood and adolescence. In her daily life, SM046 has a history of inadequate decision-making and inappropriate social behavior. WC1606 has bilateral hippocampal damage. Four years before our experiments, he suffered a series of cardiac arrests and ventricular fibrillation, which produced severe ischemia-anoxia and consequent bilateral hippocampal injury (see Fig. 1). He was left with a severe anterograde declarative memory impairment. He has low average intellect (Table 1). RH1951 has bilateral damage to both the hippocampus and amygdala because of herpes simplex encephalitis, suffered 14 years before our experiments. The disease produced bilateral medial temporal lobe lesions and a severe impairment in anterograde declarative memory. His intellectual abilities remain well above average (Table 1). Based on (i) review of the academic and occupational histories of the patients, (ii) multiple assessments over several years, which indicate stable intellectual functioning, and (iii) lack of significant "scatter" among the various subsets from the WAIS-R (*16*), there is no indication of general intellectual deterioration in these patients. The fact that SM046 and WC1606 are well-matched in intelligence quotient (IQ), but have different conditioning and declarative learning outcomes, argues against the possibility that intellectual factors could account for our findings.
5. Procedures of SCR recordings have been described in detail elsewhere [D. Tranel and H. Damasio, *Psychophysiology* **31**, 427 (1994)].
6. All participants gave informed consent before participation in the experiments. After electrodes were attached, each participant was seated in a comfortable chair, 0.45 m in front of the screens of a Caramate 4000 slide projector and of a computer for generating tones. The participant was asked to relax, to remain silent, and to attend to the color of the slides appearing on the screen. No motor or verbal response was to be given. Each slide was shown for 2 s, and the interval between two consecutive slides was between 10 and 20 s. The intertrial interval was determined by the status of the electrodermal activity. A new slide was not presented if the participant was generating, or was in the steep recovery limb, of an SCR. The auditory-auditory conditioning procedure was identical to the visual-auditory procedure, except that computer-generated tones were used instead of color slides. Each tone was presented for 2 s, and the interval between two consecutive tones was 10 to 20 s.
7. In the conditioning phase, the sequence of blue slides followed by the US, blue slides not followed by the US, and unpaired slides was as follows: (B-US)-R-(B-no US)-R-(B-US)-R-R-(B-US)-R-(B-no US)-G-R-(B-US)-Y-R-(B-no US)-(B-US)-R-G-(B-no US)-G-R-(B-no US)-G-(B-US)-(B-no US) (where B, blue; G, green; R, red; and Y, yellow).
8. In auditory-auditory conditioning, the same format of questions was used, but because it was difficult to give a verbal description of the computer tones, six tones were replayed and the participant was asked to identify the familiar tones as well as the tone followed by the horn. To quantify each participant's ability to acquire these specific facts about the experiment, we ascribed a maximum score of 4 if all answers were correct. Because the most significant fact in the conditioning experiment was to learn that the blue slide (or the one computer tone) was followed by the horn, a correct answer to this question was ascribed a score of 2.5. Any answer to this question that included more than one color (or tone), or a color other than blue (or other than the specific tone paired with the horn), resulted in a score of 0. Each of the remaining three questions was ascribed a score of 0.5 for a correct answer, and a score of 0 for an incorrect one. Participants were asked to declare their knowledge, and they were not required to guess an answer or to respond in a forced choice format. All participants answered all the questions.
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19. Supported by the National Institute of Neurological Disease and Stroke (grant PO1 NS19632), the James S. McDonnell Foundation, and the Medical Research Council (Canada). R.A. is a Burroughs-Wellcome Fund Fellow of the Life Sciences Research Foundation.

20 March 1995; accepted 24 July 1995