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Impact of Continuous Versus Intermittent CS–UCS Pairing on Human Brain Activation During Pavlovian Fear Conditioning

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During Pavlovian fear conditioning a conditioned stimulus (CS) is repeatedly paired with an aversive unconditioned stimulus (UCS). In many studies the CS and UCS are paired on every trial, whereas in others the CS and UCS are paired intermittently. To better understand the influence of the CS–UCS pairing rate on brain activity, the experimenters presented continuously, intermittently, and non-paired CSs during fear conditioning. Amygdala, anterior cingulate, and fusiform gyrus activity increased linearly with the CS–UCS pairing rate. In contrast, insula and left dorsolateral prefrontal cortex responses were larger during intermittently paired CS presentations relative to continuously and non-paired CSs. These results demonstrate two distinct patterns of activity in disparate brain regions. Amygdala, anterior cingulate, and fusiform gyrus activity paralleled the CS–UCS pairing rate, whereas the insula and dorsolateral prefrontal cortex appeared to respond to the uncertainty inherent in intermittent CS–UCS pairing procedures. These findings may further clarify the role of these brain regions in Pavlovian fear conditioning.

Keywords: fear, conditioning, functional MRI, emotion, uncertainty

The laboratory study of fear learning and memory has traditionally used a Pavlovian conditioning paradigm in which a conditioned stimulus (CS) is repeatedly paired with an aversive unconditioned stimulus (UCS). In many cases the CS is paired with the UCS on every trial (continuously paired), whereas in other studies the CS and UCS are intermittently paired. In both continuous and intermittent procedures, the CS comes to elicit a conditioned response (CR) which is taken as evidence that an association between the CS and the UCS has been formed. However, laboratory animal research indicates that intermittent procedures slow learning rates (Gottlieb, 2004), diminish CR amplitude (Leonard, 1975; Mackintosh, 1974), decrease response frequency (Huang, Krukar, & Miles, 1992), and delay extinction (Bloom & McFarlain, 1971; Haselgrove, Pearce, & Aydin, 2004; Hilton, 1969) relative to continuous procedures. Human conditioning studies have also examined differences in the behavioral response to intermittent versus continuous procedures. These studies have demonstrated that intermittent procedures decrease response frequency (Flora & Pavlik, 1990; Galbicka, 1994; Svartdal, 2003), retard CR acquisition (Leonard, 1975; Schurr & Runquist, 1973), and slow extinction (Schurr & Runquist, 1973) compared to continuous procedures.

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Fear conditioning studies in laboratory animals indicate that the amygdala, hippocampus, thalamus, cingulate, and sensory cortex support fear acquisition and expression (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Gao, Ren, Zhang, & Zhao, 2004; Helmstetter & Bellgowan, 1994; LaBar & LeDoux, 1996; Quinn, Oommen, Morrison, & Fanselow, 2002; Romanski & LeDoux, 1992). These studies have demonstrated that the amygdala is a principal site of CS–UCS convergence and CR production during Pavlovian fear conditioning (Fanselow & Kim, 1994; Helmstetter, 1992; Kim & Davis, 1993; LeDoux, 2000). Functional brain imaging studies of fear conditioning have extended these findings to humans, demonstrating that the amygdala also plays an important role in forming CS–UCS associations (Büchel, Morris, Dolan, & Friston, 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Morris, Büchel, & Dolan, 2001; Tabbert, Stark, Kirsch, & Vaitl, 2005) and producing CRs in humans (Cheng, Knight, Smith, Stein, & Helmstetter, 2003, 2006; Knight, Nguyen, & Bandettini, 2005). These studies have also shown learning-related activations within the hippocampus, thalamus, cingulate, insula, orbitofrontal, and sensory cortex to emotionally salient CS presentations (Büchel et al., 1998; Büchel, Dolan, Armony, & Friston, 1999; Knight, Cheng, Smith, Stein, & Helmstetter, 2004; Knight, Smith, Stein, & Helmstetter, 1999; LaBar et al., 1998; Morris et al., 2001; Phelps, Delgado, Nearing, & LeDoux, 2004).

Many of the brain regions that support Pavlovian fear conditioning show graded responses that vary with properties of the stimuli that are presented (Rosen & Donley, 2006; Zald, 2003). For example, several studies have observed a linear increase in amygdala and insula activity that corresponds to the perceived intensity of an aversive stimulus (Bornhovd et al., 2002; Rosen, Fanselow, Young, Sitcoske, & Maren, 1998; Small et al., 2003; Winston, Gottfried, Kilner, & Dolan, 2005), whereas anterior cingulate activity increases when individuals are more certain of receiving an aversive stimulus (Ploghaus, Becerra, Borras, & Borsook,

2003). Other studies have shown that many brain regions respond under uncertain conditions (Bornhovd et al., 2002; Critchley, Mathias, & Dolan, 2001; Keri, Decety, Roland, & Gulyas, 2004; Ploghaus et al., 2003; Whalen, 1998). For instance, insula activity increases with the level of uncertainty that an event will occur (Volz, Schubotz, & von Cramon, 2003), whereas ventromedial prefrontal cortex activity and hippocampal activity have been associated with uncertainty of receiving an aversive stimulus (Ploghaus et al., 2003).

Neuroimaging studies of fear conditioning have used both continuous and intermittent CS–UCS pairing procedures. Pairing the CS and UCS on all trials appears to lead to rapid CR acquisition (Knight, Cheng, et al., 2004; LaBar et al., 1998), whereas intermittent pairing has been used to slow the extinction process (Phelps et al., 2004). Brain imaging studies using intermittent pairing procedures have found robust insula, amygdala, and anterior cingulate activity that presumably reflects fear memory processes but that may also be associated with the unexpected outcomes inherent in intermittently paired stimuli (Büchel et al., 1998, 1999; Critchley et al., 2001; Huettel, Song, & McCarthy, 2005; Phelps et al., 2004). Although prior neuroimaging research of non-aversive conditioning suggests that varying the CS–UCS pairing rate can influence brain function (Kirsch et al., 2003), previous fMRI studies of fear conditioning have not directly investigated differences that continuous and intermittent procedures may have on brain activity. Therefore, in the present study we investigated the influence of continuous versus intermittent CS–UCS pairing on brain activity during human Pavlovian fear conditioning.

Method

Subjects

Eighteen healthy right-handed volunteers (11 female and 7 male; mean age ± SEM = 30.17 ± 1.63 years; age range = 23 to 47 years) participated in this study. All subjects provided written informed consent in compliance with the National Institute of Mental Health Institutional Review Board.

CS and UCS

Three pure tones (700, 1000, and 1300 Hz) were presented as CSs (10-s duration, 20-s intertrial interval) during the conditioning session. The CS100 (40 trials) co-terminated with a 500-ms loud (100-db) white-noise UCS on all trials, the CS50 (40 trials) was paired with the UCS on half the trials, and the CS− (40 trials) was presented alone. CSs were counterbalanced and presented in a pseudorandom order such that no more than two trials of the same CS were consecutively presented.

UCS Expectancy

We used an MRI-compatible joystick to assess subjects' expectancy of receiving the UCS. The joystick controlled a rating bar presented throughout training at the bottom of the visual display. Subjects were instructed to rate their UCS expectancy on a continuous scale from 0 to 100 (0 = *certain that the UCS will not be presented*, 50 = *uncertain whether the UCS will be presented*, 100 = *certain that the UCS will be presented*) and to continuously update (UCS expectancy was sampled at 10 Hz) their rating to reflect their current UCS expectancy. UCS expectancy was calculated as the average response during the last 1 s of the CS presentation.

Skin Conductance Response (SCR)

We used a Contact Precision Instruments (Boston, MA) Psylab Stand-Alone Monitor skin conductance monitoring system to monitor SCR throughout the conditioning session. SCR was sampled (80 Hz) with a pair of surface gel cup electrodes (silver–silver chloride, 6-mm diameter; Biopac model TSD203; Goleta, CA) attached to the distal phalanx of the middle and ring fingers of the left hand. The SCR signal was digitized at the electrodes, and a 10-Hz filter was applied. We analyzed SCRs by subtracting the average skin conductance measurement during the baseline period (5 s immediately before CS presentation) from the second interval response (SIR; peak response during the 5 s before CS termination). The SIR is generally considered an emotional response, elicited by UCS anticipation, that reflects learning the CS–UCS association (Boucsein, 1992; Prokasy & Kumpfer, 1973; Wolter & Lachnit, 1993). SCR data were square root transformed prior to statistical analysis.

fMRI

Structural and functional imaging was completed on a General Electric Signa HDx 3.0T scanner with an eight-channel RF head coil. Functional imaging of the entire brain was conducted with a gradient-echo echo-planar pulse sequence (repetition time = 2,000 ms; echo time = 30 ms; field of view = 240 mm; matrix = 64 × 64; slice thickness = 4 mm) during each of four 920-s blocks of stimulus presentations. High-resolution anatomical images (MPRAGE) were obtained to serve as an anatomical reference. Image processing was performed with the AFNI software package (Cox, 1996; Cox & Hyde, 1997). Echo-planar time series data were motion corrected, concatenated, and reregistered to the fifth volume of the first imaging block (Cox & Jesmanowicz, 1999). We obtained hemodynamic response functions by deconvolving the input for the onset of all stimulus types (CS100, CS50, and CS−) from the fMRI time series using a least-squares procedure. The percent area under the second through fourth images of the hemodynamic response curve (AUC), which occur prior to UCS presentation, was used as an index of the response magnitude produced by each CS. Functional maps reflecting the AUC were converted to a standard stereotaxic coordinate system (Talairach & Tournoux, 1988) and spatially blurred with a 2-mm full-width-at-half-maximum isotropic Gaussian filter (Cox & Hyde, 1997). Brain activity associated with each CS type was compared to a resting baseline. Further analysis was restricted to areas of activation that were larger than 250 mm^3 in volume and that showed a significant increase in activity during any of the CSs relative to baseline ($t > 3.96$, $p < .0005$). No region showed decreased activity relative to baseline. An ANOVA of fMRI data from regions meeting these criteria was then performed with a corrected $p < .05$ significance threshold (see Table 1).

Results

Behavioral Data

Learning-related changes in UCS expectancy developed within the first of five trials of the conditioning session, as demonstrated

Table 1
Brain Activity Related to the Conditioned Stimulus (CS)–Unconditioned Stimulus (UCS) Pairing Rate

Location and hemisphere	Volume (mm^3)	Coordinates (center of mass) X	Y	Z	$F(1, 17)$
Regions showing responses that increase with CS–UCS pairing rate					
Anterior cingulate					
Bilateral	3,803	−2.3	−3.5	43.9	8.10
Fusiform gyrus					
Right	2,504	22.8	−64.4	−10.3	9.93
Left	513	−23.0	−61.7	−13.4	7.86
Inferior occipital gyrus					
Left	521	−37.4	−69.9	−3.7	8.22
Precentral gyrus					
Left	4,600	−30.1	−19.1	50.2	8.10
Precuneus					
Left	5,115	−17.8	−73.9	24.9	14.12
Regions showing responses to intermittent CS–UCS pairing					
Insula					
Right	292	35.1	20.3	5.9	7.57
Left	1,698	−28.0	19.1	5.7	7.05
Dorsolateral PFC					
Left	338	−36.6	3.1	30.8	11.23

Note. For all *Fs*, $p < .05$. PFC = prefrontal cortex.

by a significant CS × Trial interaction ($F = 6.97$, $p < .05$). Over the course of the conditioning session UCS expectancy responses showed a significant linear relationship (see Figure 1a) with the rate at which the CS and UCS were paired ($F = 16.74$, $p < .05$), with the lowest UCS expectancy ratings occurring during the CS− presentations ($M \pm SEM = 43.02 \pm 1.61$), intermediate ratings during the CS50 presentations (57.71 ± 1.70), and the highest ratings during the CS100 presentations (73.04 ± 1.80). Similar learning-related changes in SCR also developed with training (see Figure 1b). SCRs were lowest during the CS− presentations (0.19 ± 0.03), intermediate during the CS50 presentations (0.23 ± 0.04), and largest during the CS100 presentations (0.25 ± 0.04), showing a significant linear relationship with the CS–UCS pairing rate ($F = 9.25$, $p < .05$).

fMRI Data

An ANOVA of fMRI data revealed two distinct patterns of activation that developed during the conditioning session. One pattern was characterized by brain areas that showed a linear increase in fMRI signal intensity that varied directly with the CS–UCS pairing rate. These regions included the anterior cingulate, left fusiform, precuneus, and inferior occipital gyrus. Response magnitude in these areas was lowest during the CS− trials, intermediate during the CS50 trials, and largest during CS100 trials (see Figure 2a). In addition, the anterior cingulate and left fusiform gyrus showed a significant CS × Block interaction in which large-magnitude responses were elicited by all CSs during the first half (Blocks 1 and 2) of the conditioning session and learning-related differences were observed only during the second half (Blocks 3 and 4) of training.

A second pattern of activation was distinguished by regional activity that was larger during the CS50 presentations than during presentations of the CS− and CS100. This activation pattern was observed within the bilateral insula and left dorsolateral prefrontal cortex (see Figure 2b and Figure 3). The fMRI signal within these regions showed a significant quadratic relationship with the CS–UCS pairing rate such that larger responses were observed during the CS50 trials than during CS− and CS100 trials. In addition, activity within the right insula showed a significant CS × Block interaction, with large amplitude responses to all CSs during the

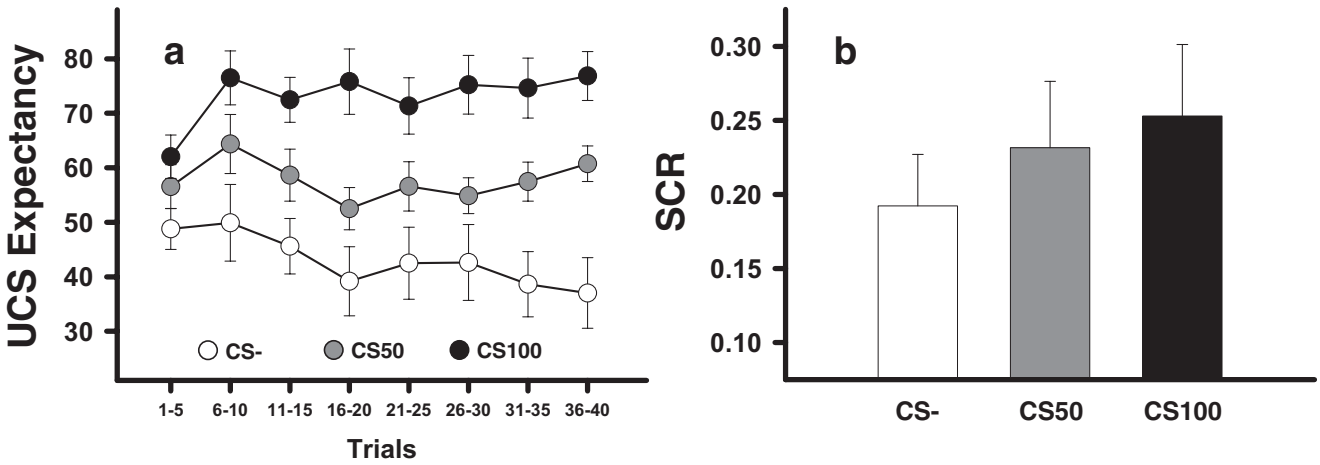

Figure 1. a: Unconditioned stimulus (UCS) expectancy. b: Skin conductance response (SCR). Learning-related changes in UCS expectancy and SCR were observed during the conditioning session. Both UCS expectancy and SCR increased linearly with the conditioned stimulus (CS)–UCS pairing rate, such that the lowest responses were observed during the CS− trials, intermediate responses during the CS50 trials, and the largest responses during the CS100 trials. A color version of this figure is available on the Web at http://dx.doi.org/10.1037/0735-7044.121.4.635.supp.

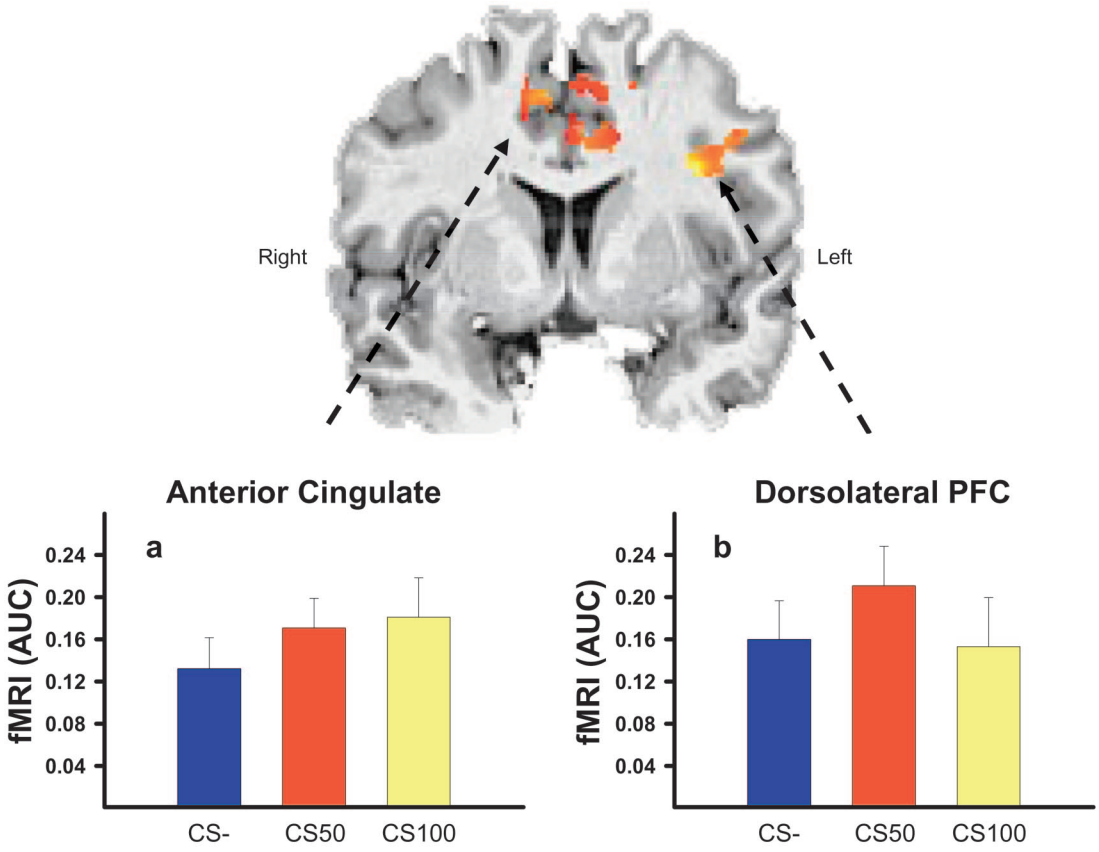

Figure 2. Area under the hemodynamic response curve (AUC) within the anterior cingulate and dorsolateral prefrontal cortex (PFC). a: Activity within the anterior cingulate increased linearly with the conditioned stimulus (CS)–unconditioned stimulus pairing rate, with the lowest responses during non-paired CS− trials, intermediate responses during intermittently paired CS50 trials, and the largest responses during the continuously paired CS100 trials. b: Activity within the left dorsolateral prefrontal cortex was larger during the CS50 trials than during the CS− or CS100 trials.

first half of the conditioning session and larger responses to the CS50 than the CS− and CS100 during the last half of the session.

Amygdala activity did not meet the cluster size and significance thresholds for the whole brain analysis. Therefore, we completed an additional region of interest (ROI) analysis of the amygdala using the AFNI Talairach–Tournoux neuroanatomical atlas (Talairach & Tournoux, 1988). Three subjects were excluded from this analysis because they did not show a sufficient temporal signal-to-noise ratio (TSNR $>$ 30) within this ROI. Both the left ($F = 6.19$, $p < .05$) and right ($F = 8.78$, $p < .05$) amygdala showed a pattern of activity that increased linearly with the CS–UCS pairing rate (see Figure 4). Amygdala responses to CSs did not differ during the first half of training. However, during the second half of training both left ($F = 7.66$, $p < .05$) and right ($F = 7.82$, $p < .05$) amygdala activity were lowest during the CS− trials, intermediate during the CS50 trials, and largest during CS100 trials.

Discussion

In the current study we utilized fMRI to investigate brain activity produced by continuous and intermittent CS–UCS pairing during Pavlovian fear conditioning. We measured SCR, UCS expectancy, and blood oxygen level dependent (BOLD) fMRI signal responses to three distinct CSs that were paired with the UCS on 0% (CS−), 50% (CS50), and 100% (CS100) of trials. Learning-related changes in SCR and UCS expectancy developed during training such that the lowest magnitude responses were elicited by the CS− trials, intermediate responses were produced by the CS50 trials, and the largest responses were observed on CS100 trials. Similar to prior research (Knight, Cheng, et al., 2004), differential UCS expectancies to CS presentations developed relatively quickly. However, the learning-related changes observed in the current study did not reach the differential response magnitude observed in prior work (Knight, Cheng, et al., 2004). This may be due to the use of auditory tones in the present study, which appear to be more difficult to discriminate than the visual stimuli used previously because of the loud gradient noise produced during scan sessions. The learning-related changes in UCS expectancy and SCR observed in the current study demonstrate that the magnitude of these learned responses increases with the CS–UCS pairing rate.

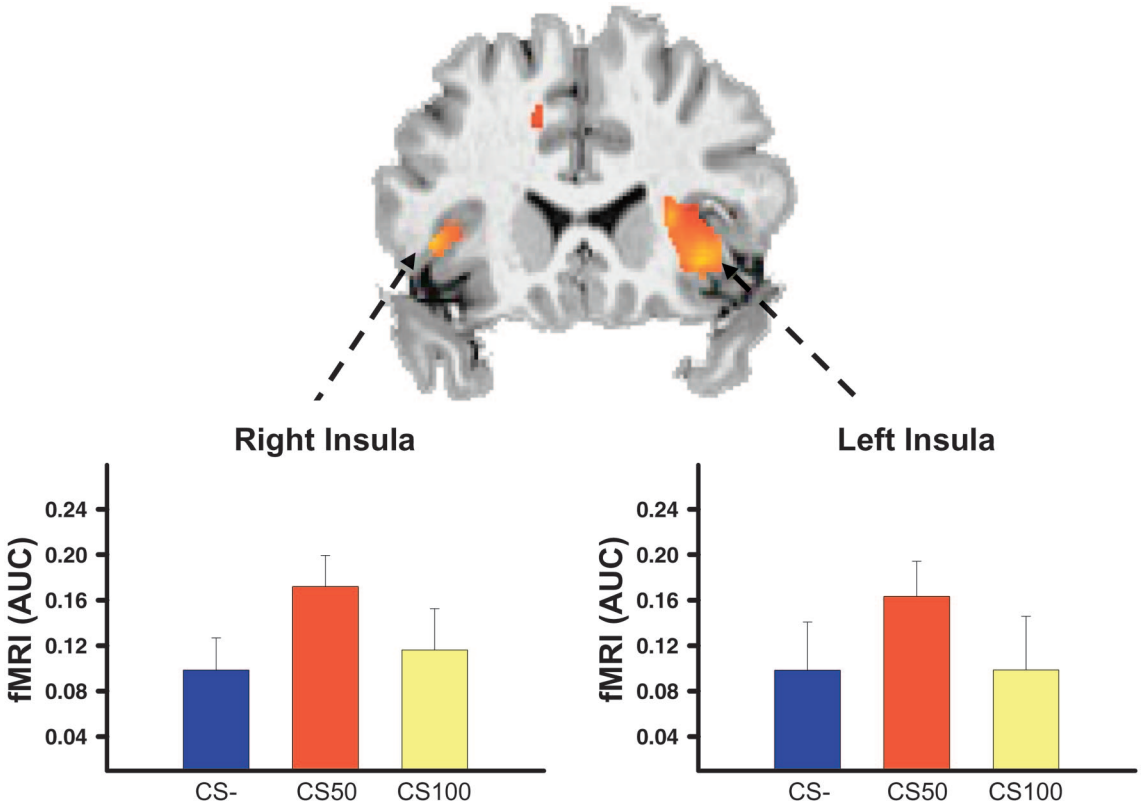

Figure 3. Area under the hemodynamic response curve (AUC) within the insula. Insula activity was larger during the CS50 trials than during the CS− and CS100 trials. CS = conditioned stimulus.

The BOLD fMRI signal was also clearly influenced by the rate at which the CS was paired with the UCS in the present study. The intensity of the fMRI signal within the anterior cingulate, amygdala, and fusiform gyrus increased linearly with the rate of CS–UCS pairing, with small responses to the CS−, intermediate responses to the CS50, and the largest responses to the CS100. These regions may code the strength of CS–UCS associations, with larger responses to CSs that better predict the UCS. This finding is consistent with prior research showing graded changes in brain activity that increase with the expectancy and intensity of aversive stimuli (Ploghaus et al., 2003; Reiman, Fusselman, Fox, & Raichle, 1989). Additionally, neuroimaging studies have shown that these regions show larger fMRI signal responses to CS+ than CS− presentations (Knight et al., 1999; Knight, Cheng, et al., 2004; LaBar et al., 1998; Morris et al., 2001; Phelps et al., 2004; Tabbert et al., 2005). Several of these studies continuously paired the CS and UCS, whereas others paired them intermittently. However, none of these prior neuroimaging studies have investigated the influence of continuous versus intermittent CS–UCS pairing on brain activity. The present results demonstrate that the amplitude of activity varies within these brain regions with the rate at which the CS is paired with the UCS.

The fMRI data also demonstrate robust activity in the bilateral insula and left dorsolateral prefrontal cortex that was greater during CS50 trials than CS100 and CS− trials. CS50 presentations may be associated with greater uncertainty compared to the CS100 and CS−, as these CSs are either always paired (CS100) or unpaired (CS−) with the UCS. Subjects' UCS expectancy ratings in this study confirm that they were uncertain of whether the UCS would be presented on CS50 trials, which may have elicited larger neural responses as a result of being intermittently paired with the UCS. Previous studies have demonstrated that the insula responds not only to emotionally salient stimuli (Adolphs, 2002; Wicker et al., 2003) but also to uncertainty (Critchley et al., 2001; Ploghaus et al., 2003). Research that has varied the level of uncertainty dynamically over time has demonstrated that insula activity increases as the level of uncertainty is raised (Huettel et al., 2005). In the current study, insula and dorsolateral prefrontal cortex activity was lower during the CS100 and CS− trials relative to CS50 presentations. These results suggest that the insula and dorsolateral prefrontal cortex are more responsive to uncertain than predictable conditioning trials, because the outcome during the CS100 and CS− presentations was more certain (either paired or unpaired with the UCS) than the outcome of CS50 trials.

Prior work has suggested the amygdala responds to the ambiguity of emotional stimuli (Whalen, 1998), and previous neuroimaging studies of fear conditioning have been somewhat consistent with that view. Specifically, neuroimaging studies of fear conditioning have shown differential amygdala responses during early acquisition trials that dissipate over the course of the training session (Büchel et al., 1998; LaBar et al., 1998). In these studies, the amygdala may have responded to the ambiguity of aversive stimuli, particularly during early trials when stimulus contingencies were uncertain (Whalen, 1998). The inclusion of habituation

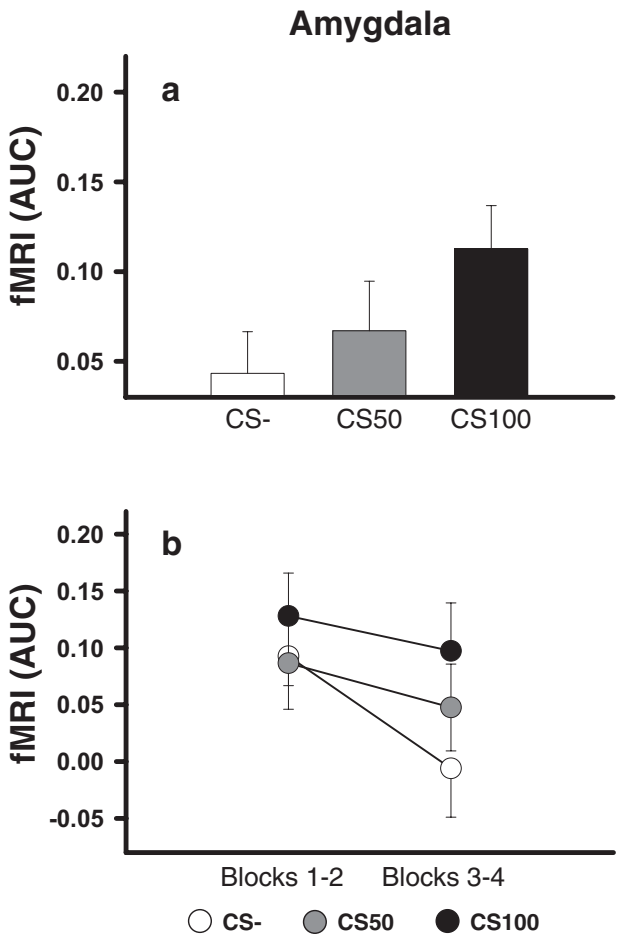

Figure 4. Area under the hemodynamic response curve (AUC) within the bilateral amygdala region of interest. a: A linear pattern of activation was observed within the amygdala, with the smallest response to the CS− trials, intermediate response to the CS50 trials, and the largest response to CS100 trials. b: During the first half of training (Blocks 1 and 2) response magnitude did not differ. However, during the second half of training (Blocks 3 and 4) learning-related differences in amygdala activity were observed, with the smallest responses during the CS− trials, intermediate responses during the CS50 trials, and the largest responses during CS100 trials. CS = conditioned stimulus. A color version of this figure is available on the Web at http://dx.doi.org/10.1037/0735-7044.121.4.635.supp.

trials in these fear conditioning studies may have increased the ambiguity associated with the CS+ on early acquisition trials (Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Whalen, 1998). For example, CS− contingencies remain unchanged (i.e., not paired with the UCS) in both habituation and acquisition phases of a conditioning study, whereas the relationship between the CS+ and the UCS varies from unpaired during habituation to paired during the acquisition phase. Therefore, the change in stimulus contingencies for the CS+ from habituation to acquisition phases may increase amygdala activity and partially explain differential responses to the CSs during early conditioning trials.

Subjects in the present study received no pre-exposure to CSs and produced large responses to all CSs early in training. These amygdala responses appear to have been maintained throughout the conditioning session by pairing the CS and UCS, whereas the response to the unpaired CS− habituated. Amygdala responses produced by the CS100 remained relatively large throughout the conditioning session, whereas responses to the CS50 fell to an intermediate level and responses to the CS− showed a pronounced decrease over time. These findings are similar to those of Tabbert et al. (2005), who demonstrated large amygdala responses to all CSs during early acquisition trials and detected differential amygdala activity only later in the training session.

In conclusion, the present study used a Pavlovian fear conditioning procedure during fMRI to investigate the effect of continuous versus intermittent CS–UCS pairing on brain activity. Amygdala, anterior cingulate, and fusiform gyrus activity increased linearly with the CS–UCS pairing rate, whereas regions such as the insula and dorsolateral prefrontal cortex showed the largest responses to stimuli intermittently paired with the UCS (i.e., CS50) and may mediate processes associated with the uncertainty of UCS presentation. The present findings indicate that many of the brain regions previously shown to support fear conditioning do not merely process the contingencies underlying CS–UCS associations but may also respond to the uncertainty of receiving an aversive UCS. These findings offer new insights into the neural mechanisms supporting human Pavlovian fear conditioning.

References

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology, 12,* 169–177.

Büchel, C., Dolan, R. J., Armony, J. L., & Friston, K. J. (1999). Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 19,* 10869–10876.

Büchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: An event-related fMRI study. *Neuron, 20,* 947–957.

Bloom, J. M., & McFarlain, R. A. (1971). Hippocampal lesions and the partial reinforcement effect. *Psychological Reports, 29,* 831–837.

Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., & Büchel, C. (2002). Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: A single-trial fMRI study. *Brain, 125*(Pt. 6), 1326–1336.

Boucsein, W. (1992). *Electrodermal activity.* New York: Plenum Press.

Cheng, D. T., Knight, D. C., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (2003). Functional MRI of human amygdala activity during Pavlovian fear conditioning: Stimulus processing versus response expression. *Behavioral Neuroscience, 117,* 3–10.

Cheng, D. T., Knight, D. C., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (2006). Human amygdala activity during the expression of fear responses. *Behavioral Neuroscience, 120,* 1187–1195.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29,* 162–173.

Cox, R. W., & Hyde, J. S. (1997). Software tools for the analysis and visualization of fMRI data. *NMR in Biomedicine, 10,* 171–178.

Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine, 42,* 1014–1018.

Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2001). Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron, 29,* 537–545.

Fanselow, M. S., & Kim, J. J. (1994). Acquisition of contextual Pavlovian fear conditioning is blocked by application of an NMDA receptor antagonist D, L-2-amino-5-phosphonovaleric acid to the basolateral amygdala. *Behavioral Neuroscience, 108,* 210–212.

Flora, S. R., & Pavlik, W. B. (1990). Conventional and reversed partial reinforcement effects in human operant responding. *Bulletin of the Psychonomic Society, 28,* 429–432.

Frankland, P. W., Bontempi, B., Talton, L. E., Kaczmarek, L., & Silva, A. J. (2004, May 7). The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science, 304,* 881–883.

Galbicka, G. (1994). Shaping in the 21st century: Moving percentile schedules into applied settings. *Journal of Applied Behavior Analysis, 27,* 739–760.

Gao, Y. J., Ren, W. H., Zhang, Y. Q., & Zhao, Z. Q. (2004). Contributions of the anterior cingulate cortex and amygdala to pain- and fear-conditioned place avoidance in rats. *Pain, 110,* 343–353.

Gottlieb, D. A. (2004). Acquisition with partial and continuous reinforcement in pigeon autoshaping. *Learning and Behavior: A Psychonomic Society Publication, 32,* 321–334.

Haselgrove, M., Pearce, J. M., & Aydin, A. (2004). A partial reinforcement extinction effect despite equal rates of reinforcement during Pavlovian fear conditioning. *Journal of Experimental Psychology: Animal Behavior Processes, 30,* 240–250.

Helmstetter, F. J., & Bellgowan, P. S. (1994). Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. *Behavioral Neuroscience, 108,* 1005–1009.

Helmstetter, F. J. (1992). Contribution of the amygdala to learning and performance of conditional fear. *Physiology & Behavior, 51,* 1271–1276.

Hilton, A. (1969). Partial reinforcement of a conditioned emotional response in rats. *Journal of Comparative and Physiological Psychology, 69,* 253–260.

Huang, I. N., Krukar, J. D., & Miles, S. P. (1992). Effects of reinforcement schedules on rats' choice behavior in extinction. *The Journal of General Psychology, 119,* 201–211.

Huettel, S. A., Song, A. W., & McCarthy, G. (2005). Decisions under uncertainty: Probabilistic context influences activation of prefrontal and parietal cortices. *The Journal of Neuroscience, 25,* 3304–3311.

Keri, S., Decety, J., Roland, P. E., & Gulyas, B. (2004). Feature uncertainty activates anterior cingulate cortex. *Human Brain Mapping, 21,* 26–33.

Kim, M., & Davis, M. (1993). Electrolytic lesions of the amygdala block acquisition and expression of fear-potentiated startle even with extensive training but do not prevent reacquisition. *Behavioral Neuroscience, 107,* 580–595.

Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., et al. (2003). Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: An event-related fMRI study. *Neuroimage, 20,* 1086–1095.

Knight, D. C., Cheng, D. T., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (2004). Neural substrates mediating human delay and trace fear conditioning. *The Journal of Neuroscience, 24,* 218–228.

Knight, D. C., Nguyen, H. T., & Bandettini, P. A. (2005). The role of the human amygdala in the production of conditioned fear responses. *Neuroimage, 26,* 1193–2000.

Knight, D. C., Smith, C. N., Cheng, D. T., Stein, E. A., & Helmstetter, F. J. (2004). Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. *Cognitive, Affective, & Behavioral Neuroscience, 4,* 317–325.

Knight, D. C., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (1999). Functional MRI of human Pavlovian fear conditioning: Patterns of activation as a function of learning. *Neuroreport, 10,* 3665–3670.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron, 20,* 937–945.

LaBar, K. S., & LeDoux, J. E. (1996). Partial disruption of fear conditioning in rats with unilateral amygdala damage: Correspondence with unilateral temporal lobectomy in humans. *Behavioral Neuroscience, 110,* 991–997.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155–184.

Leonard, D. W. (1975). Partial reinforcement effects in classical aversive conditioning in rabbits and human beings. *Journal of Comparative and Physiological Psychology, 88,* 596–608.

Mackintosh, N. J. (1974). Stimulus selection: Learning to ignore stimuli that predict no change in reinforcement. In R. A. Hinde & J. Stevenson-Hinde (Eds.), *Constraints on learning* (pp. 75–96). London: Academic Press.

Morris, J. C., Büchel, C., & Dolan, R. J. (2001). Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. *Neuroimage, 13*(6, Pt. 1), 1044–1052.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron, 43,* 897–905.

Ploghaus, A., Becerra, L., Borras, C., & Borsook, D. (2003). Neural circuitry underlying pain modulation: Expectation, hypnosis, placebo. *Trends in Cognitive Sciences, 7,* 197–200.

Prokasy, W. F., & Kumpfer, K. L. (1973). Classical conditioning. In W. F. Prokasy & D. C. Raskin (Eds.) *Electrodermal activity in psychological research* (pp. 157–202). New York: Academic Press.

Quinn, J. J., Oommen, S. S., Morrison, G. E., & Fanselow, M. S. (2002). Post-training excitotoxic lesions of the dorsal hippocampus attenuate forward trace, backward trace, and delay fear conditioning in a temporally specific manner. *Hippocampus, 12,* 495–504.

Reiman, E. M., Fusselman, M. J., Fox, P. T., & Raichle, M. E. (1989, February 24). Neuroanatomical correlates of anticipatory anxiety. *Science, 243*(4894, Pt. 1), 1071–1074.

Romanski, L. M., & LeDoux, J. E. (1992). Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. *The Journal of Neuroscience, 12,* 4501–4509.

Rosen, J. B., & Donley, M. P. (2006). Animal studies of amygdala function in fear and uncertainty: Relevance to human research. *Biological Psychology, 73,* 49–60.

Rosen, J. B., Fanselow, M. S., Young, S. L., Sitcoske, M., & Maren, S. (1998). Immediate-early gene expression in the amygdala following footshock stress and contextual fear conditioning. *Brain Research, 796,* 132–142.

Schurr, B. C., & Runquist, W. N. (1973). Acquisition and extinction of human eyelid conditioned response as a function of schedule of reinforcement and unconditioned stimulus intensity under two masked conditioning procedures. *Journal of Experimental Psychology, 101,* 398–401.

Small, D. M., Gregory, M. D., Mak, Y. E., Gitelman, D., Mesulam, M. M., & Parrish, T. (2003). Dissociation of neural representation of intensity and affective valuation in human gestation. *Neuron, 39,* 701–711.

Svartdal, F. (2003). Extinction after partial reinforcement: Predicted vs. judged persistence. *Scandinavian Journal of Psychology, 44,* 55–64.

Tabbert, K., Stark, R., Kirsch, P., & Vaitl, D. (2005). Hemodynamic responses of the amygdala, the orbitofrontol cortex and the visual cortex during a fear conditioning paradigm. *International Journal of Psychophysiology, 57,* 15–23.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* New York: Thieme.

Volz, K. G., Schubotz, R. I., & von Cramon, D. Y. (2003). Predicting events of varying probability: Uncertainty investigated by fMRI. *Neuroimage, 19*(2, Pt. 1), 271–280.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging

studies of the human amygdala. *Current Directions in Psychological Science, 7,* 177–188.

Wicker, B., Keysers, C., Plailly, J., Royet, J. P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in my insula: The common neural basis of seeing and feeling disgust. *Neuron, 40,* 655–664.

Winston, J. S., Gottfried, J. A., Kilner, J. M., & Dolan, R. J. (2005). Integrated neural representations of odor intensity and affective valence in human amygdala. *The Journal of Neuroscience, 25,* 8903–8907.

Wolter, J., & Lachnit, H. (1993). Are anticipatory first and second interval skin conductance responses indicators of predicted aversiveness? *Integrative Physiological and Behavioral Science, 28,* 163–166.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research, 41,* 88–123.

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