Fear Is Fast in Phobic Individuals: Amygdala Activation in Response to Fear-Relevant Stimuli

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Background: *Two core characteristics of pathologic fear are its rapid onset and resistance to cognitive regulation. We hypothesized that activation of the amygdala early in the presentation of fear-relevant visual stimuli would distinguish phobics from nonphobics.*
Methods: *Chronometry of amygdala activation to phobia-relevant pictures was assessed in 13 spider phobics and 14 nonphobics using functional magnetic resonance imaging (fMRI).*
Results: *Blood oxygen level–dependent (BOLD) responses in the amygdala early in picture processing consistently differentiated between phobic and nonphobic subjects, as well as between phobogenic and nonphobogenic stimuli among phobics. Furthermore, amygdalar BOLD responses associated with timing but not magnitude of activation predicted affective responses to phobogenic stimuli. Computational modeling procedures were used to identify patterns of neural activation in the amygdala that could yield the observed BOLD data. These data suggest that phobic responses were characterized by strong but brief amygdala responses, whereas nonphobic responses were weaker and more sustained.*
Conclusions: *Results are discussed in the context of the amygdala's role in rapid threat detection and the vigilance-avoidance hypothesis of anxiety. These data highlight the importance of examining the neural substrates of the immediate impact of phobogenic stimuli for understanding pathological fear.*

For an animal to survive, threat must be detected quickly (LeDoux 1996; Öhman and Mineka 2001). Efficient identification of potential threat requires detection of such stimuli based on relatively simple stimulus features and at any position in the perceptual field, thus resulting in a relatively rapid, automatic system with minimal processing of incoming sensory information (LeDoux 1996; Öhman and Mineka 2001). A growing corpus of data implicates the amygdala as a likely facilitator of rapid detection of potentially threatening stimuli (LeDoux 2000; Öhman and Mineka 2001). An independent line of research has found that specific phobics respond rapidly to phobia-relevant stimuli (Globisch et al 1999; Öhman et al 2001). One possible mechanism underlying this accelerated response is exacerbation of the amygdala's early response to fear-relevant cues. To better understand the neural substrates distinguishing pathologic fear, we examined the role of the amygdala in the early portion of responses to phobogenic stimuli among specific phobics and nonphobics.

Extensive data implicate the amygdala in negative affect, especially fear (LeDoux 2000). Lesions of the amygdala block fear conditioning in numerous sensory modalities (for review, see Maren 2001). In human neuroimaging studies increased amygdala activation has been found during viewing of negatively valenced pictures (Irwin et al 1996; Lane et al 1997) and fear faces (Breiter et al 1996; Morris et al 1996) even when presented preattentively (Whalen et al 1998). Importantly, a number of functional magnetic resonance imaging (fMRI) studies have shown that amygdala activation habituates over repeated conditioning trials or presentations of affective stimuli (Buchel et al 1998; LaBar et al 1998; Wright et al 2001). Furthermore, Phelps and colleagues (2001) found within-trial habituation of amygdala activation to threat cues. These data suggest that the amygdala may play an immediate but short-lived role in the unfolding reaction to a negative affective stimulus. Thus, the failure of several early ^{15}O positron emission tomography (PET) studies to find amygdala activation in response to phobia-relevant cues (e.g., Rauch et al 1995; Wik 1996) may be due to the inadequacy of the temporal resolution of PET for capturing these relatively fleeting patterns of activation. Consistent with this notion, fMRI work has suggested that amygdala activation in response to phobia-relevant stimuli is detected when stimuli are presented in an event-related (Dilger et al 2003), but not a block, design, which may accelerate habituation (Paquette et al 2003; but see Scheinle et al 2005). In addition, recent PET work has also revealed amygdala activation to pictures of phobic stimuli when these stimuli are presented very briefly (14 msec; Carlsson et al 2004). Taken together these data suggest that in specific phobia the amygdala is more readily recruited in response to briefly presented stimuli and that its activation is not sustained.

Independent research has suggested that phobic fear is characterized by an abnormally early onset of the fear response. Globisch and colleagues (1999) found potentiation of the startle eye-blink response to phobia-relevant pictures as early as 300 msec following picture onset, earlier than potentiation is typically found in response to nonphobic, aversive stimuli (Bradley et al 1993).

In this study, we used an event-related fMRI paradigm to assess the magnitude and timing of the amygdalar BOLD response to phobia-relevant compared with neutral and unpleasant nonphobic pictorial stimuli among female spider phobic and nonphobic control subjects. Women were chosen because previous studies have shown that 75%–80% of all specific phobics are women (Fyer 1998; Magee et al 1996). To enable fine-grained temporal sampling of signal in the amygdala, coverage of the brain was limited to five coronal slices centered on the amygdala, and a jittered design was employed, allowing for an effective time resolution of 300 msec. We predicted that among phobics, early involvement of the amygdala in response to phobia-

relevant stimuli would result in more rapid onset of the amygdala BOLD response. Importantly, differences in the observed onset of the BOLD response may not reflect differences in the time to onset of underlying neural activity; they could reflect differences in the magnitude and duration of underlying hemodynamic responses. As such, computational modeling was used to examine whether patterns other than simple facilitations or delays in underlying neural activity could account for the observed data.

Materials and Methods

Participants

Participants were female undergraduates who participated in a mass screening for course credit. Women scoring greater than 20 (94th percentile in the current sample) on the Spider Phobia Questionnaire (Klorman et al 1974) were classified as phobics, and women scoring 0 or 1 were classified as nonphobic. From this pool, thirty right-handed women (15 phobic and 15 control subjects) screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al 1995) met criteria for participation in the study, including presence or absence of spider phobia and absence of a history of depression, psychosis, or other anxiety disorders. Two phobic and one control subjects were dropped because of movement artifact, yielding a final sample of 27 participants (13 phobic subjects: M[SD] age = 18.46 [.52], 12 Caucasian, 1 Hispanic; 14 control subjects: M[SD] age = 19.21 [1.05], all Caucasian). The two groups did not differ on age ($p > .50$).

Materials and Procedures

Informed consent from the University of Wisconsin Health Sciences Human Subjects Committee was obtained before scanning. Affective pictures were presented in three functional runs. Given evidence of amygdala habituation over time, only data from the first scan are presented here. During the first run, 20 spider, 20 non-spider negative, and 20 neutral pictures were presented via Silent Vision fiber optic goggles (Avotec, Jensen Beach, Florida). Negative and neutral pictures were selected from the International Affective Picture System (Lang et al 1999). Spider pictures were selected from various Web sites. Pictures were presented in a pseudorandom order for 300 msec followed by a 15,000 msec ITI.

After scanning, subjects rated a subset (10 of each condition) of the pictures on subjective arousal. Each picture was presented for 3 sec followed by a 9-point Likert scale (higher numbers reflect greater arousal). Due to technical problems, rating data for 2 control subjects were lost.

Data Acquisition. Magnetic resonance data were acquired using a GE EchoSpeed 1.5-Tesla scanner (Waukesha, Wisconsin) equipped with high-speed, whole body gradients and a standard clinical whole-head transmit-receive quadrature birdcage head coil. A T2* weighted gradient-echo echo-planar (EPI) pulse sequence was used to collect five coronal slices centered on the amygdala (slice thickness: 5 mm, 1 mm interslice gap, echo time/repetition time (TE/TR = 50/600 msec, field of vision = 24 × 24 cm, $\alpha = 65°$, matrix = 64 × 64, 1540 images per scan). By using an ITI not evenly divisible by the TR, we were able to achieve a time resolution of 300 msec, or half of the acquisition TR. Structural images were acquired using an axial three-dimensional spoiled gradient recoil (SPGR; TE/TR = 8/20 msec, FOV = 24 × 24 cm, $\alpha = 35°$, number of excitations = 1, 256 × 256, 124 slices, slice thickness = 1.0–1.2 mm).

Data Reduction. Using the AFNI software suite (Cox 1996) data processing included offline image reconstruction, spatial smoothing with a Hamming window (FWHM = 1 voxel), motion correction, removal of skull and ghost artifacts, and introduction of high-pass temporal Fourier filter (.4 Hz). Within-run trials were aggregated such that the 20 trials per picture type (spider, negative, neutral) were averaged to create a 50-point (15 sec) time series with 300-msec resolution for each condition. A region of interest (ROI) including all functional voxels containing amygdalar tissue (as identified in the SPGR anatomies) was drawn on EPI images for each slice for each subject (for amygdala boundary criteria, see Convit et al 1999). Because of signal dropout, an average of 1.57 voxels in the amygdala was lost for each hemisphere and each subject. These voxels were not included in the ROI analyses. Time series for the average of all voxels in the ROI were calculated.

A gamma variate function was fit to the functional time series data to model three parameters of the hemodynamic response, including time to onset, percent signal change from baseline, and time to peak activation. There were no interactions or main effects for group, hemisphere, or valence for goodness of fit of the gamma-variate function ($ps > .10$). For each hemisphere averages each of the three gamma variate parameters across all voxels in the amygdala ROIs were calculated. A Group (Phobic, Control) × Picture Condition (Spider, Negative, Neutral) × Hemisphere (Left, Right) analysis of variance (ANOVA) was computed separately for each gamma variate parameter.

Regressions Using Amygdala BOLD Parameters to Predict Self-Reported Arousal Ratings. To determine whether magnitude or rapidity of the amygdalar BOLD response was more predictive of subjective reactivity to phobic stimuli, hierarchical regressions were calculated using difference scores between spider and neutral picture self-report then reversed to determine whether the two variables accounted for overlapping or independent portions of variance. Spider minus neutral time to onset and percent signal change were entered as the predictors in the first model. Identical regressions were run using time to peak rather than time to onset. A parallel set of regressions was run for negative minus neutral to explore the specificity of these effects for phobic arousal ratings for the pictures as the dependent variable.

Modeling Procedures To interpret the gamma variate timing effects properly, it is important to consider the underlying neural activity that these parameters reflect. Given the temporal smoothing and delays inherent in fMRI data, the BOLD hemodynamic response time to onset and time to peak parameters reflect an aggregation of amygdala activation over time. As such, it is possible that strong neural firing very early in response to a stimulus followed by a period of decreased firing could result in faster time to peak or onset of the BOLD signal than a more sustained neural reaction. Consequently, any effects for the timing variables may reflect differences in the timing of neuronal firing, differences in the magnitude of neuronal firing in early phases of stimulus processing, or both. Thus, computational modeling procedures were used to guide interpretation of the data.

We assumed that BOLD responses in the amygdala to spider pictures were associated with local field potentials (e.g., Logothetis and Wandell 2004) reflecting bursts of neural activity to the stimulus. Variation between groups in the onset time, magnitude, and duration of the field potentials were examined using a boxcar-deconvolution approach based on relatively standard assumptions for fMRI analyses. The boxcar profile is often adopted as a model of plausible neural activity in creating design files for event-related fMRI analyses and is standard in many popular neuroimaging packages, such as SPM and Brain Voyager (e.g., Laurienti et al 2003; Mechelli et al 2003). Convolution of boxcar

models of neural activity with a canonical hemodynamic response is a standard method for generating a plausible time course of neural activity for use in finding brain regions active in response to an fMRI design (Boynton et al 1999). Finally, allowing parameters such as the magnitude and length of presumed neural activity to vary within convolution models has often been adopted when examining individual differences in the time course of fMRI responses (e.g., Christoff et al 2001).

Thus, a multidimensional unconstrained nonlinear minimization algorithm (Neadler and Meade 1965) implemented using Matlab's "fminsearch" procedure was used to determine empirically the best fitting boxcar function which, when convolved with a the first 15 sec of the canonical double-gamma hemodynamic response used in SPM99 (Wellcome Department of Cognitive Neurology, London, UK) estimated the mean hemodynamic response observed for control and phobic participants. The boxcar was allowed to vary along three dimensions including time to onset, duration, and amplitude. Formally the boxcar was defined as a region with an amplitude of 0 everywhere except from the onset time until the onset time plus duration, with height of the amplitude, sampled at a rate of 100 Hz. At each iteration of the algorithm, the boxcar was convolved with the double-gamma hemodynamic response, also sampled at 100 Hz, which was then down-sampled to the TR, yielding an estimate of the BOLD response. The mean squared deviation of the estimated minus the observed group mean hemodynamic waveform was returned as a cost function, which was minimized. To identify the boxcar function that best fit the actual mean BOLD time series to spider stimuli for each group. The model was initially seeded with an amplitude of .2% change, a boxcar length of 1 sec, and an onset delay of 150 msec for both groups. Examination of other seeds in a range that allowed model fits sufficient to reflect group differences did not change the observed results.

Five models were computed. In the first model, just the onset delay was allowed to vary during the fitting process. In the second, just the duration varied. In the third, just the amplitude varied. In the fourth, the amplitude and duration were both allowed to vary. When a particular parameter was held constant its value was set at the mean value derived as the best fit from previous simulations (amplitude = .643% change, duration = 3.02 sec, onset = 150 msec). To examine the robustness of the obtained solutions to use of different shapes of neural responses a fifth model was also evaluated allowing the amplitude and duration to vary, using a half-sine wave for the presumed neural response. For each model, the fit was evaluated using the average-case intraclass-correlation between the model's group-difference waveform and the observed group-difference waveform. This metric evaluates both the absolute and relative agreement of the model to the empirical data. Models were compared using tests of dependent correlations.

Results

Group × Condition Comparisons: Gamma Variate Data

To demonstrate the raw time series and gamma variate fit for the main condition of interest, the spider pictures, these waveforms for the left amygdala are presented in Figure 1. Intraclass correlations demonstrated a good fit between the raw and fitted time series for both control (intraclass correlation [ICC] = .98, $p < .001$; confidence interval [CI] = .97–.99) and phobic subjects (ICC = .99, $p < .001$; CI = .98–.99).

Time to Onset. The Group × Condition × Hemisphere ANOVA revealed a Group × Condition interaction, $F(2,50) =$
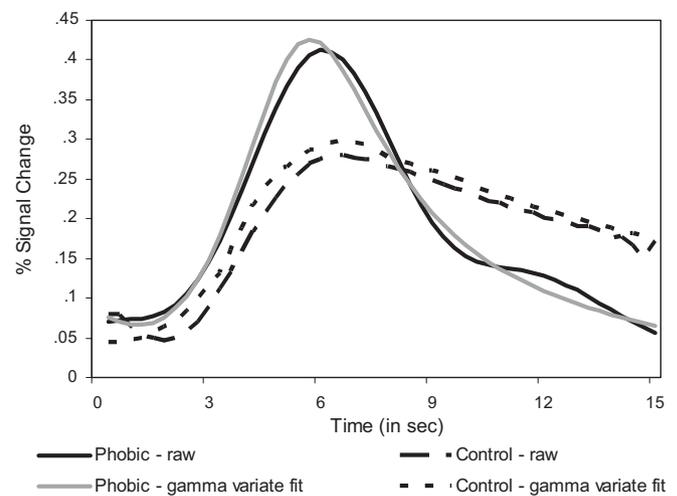

Figure 1. Mean observed blood oxygen level–dependent and gamma variate fit waveforms depicting phobic and control subjects' responses to spider pictures for the left amygdala (y axis units are percent signal change). Waveforms for the right hemisphere are similar to those depicted here. For waveforms with error bars, see supplementary materials online.

4.90, $p < .01$, for the time to onset (Figure 2). Follow-up t tests revealed that compared with control subjects, phobic subjects had faster onset of BOLD response to spider pictures for both left, $t(25) = 3.28$, $p < .003$, and right, $t(25) = 2.67$, $p < .01$, amygdalae. The two groups did not differ in time to onset for negative or neutral pictures for either hemisphere ($ps > .40$). For the left amygdala, phobic subjects also had a faster time to onset in response to spider compared with negative, $t(11) = 2.65$, $p = .02$, and neutral, $t(11) = 3.88$, $p = .002$, pictures. Among the phobic subjects there were no differences among conditions in the right amygdala ($ps > .19$). For the control subjects, there were no differences among conditions ($ps > .17$). There were no other main effects or interactions for the time to onset ANOVA ($ps > .18$).

Time to Peak. Similar to the time to onset effects, for the time to the peak of the hemodynamic response in the amygdala there was a significant Group × Condition interaction, $F(2,50) = 5.74$, $p = .006$, such that phobic subjects had a faster peak of BOLD response to spider pictures for both left, $t(25) = 3.38$, $p < .002$, and right, $t(25) = 3.02$, $p < .006$, hemispheres (Figure 2). The two groups did not differ in time to peak for negative ($ps > .50$) or neutral ($ps > .55$) conditions for either hemisphere. Phobic subjects showed faster time to peak in response to spider compared with neutral [left: $t(11) = 3.44$, $p = .005$; right: $t(11) = 1.59$, $p = .13$] and negative [left: $t(11) = 2.60$, $p = .02$; right: $t(11) = 3.12$, $p = .009$] pictures. Among control subjects there were no differences between conditions ($ps > .14$). There were no other main effects or interactions for this parameter ($ps > .12$).

Percent Signal Change. In contrast to the findings for time to onset and time to peak, there was no Group × Condition interaction, $F(2,50) = 1.33$, $p > .25$, for percent signal change (Figure 3). There was a main effect for Condition, $F(2,50) = 4.42$, $p < .02$. Bilaterally, responses were smaller to neutral pictures than to spider, $t(25) = 1.89$, $p < .07$, and negative, $t(25) = 3.46$, $p < .002$, pictures across both groups. There was no difference in percent signal change between spider and negative pictures ($p > .30$). Planned contrasts comparing percent signal change in response to spider versus neutral pictures among the phobic subjects revealed marginally greater activation in response to
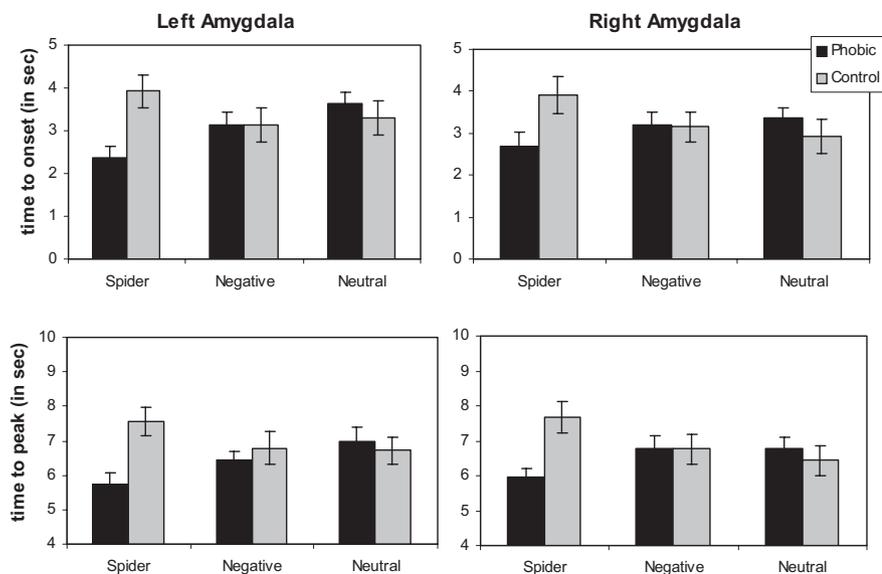
Figure 2. Mean time to onset (top) and time to peak (bottom) of the blood oxygen level–dependent signal for the amygdala regions of interest. Left and right amygdala time to onset and time to peak (in sec) are plotted on the y axis, with group and condition on the x axis.

spiders in the right, $t(11) = 2.05$, $p < .06$, but not left amygdala ($p > .30$).[1] A main effect for Hemisphere, $F(1,25) = 4.76$, $p < .04$, revealed larger percent signal change in the left than right amygdala, $t(25) = 2.21$, $p < .04$, across both groups and all picture types. There was no main effect for Group ($p > .35$). In addition, there were no significant interactions ($ps > .25$).

Specificity of Time Course Variables Versus Magnitude: Relations Between Picture Ratings and Amygdala ROI Variables

The hemodynamic response time variables were associated with self-reported arousal in response to the pictures, whereas percent signal change of activation was not (Figure 4). Entered as the first step in a hierarchical regression, left amygdala spider–neutral time to onset predicted 27.3% of the variance in arousal ratings, $F(1,23) = 8.63$, $p < .007$, with left amygdala percent signal change adding .1% of variance ($p > .80$). Reversing the order of entry, spider–neutral percent signal change predicted a nonsignificant .6% of variance in arousal ratings ($p > .70$), with time to onset contributing an additional 26.8% of variance, $F(2,22) = 8.13$, $p < .009$. Similarly, for time to peak when entered as the first step in the regression, left hemisphere time to peak predicted 36.0% of the variance in spider–neutral arousal ratings, $F(1,23) = 12.93$, $p < .002$, with percent signal change adding .5% of the variance ($p > .65$). When entered first, percent signal change predicted an almost identical .6% of the variance in arousal difference scores, $F(1,23) = .14$, $p > .70$, with the bulk of the variance being predicted by time to peak (35.9%), $F(2, 22) = 12.43$, $p < .002$. Similar results were present for the right

amygdala, with percent signal change accounting for 2.6% of the variance when entered as the first step, $F(1, 23) = .62$, $p > .40$, time to peak adding 21.5%, $F(2,22) = 6.22$, $p < .02$, and in a separate regression time to onset adding a marginally significant 14.3%, $F(2,22) = 3.78$, $p < .06$. No significant effects were found for time to onset, time to peak, or percent signal change in predicting negative–neutral activation, suggesting that variations in amygdala hemodynamics are consequential for subjective reactivity to phobic stimuli specifically. As is evident in the scatterplot the phobic subjects rated spider pictures as more arousing than the controls, $t(23) = 9.79$, $p < .001$.

Modeling Results

To understand the patterns of neural activity that could lead to the observed BOLD responses for spider pictures (Figure 1), a series of models was calculated in which a boxcar function representing the hypothetical neural left amygdala response was allowed to vary in terms of amplitude, onset, duration, or any combination of these parameters and then convolved with a canonical hemodynamic response. To determine the goodness of fit of these models, difference waveforms were created (phobic minus control) for both the estimated and empirically observed time series. Intraclass correlations were computed between these empirical and estimated difference waveforms. Although the model allowing only amplitude to vary also resulted in a fit that yielded a significant intraclass correlation between estimated and empirical group difference waveforms (Figure 5, model 3; ICC = .50, $p < .009$), the model allowing both amplitude

[1]To determine whether any voxels in the amygdala exhibited greater percent signal change for spider compared with neutral pictures for the phobic subjects, a voxelwise Group × Condition ANOVA on this variable was calculated using AFNI. Image data were converted to Talairach space (Talairach and Tournoux 1988). An alpha level of .05 (two-tailed) corrected for multiple comparisons was determined by combining an alpha significance threshold of .005 (uncorrected) with a Monte-Carlo simulation estimated spatial extent threshold of 110 mm³. Using these criteria no Group × Condition interaction was detected in the amygdala for percent signal change. A subsequent t test, however, did reveal a small cluster, indicating greater percent signal change to spiders compared with neutral pictures in the left amygdala among the phobic subjects (centroid: x: −19, y: −1, z: −12).
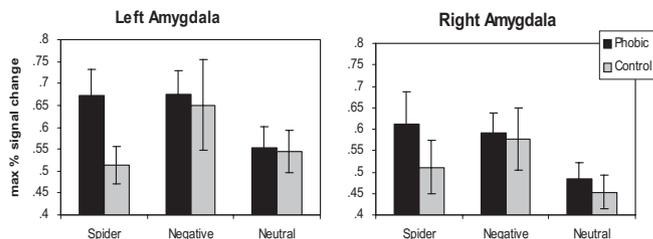

Figure 3. Mean percent signal change of the blood oxygen level–dependent signal for the amygdala regions of interest. Left and right amygdala percent signal change from baseline is plotted on the y axis, with group and condition on the x axis.
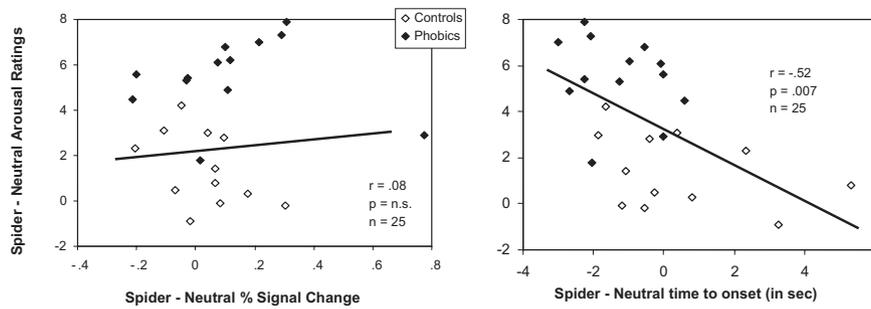
Figure 4. Scatterplots of the correlations between self-reported arousal ratings of the picture stimuli and amygdala time to onset and percent signal change of blood oxygen level–dependent (BOLD) response across all subjects. The Likert scale ranged from 1 to 9, with higher numbers reflecting greater subjective arousal. As can be seen in the figure, time to onset (right) of left amygdala BOLD signal accounts for significant variance in ratings of stimulus arousal, whereas percent signal change (left) does not. All variables are spider–neutral difference scores. Correlations were also computed separately for each group. For the control subjects, % signal change: $r = -.44$, $p = .15$, and time to onset: $r = -.37$, $p = .24$. For the phobic subjects, % signal change: $r = -.02$, $p > .90$, and time to onset: $r = -.23$, $p > .40$. After removal of the outlier for the phobic group for the % signal change correlation, $r = .59$, $p = .04$.

and duration to vary was a significantly better fit (Figure 5, model 4; ICC = .96, $p < .0005$; comparison of dependent r values: $t(49) = 27.4$, $p < .005$). No other model tested achieved a significant fit between observed and estimated group difference waveforms ($ps > .38$). Intraclass correlations between estimated and empirical group difference waveforms were significantly greater for the model allowing amplitude and duration to vary than for all other models tested ($ps < .005$). As shown in Figure 5, model 4, the boxcar model of hypothetical neural activity that best generated the observed

hemodynamic responses suggested that spider phobic subjects had a larger but shorter lasting amygdala response to spider pictures than control subjects.

To examine whether these results were robust to variation in the shape of the presumed underlying neural response, the variation in the amplitude and duration of a half-sine wave shaped neural response was also fit. The results, shown in Figure 5, model 5, are similar to those shown using the boxcar responses; patients were predicted to have stronger but less sustained neural responses. The
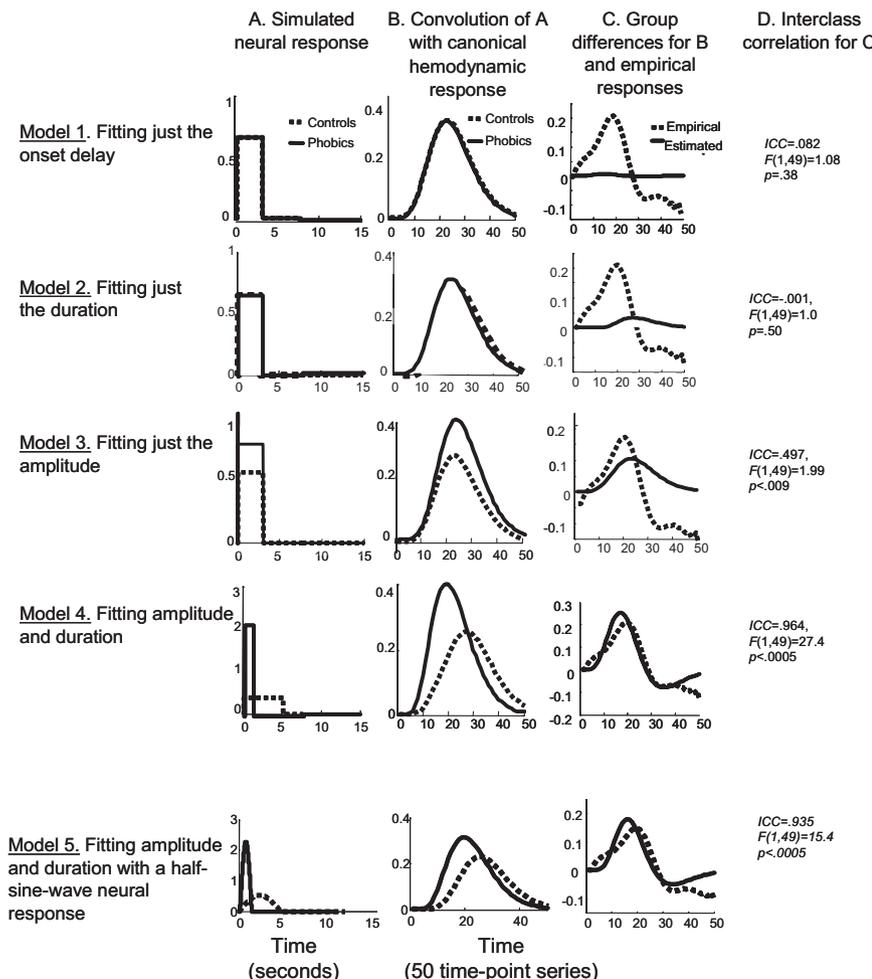

Figure 5. Results of the modeling procedures. The first column identifies the parameter of the boxcar function that was allowed to vary for each model. The second column depicts the boxcar representing the hypothetical neural response that yielded the best fit between observed and estimated waveforms for that model. The third column represents the result of convolving this best-fitting boxcar with a canonical hemodynamic response. The ideal outcome would be waveforms identical to the observed blood oxygen level–dependent (BOLD) responses depicted in Figure 1. The fourth column depicts the degree to which the estimated response (from the model fitting) actually fits the empirical data (the raw BOLD time courses from Figure 1). The waveforms presented are difference curves representing the difference in time course between phobic and control subjects for both the empirically observed and estimated data. Intraclass correlations between the empirical and estimated curves are presented in the last column. Models 1–4 used a boxcar function as the input for the hypothetical neural response. For comparison purposes, Model 5 shows the results for the best-fitting model when a half-sine-wave function is used.

fit for this model was significant and comparable to the corresponding boxcar model (ICC = .94, $p < .0005$).

Discussion

These data suggest that amygdala activation in the very early stages of stimulus processing distinguish phobic from nonphobic responses. Faster time to onset and time to peak of amygdala BOLD responses to spiders consistently discriminated between groups and conditions. Model-fitting procedures demonstrated that these data could reflect a strong but brief activation among the phobic subjects and weaker but more sustained activation among the nonphobic subjects. Although the observed data could, of course, reflect other group differences in the shape of the neural response, the consistent observed qualitative pattern of group differences using multiple profiles of plausible neural responses suggests that at least the observed facilitation in the BOLD signal could result from factors other than a faster amygdala response. The simulations further suggest that strong neuronal firing in the amygdala occurring early during stimulus processing followed by decreased firing could represent key components of the phobic fear response. In contrast a more sustained pattern of amygdala activity, potentially lasting for multiple seconds in response to spider stimuli, could be present in healthy individuals.

In addition, although the time to onset and time to peak variables (reflecting early differences in amygdala activation) predicted ratings of arousal in response to the phobia-relevant pictures, magnitude of activation did not. Within- and between-group effects for magnitude of response were also somewhat less robust than those observed for time to onset and time to peak. As peak magnitude of response typically occurs several seconds into the trial, the more modest effects for magnitude of amygdala activation seen here are also consistent with the notion that responses in the initial phase of stimulus processing in particular are related to phobic fear. In contrast, early processing differences robustly discriminated responses to phobogenic stimuli.

Amygdala and Rapid Detection of Threat

Evolutionary accounts of the instantiation of fear systems in the brain have emphasized early and reliable recognition of threatening stimuli as a crucial key to survival (Öhman and Mineka 2001). Individuals with specific phobia exhibit an exaggerated preattentive bias for identifying threatening animals embedded in a complex visual display (Miltner et al 2004; Öhman et al 2001). Phobic individuals also exhibit rapid onset of fear-potentiated blink response to phobogenic pictures (Globisch et al 1999), and elevated skin conductance responses to masked phobia-relevant stimuli (Öhman and Soares 1994). Phobic fear responses are thought to operate in a relatively crude fashion with an emphasis on minimizing false negatives at the risk of an increased number of false positives (LeDoux 1996; Öhman and Mineka 2001). Indeed, previous investigators have suggested that individuals with phobias fail to circumvent "false" fear reactions that may normally be circumvented via more extensive cortical processing (Wik 1997).

These findings are in keeping the mounting evidence implicating the amygdala in automatic processing of stimuli signaling potential threat. Amygdala activation is evident in response to backwardly masked fear faces (Etkin et al 2004; Whalen et al 1998) and masked faces that have been paired with an aversive stimulus (Morris et al 1998). Importantly, patients with posttraumatic stress disorder exhibit accentuated amygdala activation to masked fear faces, suggesting that the amygdala may play a key

role in mediating preconscious response biases evident in anxiety disorders (McNally 1995). Consistent with the notion that an adaptive fear detection system will function independently of the current focus of attention, amygdala responses to fear-related stimuli are unaffected by manipulation of spatial attention (Vuilleumier et al 2001) or instructions to focus on nonaffective aspects of the stimulus (Bishop et al 2004; Mathews et al 2004). These data are consistent with the notion that in its role as a detector of emotionally relevant stimuli, the amygdala may act relatively automatically, independent of input from higher cognitive control (LeDoux 2000; Morris et al 1998, 1999). Although in many instances this automaticity clearly serves an adaptive function, in clinical populations the intensity of this response may hinder habituation over time and facilitate the maintenance excessive fear, such as that seen in specific phobia.

In keeping with these data on the automaticity of amygdala responses to potential threat, Öhman and Soares (1994) suggested that rapid, automatic activation of the amygdala in particular facilitates phobic responses, perhaps via the "quick and dirty transmission route" described by LeDoux (2000). The amygdala can be rapidly activated by incompletely processed stimuli via a direct pathway from thalamic nuclei with minimal input from higher cortical regions (Amaral et al 1992; Doron and LeDoux 1999). Supporting the claim that rapid processing can occur via the direct thalamoamygdalar pathway, auditory fear conditioning induces plasticity in amygdala neurons (Quirk et al 1995, 1997), and this plasticity is evident earlier than that seen in auditory cortex, suggesting that the early plasticity in amygdala neurons results from direct thalamoamygdala projections (Öhman and Mineka 2001). A direct visual thalamoamygdalar pathway has also been identified and implicated in fear conditioning (Shi and Davis 2001), with particular emphasis on fear-conditioning-induced plasticity in the lateral amygdala (Pare et al 2004). In humans, covariation between the amygdala and posterior thalamus has been found in response to masked conditioned faces (Morris et al 1999, 2001) and fearful faces presented at low spatial frequency (Vuilleumier et al 2003). Furthermore, a normal pattern of posterior thalamic-amygdala covariation is evident in a patient with an extensive lesion to left primary visual cortex, even when stimuli are presented to his blind hemifield and thus not consciously detectable (Morris et al 2001). These data suggest that the thalamoamygdalar pathway may be specialized for processing of relatively coarse fear-related stimuli. Although this circuitry may be adequate only for processing very crude environmental stimuli, the existence of this pathway underscores the possibility that the amygdala is involved in rapid, automatic processing of emotional stimuli. In specific phobia, the amygdala may be overly tuned to respond to incoming sensory information related to the target of the phobia.

Vigilance–Avoidance Model

The computational modeling results indicating strong but brief activation of the amygdala in phobia are consistent with the "vigilance–avoidance" model of anxiety (Amir and Foa 2001; Mogg and Bradley 1998; Mogg et al 1987), which suggests that when phobic individuals perceive a threatening stimulus, they have a strong immediate fear response and then quickly avert their attention. Reaction time data in evaluation of threat-related words suggest that phobic individuals show initial engagement followed by avoidance (e.g., Amir et al 1998). Recent eye-tracking data indicate that when scanning a complex scene that includes spiders, phobic individuals quickly make a first fixation on a spider, but after the first several fixations, they consistently

fixate on locations further away from spider targets than do nonphobic individuals (Pflugshaupt et al 2005).

Our data are also consistent with the vigilance–avoidance hypothesis and could suggest that the amygdala is primarily involved in the early vigilance response associated with phobia. Previous work has suggested that the amygdala is associated with vigilance and attending to potentially salient stimuli in the environment (Davis and Whalen 2001). As described previously, hypervigilance and rapid, automatic responding to phobia-relevant stimuli are key features of specific phobia (Öhman et al 2001; Globisch et al 1999). Strong, early activation of the amygdala may embody the "vigilance" portion of the vigilance–avoidance hypothesis. In addition to its role in vigilance, other investigators have suggested that the amygdala also controls phobia-related avoidance behaviors (McNaughton and Corr 2004). Thus, the amygdala may be implicated in both initial vigilance to threat and subsequent avoidance. Although other evidence suggests that in some cases anxious individuals sustain attention to threat-related stimuli longer than other people (e.g., Fox et al 2002), our data do not suggest that the amygdala is involved in that process in specific phobia.

Finally, the model prediction that nonphobic individuals may have relatively sustained responses to emotional stimuli is also consistent with existing data. There are few data regarding whether this time course of activity is present in animals or primates to the types of stimuli shown in the current experiment, but related data supports this notion. Event-related-potential data, which are not subject to the same lagged measurements in BOLD imaging, suggests that healthy individuals have observable slow-wave brain responses to emotional picture stimuli lasting at least 5 sec (e.g., Cuthbert et al 2000). Similarly pupillary reactions (an index of cognitive and emotional processing [Beatty and Lucero-Wagoner 2000] known to reflect amygdala activity indirectly [Koikegami and Yoshida 1953]) lasting over 4 sec following behavioral reactions to affective words in healthy individuals have also been observed (Siegle et al 2001). These are summative indices of brain activity and do not uniquely reflect amygdala activity but rather suggest that human brain reactions to emotional stimuli may be sustained. Animal data more directly suggest that amygdalar reactions to aversive behavioral stimuli may be sustained for minutes or hours (McIntyre et al 2002; Pelletier et al 2005). Together these data are consistent with the idea that in healthy individuals, brain reactions potentially involving the amygdala might be sustained for at least seconds in response to an aversive stimulus.

From Phobic Response to Phobic Disorder: Decreased Sustained Activity and Failure to Habituate

Sustained strong amygdala activity could be associated with undesirable sustained emotional processing and elaboration (Siegle et al 2002). Thus, the shorter duration of observed high magnitude activity in the phobic individuals could be considered adaptive in the moment. If engagement is necessary to extinguish fear reactions, however, quick disengagement among phobic individuals could contribute to failure to habituate and extinguish phobic fear. This notion is consistent with thinking on the mechanisms via which the vigilance–avoidance model is associated with maladaptive anxiety and fear. As Mogg and Bradley (1998) postulated, the vigilance–avoidance pattern of fear responding may maintain anxious responses over time through a two-stage process. First, the enhanced vigilance leads to more ready detection of threatening stimuli, and second, the subsequent cognitive avoidance interferes with habituation to the

stimuli as well as opportunities for objective assessment of the true extent of the threat potential of the stimulus. The data from our study suggest that specific phobia may be characterized by dysregulation in both the initial response, as well as the capacity to subsequently downregulate the fear response due to avoidance-mediated disruption of habituation. The amygdala in particular may play a role in one or both of these dysregulated processes and thus be an important link in the neural circuitry that maintains a phobic disorder.

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