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Neural Correlates of Anticipation and Uncontrollability in Snake Phobia

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INTRODUCTION

Anticipation and uncontrollability have been implicated as major contributors to anxiety disorders in general (Barlow, 2002). Consistent with a large literature on brain responses to aversion, a recent study in our laboratory (Nitschke et al., 2006) implicated a number of brain regions in the anticipation of and response to aversive pictures, including the anterior cingulate cortex (ACC), insula, amygdala and orbital frontal cortex (OFC). The present event-related fMRI study enrolled volunteers both with and without specific phobia of snakes to identify the neural areas recruited in the anticipation of and response to videos of differing emotional content (snake, fish, disgust). Uncontrollability was manipulated by giving subjects control on half of the trials to avoid viewing the videos. Barlow's theory of anxiety emphasizes uncontrollability as one of the most important generalized psychological influences on the development of specific phobia. Research on anxiety has investigated controllability (Armfield et al. 1996; Drugan et al. 1997; Gladstone et al. 2003), but no study has examined its effects on the neural correlates of anxiety.

HYPOTHESES

1. In phobics, anticipation of snake videos will activate regions identified in Nitschke et al. (2006), including the insula and amygdala.

2. Uncontrollability over video presentation will result in larger neural responses than when video presentation can be controlled.

3. Non-phobics are expected to show anticipation and uncontrollability effects for the disgust videos but not the snake videos.

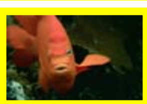
METHODS

Participants

Two groups of participants were studied. **Snake phobics** consisted of 12 participants (9 females, mean age 23, range 18-46) and **Non-phobics** consisted of 12 participants (4 females, mean age 23, range 19-35). Participants were right-handed and neurologically healthy. Phobics met criteria for DSM-IV diagnosis of specific phobia of snakes and were absent of all other clinical disorders as assessed by the Structured Clinical Interview for the DSM-IV (First et al. 1996). Non-phobics were absent of all clinical disorders including specific phobia of snakes as assessed by the SCID. Informed consent in accordance with rules set by the University of Wisconsin at Madison Human Studies Committee was obtained from all participants prior to the experiment.

Stimuli

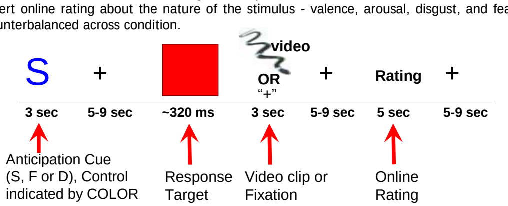
The stimuli consisted of 3-s snake, fish, and disgust videos (24 each). Each video was standardized for several psychological attributes (e.g. arousal, valence, disgust, fear) during pilot rating sessions prior to the study. Physical attributes such as brightness, contrast, scene complexity and movement of the stimuli were equalized. Videos were presented to participants in the scanner using Avotec goggles mounted on the head coil of a 3.0 Tesla GE SIGNA Scanner (TR=2 s).



Procedure

Experimental Paradigm:

Participants were administered several anxiety and phobia questionnaires, followed by a mock scanner session during which they practiced the experimental task. Each trial began with an anticipation period signaled by a cue. An S preceded snake videos, a D preceded disgust videos, and an F preceded fish videos. Subjects were instructed at the onset of the study that they would be receiving these videos. Uncontrollability was indicated by the color of the anticipation cue. A blue or yellow cue indicated a controllable trial, and the other color indicated an uncontrollable trial. When a subject had an uncontrollable trial, they invariably receive the video. When a subject had a controllable trial, if reaction time (RT) was fast enough to a red target square that followed the cue after a variable delay, they received a fixation cross rather than the anticipated video. Otherwise, they received the anticipated video. Of the 72 total video trials, half were cued as uncontrollable and the other half controllable. A success rate of approximately 50% was achieved with online monitoring of RT by DMDX software. Each trial ended with one Likert online rating about the nature of the stimulus - valence, arousal, disgust, and fear - counterbalanced across condition.



Data Analysis

Our fMRI analysis procedures (artifact removal, head movement compensation and atlas transformation) are detailed in previous publications (Mackiewicz et al. 2006) and are available in a handout. The data were analyzed using a least-squares general linear model (GLM) fit to the gamma variate hemodynamic response function (GAM) to fit the cue (Epoch 1), video/fixation (Epoch 2), and rating/fixation (Epoch 3) periods upon which voxel wise t tests were performed. Cluster extraction analyses were then performed on the resultant percentage signal change maps with a threshold of $p<.005$ with a voxel size of 1 mm^3 (voxel sizes of each cluster are indicated in Figures).

RESULTS

Anticipation

In phobics, anticipation of snake videos activated ACC, bilateral insula and bilateral amygdala more than anticipation of fish and disgust videos **(Figure 1, 2).** In non-phobics, anticipation of disgust videos activated bilateral insula, bilateral OFC and dorsal and perigenual ACC more than anticipation of fish or snake videos **(Figure 4).** There was a significant difference between anticipation of fish and snake videos in non-phobics in that anticipation of the fish video activated the right insula. Activation effects were mirrored in the video response data **(Figure 3a, 3b, 5).**

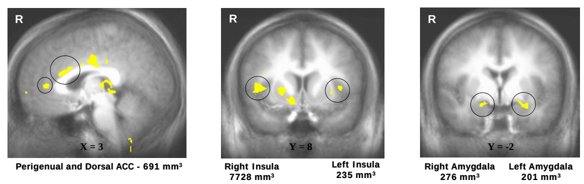


Figure 1. Phobics - ROI that distinguish activity to anticipation of a snake cue as compared to fish in the ACC, bilateral insula and bilateral amygdala. All differences are significant at $p<0.005$ (see Figure 3a for complementary video response data).

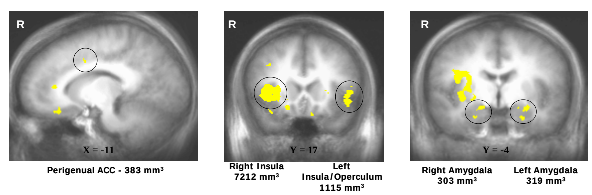


Figure 2. Phobics - ROI that distinguish activity to anticipation of a snake cue as compared to disgust in the perigenual ACC, bilateral insula/operculum and bilateral amygdala. All differences are significant at $p<0.005$ (see Figure 3b for complementary video response data).

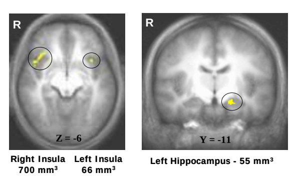


Figure 3a. Video Responses for Phobics ROI that distinguish activity to viewing snake videos as compared to fish in the bilateral insula and left hippocampus ($p<0.005$).

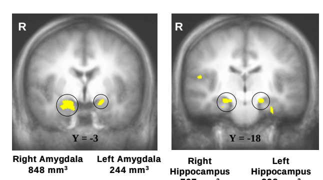


Figure 3b. Video Responses for Phobics ROI that distinguish activity to viewing disgust videos as compared to fish in the bilateral amygdala and bilateral hippocampus ($p<0.005$).

RESULTS

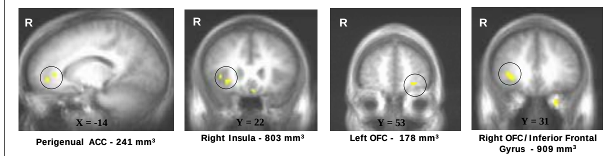


Figure 4. Non-phobics - ROI that distinguish activity to anticipation of a disgust cue as compared to snake in the perigenual ACC, right anterior insula and bilateral OFC/inferior frontal gyrus. All differences are significant at $p<0.005$.

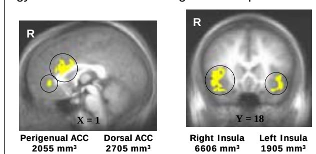


Figure 5. Video Responses for Non-Phobics ROI that distinguish activity to viewing of disgust videos as compared to fish in the perigenual and dorsal ACC and bilateral insula. All differences are significant at $p<0.005$.

Uncontrollability

The most salient stimuli for the phobic participant group showed accentuated activity in the insula and ACC when it was uncontrollable, versus controllable as a function of worry, as measured by the Penn State Worry Questionnaire **(Figure 6a)**, and anxiety, as measured by the Hamilton Rating Scale for Anxiety **(Figure 6b).**

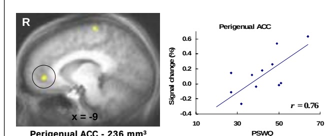


Figure 6a. Phobics - ROI that distinguishes larger activity during anticipation of an uncontrollable snake cue as compared to a controllable snake cue in the perigenual ACC was associated with increased worry on the PSWQ ($p<0.005$).

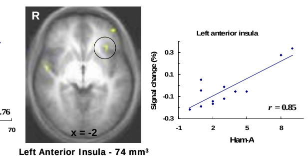


Figure 6b. Phobics - ROI that distinguishes larger activity during anticipation of an uncontrollable snake cue as compared to a controllable snake cue in the left insula was associated with increased anxiety on the HAM-A ($p<0.005$).

CONCLUSIONS

1. As predicted, anticipation of aversive events led to greater activation in the ACC, bilateral insula, amygdala and OFC. For the phobics, this was especially the case for the anticipation of snake videos. The non-phobics predominantly showed anticipation effects for the disgust videos in comparison to the snake. Uncontrollability appeared to act as a moderator on the activation observed in phobics with elevated worry and anxiety.

2. These anticipation and uncontrollability effects indicate that for the phobics, the snake stimuli are most salient. On the other hand, for the non-phobics, the disgust stimuli are most salient and show anticipation effects similar to that of the phobics for the snake stimuli.

REFERENCES

1. Barlow DH, 2002. Anxiety and its disorders (2nd ed.). New York: Guilford Press.
2. Armfield JM, Mattiske JK, 1996. Behavior Research Therapy 34, 899-909.
3. Drugan RC, Basile AS, Ha JH, Healy D, Ferland RJ, 1997. Brain Res Brain Res Protoc 2, 69-74.
4. Gladstone G, Parker G, 2003. Australian and New Zealand Journal of Psychiatry 37, 347-354.
5. Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ, 2006. NeuroImage 29,106-116.
6. First MG, Gibbon M, Spitzer R, Williams J, 1996. User's Guide for the Structured Clinical Interview for the DSM-IV Axis I Disorders—Research Version. Biometrics Research Dept, NY.
7. Mackiewicz KL, Sarinopoulos I, Cleven KL, Nitschke JB, 2006. Proc Natl Acad Sci USA Sep 19;103(38):14200-5.

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