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Brain, body, and cognition: Neural, physiological and self-report correlates of phobic and normative fear

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ABSTRACT

The phobic fear response appears to resemble an intense form of normal threat responding that can be induced in a nonthreatening situation. However, normative and phobic fear are rarely contrasted directly, thus the degree to which these two types of fear elicit similar neural and bodily responses is not well understood. To examine biological correlates of normal and phobic fear, 21 snake phobic and 21 nonphobic controls saw videos of slithering snakes, attacking snakes and fish in an event-related fMRI design. Simultaneous eletrodermal, pupillary, and self-reported affective responses were collected. Nonphobic fear activated a network of threat-responsive brain regions and involved pupillary dilation, electrodermal response and self-reported affect selective to the attacking snakes. Phobic fear recruited a large array of brain regions including those active in normal fear plus additional structures and also engendered increased pupil dilation, electrodermal and self-reported responses that were greater to any snake versus fish. Importantly, phobics showed greater between- and within-subject concordance among neural, electrodermal, pupillary, and subjective report measures. These results suggest phobic responses recruit overlapping but more strongly activated and more extensive networks of brain activity as compared to normative fear, and are characterized by greater concordance among neural activation, peripheral physiology and self-report. It is yet unclear whether concordance is unique to psychopathology, or rather simply an indicator of the intense fear seen in the phobic response, but these results underscore the importance of synchrony between brain, body, and cognition during the phobic reaction.

1. Introduction

The expression of fear is associated with an adaptive set of behaviors and central and autonomic nervous system responses that serve to protect the organism in the face of danger (Ohman & Mineka, 2001). When presented with a threat, physiological changes including increased heart rate (Moratti & Keil, 2005; Sartory, Rachman, & Grey, 1977) and dilated pupils (Reinhard, Lachnit, & König, 2006) ready the body to fight or flee. This evolutionarily adaptive response becomes maladaptive in simple phobic fear, in which an intense fear response can be provoked by a stimulus not immediately threatening to the body, such as a photograph of a snake. Autonomic reactions to phobic provocation mimic those in normative fear responding (Davidson, Marshall, Tomarken, & Henriques, 2000; Sarlo, Palomba, Angrilli, & Stegagno, 2002), and neuroimaging studies of phobic fear demonstrate activation in visual, motor, affective, and sensory brain networks (Schienle, Schafer, Hermann, Rohrmann, & Vaitl, 2007; Straube, Mentzel, & Miltner, 2006). These networks overlap with regions implicated in fear conditioning (Knight, Cheng, Smith, Stein, & Helmstetter, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004), and presentation of fearful images (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005), which find activation patterns involving similar regions such as the supplementary motor area and amygdala.

Despite similarities in autonomic responding and overlapping brain networks, some sequelae may be unique to phobic fear. Behavioral avoidance (Hamm, Cuthnert, Globisch, & Vaitl, 1997) and increased environmental vigilance (Kindt & Brosschot, 1997; Koch, O'Neill, Sawchuk, & Connolly, 2002) have been strongly associated with phobic fear. In addition, although phobics often overestimate the inherent danger of their feared stimuli (e.g. Arntz, Lavy, Van den Berg, & Van Rijsoort, 1993; Mizes, Landolf-Fritsche,

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& Grossman-McKee, 1987), many phobics also recognize that their fear is irrational and are quite embarrassed by it (Davidson, 2005; Mayer, Merckelbach & Muris, 2000). This apparent conflict between explicit cognition and emotional reaction may be explained by the uncontrollable, automatic nature of the phobic reaction and its involvement of many brain and bodily systems (Ohman & Mineka, 2001). This conflict may also lead to increased attempt at emotion regulation during fear provocation in phobic individuals, in an effort to dampen or control the reaction, although they are ultimately unable to do so (Hermann et al., 2009).

This uncontrollable and automatic sensation across multiple body systems is suggestive of the theory of concordance, the notion that indices of emotion should correlate, or cohere. However, empirical support for this theory has been mixed (Fernández-Dols, Sánchez, Carrera, & Ruiz-Belda, 1997; Matsumoto, Nezlek, & Koopmann, 2007; Rosenberg & Ekman, 1994), even in the study of specific phobia (Duinen, Schruers, & Griez, 2010). Particularly important are negative findings for correlation between subjective self-report and physiology (e.g. Gross & Levenson, 1993), which call into question the reliability of self-reported experiences of emotion. However, the concordance of systems associated with emotion has been observed to vary as a function of perceived intensity, with higher intensity responding linked to greater systemic concordance (Mauss, Levenson, McCarter, Willhelm, & Gross, 2005; Rosenberg & Ekman, 1997). Intense phobic responses have likewise shown concordance between self-reported fear and physiological response (Sartory et al., 1977), and this concordance may be important to intense experiences that feel subjectively automatic or overwhelming.

The current study sought to contrast normative and phobic fear to discern similarities and distinctions in their neural and physiological correlates. To this end, phobic and nonphobic participants were presented with videos of snakes, both threatening clips of snakes striking in the direction of the viewer, and nonthreatening snakes slithering along the ground. In this way, the normative reaction of a nonphobic person to an attacking fearful snake stimulus can be compared to the phobic response to a less obviously threatening snake and a more complete picture of fear can be obtained. We hypothesized that normative fear would recruit regions frequently associated with threat and fear such as the amygdala, thalamus and insula (Hariri et al., 2003; Williams et al., 2005). In contrast, we hypothesized the neural correlates of phobic fear would involve an overlapping, but much more extensive set of brain regions. Unlike normative threat responding, phobic fear is often associated with feelings of disgust (de Jong, Peters, & Vanderhallen, 2002), and greater environmental awareness (Öhman, Flykt, & Esteves, 2001). Therefore, we hypothesized that phobia-specific activation in the insula (Wicker, Keyeere, Plially, Gallese, & Rizzolatti, 2003) and visual processing regions in temporal and parietal cortices (Lloyd, Morrison, & Roberts, 2006) would be observed. Further, as phobics report embarrassment and self-consciousness during fear responses (Davidson, 2005), we expected prefrontal activation unique to phobic fear in regions associated with emotion regulation (Goldin, McRae, Ramel, & Gross, 2008).

We were also specifically interested in whether responses would correlate across the multiple systems being measured, and whether this occurred in both phobic and normative fear. To test for concordance during phobic fear provocation across multiple systems, we collected self-reported affect, functional brain data and several measures of peripheral physiology. Given the intensity of phobic symptom provocation, we hypothesized that phobic fear would be associated with greater and more consistent relationships among indices.

2. Methods

2.1. Participants

A total of 24 snake phobic and 25 nonphobic control female subjects were enrolled in the study. Potential participants were recruited through an Introductory Psychology class and flyers displayed throughout the community requesting participants for a study of snake phobia. Exclusion criteria for all subjects included MRI contraindication (e.g. pacemaker), claustrophobia, left-handedness, and history of head trauma. Enrollment was limited to females due to the higher incidence of snake phobia in women as compared to men; creating a sample that was balanced across gender in the snake-phobic group may have proven difficult. Eligible phobic participants scored greater than 18 on the Snake Questionnaire (SNAQ; Klieger, 1987); control participants scored 3 or less. Diagnostic interviews were not conducted to evaluate phobics for clinically relevant simple phobia because it was felt that the rarity of snakes in Wisconsin limited the daily impact of the fear; restricting the sample to clinical significance was unnecessarily strict. Three phobic subjects completed the simulation session but were not scanned: two subjects discontinued their enrollment due to fear of the stimuli and one subject could not be comfortably positioned in the MRI simulation mock scanner used to prepare participants for the scanning environment. Technical difficulties caused data from four control subjects to be unusable, due to spatial warping of the functional data and/or problems with acquisition of functional data. The final sample size was 42, 21 of each phobic and control participants. The average age of phobic participants was 19.6 years; control subjects were on average 20.4 years old.

2.2. Procedure

Enrolled participants first completed a simulation session in a mock MRI scanner to familiarize them with the scanning environment and ensure tolerability of the fearful stimuli. Subjects were placed in the mock MRI scanner and shown stimuli similar but not identical to those used in the experimental trials. The real MRI scanning session occurred a few days to at most two weeks later, during which video clips were presented as MR images, pupillary response, and electrodermal activity data were collected. After MR scanning, subjects rated half of the video clips (randomly presented, half counterbalanced) presented on a computer outside the scanner. Valence and arousal ratings were collected for each video clip on a 1–7 Likert scale. Written informed consent was given in accordance with the Human Subjects Committee of the University of Wisconsin and subjects were paid eighty dollars for participation.

2.3. Design and materials

Subjects were presented with 48 video clips approximately 2 s in duration, 16 exemplars each of 3 types of videos. Video clip types included: snakes threatening in the direction of the camera, snakes slithering across the ground, and fish. Clips were selected from a variety of nature programs. Slithering snakes and fish were equated for direction of movement, i.e. toward versus away from the camera. Clips were presented in random order in an event-related design with an average of 8 s of black screen between clips (average ITI = 10 s, range 8–12 s).

2.3.1. Pupillary, electrodermal and self-report data collection and analysis

An iView × system (v. 1.3.31) with eyetracking capabilities was integrated with the fiber optic goggles used to present the video stimuli. Horizontal pupil diameter was acquired during fMRI scanning at a sampling rate of 60 Hz, and data were processed using algorithms developed by Siegle, Steinhauer, and Thase (2004) using MatLab software (MathWorks, Natick, MA). Blinks were identified and removed using amplitude thresholds and remaining data were *Z*-scored within each participant. Pupillary data were lost from 2 phobic subjects for which heavy eye makeup caused difficulties in the software identifying the pupil. In remaining subjects, for each video the average pupillary diameter was calculated for an 8-s window from video onset, and the average response across all video presentations of each type threatening snake, slithering snake and fish were entered into a Video Type × Group ANOVA. Estimated pupil response for individual videos were used for the concordance analyses described below.

Electrodermal response (EDA) was also collected simultaneous to fMRI trials, using 8 mm Ag–Ag/Cl electrodes placed on the distal phalanges of the index and middle fingers of the left hand. EDA signal was processed with a Matlab routine developed in-house which low-pass filtered the data (0.7 Hz cutoff), and identified peaks exceeding 0.05 μS in height. Due to the cold temperature in the scan room and high-frequency noise interference from the MR signal, only 13 subjects from each group showed a reliable EDA response, which was defined as having at least 2 identified peaks exceeding the 0.05 μS cutoff from each of the 3 video conditions. For these subjects, amplitude and frequency of response was calculated across each video type, and these values were entered into separate Video Type × Group ANOVAs. Generally, participants excluded from EDA analyses did not show suprathreshold responses to the fish videos, and to the slithering snakes for control participants. Had all data been included, the resultant ANOVAs would have been highly imbalanced.

Self-reported valence and arousal ratings were collected after completion of MR data acquisition on a computer outside the scanning room. To constrain the length of

the experiment, each participant viewed half (order counterbalanced) of the videos presented during the functional trials and rated them on a 1–7 Likert scale on valence and arousal. Ratings data were lost from one control subject due to computer failure. The average valence and arousal rating was computed for each video type, and these values were entered into separate Video Type × Group ANOVAs.

To assess whether these ancillary measures were describing overlapping variance in response, Bartlett's test of equality of covariance matrices was run comparing phobics and controls separately for each video type (threatening snake, slithering snake and fish) across the variables: average EDA amplitude, pupillary response, self-reported valence rating and self-reported arousal rating.

Significant interactions were probed with pairwise comparisons using a Least Significant Difference adjustment for multiple comparisons. Only post hoc comparisons of $p < 0.05$ are reported. Bartlett's test was computed with R software version 2.6.0 for Macintosh.

2.3.2. MR data collection and analysis

MR images were collected with GE SIGNA 3.0 Tesla scanner equipped with high-speed, whole-body gradients and a whole-head transmit-receive quadrature birdcage headcoil. After scanner calibration, a T1-weighted, high-resolution SPGR anatomical scan was collected for localization of function (124 axial slices, each 1.2 mm thick). Functional data were collected in one 9-min run of 272 echo-planar images (EPI timepoints).

A TR of 2 s was used (TE = 30 ms), to collect 30 interleaved 4 mm sagittal slices, gap = 1 mm. The field-of-view for each slice was 240 by 240 mm, with a 64 by 64 matrix. The resulting voxel size was 3.75 by 3.75 by 5 mm.

Data were processed with in-house software and the AFNI software package, version 2.52 for Mac OSX. Data processing steps included: data reconstruction with a 1-voxel radius Fermi filter, correction for differences in slice-timing, 6 parameter rigid-body motion correction and removal of skull and ghost artifacts. A least-squares GLM was run, fitting the timeseries from each voxel to an ideal Gamma Variate hemodynamic response and entering the motion parameters in as covariates. For the analyses of concordance described below, the response to each video was extracted separately; all other analyses were conducted on the average response to each stimulus type (threatening snakes, slithering snakes, fish). The heights of activation to each video type or individual video were transformed into Talairach space via identification of anatomical landmarks on the high-resolution anatomical scan, and then blurred with a Gaussian filter (FWHM = 2 mm).

Voxel-by-voxel ANOVAs were run, inputting the activation maps from each subject and stimulus type. The Group (phobic, control) by Video Type (threatening snake, slithering snake, fish) interaction was screened at $p = 0.005$ (mapwise $p = 0.05$ corrected). Voxels making the initial threshold for the Group by Video Type interaction were subjected to simple effects contrasts, thresholded at the $p < 0.005$ level, to determine the source of the interaction. Two a priori patterns of significance were extracted: (1) brain regions active during a normative fear response were those voxels showing greater response to threatening snakes versus slithering snakes within control subjects, and not showing significantly greater activation to slithering snakes versus fish in controls (2) brain regions active during phobic response were those showing greater activation to threatening and slithering snakes versus fish within phobic subjects and also showing greater activation in phobic versus control subjects during the viewing of all snakes. Given the size and extent of clusters showing a significant phobic response effect, some extending across multiple brain regions, clusters meeting significance for the phobic fear reaction were screened with the Talairach atlas provided with the AFNI suite (Cox, 1996) dividing clusters according to anatomical boundaries. Correction for multiple testing was achieved by imposing a voxelwise F-threshold and minimum cluster size, which has been demonstrated a sensitive method of alpha control (Logan and Rowe, 2004). Given the spatial correlation of the activation maps, Monte Carlo simulations determined that a voxel-wise cutoff of $p = 0.005$ and a minimum cluster size of 100 mm^3, a map-wise p-value of 0.05 was achieved.

Additional tests were run to examine the relationships between activation in identified brain regions, and between brain activation and ancillary measures. Analyses of concordance were run, both across- and within-subjects, to address how measures might be related. To assess whether activation across brain regions was more highly correlated in one group versus another across subjects, Bartlett's test of equality of covariance matrices was run comparing brain activation in phobics and controls separately for each video type (threatening snake, slithering snake and fish). This test compares shared variance between two matrices of data and can determine whether a set of variables is more related in one condition versus another. Clusters used in this analysis were those identified in the normative fear reaction, as these regions are active in both phobics and controls. To determine whether brain activation and ancilliary measures were correlated within-subjects, analysis of within-subject concordance was obtained by generating rank-order Spearman's R correlation maps between brain activation and pupillary response to each video of threatening snakes. Separate Spearman's R maps were obtained for each subject and these values were entered into a voxel-by-voxel t-test comparing the correlation between pupillary and brain response in phobics versus controls. Data from the threatening snakes condition was used in order to test for concordance specifically in the maximally salient condition for both groups. Pupillary response was used for concordance analyses because this variable provided the greatest range of response for both groups, as ratings data were near ceiling level for the phobic group and the modal electrodermal data response to the individual videos was less than 0.05 μS. Clusters meeting thresholds of $p < 0.005$ voxelwise and cluster size > 100 mm^3 were extracted and linear mixed models were run on cluster means to determine: (1) whether the ratings metrics also demonstrated within-subject concordance across either or both groups, and (2) if there were group by condition effects indicating significant activation to snake videos versus fish in one or both groups.

3. Results

3.1. Self-report

Both ratings metrics showed a significant Group (phobic, control) × Video Type (threatening snake, slithering snakes, fish) interaction [$F(2,38) = 59.3$, $p < 0.001$ for valence; $F(2,38) = 40.3$, $p < 0.001$ for arousal; see Fig. 1]. Planned comparisons showed that phobics found the threatening and slithering snakes to be more arousing and less pleasant than fish, $ps < 0.001$, and rated the threatening snakes as more arousing and less pleasant than the slithering snakes, $ps \leq 0.01$. Controls rated the threatening snakes as more arousing and less pleasant than either slithering snakes or fish, $ps \leq 0.001$, and rated the slithering snakes as less pleasant than fish, $p = 0.041$. Valence and arousal ratings of threatening snakes were lower in controls than in phobics, $ps \leq 0.01$.

3.2. Electrodermal activity

A Group (phobic, control) × Video Type (threatening snake, slithering snakes, fish) ANOVA on EDA data revealed a main effect for video type ($F(2,23) = 5.52$, $p = 0.011$). Planned comparisons demonstrated that threatening snakes increased the number and amplitude of electrodermal responses across both groups, $ps \leq 0.002$, see Fig. 2. No group differences or Group by Video Type interactions emerged.

3.3. Pupillary response

Average pupil dilation across 8 s from video onset showed a significant Group × Video Type interaction, $F(2,35) = 3.58$, $p = 0.039$. Planned comparisons showed that for phobics: threatening snakes > slithering snakes > fish (all $ps < 0.005$), and for controls: threatening snakes > slithering snakes or fish ($ps < 0.001$; Fig. 3). In comparison to controls, phobics showed greater dilation to slithering snakes ($p = 0.021$), and less dilation to fish ($p = 0.034$).

3.4. FMRI

Normative fear. A Group (phobic, control) × Video Type (threatening snakes, slithering snakes, fish) voxel-by-voxel ANOVA was screened for two a priori effects of interest, normative and phobic fear. To determine brain regions involved in a normative fear response, regions were extracted that demonstrated a higher response to threatening versus slithering snakes in control subjects in post hoc simple effects. Active regions included bilateral amygdala and insula, thalamus, anterior cingulate cortex, right inferior frontal gyrus, supplementary motor area, right precentral gyrus, bilateral fusiform gyri and primary visual cortex (Table 2 and Fig. 4). In controls, activation to threatening snakes was greater than activation to slithering snakes or fish. Interestingly, these same regions were significantly more active in phobics in response to threatening and slithering snakes versus fish. No regions showed greater activation to attacking snakes in controls versus phobics. All regions except cuneus and right fusiform gyrus showed significantly greater activation in phobics versus controls in response to both slithering and threatening snakes; these regions showed a higher response in phobics versus controls in response to slithering snakes only.

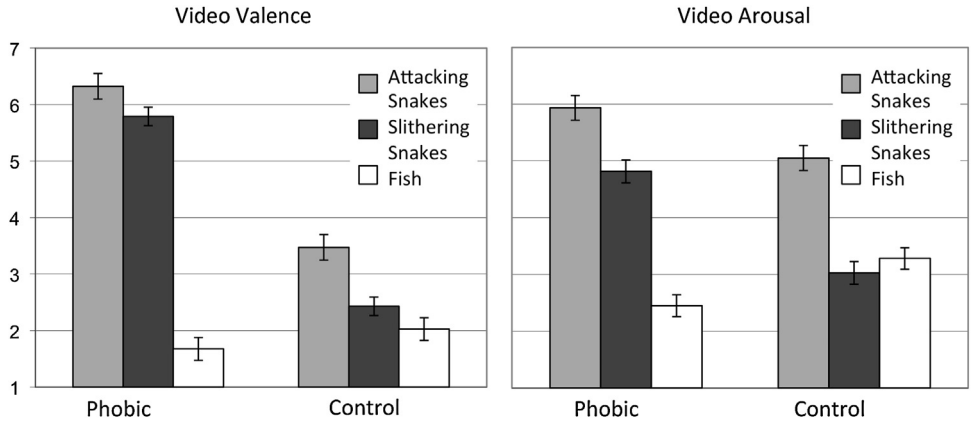

Fig. 1. Self-reported ratings of valence and arousal, given after the functional scanning session. Phobics rated the snakes as more arousing and more negative than controls, and controls rated only the attacking snakes as more arousing and negative than other stimuli. Error bars are ±1 SE.

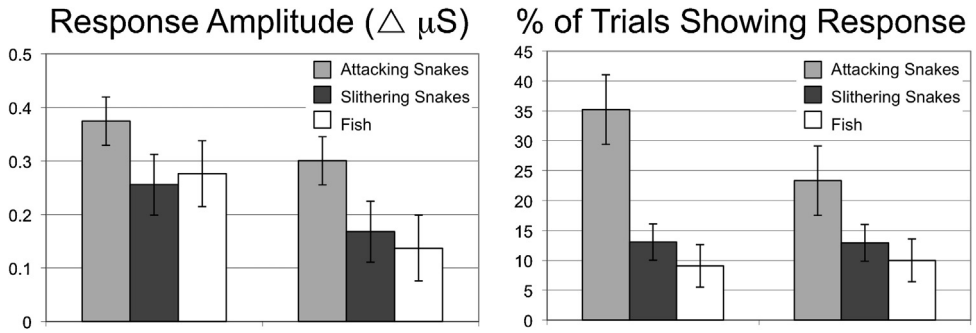

Fig. 2. Electrodermal responses. Attacking snakes produced greater electrodermal activity and more frequent trials with greater than 0.05 μS, versus other stimuli in both phobics and controls. Error bars are ±1 SE. $N = 13$ in each group.

Phobic fear. To determine brain regions involved in phobic response, the same Group (phobic, control) × Video Type (threatening snakes, slithering snakes, fish) voxel-by-voxel ANOVA was tested for regions with a significant interaction and simple effects determined areas with significantly higher activation in phobic subjects in response to slithering snakes and threatening snakes versus fish. To isolate regions for those showing a uniquely phobic response, voxels were also screened for clusters showing a significantly higher response in phobics versus controls in response to all snakes. A large network of regions was identified, showing some overlap with the network identified in the normative fear response. Regions significantly more active in the phobic response included an array of cortical regions including the left orbital gyrus, and bilateral anterior cingulate, supplementary motor, pre- and postcentral, temporal, occipital gyri and bilateral parietal lobules (see Table 4 and Fig. 5). Subcortical regions included bilateral amygdalae, hippocampi, caudate, putamen, and the thalamus.

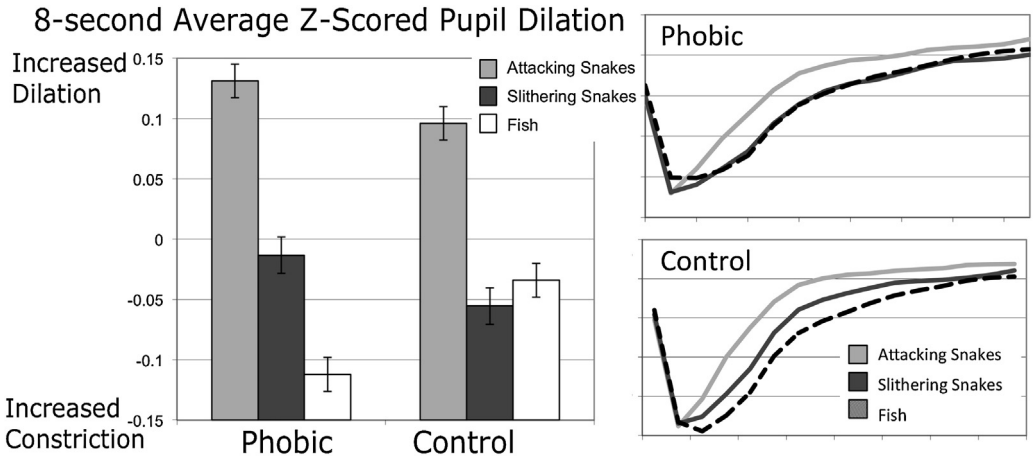

Fig. 3. 8-s average of *Z*-scored pupillary response to each video. On the left, attacking snakes produced greater average pupil dilation versus other stimuli in both phobics and controls, and slithering snakes produced more dilation than fish only in phobics. Error bars are ±1 SE. On the right, the same *Z*-scored data are presented over the 8-s window.

Table 1
Bartlett's test of equality of covariance matrices and pairwise correlations between metrics for ancillary data.

Bartlett's test[a]	χ^2	p-Value	Pairwise correlations for phobics and controls[b]				
					ArR	Pupil	EDA
Threatening snakes	27.81	0.0019	ValR		0.95	0.14	0.46
Slithering snakes	13.48	0.19	ArR	0.27		0.24	0.60
Fish	5.75	0.83	Pupil	−0.26	−0.47		0.30
			EDA	−0.01	−0.48	0.27	

[a] Bartletts' χ^2 value comparing the covariance matrices of phobics and controls as measured by self-reported valence and arousal, pupil dilation, and electrodermal reponse (EDA).
[b] Pairwise correlations between measures for the threatening snakes. The values on the upper right are within phobics, and those on the lower right are within controls.

Table 2
Brain regions involved in normative fear.

Location	L/R	BA	Talairach coordinates			Cluster volume	F	p-Value
			x	y	z			
Frontal								
Anterior Cingulate	L	32	−6.5	13.5	33.5	276	8.83	0.00034
Inferior frontal	R	9	33.9	14.8	8.7	1217	8.77	0.00036
Supplementary motor	med	6	0.4	0.9	50.2	1166	9.81	0.00016
Middle frontal	R	6	48.8	−0.9	42.2	93	8.42	0.00048
Subcortical								
Insula	R	13	41.0	14.8	10.5	597	9.12	0.00027
	L	13	−30.2	16.9	5.5	2429	9.49	0.00020
Amygdala	R	28	18.2	−4.1	−9.8	133	7.46	0.0011
	L	28	−16.9	−6.3	−10.1	159	11.3	0.000046
Thalamus and Substantia Nigra	med	–	2.2	−20.8	0.7	5398	12.1	0.000025
Temporal and occipital								
Fusiform	R	20	38.0	−43.0	−15.9	298	9.87	0.00015
	L	37	−41.4	−55.7	−18.2	95	9.63	0.00018
Cuneus	med	18	0.3	−77.8	12.7	605	7.30	0.0012
	L	19	−17.0	−82.9	33.2	200	7.09	0.0015

L/R, left or right hemisphere; med, medial; BA, Brodman's area; Talairach coordinates are based on the center of mass for each cluster. Cluster volumes are in mm^3; F-statistic and p based on (2,80) degrees of freedom.
All clusters meet $p < 0.05$ mapwise corrected and are listed in anterior-to-posterior order within each region.

3.5. Concordance analyses

Between-subjects. Barlett's test of equality of covariance matrices revealed that there was significantly greater covariance among EDA amplitude, pupillary response, self-reported valence and self-reported arousal within phobics versus controls, specifically in response to threatening snakes ($\chi^2 = 27.81$, $p = 0.0019$; Table 1). There were no significant differences between covariance matrices within phobics and controls for the slithering snakes or fish conditions (slithering snakes: $\chi^2 = 13.38$, $p = 0.19$; fish: $\chi^2 = 5.75$, $p = 0.83$).

Bartlett's test of equality of covariance matrices was also run on the mean activation in each of the 17 clusters identified in the normative fear reaction, to assess whether these brain regions showed greater concordance in either subject group (Table 3). Phobics showed greater concordance than controls across brain regions during videos of threatening snakes ($\chi^2 = 153.3$, $p = 0.02$). There was no difference between groups in the covariance between brain regions in response to fish or slithering snakes (slithering snakes: $\chi^2 = 135.9$, $p = 0.15$; fish: $\chi^2 = 130.0$, $p = 0.25$).

Within-subject concordance. A t-test comparing the within-subject Spearman's R correlation between brain activation and pupil dilation for phobic individuals versus controls revealed brain regions where phobics demonstrated greater concordance in response to videos of threatening snakes (Table 5 and Fig. 6). Brain areas showing this concordance included the following left-sided regions: insula, amygdala, precentral gyrus, and superior temporal gyrus, and these regions bilaterally: putamen, parahippocampal gyrus, supplementary motor area, cuneus, precuneus and cingulate gyrus. In these regions there was a greater positive correlation between pupil area and brain activation within phobic subjects than within controls. Of these regions, in the left insula,superior temporal gyrus and precentral gyrus, linear mixed models demonstrated that arousal ratings also showed significantly greater correlation with activation in phobics than in controls (all

Table 3
Bartlett's test of equality of covariance matrices and pairwise correlations between brain activation for regions in the normative fear analysis.

Bartlett's test[a]			Pairwise correlations for phobics and controls[b]					
	χ^2	p-Value		Thal	RIns	LIns	RPuta	ACC	LAmg
Threatening snakes	153.3	0.02	R Amygdala	0.68	0.65	0.53	0.72	0.60	0.67
Slithering snakes	135.9	0.15	SMA	0.79	0.60	0.60	0.78	0.54	0.74
Fish	130.0	0.25	R Amygdala	0.20	0.54	0.21	0.06	0.01	0.50
			SMA	0.37	0.31	0.14	0.33	0.58	0.22

[a] Barlett's χ^2-value comparing the covariance matrices of phobics and controls for clusters identified in the normative fear contrasts.
[b] Pairwise correlations between activation in the right amygdala and supplementary motor area (SMA), and other regions thalamus, right and left insula, right putamen, left nucleus accumbens, anterior cingulate and left amygdala. The values on the top are within phobics, and those on the bottomare within controls.

Table 4
Brain regions involved in phobic fear.

	Talairach Coordinates			Cluster volume	*F*	*p*-Value
	x	*y*	*z*			
Left hemisphere						
Frontal						
Orbital gyri	−19	26	−11	726	10.42	0.000095
Olfactory cortex	−7	11	−4	332	8.93	0.00032
Inferior frontal gyrus	−38	12	9	4284	9.73	0.00017
Middle frontal gyrus	−26	28	31	1931	9.08	0.00028
Superior frontal gyrus	−17	2	53	680	9.01	0.00030
Supplementary motor area	−4	9	46	5533	10.49	0.000090
Cingulate gyrus	−6	9	31	4117	9.74	0.00016
Precentral gyrus	−30	−15	48	1915	8.65	0.00040
Subcortical						
Insula	−31	12	4	3187	8.96	0.00031
Caudate	−9	9	6	1787	10.52	0.000088
Putamen	−16	10	−1	4165	9.15	0.00027
Pallidum	−15	−1	4	1239	11.08	0.000057
Thalamus	−11	−19	8	4540	14.35	0.000005
Subthalamic nucleus	−11	−7	−3	905	9.32	0.00023
Red nucleus	−11	−18	−3	647	8.89	0.00033
Midbrain	−1	−21	−9	358	11.99	0.000028
Temporal						
Amygdala	−18	−5	−10	220	9.82	0.00015
Hippocampus	−21	−23	−3	1131	8.95	0.00031
Parahippocampal gyrus	−24	−30	−8	205	8.19	0.00058
Superior temporal gyrus	−49	−15	4	1089	7.55	0.00099
Parietal						
Postcentral gyrus	−17	−31	58	6313	9.88	0.00015
Parietal lobule	−32	−48	46	2357	7.96	0.00070
Supramarginal gyrus	−52	−43	29	635	7.63	0.00093
Precuneus	−8	−49	53	2309	10.07	0.00013
Lingual gyrus	−13	−49	0	614	8.42	0.00048
Angular gyrus	−42	−50	26	128	7.18	0.00136
Occipital						
Fusiform gyrus	−35	−58	−13	388	10.65	0.000079
Calcarine gyrus	−8	−57	8	300	8.28	0.00054
Cuneus	−9	−79	32	175	8.13	0.00061
Occipital gyri	−22	−77	30	487	8.26	0.00055
Right hemisphere						
Frontal						
Olfactory cortex	4	14	0	484	13.17	0.000011
Inferior frontal gyrus	43	14	9	3658	9.14	0.00027
Middle frontal gyrus	32	29	33	131	8.05	0.00065
Superior frontal gyrus	19	−7	58	822	7.95	0.00071
Supplementary motor area	6	−10	56	3014	8.48	0.00046
Cingulate gyrus	8	−5	26	3171	8.62	0.00041
Precentral gyrus	28	−23	55	3679	10.00	0.00013
Subcortical						
Insula	38	9	4	2861	10.39	0.000097
Caudate	12	13	2	1160	10.79	0.000071
Putamen	21	10	−2	2049	7.93	0.00072
Pallidum	16	0	3	474	8.79	0.000354
Thalamus	12	−18	9	3675	14.37	0.000005
Subthalamic Nucleus	12	−8	−4	905	10.76	0.000073
Red nucleus	11	−18	−4	505	9.91	0.00014
Temporal						
Amygdala	25	−2	−12	297	7.20	0.00133
Hippocampus	27	−19	−7	803	8.41	0.00048
Parahippocampal gyrus	22	−15	−13	469	8.35	0.00051
Superior temporal gyrus	47	−24	2	1366	7.45	0.00108
Inferior temporal gyrus	53	−48	−7	281	8.52	0.00044
Parietal						
Postcentral gyrus	17	−36	57	6853	9.99	0.00013
Parietal lobule	31	−50	49	1513	8.30	0.00053
Supramarginal gyrus	50	−34	30	550	8.26	0.00055
Precuneus	13	−49	−2	934	8.65	0.00040
Lingual gyrus	10	−56	48	985	9.66	0.00018
Occipital						
Fusiform gyrus	31	−44	−15	376	8.56	0.00043
Calcarine gyrus	15	−60	11	116	8.57	0.00043
Cuneus	17	−72	33	253	8.34	0.00051
Occipital gyri	32	−70	15	1356	8.93	0.00032

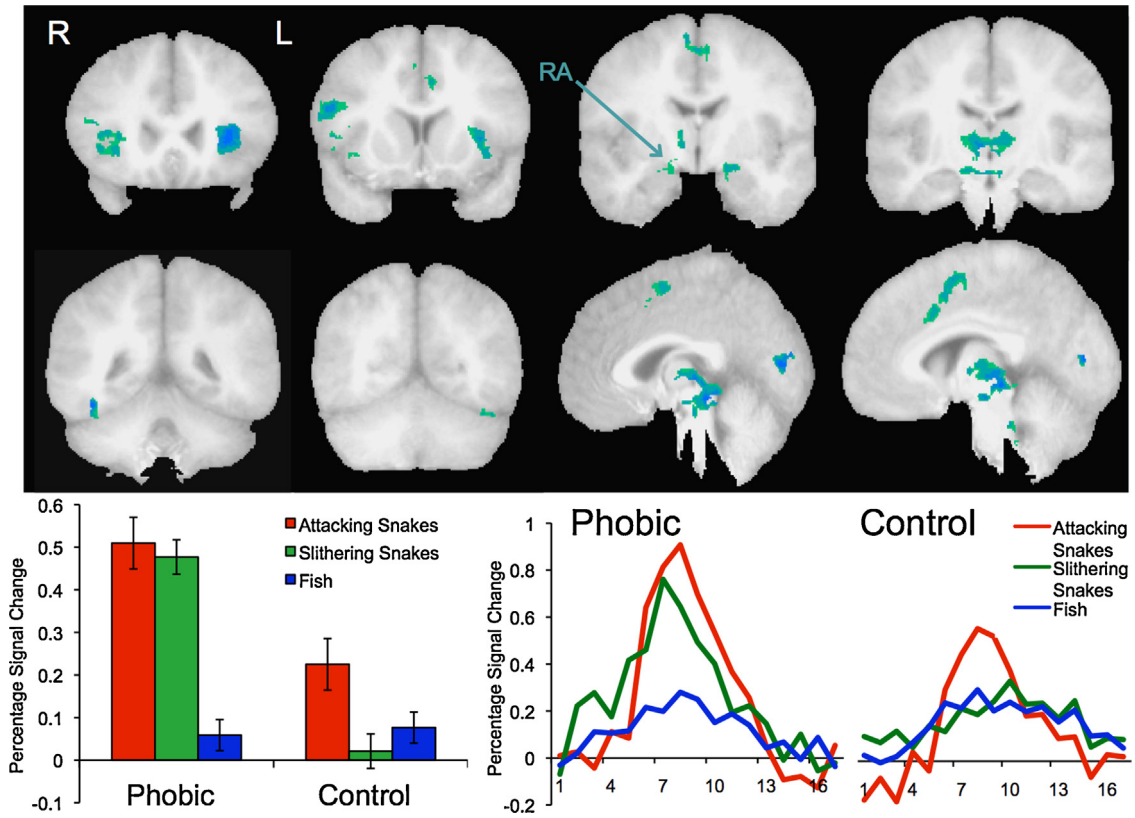

Fig. 4. Brain regions showing activation consistent with normative fear, e.g., greater activation in controls to attacking snakes versus slithering snakes. Bottom: Bar graph and activation traces are taken from the right amygdala (RA), but all clusters showed the same pattern of significance. Phobics also showed greater activation to all snakes versus fish in these clusters, and activation in phobics was greater than that in controls to the snake stimuli.

p's < 0.05), signifying concordance across both self-report and pupil reaction in predicting brain activation. For the left hemisphere clusters anterior insula, insula and superior temporal gyrus, brain activation in control subjects was significantly greater in response to threatening snakes than to slithering snakes or fish (all *p*'s < 0.05), suggesting that these brain regions garner a reliable normative fear response, but that activation does not correlate with self-report or pupil dilation.

Table 5
Brain regions showing coherence between brain and pupillary response within phobics.

	Hemi	Talairach coordinates			Cluster volume	*t*	*p*-Value
		x	*y*	*z*			
Frontal							
Supplementary motor area	R	2	8	48	131	3.28	0.0023
Precentral gyrus	L	−44	0	39	150	3.37	0.0018
Cingulate gyrus	medial	0	−11	36	108	3.27	0.0023
Subcortical							
Anterior insula	L	−26	20	−5	100	3.20	0.0028
Insula	L	−38	11	−5	787	3.41	0.0016
Putamen	R	25	2	0	598	3.29	0.0022
	L	−23	−2	2	831	3.39	0.0022
Lentiform nucleus	L	−30	−19	4	493	3.31	0.0021
Temporal							
Amygdala	L	−22	−2	−8	170	3.36	0.0018
Superior temporal gyrus	L	−51	−4	−2	1149	3.47	0.0013
	L	−58	−34	19	128	3.32	0.0020
	L	−53	−48	14	865	3.34	0.0019
Parahippocampal gyrus	R	12	−33	−4	103	3.32	0.0021
	L	−11	−36	0	210	3.59	0.0010
Parietal							
Lingual gyrus	L	−18	−61	−2	159	3.19	0.0029
Precuneus	R	7	−72	41	411	3.34	0.0020
Occipital							
Cuneus	medial	6	−71	31	140	3.15	0.0032
	medial	0	−73	14	380	3.29	0.0022
Middle occipital gyrus	L	−22	−86	20	242	3.58	0.0010

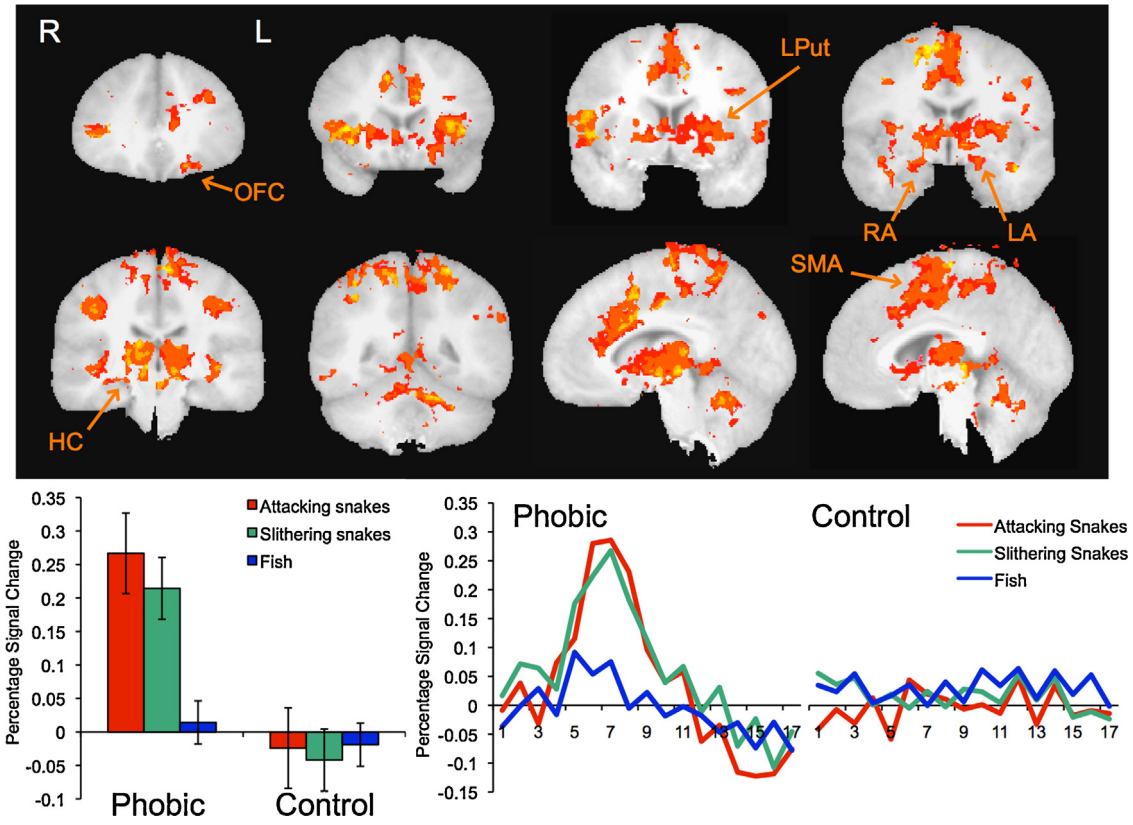

Fig. 5. Brain regions showing activation consistent with phobic fear, e.g., greater activation in phobics to either attacking or slithering snakes versus fish and also greater activation in phobics than controls in response to snakes. Labeled regions of interest include the orbitofrontal cortex (OFC), right and left amygdala (RA, LA), hippocampus (HC), and supplementary motor area (SMA). Bottom: bar graph and activation traces are taken from the left putamen (LPut), but all clusters showed this pattern of significance. Phobics also showed greater activation to all snakes versus fish in these clusters, and activation in phobics was greater than that in controls to the snake simuli.

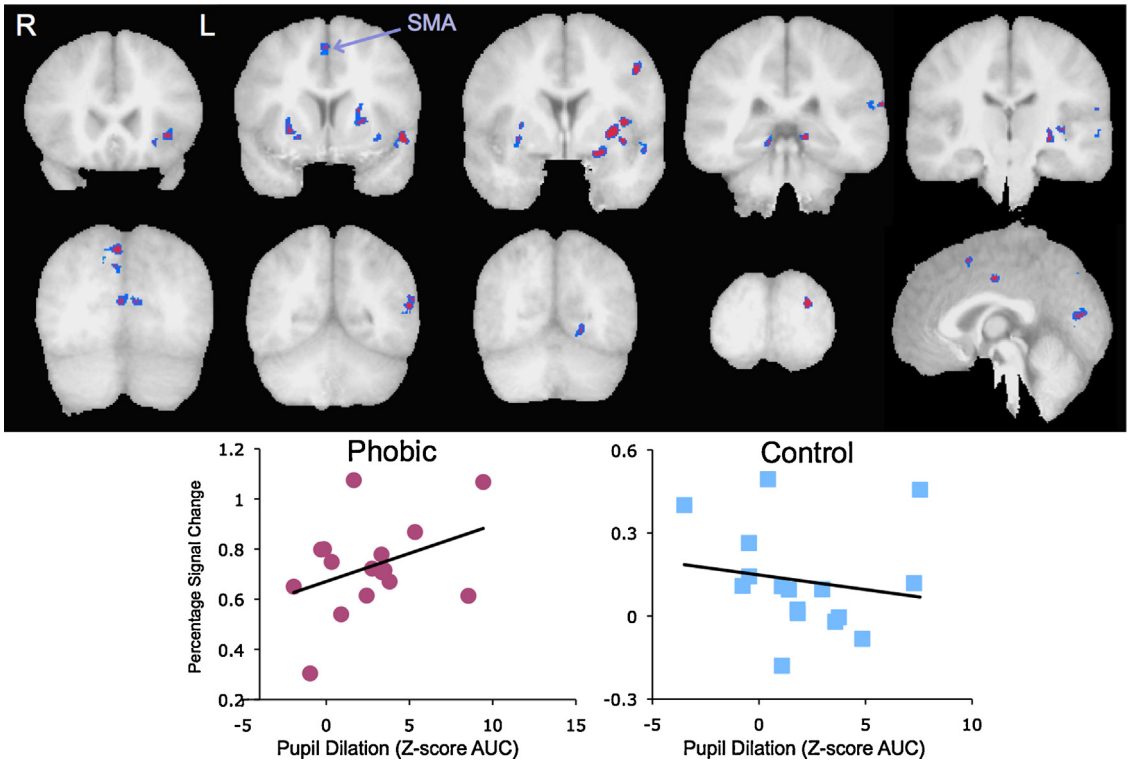

Fig. 6. Top: brain regions showing concordance between brain activation and pupil response for phobics more than controls in response to videos of attacking snakes. Bottom: correlation between pupil dilation and brain activation in response to each of the 16 video clips of threatening snakes. These data are taken from the supplementary motor area cluster (SMA), but all clusters show significantly greater positive correlation between pupil and brain activity for phobics versus controls. Pupil dilation is expressed in area under the curve (AUC) across and 8-s window of the *Z*-transformed time course.

4. Discussion

This study is unique in its direct and simultaneous comparison of normative and phobic fear, finding overlapping yet distinct networks that characterize each. While other investigations have added to the understanding of phobic fear, and compared phobic fear to normative responses to phobogenic stimuli, (e.g. Ahs et al., 2009), the current study adds to this literature a direct comparison between phobic fear and normative *fear* reactions. Normative fear is characterized by a series of brain regions frequently implicated in threat responding and negative affect, including the anterior cingulate, supplementary motor area, insula, amygdala, and thalamus, as well as visual processing regions such as the fusiform gyrus and cuneus. Significant eletrodermal responses, pupil dilation, and self-reported reaction to the attacking snakes within nonphobic persons confirms a reliable normative threat response across brain, periphery and self-reported perception, under conditions where emotional intensity is high. Phobic fear was characterized by more widespread activation, and more intense physiological and self-reported reactions. While participants were not formally diagnosed with a clinically significant phobic disorder, their behavioral, physiological and neural responses indicate that their experience was far more affectively evocative than that of nonphobics.

4.1. Phobic versus normative fear

Phobic fear, in contrast, recruits, on the one hand, larger volumes within the same brains regions identified in normative fear, and, on the other hand, several cortical and subcortical regions not associated here with normal fear. Widespread activation across parietal and occipital regions in the phobic reaction suggests extensive visual processing and environmental vigilance that is frequently associated with phobic fear (Ohman & Mineka, 2001). A larger network of the motor system was also recruited in phobia versus normative fear, including precentral cortex, red nucleus and larger volumes of the supplementary motor area (SMA), and putamen. While a small region of SMA was activated during normative fear, in phobic fear widespread activation across multiple motor regions implies a more concerted, intense fight-or-flight response.

The current paradigm replicated activation in brain regions commonly associated with phobic responses, notably the insula, amygdala, anterior cingulate, and thalamus, (e.g. Del Casale et al., 2012). In agreement with a large literature on fear and threat responding, the amygdala reliably responded to both types of fear, but the phobic reaction again recruited a larger volume of this structure. Orbitofrontal cortex and hippocampal regions, which were uniquely active during phobic fear, might underlie the conditioned avoidance characteristic of phobic, but not normative fear. OFC has been implicated in conditioning paradigms, specifically signaling the reinforcement value of stimuli (Phelps et al., 2004) in a top-down manner (Wright et al., 2008), while hippocampal regions trigger contextual memory of threat (Milad et al., 2007). Together, these regions may serve to maintain the phobia by recalling previous episodes of fear and associating the snake with a fearful response. This interpretation agrees with previous work suggesting that the phobic response may arise from conditioning mechanisms operating within the normative fear network (Schweckendiek et al., 2011). Additional prefrontal regions were implicated during phobic fear in areas previously associated with emotion regulation (Goldin et al., 2008) and awareness of the self (Macrae, Moran, Heatherton, Banfield, & Kelley 2004). Conceptually this aligns with the experience of phobic versus normative fear, with the former often associated with self-reports of embarrassment and attempts to downregulate the fear response. As with the normative fear response, self-reported experience, electrodermal activity and pupil reactivity show greater response to images of snakes than non-snake videos in phobic persons, suggesting phobic and normative fear share some experiential and physiological characteristics. Overall, the phobic response overlaps with the normative fear response in self-report, autonomic activity and threat-responsive brain regions. Within these regions, phobia is associated with greater strength of activation than normative fear responding, except for regions implicated in primary visual processing, such as the cuneus. Further, the phobic reaction recruits additional structures involved in environmental vigilance, motor control, emotion regulation, and memory traces that may maintain the phobic response.

4.1.1. Phobic versus normative fear concordance

Moreover, the phobic response demonstrates concordance between subjective self-report, autonomic physiology, and brain activity whereas normative fear does not. This certainly holds true *across* subjects, that is, phobic individuals showing greater brain activation in response to images of snakes also experienced strong peripheral responses and reported more intense emotions. This effect was not present in normative fear. In fact, within controls, measures of peripheral physiology were somewhat positively related to each other, but were inversely related to self-report. The finding implies that concordance was not present across systems in normative fear, and agrees with previous work suggesting that individuals who are behaviorally less expressive are more physiologically reactive (e.g. Gross & Levenson, 1993). Importantly, however, concordance was also observed *within* individuals with snake phobia; those images that induce greater brain response for a given phobic person also induce stronger pupillary dilation and are rated are more arousing. Although this result arose from a subset of study participants due to data quality concerns, the phenomenon of concordance between brain, body, and behavior that is suggested adds an important facet to better understanding the phobic response. Brain regions demonstrating this within-subject correlation involve a subset of those previously identified during the phobic fear reaction and several that are also implicated in normative fear reactions. Concordance observed within the amygdala is not surprising as it is the structure most commonly associated with the experience of fear (Phan, Wager, Taylor, & Liberzon, 2002) and has shown functional connectivity with visual processing regions in fear perception (Sabatinelli et al., 2005). Further, the phobic reaction has been associated with feelings of disgust and several regions found to be coherent between brain and autonomic activity, such as the anterior insula and putamen, are frequently associated with feelings of disgust. Stark et al. (2007) found disgust-related insula activation that correlated with self-reported disgust, suggesting that the concordance seen here might be specifically related to a disgust component of phobia. The overall pattern of concordance among brain regions implies that fear, visual processing, motor preparation, autonomic activity and disgust act in concert during the most intense phobic reactions.

The normative fear reaction brings about reliable changes in brain activation, pupil dilation and self-reported affect, but these systems do not systematically relate to each other as in phobic fear. It remains to be determined whether this concordance during the phobic reaction is a function of intensity of experience or is characteristic of psychopathology in particular. This is an important qualification, as it is yet unclear whether concordance could be considered a marker of pathology or is simply a barometer of intensity of experience. Further, the current work was limited with respect to the size of the sample, which prohibited analysis of subgroups, as well as the demographics (predominantly Caucasian college-aged females). Other studies looking for concordance across subjects have suggested that some groups, such as older adults or males,

may show this relationship less than others during anxiety provocation (Stoyanova & Hope, 2012; Teachman & Gordon, 2009). In the current study, concordance was observed singularly in the most salient condition, e.g. the phobic response to attacking snakes, and not in normative fear or in the phobic response to less threatening snakes. This was true across subjects, in that phobic individuals who were highly reactive on one measure were highly reactive on another. Importantly, concordance was also found within subjects, i.e. within a given individual videos that were rated as particularly distressing also engendered high behavioral and physiological responses, and those videos that were less arousing had lower reactions across measures. This implies that concordance is primarily a function of strength of response, and failure to find such correlations in less salient experimental conditions may explain why concordance has been difficult to demonstrate. Phobic provocation is an intensely fearful experience and it may be challenging to ethically induce a comparable level of fear, particularly in a functional imaging paradigm. Nonetheless, could such a salient and fearful condition be produced in a nonphobic person, concordance may result.

While a picture of phobic and normative fear reactions appears from these data, there are several avenues yet to be explored. While the prefrontal activations observed align with studies of emotion regulation, other investigations of simple phobia have attributed prefrontal activity to cognitive misattributions commonly reported in phobia, such overestimation of threat (Straube, Mentzel, & Miltner, 2007). More precise differentiation of prefrontal activation into those regions attempting to regulate, or dampen the phobic response, versus those regions that are cognitively exacerbating it would provide insight into the processes underlying and maintaining phobias as well as other ruminative disorders such as depression and generalized anxiety disorder. While outside the scope of the current investigation, functional connectivity analyses may better illuminate the relationship between brain regions active in the phobic response. Such analyses may provide additional support to the hypothesis that concordance is a significant factor in phobic symptom provocation.

In a different vein, treatment of simple phobia with exposure therapy remains an extremely effective method for symptom alleviation, but whether concordance may fit into this effect is yet unclear. Treatment of simple phobia via exposure therapy has been associated with reduction in activity in regions implicated in conditioned responses and emotion regulation (Paquette et al., 2003), as well as in regions frequently associated with phobic symptom provocation, including the anterior cingulate and insula (Straube, Glauer, Dilger, Mentzel & Miltner, 2006), and basal ganglia and right PFC (Ipser, Singh, & Stein, 2013). Given that many of these regions demonstrated concordance in the current study, it is possible that treatment effects could result from a gradual reduction in concordance with continued exposures. Alternatively, the effect of treatment might be explained by additional cognitive regulation strategies being brought online to dampen automatic and coherent responses. While simultaneous activity across autonomic, motor, visual and affective systems may characterize phobic fear episodes, how these systems relate during treatment and recovery is important to better understand phobic fear reduction and may also apply to the treatment of other intense affective conditions, such as panic and post-traumatic stress.

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