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Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence

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Abstract

Background—Intimate partner violence (IPV) is one of the most common causes of posttraumatic stress disorder (PTSD) in women. Victims of IPV are often preoccupied by the anticipation of impending harm. This investigation tested the hypothesis that IPV-related PTSD individuals show exaggerated insula reactivity to the anticipation of aversive stimuli.

Methods—Fifteen women with a history of IPV and consequent PTSD (IPV-PTSD) and 15 non-traumatized control (NTC) women performed a task involving cued anticipation to images of positive and negative events during functional magnetic resonance imaging.

Results—Both groups showed increased activation of bilateral anterior insula during anticipation of negative images minus anticipation of positive images. Activation in right anterior/middle insula was significantly greater in the IPV-PTSD relative to the NTC group. Functional connectivity analysis revealed that changes in activation in right middle insula and bilateral anterior insula were more strongly associated with amygdala activation changes in NTC than in IPV-PTSD subjects.

Conclusions—Increased activation in the anterior/middle insula during negative anticipation in women with IPV-related PTSD. These findings in women with IPV could be a consequence of the IPV exposure, reflect pre-existing differences in insular function, or due to the development of PTSD. Thus, future longitudinal studi4s need to examine these possibilities.

INTRODUCTION

Intimate partner violence (IPV) is a leading cause of injury to women in the US (1), accounting for 20% of non-fatal injuries (2). IPV frequently causes posttraumatic stress disorder (PTSD), which is a severe consequence of extraordinarily stressful events that occurs when the combination of re-experiencing aspects of the stressful event, hyperarousal to one's surroundings, and avoidance of specific situations significantly impairs daily functioning. PTSD is twice as common in women as men, a difference that is in part due to higher rates of exposure among women to IPV (3). IPV-related PTSD is one of the most prevalent and impairing forms of PTSD among women (4). This impairment is not limited to situations in which individuals are exposed to reminders of traumatic stressors. Individuals with IPV-related

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PTSD frequently anticipate the occurrence of harmful stimuli, and go to great lengths to avoid situations (and thoughts or feelings) that may cue remembrances associated with prior trauma, in addition *anticipation* of fear and discomfort (e.g., hyperarousal) contributes substantially to behavioral and emotional avoidance that are hallmarks of PTSD (5).

Despite the public health importance of IPV-related PTSD, its underlying neurobiology is poorly understood. Although a number of studies have used blood-oxygen-level dependent (BOLD) imaging to examine brain function in PTSD patients versus nontraumatized controls (6–26), these studies are highly heterogeneous regarding both the tasks performed, and the analysis techniques employed. Seven studies have utilized tasks involved face viewing/ judgment and four studies have used imaging during symptom provocation paradigms. However, there have been no studies to date that have used BOLD imaging to examine the neural correlates of anticipatory processes in individuals with PTSD.

Functional neuroimaging studies of PTSD have focused primarily on amygdala and ventral medial prefrontal gyrus (MPFG)(27–33). A meta-analysis of imaging studies in a variety of anxiety disorders recently published by Etkin and Wager (34) indicated that right middle insula and amygdala are two primary areas with the most robust imaging findings in PTSD. The studies summarized in Table 1 show that individuals with PTSD, when compared to nontraumatized controls (NTC), frequently have increased amygdala activation (supplementary Figure 1). Additionally, although the insula is significantly engaged during anticipatory processing (35–39), this structure has shown differential activity in some but not all functional magnetic resonance imaging (fMRI) studies in PTSD. These seemingly discrepant findings raise the question of whether these tasks activated fear and anticipatory circuits. In fact, in the meta-analysis discussed above the authors highlight the role of the amygdala and anterior/middle insula in fear conditioning, phobias, and anticipatory processing (34). Examining the neural correlates related to anticipation and fear is of specific interest for understanding the neurobiology of a condition like PTSD that is characterized by symptoms that involve hyperarousal (i.e., physiologically activating), as well as numbing and avoidance (i.e., physiologically deactivating) experiences. Hyper-arousal may be expressed in the response of the anterior/middle insula, which has substantial physiological afferents (40-2), and numbing and avoidance may lead to regulation of the amygdala when controlling anticipatory stress (43).

Prior research suggests a conceptual framework in which altered anticipation of aversive events is fundamentally involved in both the initiation and maintenance of symptoms associated with IPV-related PTSD. This conceptualization is supported by a burgeoning functional neuroimaging literature which indicates that some of the same brain structures that are abnormally active in PTSD are also critically involved in anticipatory processing. Neuroimaging studies of various PTSD samples have shown differential activation in the amygdala, medial prefrontal cortex (MPFC), and anterior insula (30). Anticipatory tasks reliably activate the anterior insula (35,37,38,44,45) and studies examining anticipation of an electric shock or noxious thermal stimuli show increased response in the MPFC (35) and anterior insula (35,44). Related evidence indicates that the anterior insula is involved not only in anticipatory processing, but also in the integration of motor, sensory and visceral afferent information, as well as in mounting affective (46) and autonomic (47) responses. This evidence converges with elegant anatomical research which describes the connections between the anterior and middle insula and the frontal lobes and limbic system (48). Although neural pain response can usefully probe these systems (44), aversive images may be stimuli that are more tailored toward the understanding of PTSD and related disorders.

This aim of this study was to determine whether women with PTSD related to IPV would show altered anticipatory processing and whether this altered processing is reflected in increased

activation of the anterior/middle insular cortex. Specifically, we hypothesized that women with IPV-PTSD relative to female NTC would show increased anterior/middle insula activation during anticipatory processing, and that increased insula activity would be functionally connected to increased amygdala activity during the anticipation of aversive stimuli. Given that the insula is thought to play a key role in the physiological experience of PTSD, we also hypothesized that anterior/middle insula activation would relate most strongly to the hyperarousal component of PTSD, and less strongly to the re-experiencing and avoidance components.

METHODS

Subjects

Fifteen women with IPV-PTSD (full or subthreshold; see below) and 15 non-traumatized control (NTC) subjects who had never experienced a PTSD "Criterion A" event (Table 1) completed a cued anticipation task during fMRI. Subjects were excluded if they had: (1) abused substances in the past year, (2) a history of >2 years of alcohol abuse, (3) used psychotropic medication within the last 4 weeks (or fluoxetine within the last 6 weeks), (4) irremovable ferromagnetic material, pregnancy, claustrophobia, bipolar disorder, or schizophrenia. PTSD subjects were included if they had other comorbid affective or mood disorders, such as major depressive disorder, as long as PTSD was the clinically predominant disorder. All participants gave informed written consent to participate in this study, which was approved by the University of California San Diego Human Research Protection Program.

Groups were statistically matched on demographic variables except years of education (i.e., lower in IPV-PTSD subjects), which was used as a covariate in subsequent group contrasts. Twelve of the 15 subjects with IPV exposure met DSM-IV criteria for PTSD and 3 had subthreshold PTSD (i.e., fulfilled Criterion A and the impairment/distress criterion, and had subthreshold Criteria C, and/or D symptoms; CAPS range: 17 to 31). Excluding the 3 subjects with subthreshold PTSD did not change the results in any meaningful way. Therefore, we have reported results from the entire group of 15 subjects with IPV exposure.

Psychological Measures, Stimulus, and Apparatus

Description of the task and the psychological measures are reported in the supplementary section.

Image Acquisition

During the task, an fMRI run sensitive to BOLD contrast was collected for each subject using a Signa EXCITE (GE Healthcare, Milwaukee) 3.0T scanner (T2* weighted echo planar imaging, TR=2000ms, TE=32ms, FOV=250×250 mm^3, 64×64 matrix, 30 2.6mm axial slices with 1.4mm gap, 290 scans). During the same experimental session, a high resolution T1-weighted image (SPGR, TI=450ms, TR=8ms, TE=4ms, flip angle=12°, FOV=250×250, ~1 mm^3 voxels) was obtained for anatomical reference.

Data were preprocessed and analyzed with the Analysis of Functional NeuroImages (AFNI) software package. Preprocessed time series data for each individual were analyzed using a multiple regression model. Regressors of interest included four regressors: 1) the API, i.e. what activated during anticipation of a positive image, 2) the ANI, i.e. what activated during anticipation of a negative image, 3) the positive image (PI) phase, i.e., what activated during processing of positive stimuli, and 4) the negative image (NI) phase, i.e., what activated during processing of negative stimuli. In addition, six nuisance regressors were entered into the linear regression model: three movement-related regressors used to account for residual motion (roll, pitch, and yaw), a white matter mask to control for physiological noise (58), and regressors for

baseline and linear trends used to eliminate slow signal drifts. In this model the CPT task comprises an active baseline. Subsequently, contrasts were constructed on an individual subject level for all anticipation (i.e. ANI+API), differential anticipation of negative and positive (i.e. ANI−API), all images (i.e. NI+PI), and difference between viewing negative and positive images (i.e. NI−PI). A Gaussian filter with full width- half maximum 6 mm was applied to the dataset to account for individual variations in anatomical landmarks. Data of each subject were normalized to Talairach coordinates as defined by AFNI's built-in atlases.

Voxel-wise percent-signal change data for whole brain were entered into an independent-samples t-test for group differences in activation during anticipation and image presentation between IPV-PTSD and NTC subjects. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation. A prior voxel-wise probability of $p < 0.05$ in a cluster of 1024μL resulted in a-posteriori probability of $p < 0.05$. Finally, the average percent-signal difference was extracted from regions of activation that were found to survive this threshold/cluster method (determined by the AFNI program AlphaSim) and the t-values were calculated with and without education as a covariate. All analyses for the behavioral data were carried out with SPSS 12.0.

In addition, a region of interest (ROI) based analysis was performed on several *a priori* areas of interest: the bilateral anterior/middle insula, bilateral amygdala, ventral medial frontal gyrus, and dorsal medial frontal gyrus. Stereotactic coordinates of the ROIs were based on standardized atlas locations taking from the Talairach atlas (59). To further refine our analyses, we divided the insular cortex into an anterior portion ($y >= 0$), which was of primary interest here, and excluded the posterior insula, which is primarily related to direct processing of ascending c-fibers(48). Using the threshold/clustering method as above, resulted in minimum clusters sizes of 128μL for the amygdala ROIs and 256μL for all remaining ROIs. While the cluster significance is $p < .05$ for the ROIs, the corrected voxel-wise probabilities are as follows: amygdala $p < 0.012$, anterior/middle insular cortex $p < 0.000068$, ventral medial prefrontal cortex $p < 0.000145$, and dorsal medial prefrontal cortex $p < 0.000145$.

Functional connectivity analysis

Functional connectivity analysis was performed using methods described previously (60). Due to an attempt to maximize power for this event-related design, we selected this technique and examined the entire time series rather than selecting only connectivity within a circumscribed period. Before conducting the functional connectivity analysis, echoplanar signals were corrected for slice-dependent time shifts, spatially filtered using a 6mm FWHM Gaussian filter and bandwidth filtered ($0.009 < f < 0.08$). The resulting echoplanar time series was subsequently transformed to the Talairach atlas. Individual time courses were extracted from these processed echoplanar signals for a seed ROI that showed task dependent activation, specifically in the anterior and anterior/middle insula. Time points in each individual's time course were censored if they were more than 2 SD from the individual's average activation for the given seed ROI then entered into a deconvolution analysis as the regressor of interest along with the movement, baseline, and linear regressors. An independent-sample t-test was performed for each seed ROI that contrasted the Fisher Z transforms of the correlation coefficient obtained for IPV and NTC groups to determine differences in functional connectivity between groups.

ROI based connectivity analysis was performed by seeding regions that showed differential group activation (see below) using volume dependent clustering thresholds based on minimum clusters sizes of 256μL. Voxel-wise percent-signal change data were entered into an independent sample t-test to examine group differences in activation during aversive anticipation IPV and NTC. A prior voxel-wise probability of $p < 0.05$ in each ROI cluster resulted in an a-posteriori probability of $p < 0.05$. Finally, the Fisher Z transformed correlations

were extracted from each ROI that was found to survive this threshold/cluster method (AFNI program AlphaSim).

RESULTS

Behavioral

NTC and IPV-PTSD subjects did not differ significantly on response latency ($F(1,29)=1.991$, p=ns) and accuracy ($F(1,29)=2.475$, p=ns, Figure 2) during the task. Furthermore, there were no significant task differences in latency ($F(1,28)=2.129$, p=ns) or accuracy ($F(1,28)=0.898$, p=ns) when education was used as a covariate.

Brain Activation

Two primary main effect analyses were performed. First, ROI analysis revealed increased activation related to the differential anticipation contrast (i.e. ANI-API) in bilateral anterior insula, and right anterior/middle insula in both groups (Figure 3, Table 2). ROI findings were corroborated by whole brain results, which showed increased activation related to the differential anticipation contrast in bilateral anterior insula, bilateral prefrontal cortex, bilateral inferior parietal lobule, and right caudate (Table 3). Second, increased activation in IPV-PTSD relative to NTC individuals was observed in right anterior/middle insula. This finding remained significant after covarying for education (Figure 3). As the contrast of interest is between positive and negative image anticipation it should be noted that both conditions ultimately contribute to this contrast.

Functional Connectivity

Functional connectivity analyses using bilateral anterior insula and right anterior/middle insula seed regions revealed the following two results: (1) Within each group, significant correlations were observed between activation in bilateral anterior insula and bilateral amygdala and dorsal MPFC, and between right anterior/middle insula and bilateral amygdala and dorsal MPFC, (2) Correlations between activation in bilateral anterior insula and bilateral amygdala, and between right anterior/middle insula and bilateral amygdala were significantly weaker in IPV-PTSD relative to NTC individuals (Table 4 and Figure 4) but dorsal MPFC activations did not differ significantly between groups (supplementary Figure 2). These correlation differences remained significant after including education as a covariate.

Brain Behavior Relationships

Two main correlative findings were observed. First, controlling for the degree of intrusions and avoidance, we observed partial correlations between subscales of the IES-R (for which there were no missing data) and brain activity in the anterior/middle insula. Within IPV-PTSD individuals, a significant positive correlation between IES-R Hyperarousal scores and activity in the left anterior insula ($r_p=.647$;x=−32, y=20, z=3) was observed. Correlations with IES-R scales were performed that did not reach statistical significance. Second, within the IPV-PTSD group, significant negative correlations were observed between CES-D scores and strength of functional connectivity between (1) left anterior insula and right amygdala, (2) right anterior insula and bilateral amygdala, and (3) right anterior/middle insula and bilateral amygdala (Figure 5 and Table 5). That is, higher levels of depression were associated with weaker connectivity between insula regions and amygdala. If the alpha levels for these correlations are bonferroni-corrected, only three correlations are significant (Table 5). For this reason findings should be considered hypothesis-generating until replicated. There were no significant correlations between task-related (i.e., within or between groups) activation and other symptom measures (e.g., CAPS, DES-T, CES-D, total IES) or behavioral performance (e.g., RT or response accuracy).

DISCUSSION

This experiment yielded several findings. First, in both ROI and whole brain analyses, both groups activated bilateral anterior insula during anticipation of negative compared to positive stimuli. Second, IPV-PTSD relative to NTC subjects showed greater activation in right anterior/middle insula during anticipation of negative compared to positive stimuli. Third, functional connectivity between activation in bilateral anterior insula and bilateral amygdala, and between right anterior/middle insula and bilateral amygdala were significantly weaker in IPV-PTSD relative to NTC individuals. We also observed within IPV-PTSD subjects had a significant positive correlation between IES-R Hyperarousal scores and activity in left anterior insula. Taken together, these results support the notion that in women with IPV-related PTSD: (1) the anterior and anterior/middle insula are important in cued anticipation of negative stimuli, (2) subregions of the insula, such as the anterior/middle insula, are hyperactivate during negative anticipation, and (3) anterior/middle insula activity may be most strongly related to symptoms of hyperarousal in IPV-related PTSD.

The insula, a part of the extended limbic system, can be subdivided into anterior agranular (Ia), central/middle dysgranular (Id) and posterior granular (Ig) subregions based on function and cytoarchitectural structure (48,61). Anterior and middle insula have reciprocal connections with ventral frontal brain regions such as the anterior cingulate and orbital frontal gyrus, as well as with the amygdala, and surrounding, areas, regions that comprise a critical emotion processing circuit. Posterior insula also has reciprocal connections with the frontal cortex, as well as the temporopolar cortex and secondary somatosensory area (61). Some investigators have suggested that the anterior aspect of the insula (including Ia and part of Id) is more closely linked to the executive control system, which includes the anterior cingulate and the dorsolateral prefrontal cortex, whereas the posterior insula (Ig and caudal aspect of Id) primarily integrates afferent information from unmyelinated C-fibers to provide a global sense of the physiological condition of the body (42). Further supporting the notion that the insula is critically involved in emotional and interoceptive processing are studies reporting correlations between insula activation and autonomic arousal (62), anxiety, and visceral changes associated with facial emotion processing (63), as well as the evidence that aversive physiological reactions are key in the establishment and maintenance of avoidant behavior in the development of phobias (e.g. agoraphobia) (64). Neuronal measurements in fear conditioning also show strong involvement of the various aspects of the insular cortex (65). These processes take place in full, and sometimes painful, awareness, which is consistent with the role of the middle/posterior insula in mediating self-awareness (66). Lesion studies in both humans and animals also support the notion that the entire insular cortex is important for emotional and interoceptive processing (67). Additionally, although activation across the entire insula has been frequently associated with disgust (68), there is increasing evidence of a broader role for this brain structure in emotion processing (69). Similarly, anterior/middle insula activation is thought to be involved in differential positive versus negative emotion processing (70), in particular fearful face processing (71), pain perception (72), and judgments about emotions (73).

These findings are consistent with a recent model which explains the critical involvement of the anterior insula in anxiety states and anxiety disorders (46), which are characterized by altered emotional and interoceptive processing. Prior studies have shown that phobic individuals relative to non-phobic comparison subjects showed increased anterior/middle insula activation during emotionally evocative paradigms that used both pictures (74) and words (75) of spider-related stimuli. In a related study, we reported that anxiety prone individuals relative to healthy controls showed exaggerated insula responses during the anticipation of images of spiders and snakes – which are among the most commonly reported phobic stimuli. This evidence is in line with research showing that social phobic individuals

show increased activation to fearful faces in the right anterior/middle insula (76) and to angry faces in the bilateral anterior/middle insula (77). These, and related studies in which healthy volunteers processed aversive sensory stimuli (37), are consistent with the notion that anterior insular activity may not only underlie the affective process of emotional distress in normal and phobic individuals, but may also be involved in action planning, i.e., mediation of anxiety-related avoidant behavior (46).

Based on this evidence, we speculate that the increased activation in anterior/middle insula observed in IPV subjects with PTSD, in particular on the left side, may represent a neural substrate linking emotional distress, anticipatory processing, and autonomic arousal, which can advance action planning to reduce exposure to the aversive stimuli. Therefore, the anterior/middle insula activation may be interpreted as a "warning signal" that is associated with the anticipation of aversive symptoms such as hyperarousal. This interpretation is supported by the strong functional connectivity between anterior/middle insula and amygdala observed in the current study, and by the strong correlations between activity in the middle insula and the parietal cortex in a prior study (38).

The pathways between the insula and the amygdala have been mapped out in great detail in animal studies. The basomedial and basolateral nuclei of the amygdala, areas that are involved with conditioned fear, show connections to the various regions in the insula (78), particularly the central dysgranular insula (61). The anterior/middle insula shows the greatest differentiation between groups in the current study, suggesting differential connectivity with the amygdala. This interpretation is consistent with a prior study by Lanius et. al. (25), which found differential activation in the dorsal anterior cingulate (dACC) between individuals who had experienced trauma and had developed PTSD versus those who had experienced significant trauma but did not develop PTSD. In this study, connectivity with the dACC differed in these two groups in a mostly lateralized way, with the PTSD subjects showing greater activation in the right side and the non-PTSD subjects showing greater activation in the left side. We found strong connectivity with the dorsal MPFC in the current study but this connectivity strength did not differ significantly between groups. To our knowledge, ours is the first study to identify altered insularamygdala connectivity in PTSD.

There are several mechanisms which may explain the functional connectivity in the current study. Due to the varying directionality of amygdala activation in PTSD fMRI studies (34) the connectivity with the insula may be highly dependent on the stimulus, task, and population. Therefore, it is not expected that this finding will be generalizable to other situation and should be interpreted with great caution. In the current study, this somewhat paradoxical relationship may imply that insula hyperactivation results in compensatory functional weakening with other brain areas, similar to what has been reported elsewhere (38). Alternatively, the amygdala may receive input from other regions such as the MPFC (19,24,25), which in turn could attenuate the functional connectivity to interoceptive stimuli provided by the anterior/middle insula cortex. These possibilities need to be further investigated with a greater number of subjects that exhibit different insula activation patterns or show significant differences in MPFC. The prevalence of PTSD in females is much higher than in males, which is related to differences in the rates and types of assault (79) and that the accumulation of traumas makes females more vulnerable to retraumatization (80). Structural equation modeling has suggested that the symptom cluster of hyperarousal may relate more to the incidence of retraumatization in females (81). This may suggest that the anterior/middle insula, and subsequent functional correlation findings, may be more pronounced in this population. Combat-related PTSD has received greater investigation in the literature and appears to have higher rates of PTSD subsequent to trauma and potentially reporting compared to other forms of PTSD (82). However, there is no research to date on the neural differences between IPV and combat - related PTSD.

This study has several limitations. First, this group was comprised of women who had experienced relatively recent IPV. These findings cannot be presumed to extend to males, to those with more chronic PTSD, or to those with PTSD stemming from exposure to other types of trauma (e.g., combat). Second, we cannot determine whether the current findings reflect pre-existing processing differences in individuals who are more susceptible to developing PTSD (e.g., it should be noted that the IPV-PTSD group has slightly lower education levels, which might reflect subtle group differences in pre-trauma cognitive ability, thought to be a risk factor for PTSD development (83,84), or are a consequence of the trauma and the post-trauma alterations. Third, future longitudinal studies with individuals exposed to IPV but failing to develop PTSD – a "resilient" comparison group that was lacking from the current study – would help distinguish neural systems involved in trauma exposure from those associated with PTSD, per se. Fourth, the lack of behavioral differences on the CPT task both within and between groups may indicate that the images have only a modest emotional impact. However, due to concerns about distressing subjects we did not include images we deemed too violent. We expect that we may see behavioral differences if stronger images were utilized. Fifth, we used the time series of the entire task as subjects to inspect connectivity rather than just during a single condition. This was done to maximize the within subject power of the connectivity analysis and to see how these networks behaved across anticipatory conditions, thus we do not assert that the functional relationships in this network are highly state dependant.

Anticipation of impending adverse events is potentially a major aspect of the negative effects of PTSD in IPV and may reflect the relationship between hyperarousal and avoidance. Pathological trauma reactions may be perpetuated via increased involvement of the anterior/middle insular cortex in processing negative anticipation, leading to avoidance of affective processing (which may be experienced as "numbing"), as indicated by decreased connectivity with the bilateral amygdala. Important follow up work should determine the heritability (e.g., through twin studies) of this pattern of connectivity and the degree to which treatment may effect this neuronal behavior in individuals with PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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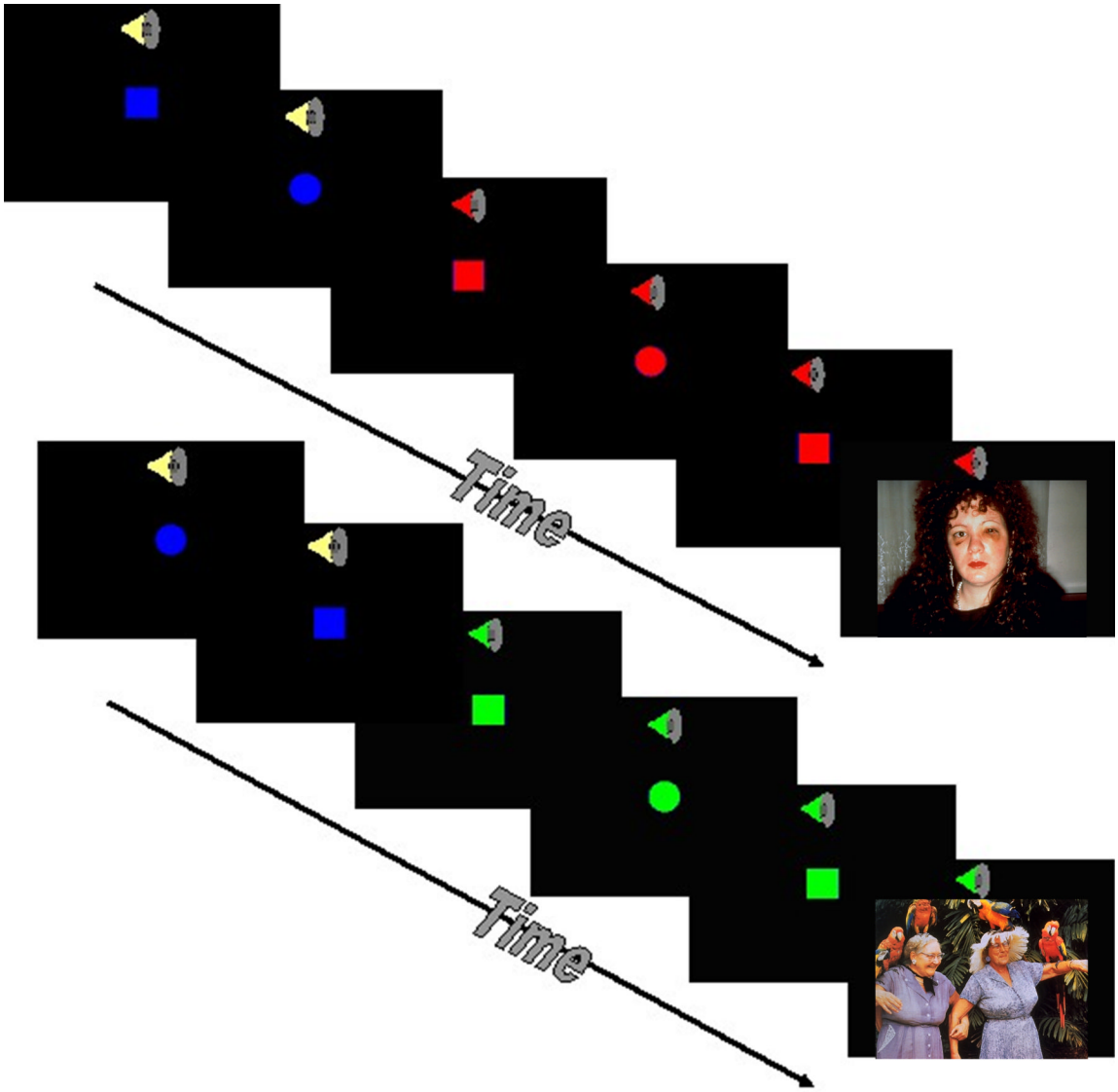

Figure 1.
Anticipation Task. The fMRI task combined a continuous performance task with the interspersed presentation of affective stimuli. Subjects were asked to press the left or right button on a touch pad based on the shape on the screen. Subjects were instructed prior to the task that a switch from a blue to a green shape accompanied by a low tone would indicate that a positive image was going to appear on the screen. In contrast, a switch from a blue to a red shape accompanied by a high tone signaled an impending negative image.

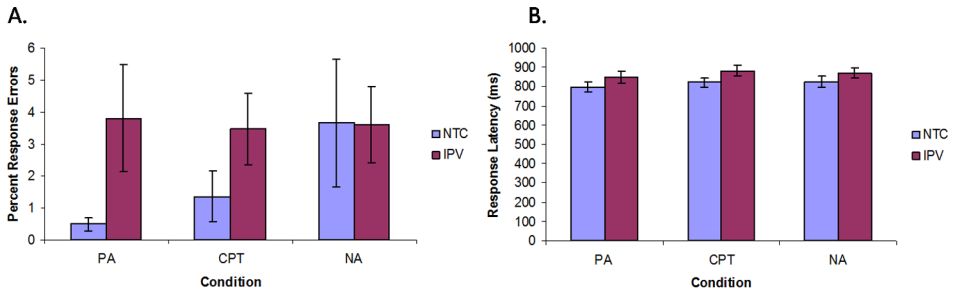

Figure 2.

Response errors (%) (A) and latency (ms) (B) to the Anticipation Task during positive anticipation (PA), negative anticipation (NA), and continuous performance task (CPT). No statistically significant group differences were found.

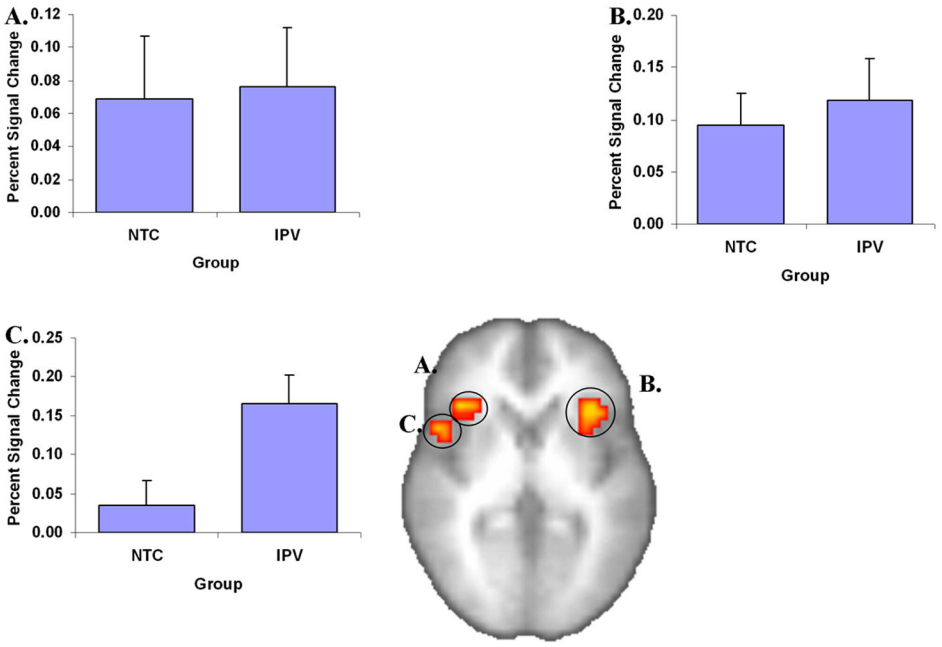

Figure 3.

Anticipation of images of negative versus positive images leads to increased activation in bilateral anterior insula (A shows right-sided activation and B shows left-sided activation), and (C) right anterior/middle insula, which was significantly more active in IPV relative to NTC subjects.

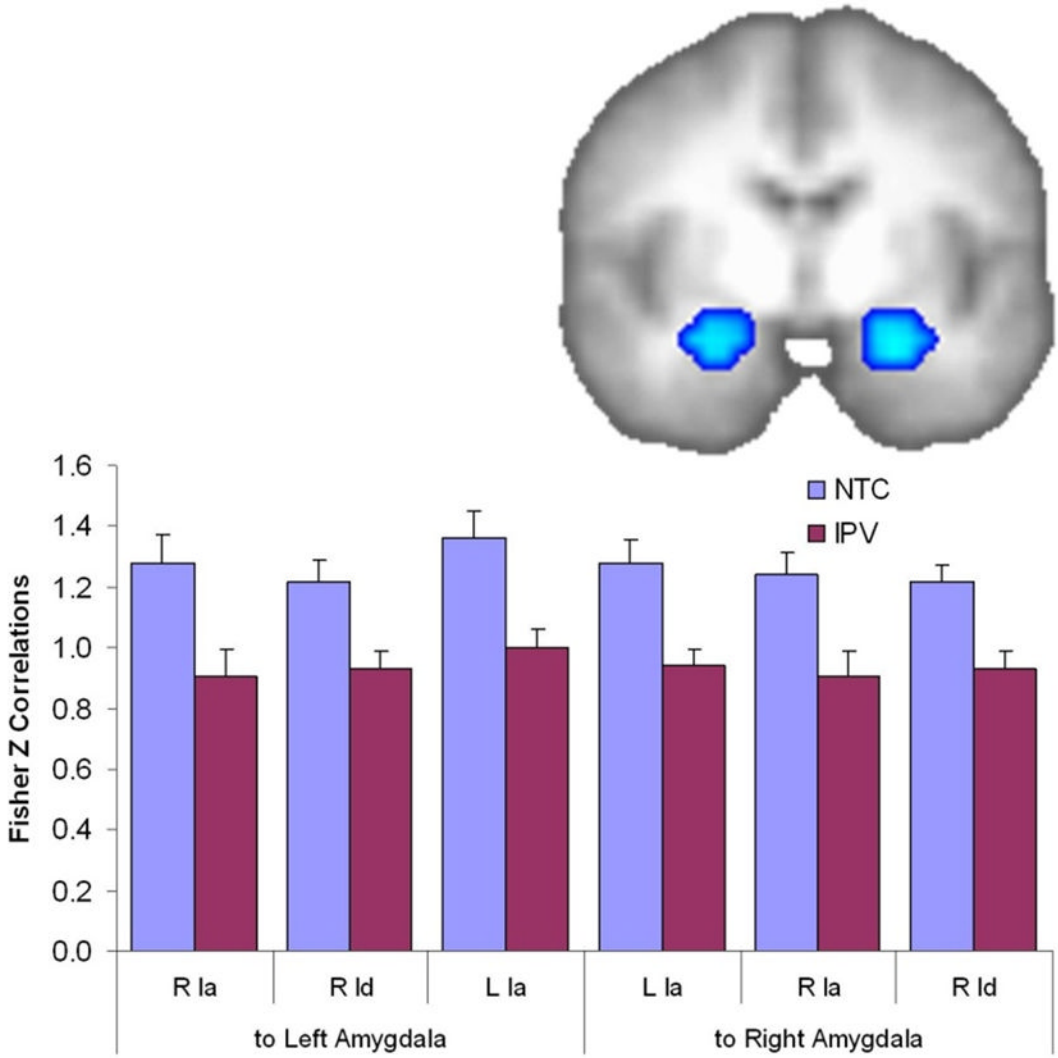

Figure 4.
Reduced Functional Connectivity from the anterior insula (Ia), middle insula (Id), and posterior insula (Ig) to the Amygdala in the IPV group. ROI image shows the regions in the amygdala of significantly reduced functional connectivity from a left anterior insula seed; functional connectivity from the other insula regions is very similar to that displayed in the graph.

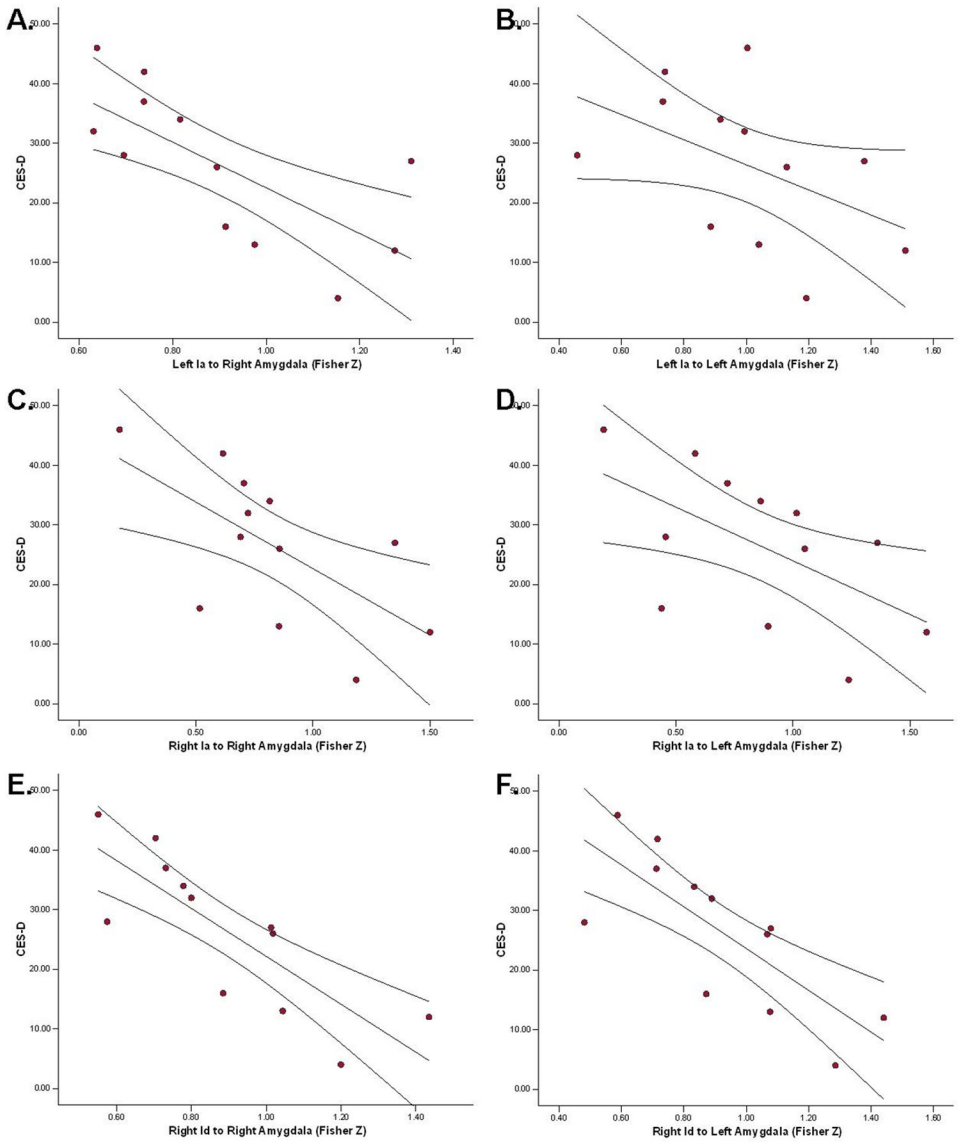

Figure 5.

CES-D correlated with Fisher-Z transform of the connectivity for the left anterior insula (Ia; A and B), right Ia (C and D), and right anterior/middle insula (Id; E and F) with the right (A, C, and E) and left (B, D, and F) amygdala in IPV subjects.

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Table 1

Demographic and Psychological Variables.

		NTC			IPV				
Demographic Variables		**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**t/χ2**	**p**
Age (yrs)		37.13	7.14	(25–50)	34.33	7.83	(24–49)	−1.33	NS
Education (yrs)		15.57	1.72	(12–18)	13.13	1.73	(9–16)	−3.87	<0.001
Marital Status	Married/Living w/Partner	3			0			10.92	<0.05
	Never Married	11			6				
	Separated/Divorced	1			8				
	Separated	0			1				
Race	African American	N=2			N=3			5.59	NS
	Caucasian	N=8			N=9				
	Hispanic	N=0			N=2				
	Filipino-American	N=1			N=0				
	Asian-American	N=1			N=0				
	Mexican-American	N=1			N=0				
	Other	N=2			N=1				
Comorbid Diagnosis (Lifetime or Current)									
Major Depressive Disorder					N=8				
Generalized Anxiety Disorder					N=4				
Panic Disorder					N=3				
Psychological Variables									
CAPS	Total	-	-	-	68.5	26.3	(17–110)		N/A
CTS-2	Negotiation	9.4	7.2	(0–20.83)	3.9	3.5	(0–9.3)	−2.37	<0.05
	Psychological Aggression	0.5	1.0	(0–3.38)	9.3	6.8	(0–18.75)	4.94	<0.001
	Physical Assault	0.0	0.0	(0–0.08)	4.3	5.3	(0–17.83)	3.14	<0.005
	Sexual Coercion	0.0	0.0	(0–0)	2.7	3.9	(0–12.6)	2.68	<0.05
	Injury	0.0	0.1	(0–0.33)	2.7	3.4	(0–12.17)	3.04	<0.005
CTQ	Emotional Abuse	9.2	4.4	(5–21)	13.6	5.7	(5–20)	2.37	<0.05
	Physical Abuse	6.3	2.2	(5–13)	9.1	3.9	(5–18)	2.45	<0.05
	Sexual Abuse	6.1	2.4	(5–13)	8.1	5.6	(5–24)	1.31	NS
	Emotional Neglect	9.2	5.0	(5–24)	13.1	5.0	(5–22)	2.10	<0.05

Demographic Variables		NTC Mean	NTC SD	NTC Range	IPV Mean	IPV SD	IPV Range	t/χ2	p
	Physical Neglect	6.4	1.8	(5–10)	8.2	3.9	(5–20)	1.62	NS
DES-T		1.2	3.9	(0–15)	6.4	8.9	(0–30)	2.09	<0.05
CES-D		4.5	5.5	(0–18)	42.0	13.2	(4–46)	6.85	<0.001
AUDIT		1.4	1.6	(0–6)	3.5	2.4	(1–9)	2.58	<0.05
DAST		0.0	0.0	(0–0)	0.6	1.0	(0–3)	2.28	<0.05
IES-R	Total	0.0	0.0	(0–0)	37.00	21.84	(7–66)	6.35	<0.001
	Avoidance	0.0	0.0	(0–0)	1.75	1.05	(0.13–3.50)	6.27	<0.001
	Hyperarousal	0.0	0.0	(0–0)	1.59	1.02	(0.13–3.00)	5.80	<0.001
	Intrusion	0.0	0.0	(0–0)	1.68	1.03	(0.00–3.17)	6.09	<0.001

Table 2

ROI brain activation differences for negative minus positive anticipation. Increased activation for negative versus positive anticipation. The t-values are shown for the task effect (t-test versus the null hypothesis) and the group effect in these regions (with education covaried out).

						Task Effect		Group Effect	
Volume	**x**	**y**	**z**	**Side**	**Area**	**t-value**	**Sig**	**t-value**	**Sig**
1024	−32	20	3	Left	Anterior Insula (Ia)	2.66	<0.01	0.47	NS
896	34	22	6	Right	Anterior Insula (Ia)	4.26	<0.001	0.32	NS
320	47	10	6	Right	Anterior/Middle Insula (Ia/Id)	3.91	<0.001	4.38	<0.05

Table 3

Whole brain task activation differences for negative minus positive anticipation. The t-values are shown for the task effect (t-test versus the null hypothesis) and the group effect with in these regions (with education covaried out).

						Task Effect		Group Effect	
Volume	**X**	**y**	**z**	**Side**	**Area**	**t-value**	**Sig**	**t-value**	**Sig**
11264	36	16	35	Right	Dorsal Lateral Prefrontal	5.169	<0.001	0.499	NS
11072	42	−44	40	Right	Inferior Parietal Lobule	5.476	<0.001	1.915	NS
8768	−39	−40	42	Left	Inferior Parietal Lobule	5.729	<0.001	1.660	NS
4352	6	7	16	Right	Caudate Body	3.401	<0.05	2.684	NS
3520	32	25	4	Right	Inferior Prefrontal & Anterior Insula	4.955	<0.001	0.080	NS
2816	11	12	46	Right	Dorsal Medial Frontal Gyrus	4.663	<0.001	0.446	NS
2048	−13	−3	50	Left	Dorsal Medial Frontal Gyrus	3.127	<0.005	0.687	NS
1856	−31	22	4	Left	Anterior Insula	2.788	<0.01	0.157	NS
1664	−41	14	19	Left	Inferior Prefrontal	2.303	<0.05	0.809	NS
1344	−15	13	56	Left	Superior Frontal Gyrus	3.299	<0.001	0.945	NS
1152	51	13	8	Right	Inferior Prefrontal & Anterior Insula	3.788	<0.001	3.819	<0.05
1024	10	30	41	Right	Medial Frontal Gyrus	2.573	<0.05	0.582	NS

Table 4

Insula and amygdala connectivity correlations after Fisher Z transformations for each group. The significance of the correlations is shown for the task effect (t-test versus the null hypothesis) and the group effect with education covaried out

Seed ROI	Connection ROI	NTC Fz	IPV Fz	Task Effect		Group Effect	
				t-value	Sig	F	Sig
Left anterior insula	Right Amygdala	1.279	0.936	18.976	>0.001	8.143	<0.005
Left anterior insula	Left Amygdala	1.358	0.978	17.352	>0.001	5.775	<0.01
Right anterior insula	Right Amygdala	1.242	0.892	15.645	>0.001	5.098	<0.05
Right anterior insula	Left Amygdala	1.277	0.870	13.684	>0.001	3.776	<0.05
Right anterior/middle insula	Right Amygdala	1.214	0.923	20.546	>0.001	7.021	<0.005
Right anterior/middle insula	Left Amygdala	1.216	0.911	18.175	>0.001	4.276	<0.05

Table 5

Correlations of Functional connectivity Fisher Z transforms with depression severity in the IPV subjects.

Seed ROI	Connection ROI	CES-D	
		r	Sig
Left anterior insula	Right Amygdala	−0.716	<0.01
Left anterior insula	Left Amygdala	−0.482	NS†
Right anterior insula	Right Amygdala	−0.664	<0.05†
Right anterior insula	Left Amygdala	−0.598	<0.05†
Right anterior/middle insula	Right Amygdala	−0.808	<0.001
Right anterior/middle insula	Left Amygdala	−0.763	<0.005

† not significant after bonferroni-correction