Supplemental Material

Methods and Materials

Participants

Three BPD patients, 1 AvPD patient, and 2 HC's were excluded for excessive head motion, and 1 BPD patient, 3 AvPD patients, and 1 HC were excluded for inadequate numbers of task responses (responding to less than 2/3 of all trials). One HC participant made the same affect self-report response for all $Repeat_{Neg}$ trials, and thus parametric regressor beta weights could not be estimated for that condition for that participant. Therefore, that participant was excluded from the HC $Repeat_{Neg}$ parametric analysis but remained in all other analyses.

Specific Exclusion Criteria

BPD and AvPD participants were excluded if they met DSM-IV criteria for past or present PTSD, bipolar I disorder, schizoaffective disorder, substance dependence, organic mental syndromes, head trauma, CNS neurological disease, seizure disorder, substance abuse disorder in the previous 6 months or current major depressive disorder. Participants with significant medical illness, contraindications to functional magnetic resonance imaging (fMRI), pregnant women and those with current active suicidal ideation were excluded.

Comorbid Diagnoses

Among the BPD patients, 3 were comorbid for narcissistic, 7 for paranoid, 8 for obsessive-compulsive, 5 for antisocial, and 1 for dependent personality disorder. Three BPD patients met criteria for generalized anxiety disorder (GAD), 3 for binge eating disorders, 1 for dysthymic disorder, 1 for obsessive-compulsive disorder, and 1 for specific phobia. Seven BPD patients had histories of prior major depressive disorder (MDD), and 9 of past substance disorder. Among AvPD patients, 13 were comorbid for obsessive-compulsive, 1 for paranoid and 1 for dependent personality disorder. Three met criteria for GAD, and 1 for dysthymic disorder. One had a past history of MDD and 1 of a prior substance use disorder.

Picture Set

The pictures included in the task consisted of 22 negative pictures (mean valence = 2.35 [1 = most negative to 9= most positive], mean arousal = 5.80 [1= least arousing to 9= most arousing]) selected from the IAPS and 48 neutral pictures (mean valence = 5.14, mean arousal = 3.81) also selected from the IAPS, and 26 negative pictures (mean valence = -1.47 [-3 = most negative to 3 = most positive]) selected from the Empathy Picture System. The mean valence and arousal ratings were derived from the canonical data provided with each picture set.

Image Acquisition and Analysis

BOLD images were obtained with a GE-EPI sequence employing the following protocol: 42 axial slices, 2.5 mm thick, skip=0.825 mm, TR= 3s, TE= 27 ms, Flip angle = 85 degrees, FOV= 21 cm, matrix= 64 x 64. Anatomical localization was obtained using a high resolution T2-weighted anatomical scan acquired on an axis plane parallel to the AC-PC line using a turbo spin-echo pulse sequence.

Slice timing correction, realignment, normalization (to a standard Montreal Neurological Institute template) using 3 mm isotropic voxels, and spatial smoothing (7mm full-width at half maximum [FWHM] with a Gaussian kernel) were performed. General linear modeling for each participant was carried out with Neuroelf software (neuroelf.net) using the canonical hemodynamic response function convolved with the vectors of events (1). The linear combination of 4 regressors was used to model the BOLD response ($Novel_{Neg}$, $Repeat_{Neg}$, $Novel_{Neut}$, and $Repeat_{Neut}$) as well as a regressor modeling the rating period, undifferentiated by condition. Six motion parameters were modeled as covariates of no interest.

Supplemental Results

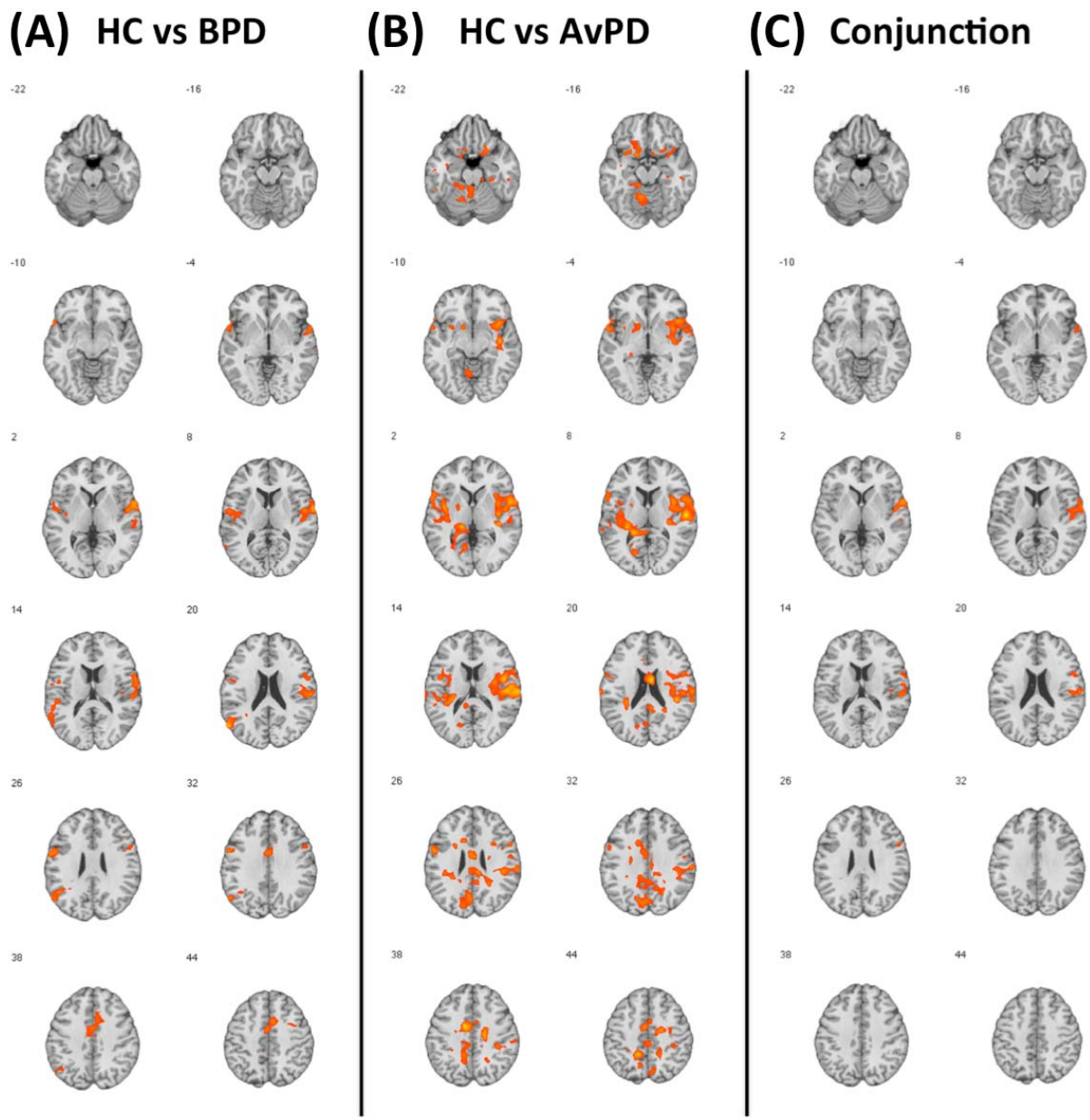
Behavioral Comparisons to Neutral Pictures

Repeated measures ANOVA of participants' ratings of picture valence, with novelty (novel vs. repeat) and picture type (negative vs. neutral) as repeated measures and group (BPD, AvPD, HC) as a between-subjects measure showed that there was a main effect of picture type, with negative pictures rated more negatively than neutral pictures ($F(64,2,1)=1103.4$, $p < 0.01$) and a Novelty X Picture-Type interaction ($F(64,2,1)=18.7$, $p < 0.01$).

BPDs compared to HCs and to AvPDs During Viewing of Negative Pictures Independent of Novelty Condition

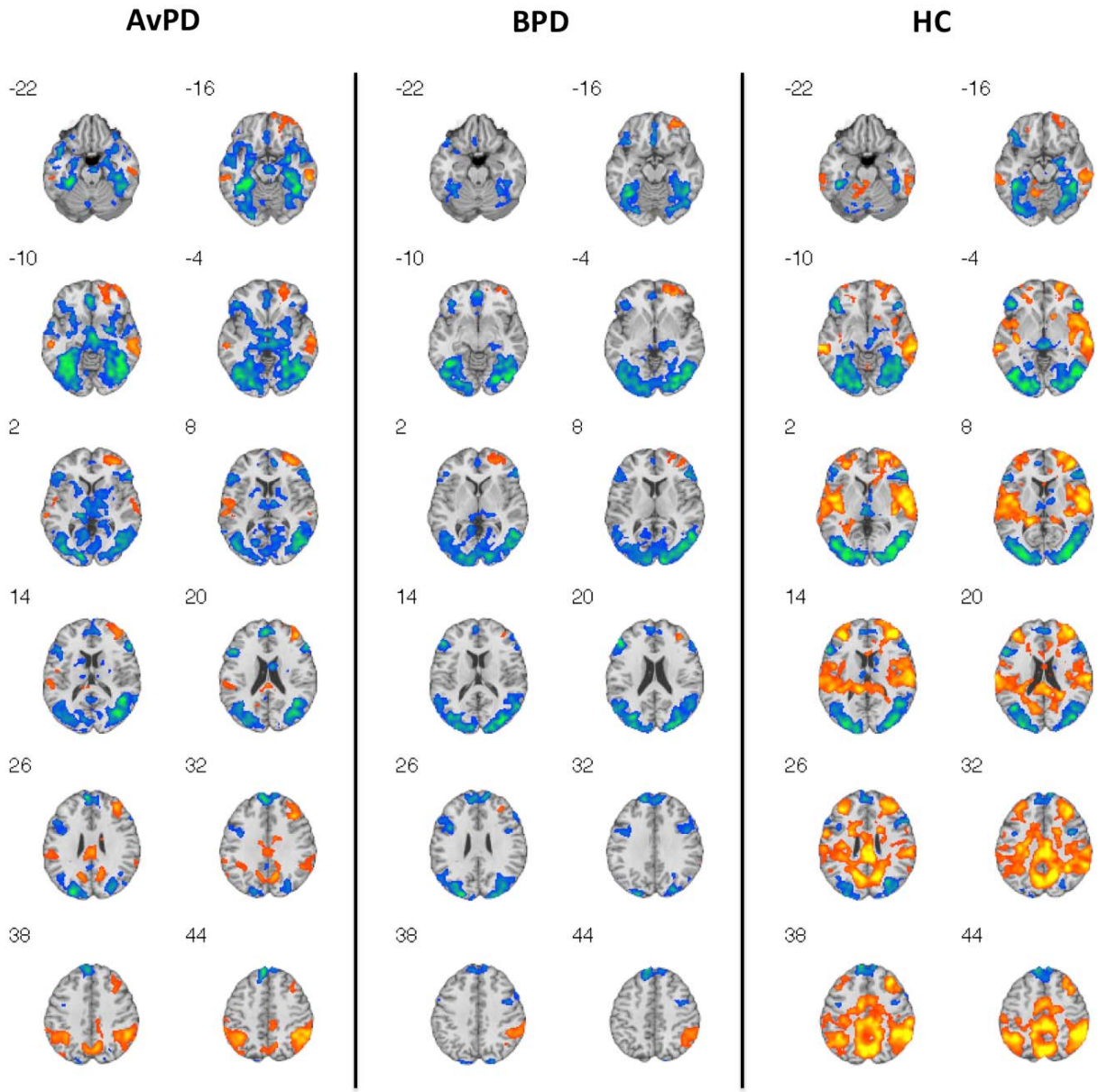
The loci of significant differences in activation between each patient group and HC's when viewing negative pictures, collapsed across novelty condition, are displayed in Table S5. We were particularly interested to interrogate activity differences between BPD participants and the other two groups in two *a priori* ROI's, insula and amygdala. At our FWE whole-brain threshold, we found no group difference in insula or amygdala activation. However, BPD participants showed significantly greater activation in the right middle-posterior insula than either HCs or AvPDs when viewing negative pictures at a relaxed extent threshold (Figure S3A; 73 voxels; peak at [45, 0, 0]). Further, because a group difference was hypothesized on the basis of prior studies reviewed previously, we interrogated the amygdala region at a relaxed threshold ($p = 0.05$, height threshold only) for an absolute value conjunction of regions showing BPD vs. HC and BPD vs. AvPD differences when viewing negative pictures ($Novel_{Neg}$ & $Repeat_{Neg}$) versus baseline. This revealed a 6 voxel locus in the right amygdala in which BPD participants showed greater activation than both HC's and AvPD's when viewing both novel and repeat negative pictures (Figure S3B; peak at [24, -9, -24]).

FIGURE S1 – Neural Activation Differences Between Groups When Viewing Repeat vs. Novel Negative Pictures



(A) HC vs. BPD, (B) HC vs. AvPD, (C) displays the conjunction of (A) and (B). No regions met whole-brain correction thresholds for BPD vs AvPD. Warm colors indicate greater activation in HC compared to the patient groups. $p<0.05$, $k=150$ (A & B), $k=86$ (C), FWE-corrected, $p<0.05$

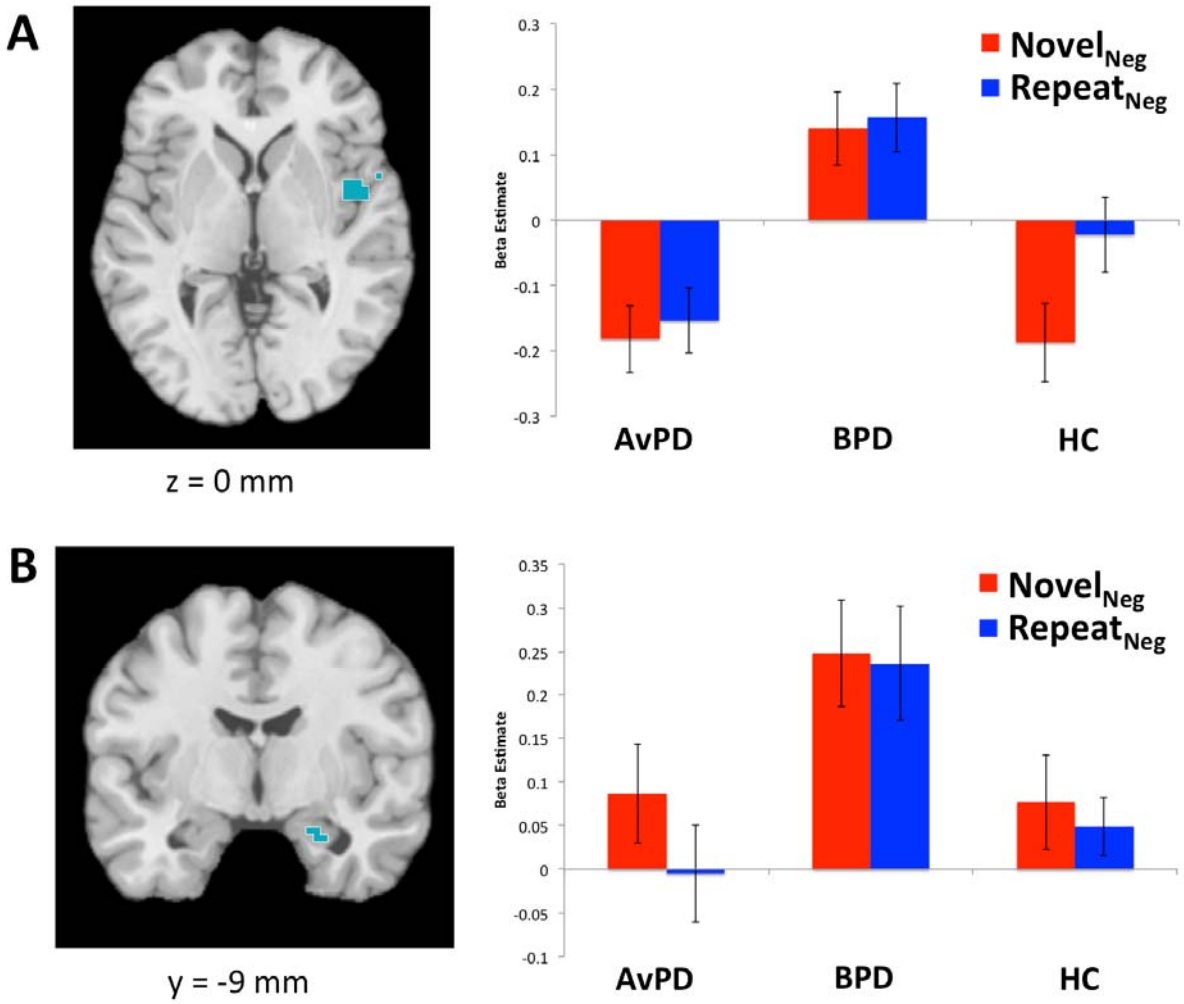
FIGURE S2 – Repeat vs. Novel Activation When Viewing Negative Pictures Within Each Group



Cool colors indicate novel > repeat activation (neural habituation) and warm colors repeat > novel activation (neural sensitization).

FWE Corrected $p < .05$, k=300

FIGURE S3 - Neural Activation Differences Between Groups When Viewing Negative Pictures Collapsed Across Novelty ($Novel_{Neg}$ & $Repeat_{Neg}$) Showing Increased BOLD Signal in BPD Compared to Both HC and AvPD participants in A.) Right Middle-Posterior Insula and B.) Right Amygdala



Maps display conjunction ROI's of with significant (BPD vs. HC) and (BPD vs. AvPD) differences collapsed across novelty condition ($p<0.05$). Accompanying graphs show extracted beta estimates for each group and novelty condition.

FIGURE S4 – Repeat vs. Novel Connectivity Changes to Left Insula Seed for Each Group (FWE-corrected, p<0.05, k = 300). Warm colors represent increases in connectivity from novel to repeat condition and cool colors represent decreases in connectivity.

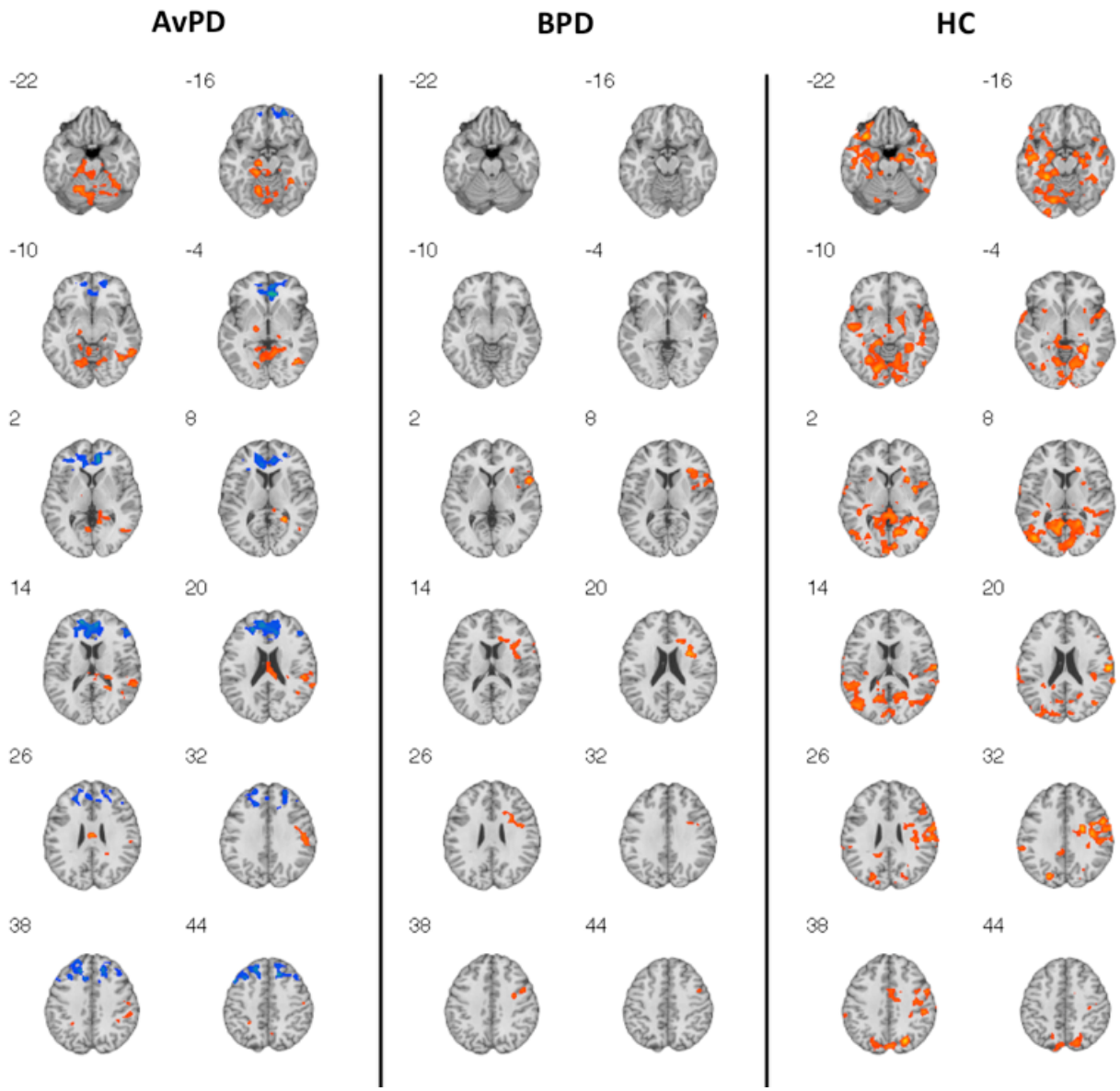


FIGURE S5 – Correlations of changes in insula-amygdala connectivity and change in average negative ratings for repeat vs. novel negative pictures for each group. Warm colors correspond to positive correlation; cool colors to negative correlation.

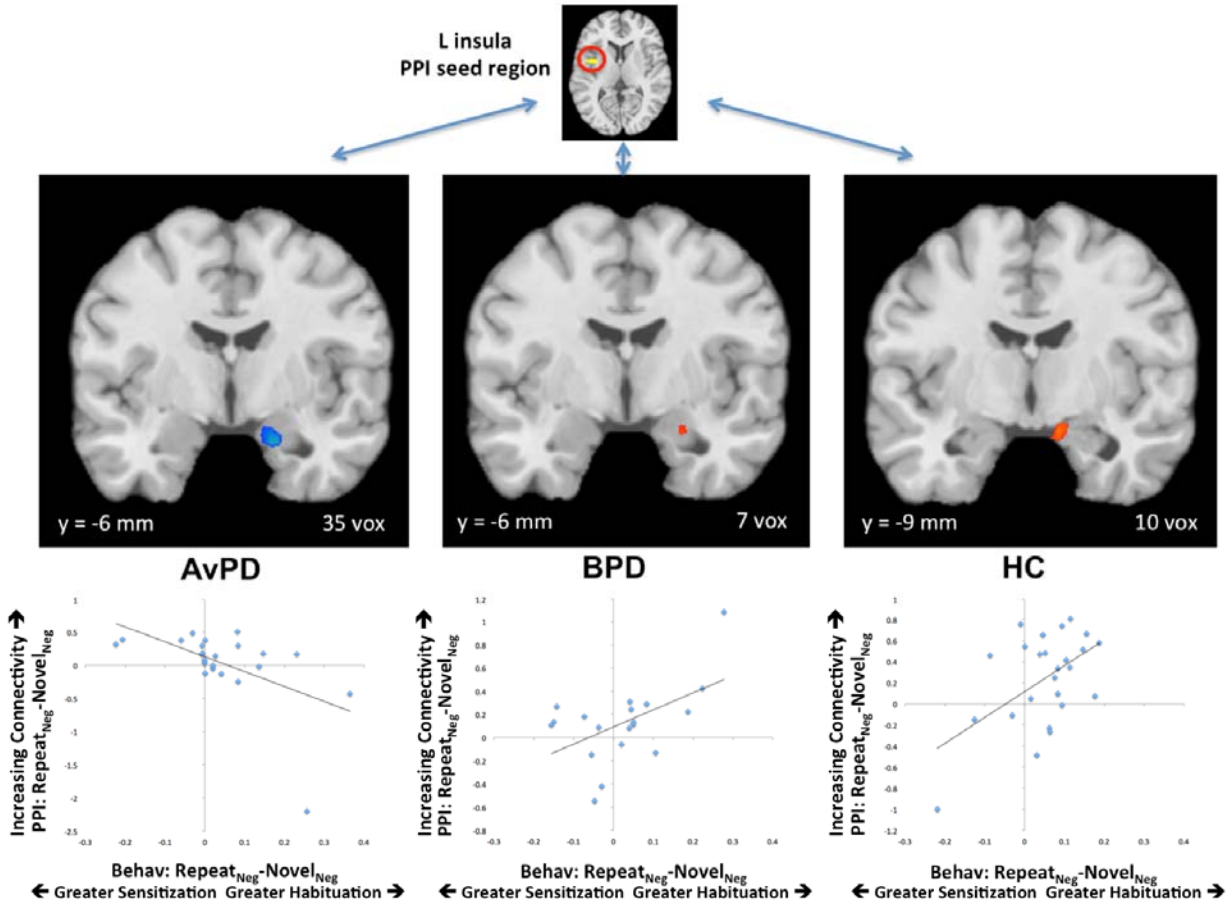
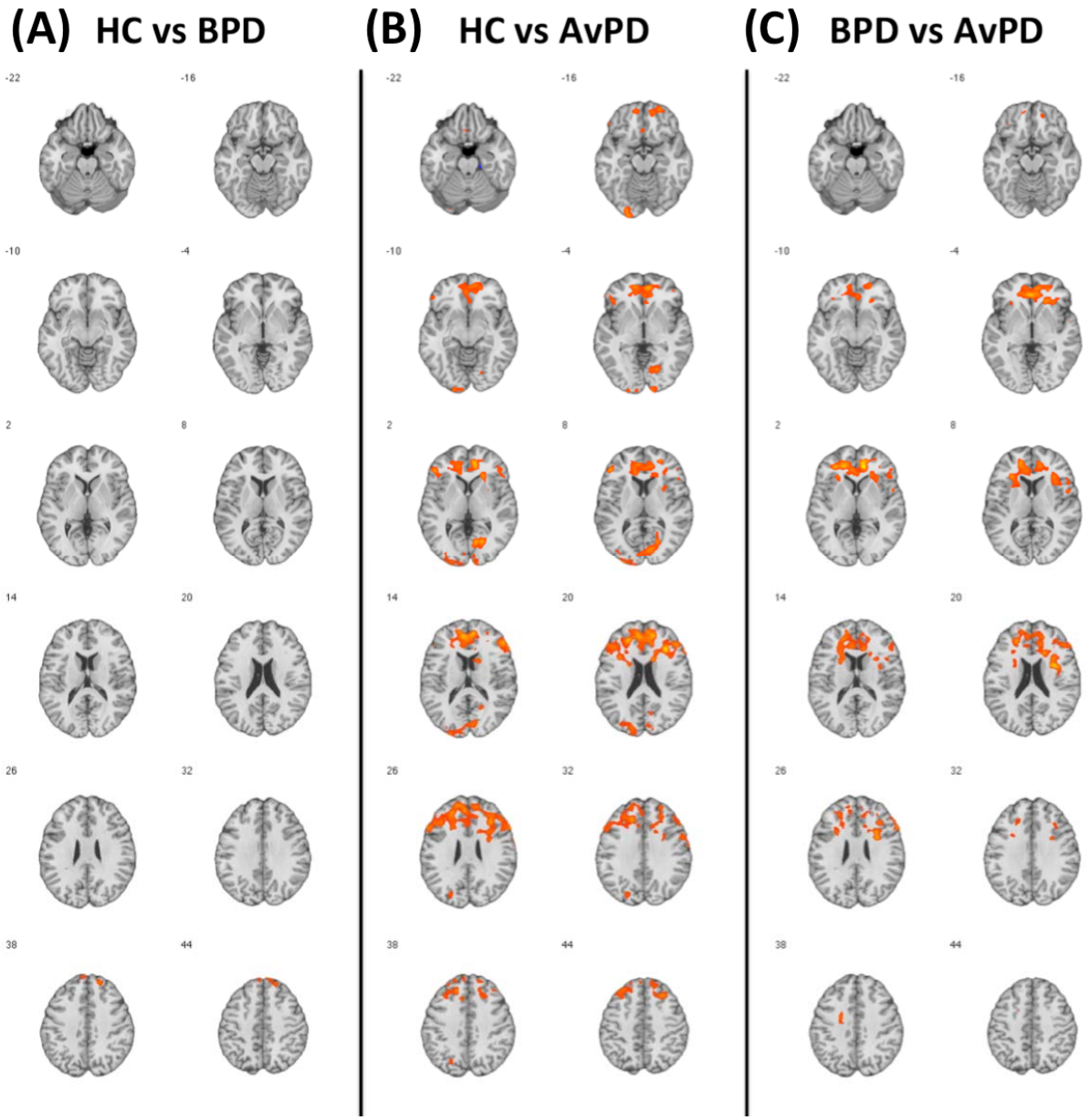
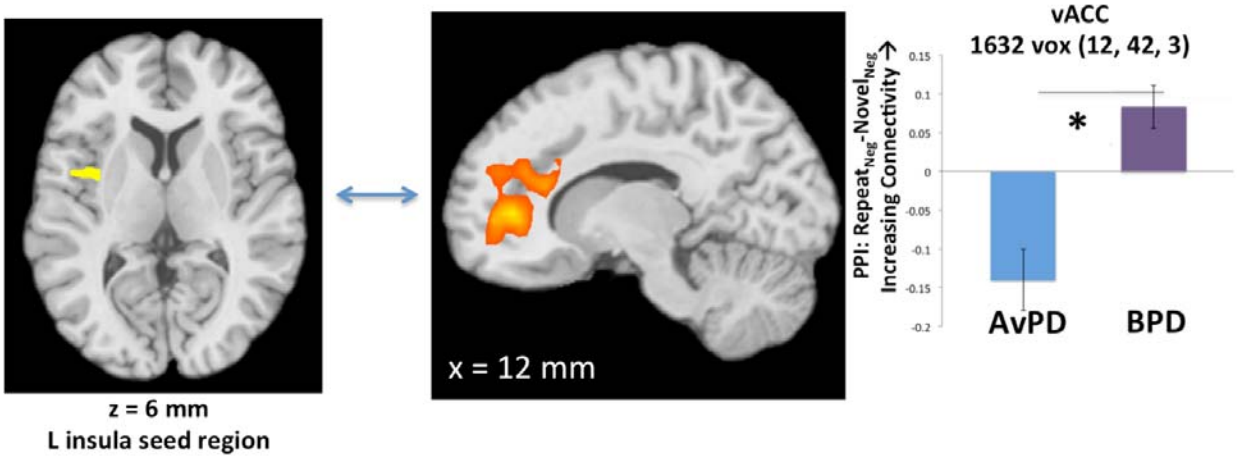


FIGURE S6 – Montages Contrasting Functional Connectivity Changes for (A) HC vs. BPD, (B) HC vs. AvPD, (C) BPD vs. AvPD. No regions met whole-brain correction thresholds for the conjunction of (A) and (B).



Warm colors indicate relatively greater functional connectivity between the indicated region and the insula seed region for repeat vs. novel negative pictures. FWE Corrected $p < .05$, $k=150$

FIGURE S7 – Between-group connectivity changes between the insula seed region and ventral ACC when viewing repeat vs. novel negative pictures in BPD patients compared to AvPD patients.



Whole-brain corrected FWE, $p < .05$, $k = 150$

Supplemental Tables

TABLE S1 – Neural Activation Differences Between Groups When Viewing Repeat vs. Novel Negative Pictures

HC > BPD ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Sub-Gyral (BA 6)	RH	195	12	0	57	3.707
Middle Temporal Gyrus (BA 39)	LH	197	-57	-69	21	3.705
Transverse Temporal Gyrus (BA 42)	RH	364	66	-3	6	3.702
Superior Temporal Gyrus (BA 22)	LH	176	-57	12	-6	3.228
Dorsal Anterior Cingulate Cortex (BA 24)	LH	156	-3	0	33	3.188

BPD > HC ($Repeat_{Neg}$ > $Novel_{Neg}$)

No significant clusters.

HC > AvPD ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Transverse Temporal Gyrus (BA 41)	RH	1455	57	-12	9	4.597
Thalamus	RH	1588	6	-3	21	4.547
Parahippocampal Gyrus (BA 30)	LH	762	-21	-39	6	4.180
Sub-Gyral (BA 20)	LH	155	-48	-18	-30	3.991
Inferior Frontal Gyrus (BA 47)	LH	204	-24	15	-27	3.591
Culmen	RH	258	24	-33	-27	3.217
Precuneus (BA 31)	LH	224	-3	-69	24	3.030
Dorsal Anterior Cingulate Cortex (BA 24)	LH	162*	-9	-3	39	4.074

AvPD > HC ($Repeat_{Neg}$ > $Novel_{Neg}$)

No significant clusters.

BPD > AvPD ($Repeat_{Neg}$ > $Novel_{Neg}$)

No significant clusters.

AvPD > BPD ($Repeat_{Neg}$ > $Novel_{Neg}$)

No significant clusters.

(p = .05, k=150, FWE-corrected, p<0.05).

* reflects local maximum within dACC meeting whole-brain FWE-correction.

TABLE S2 – Repeat vs. Novel Activation When Viewing Negative Pictures Within Each Group

AvPD

Habituation ($Novel_{Neg}$ > $Repeat_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Fusiform Gyrus (BA 37)	LH	9657	-30	-39	-18	7.621
Superior Frontal Gyrus (BA 9)	LH	771	-6	57	27	6.177

Sensitization ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Inferior Parietal Lobule (BA 40)	RH	724	57	-45	48	5.88
Middle Temporal Gyrus (BA 21)	RH	308	60	-30	-15	5.716
Inferior Parietal Lobule (BA 40)	LH	890	-57	-42	51	5.561
Middle Frontal Gyrus (BA 9)	RH	763	39	27	30	5.267
Cuneus (BA 7)	RH	640	9	-66	36	4.811

BPD

Habituation ($Novel_{Neg}$ > $Repeat_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Inferior Occipital Gyrus (BA 19)	RH	5882	42	-78	-9	11.182
Middle Frontal Gyrus (BA 46)	LH	609	-48	33	18	7.439
Medial Frontal Gyrus (BA 11)	LH	891	0	51	-12	5.475
Inferior Frontal Gyrus (BA 45)	RH	393	51	33	6	4.454

Sensitization ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Sub-Gyral	RH	342	27	48	-3	5.025
Supramarginal Gyrus (BA 40)	RH	401	45	-42	39	4.359

TABLE S2 (cont.) – Repeat vs. Novel Activation When Viewing Negative Pictures

Within Each Group

HC

Habituation ($Novel_{Neg}$ > $Repeat_{Neg}$**)**

Region	Hemisphere	k	x	y	z	T max
Middle Occipital Gyrus (BA 37)	RH	5408	48	-69	0	7.729
Inferior Frontal Gyrus (BA 45)	RH	461	48	33	-3	6.137
Inferior Frontal Gyrus (BA 47)	LH	500	-45	33	-6	5.936
Superior Frontal Gyrus (BA 8)	LH	609	-9	51	48	5.213

Sensitization ($Repeat_{Neg}$ > $Novel_{Neg}$**)**

Region	Hemisphere	k	x	y	z	T max
Inferior Frontal Gyrus (BA 46)	RH	15731	42	48	12	9.051
Culmen	LH	336	-15	-54	-18	3.93

(p = .05, k = 300, FWE-corrected, p<0.05)

TABLE S3 – Functional Connectivity Change Differences Between Groups When Viewing Repeat vs. Novel Negative Pictures

HC > BPD: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Superior Frontal Gyrus (BA 9)	RH	220	18	45	39	3.160

BPD > HC: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

No significant clusters.

HC > AvPD: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Middle Frontal Gyrus (BA 9)	RH	2603	33	27	21	4.773
Posterior Cingulate (BA 30)	RH	573	21	-69	3	3.693

AvPD > HC: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Culmen	RH	250	9	-33	-39	4.060
Inferior Semi-Lunar Lobule	LH	164	-9	-63	-51	3.677

BPD > AvPD: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Anterior Cingulate (BA 32)	RH	1632	12	42	3	4.924

AvPD > BPD: PPI ($Repeat_{Neg}$ > $Novel_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Cerebellar Tonsil	LH	177	-21	-63	-45	3.657

($p = .05$, $k=150$, FWE-corrected, $p<0.05$)

TABLE S4 – Neural Activation Differences Between Groups When Viewing Negative Pictures Collapsed Across Novelty

BPD > HC ($Novel_{Neg}$ & $Repeat_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Superior Temporal Gyrus (BA 22)	RH	782	63	-18	-3	4.169
Middle Frontal Gyrus (BA 10)	LH	999	-42	57	12	4.165
Sub-Gyral (BA 37)	LH	231	-51	-39	-9	3.697

HC > BPD ($Novel_{Neg}$ & $Repeat_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Parahippocampal Gyrus (BA 30)	RH	456	18	-36	-12	3.354

BPD > AvPD ($Novel_{Neg}$ & $Repeat_{Neg}$)

Region	Hemisphere	k	x	y	z	T max
Middle Temporal Gyrus	LH	9343	-51	-36	-9	5.068

AvPD > BPD ($Novel_{Neg}$ & $Repeat_{Neg}$)

No significant clusters.

p = .05, k = 203, FWE-corrected, $p<0.05$.

References

1. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. NeuroImage. 1998;7(1):30-40.