Supplemental Material

Participants

Among borderline patients, 2 were excluded for falling asleep repeatedly during scanning, 1 was excluded due to excessive motion during scanning, and 1 was excluded due to poor image quality. Among avoidant patients, 1 was excluded for repeatedly falling asleep during scanning, 1 was excluded for excessive motion, and 4 were excluded due to poor image quality. Among healthy controls, 1 was excluded due to excessive motion, 1 was excluded due to technical problems with the response glove, and 7 were excluded due to poor image quality. 2 borderline patients and 1 healthy control had 1 slightly shorter run due to an incorrectly entered number of volumes resulting in that run being 1.58 min shorter; these runs were maintained in the analysis. 1 borderline patient and 1 avoidant patient had 1 run excluded from analysis due to participant motion unique to that run (with the remaining runs unaffected), and thus those participants were retained overall in the analysis with the 1 run excluded. 1 run for 1 borderline patient was excluded due to poor signal quality, but that participant was retained in the analysis with the 1 run excluded.

Comorbid axis I diagnoses among the borderline patients included: 7 current major depression, 1 past major depression, 5 PTSD, 8 past substance abuse, 3 social phobia, 2 specific phobia, 1 panic disorder, 5 eating disorders, 3 dysthymic disorder, 1 cyclothymic disorder, 3 somatoform disorders, 4 intermittent explosive disorder. Among the avoidant patients comorbid axis I disorders included: 4 current major depression, 1 past major depression, 6 past substance abuse, 11 social phobia, 1 panic disorder, 1 eating disorder, 1 dysthymic disorder, 1 generalized anxiety disorder, 1 adjustment disorder.

Among the borderline patients comorbid Axis II disorders included: 2 schizoid, 1 schizotypal, 5 antisocial, 4 narcissistic, 9 obsessive-compulsive, 4 dependent, 2 histrionic personality disorders. Axis II disorders among the avoidant patients included: 2 schizoid, 4 schizotypal, 2 paranoid, 2 antisocial, 1 narcissistic, 5 obsessive-compulsive, 2 dependent personality disorders.

Materials

Images consisted of 3 negative and 5 neutral images from the Empathy Picture System (Geday, Gjedde, Boldsen, & Kupers, 2003) as well as 27 negative and 25 neutral images purchased from online image repositories. Neutral images depicted individuals interacting in emotionally neutral ways. To be comparable to one another, all images used in this experiment were rated by a separate group of healthy adult participants using the Self-Assessment Manikin (Bradley & Lang, 1994) for assessment of valence (on a scale of 1=most negative to 9=least negative) and arousal (on a scale of 1=least arousal to 9=most arousal). Negative images were rated as valence = 3.36 (standard deviation = 0.90) and arousal = 4.81 (standard deviation = 1.16), whereas neutral images were rated as valence = 5.92 (standard deviation = 0.67) and arousal = 3.74 (standard deviation = 0.89).

Functional MRI

Whole-brain fMRI data were acquired using a 3.0T Philips Achieva scanner using an echo-planar imaging sequence using the following protocol: 45 axial slices, 3.0 mm thickness, no interslice gap, repetition time = 2.5 s, TE = 27 ms, flip angle = 90 degrees. Slices were acquired in ascending sequential order. At each session, data were acquired in three functional runs of 296 volumes each, incorporating 20 s of leading and 20 s of

trailing fixation, for a total of 12.3 min per run. A high-resolution T1-weighted anatomical scan was also acquired for each participant during Session 1 only.

Preprocessing was completed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) using standard parameters: slice-timing correction, realignment and coregistration between each participant's functional and anatomical data, normalization to a standard template (Montreal Neurological Institute) using 3 mm isotropic voxels, and spatial smoothing with a Gaussian kernel (full-width at half maximum = 6 mm).

At the first level, general linear modeling (GLM) was carried out using NeuroElf software (neuroelf.net) by convolving task event epochs (defined below) with the canonical hemodynamic response function for each participant. Two epochs were modeled: the stimulus presentation period (differentiated by an interaction of Session, Valence, and Presentation Order), and the negative affect rating period (undifferentiated by condition). Participants' six motion parameters were also included in the GLM. Data were high-pass filtered (cut-off = 130 s), and participant timecourses underwent percent signal change transformation. Parameter estimates were then extracted for each participant for each condition (i.e. the interaction of Session, Valence, and Presentation Order).

Exploratory Whole-Brain Analysis

In order to examine post-hoc regions-of-interest involved in habituation or sensitization across interactions of Group and Session, an exploratory whole-brain analysis was conducted by creating contrast images using random-effects between-subjects comparisons of beta weights obtained from the GLM described above using

NeuroElf software. Specifically, average activity at Session 1 was subtracted from average activity at Session 2 for each Valence for each Group.

Anatomical Definitions of Regions-of-Interest (ROI's)

Right and left amygdala ROI's were defined using the TD Brodmann atlas within the WFU Pickatlas (Lancaster et al., 2000; Maldjian, Laurienti, Kraft, & Burdette, 2003) (Right amygdala: 50 voxels, center at [24, -4, -19]; Left amygdala: 49 voxels, center at [-23, -4, -19]). Right and left anterior insula ROI's were defined using the AAL atlas within the WFU Pickatlas (Right anterior insula: 302 voxels, center at [33, 17, -2]; Left anterior insula: 278 voxels, center at [-37, 18, -4]). The dACC ROI was defined using the AAL atlas within the WFU Pickatlas (687 voxels, center at [2, 34, 18]).

Supplemental Results

Salience Network Activity

Overall, there was a main effect of Presentation Order, $F(4,1368)=11.55$, $p<0.01$, reflecting within-session habituation across all groups, as detailed below. Among borderline patients, for negative images, Session 1 presentation 5 < Session 1 presentation 1, $t(25)=2.79$, $p<0.01$, two-tailed, and Session 2 presentation 5 < Session 2 presentation 1, $t(25)=3.43$, $p<0.01$, two-tailed; for neutral images, Session 2 presentation 5 < Session 2 presentation 1, $t(25)=2.31$, $p<0.03$, two-tailed. Among avoidant patients, for negative images, Session 1 presentation 5 < Session 1 presentation 1, $t(24)=2.93$, $p<0.01$, two-tailed, and Session 2 presentation 5 < Session 2 presentation 1, $t(24)=4.61$, $p<0.01$, two-tailed. Among healthy controls, for negative images, Session 1 presentation 5 < Session 1 presentation 1, $t(23)=4.43$, $p<0.01$, two-tailed, and Session 2 presentation 5

< Session 2 presentation 1, $t(23)=4.37$, $p<0.01$, two-tailed; for neutral images, Session 1 presentation 5 < Session 1 presentation 1, $t(23)=2.17$, $p<0.05$, two-tailed.

Exploratory Comorbidity Analyses

As an exploratory analysis, we further examined self-reported negative affect and salience network activity in avoidant patients as a function of presence or absence of comorbidity with social phobia (i.e. the comorbidity with the largest sample size across participants, with 11 avoidant patients comorbid with social phobia and 14 avoidant patients not meeting criteria for social phobia; details of comorbidities are given above).

Self-reported negative affect results were very consistent across avoidant patients with and without comorbidity with social phobia. No main effect of social phobia comorbidity nor any significant interaction with other task factors (i.e. Session, Valence, and Presentation Order) was present.

Salience network activity in avoidant patients comorbid with social phobia showed somewhat more similarity to activity in borderline patients than in avoidant patients not comorbid with social phobia, particularly for responses to negative images across sessions (Figure S1). This is illustrated by a significant Session-by-Valence-by-Social Phobia Comorbidity interaction among avoidant patients, $F(1,437)=4.76$, $p<0.04$. However, post-hoc analyses showed no significant between-session sensitization or habituation for avoidant patients comorbid with social phobia for either negative images ($t(10)=0.62$, n.s.) or neutral images ($t(10)=1.14$, n.s.), nor for avoidant patients not comorbid with social phobia for either negative images ($t(13)=1.19$, n.s.) or neutral images ($t(13)=0.57$, n.s.).

Finally, there was also a marginal Valence-by-Social Phobia Comorbidity interaction, $F(1,437)=3.51$, $p<0.07$, such that social phobia comorbidity differences in salience network activity among avoidant patients were somewhat more pronounced for negative relative to neutral images. No main effect of social phobia comorbidity was present on salience network activity, and no other interactions with any other task factors were significant.

Right Amygdala

Right amygdala ROI definition and activity are shown in Figure S2. Across both valences and all sessions, a robust main effect of Presentation Order was present, showing decreasing activity overall over time within a session (i.e. a main effect of within-session habituation), $F(4,1368)=12.45$, $p<0.01$. Importantly, there was also a robust Group-by-Session interaction, $F(2,1368)=23.38$, $p<0.01$, driven by the marked increase (i.e. sensitization) specifically for borderline patients relative to the other two groups from Session 1 to Session 2 in both valences (in borderline patients for negative images, Session 2 > Session 1, $t(25)=1.97$, $p<0.04$, one-tailed, other groups n.s.; in borderline patients for neutral images, Session 2 > Session 1, $t(25)=1.92$, $p<0.04$, one-tailed, other groups n.s.). A marginal main effect of Group was also present, with activity slightly greater overall in borderline patients across both valences and sessions, $F(2,72)=2.54$, $p<0.09$.

Left Amygdala

Left amygdala responses (Figure S3) showed a main effect of Presentation Order ($F(4,1368)=9.54$), $p<0.01$), indicating global within-session habituation. Further, there was a significant Session-by-Valence interaction, $F(1,1368)=41.40$, $p<0.01$, as well as a

significant Group-by-Session-by-Valence interaction, $F(2,1368)=8.15$, $p<0.01$, indicating greater between-session sensitization for negative images, and for avoidant patients (for negative images, Session 2 > Session 1, $t(24)=2.46$, $p<0.03$, two-tailed) and healthy adults (for negative images, Session 2 > Session 1, $t(23)=1.77$, $p<0.10$, two-tailed), in particular (borderline patients n.s.).

Right Anterior Insula

Right AI activity (Figure S4) showed a pattern similar to that of right amygdala. A main effect of Presentation Order was present, showing decreasing activity overall over time within a session (i.e. habituation), $F(4,1368)=4.58$, $p<0.01$. As with right amygdala activity, there was also a robust Group-by-Session interaction, $F(2,1368)=15.68$, $p<0.01$, illustrating the sensitization shown for borderline patients overall relative to the other two groups from Session 1 to Session 2 across valences (in borderline patients for negative images, Session 2 > Session 1, $t(25)=1.65$, $p<0.04$, one-tailed, other groups n.s.; in borderline patients for neutral images, Session 2 > Session 1, $t(25)=1.76$, $p<0.05$, one-tailed, other groups n.s.). A main effect of Valence was also present (negative>neutral), $F(1,1368)=19.76$, $p<0.01$.

Left Anterior Insula

Left AI activity showed a similar pattern across groups overall (Figure S5), with a significant main effect of Presentation Order, indicating habituation within-session across groups ($F(4,1368)=7.90$, $p<0.01$). Main effects of Session (Session 1 > Session 2), $F(1,1368)=50.34$, $p<0.01$, and Valence (negative > neutral), $F(1,1368)=51.73$, $p<0.01$, were also present. However, in contrast to right amygdala and right AI, left AI showed no longitudinal sensitization effect in borderline patients. Instead, a significant Group-by-

Session interaction was present ($F(2,1368)=8.91$, $p<0.01$), though driven by between-session habituation in healthy controls (in healthy controls for negative images, Session 2 < Session 1, $t(23)=2.78$, $p<0.02$, two-tailed, in avoidant patients for negative images, Session 2 < Session 1, $t(24)=2.04$, $p<0.06$, two-tailed, borderline patients n.s.; in healthy controls for neutral images, Session 2 < Session 1, $t(23)=2.20$, $p<0.04$, two-tailed, other groups n.s.). A Presentation Order-by-Valence interaction was also present, $F(4,1368)=2.94$, $p<0.03$, as was a marginal Group-by-Valence interaction, $F(2,1368)=2.87$, $p<0.06$, reflecting greater within-session habituation for negative images, and marginally greater group differentiation for negative images, respectively.

dACC

dACC activity showed a pattern consistent with right amygdala and right anterior insula activity (Figure S6). While there was no overall within-session effect of habituation, there was a significant Group-by-Session interaction ($F(2,1368)=16.37$, $p<0.01$), illustrating sensitization for borderline patients relative to the other two groups from Session 1 to Session 2 in both valences (in borderline patients for negative images, Session 2 > Session 1, $t(25)=1.78$, $p<0.05$, one-tailed, other groups n.s.; in borderline patients for neutral images, Session 2 > Session 1, $t(25)=2.07$, $p<0.03$, one-tailed, other groups n.s.). A marginal main effect of Session was also present (Session 2 > Session 1), $F(1,1368)=3.66$, $p<0.06$.

Laterality Analysis

An exploratory analysis incorporating laterality as a factor among lateralized regions (i.e. bilateral amygdala and bilateral AI) indicated both a main effect of laterality (i.e. more activity overall in the left relative to right hemisphere among these four ROI's

across groups and valences when viewing social picture stimuli), $F(1,5808)=3.91$, $p<0.05$, as well as a Group-by-Session-by-Laterality interaction, $F(2,5808)=10.08$, $p<0.01$, substantiating observations above that the between-session sensitization observed for borderline patients was strongest on the right relative to the left hemisphere.

Exploratory Whole-Brain Analysis

While our primary hypotheses concerned activation in salience network ROI's, we also performed a whole-brain exploratory analysis to identify post-hoc regions showing sensitization or habituation effects (i.e. average Session 2 – average Session 1 activity for each Valence for each Group). No post-hoc regions emerging from a whole-brain exploratory analysis met familywise-error thresholds for multiple comparison correction, as determined by Alphasim (Ward, 2000), for either Valence in any Group (correction threshold: $p<0.001$, two-tailed, uncorrected; extent threshold = 38 voxels; FWE-corrected, $p<0.05$).

References

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Ward, B. D. (2000). Simultaneous inference for FMRI data. Retrieved July 3, 2011, from http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf

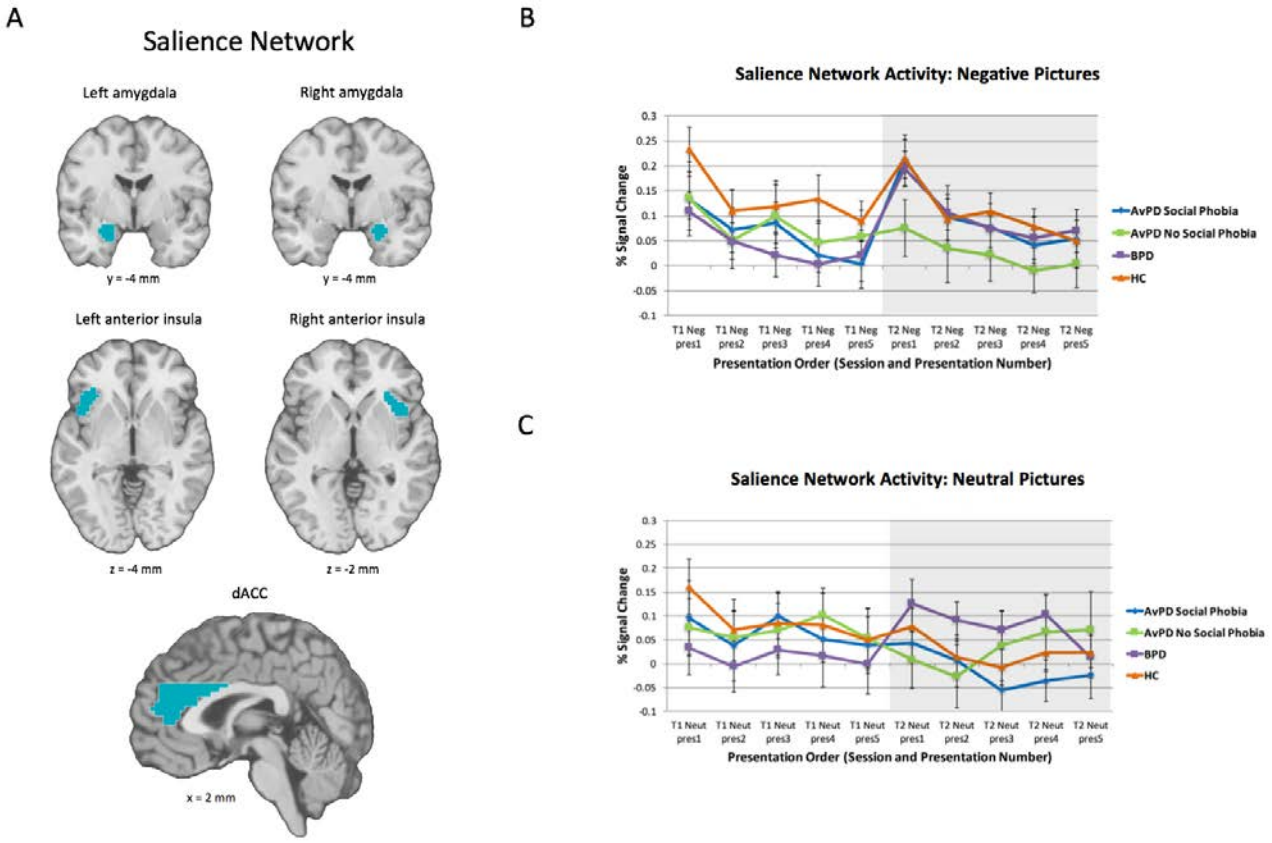

Figure S1. Salience network activity during the longitudinal habituation task for avoidant patients comorbid with social phobia, avoidant patients not comorbid with social phobia, borderline patients, and healthy controls. (A: network component ROI definitions; B: activity for negative images; C: activity for neutral images). T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.

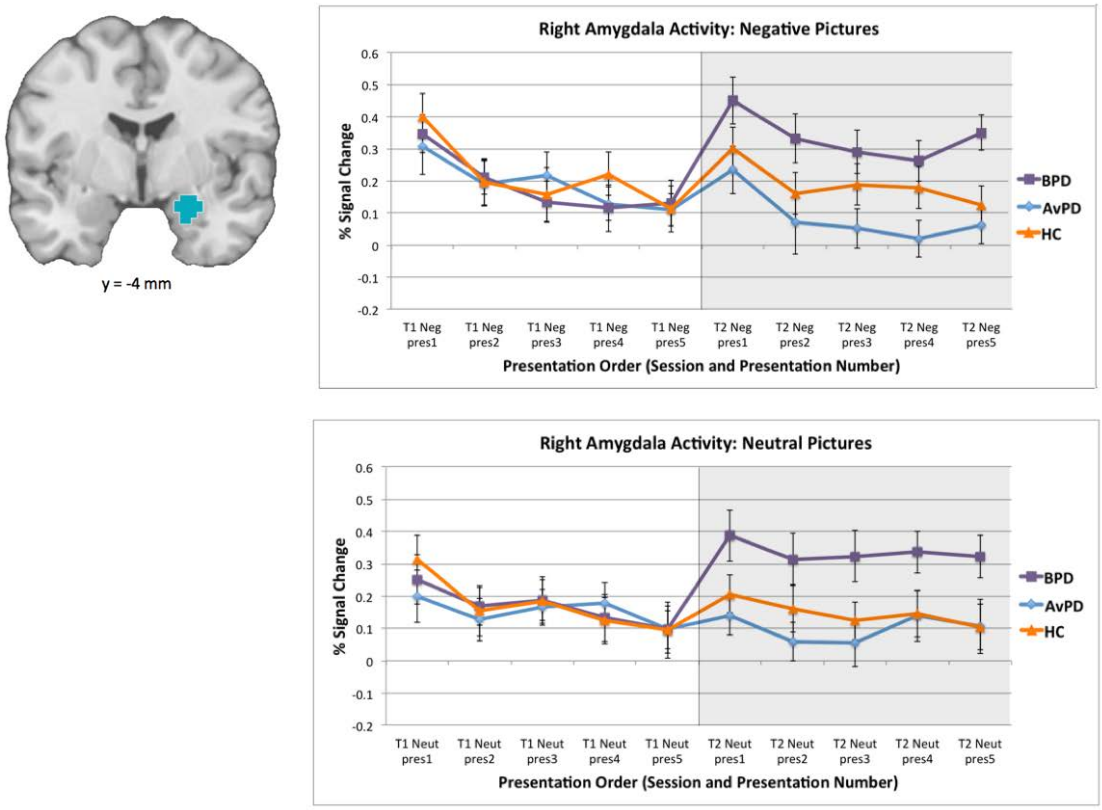

Figure S2. Right amygdala activity during the longitudinal habituation task. T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.

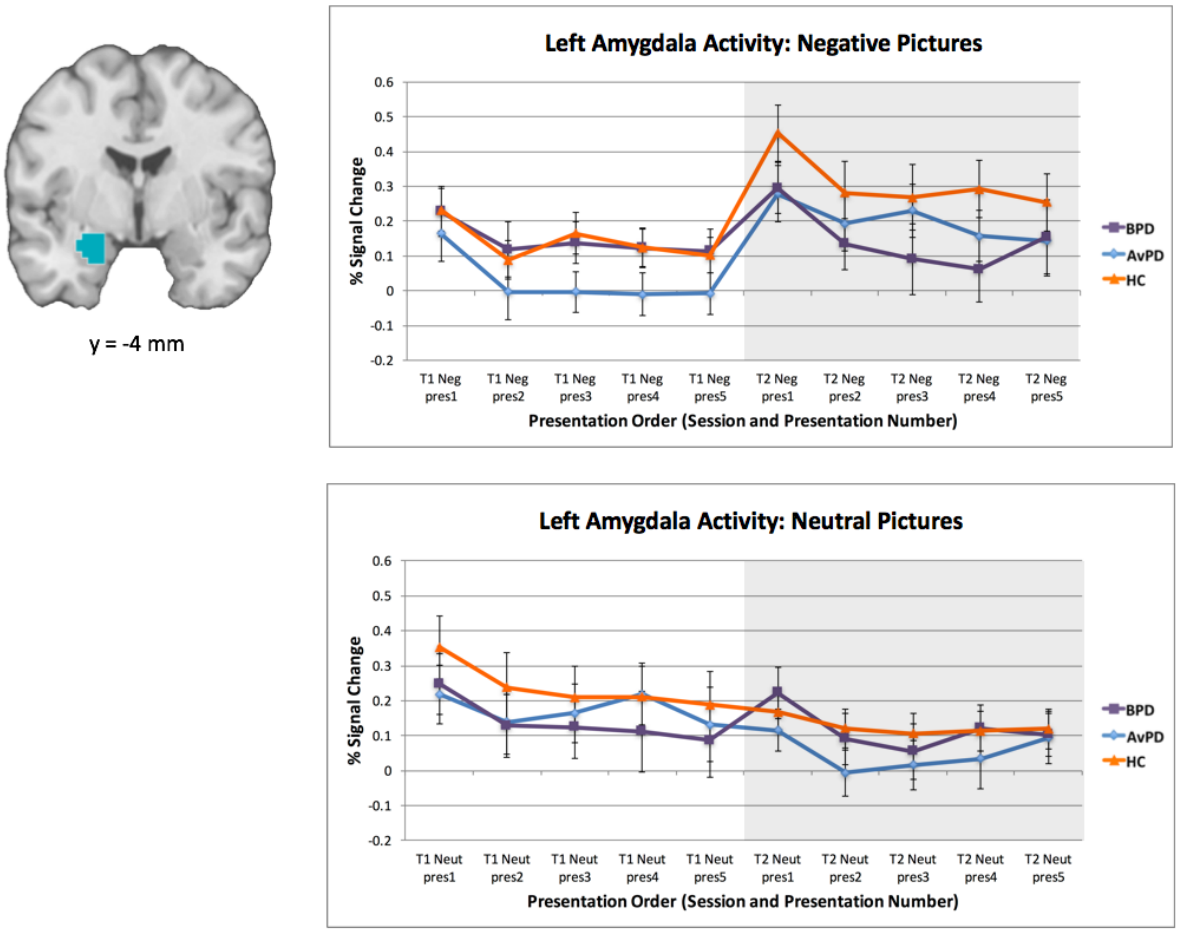

Figure S3. Left amygdala activity during the longitudinal habituation task. T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.

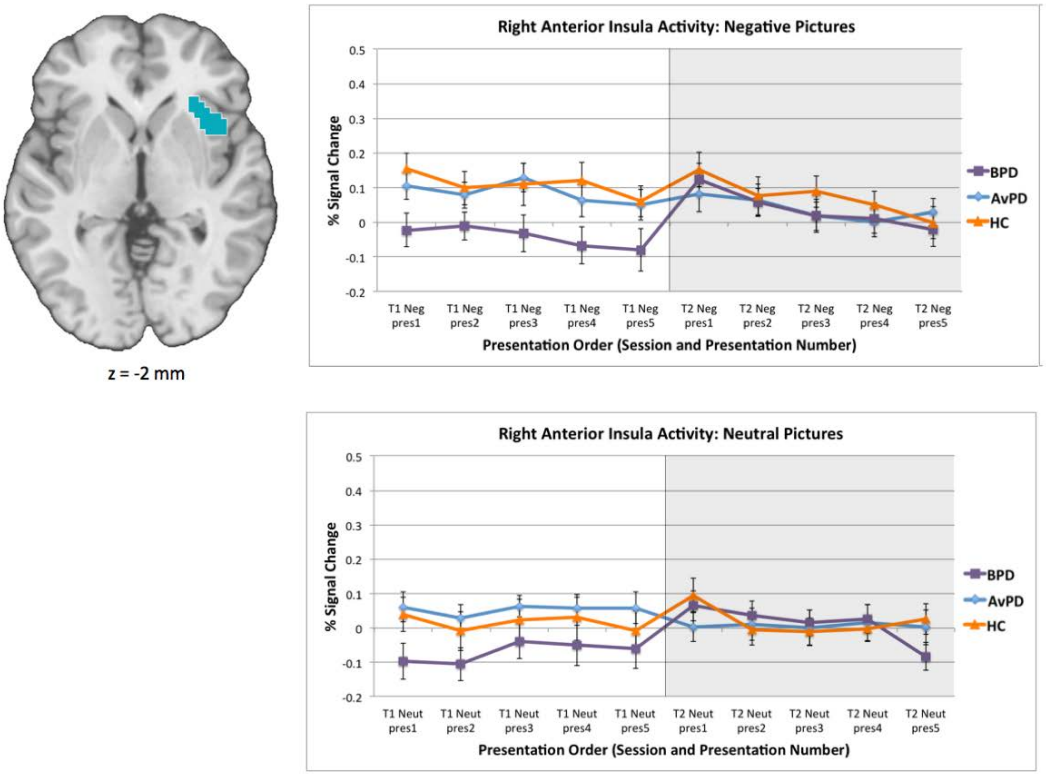

Figure S4. Right anterior insula activity during the longitudinal habituation task. T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.

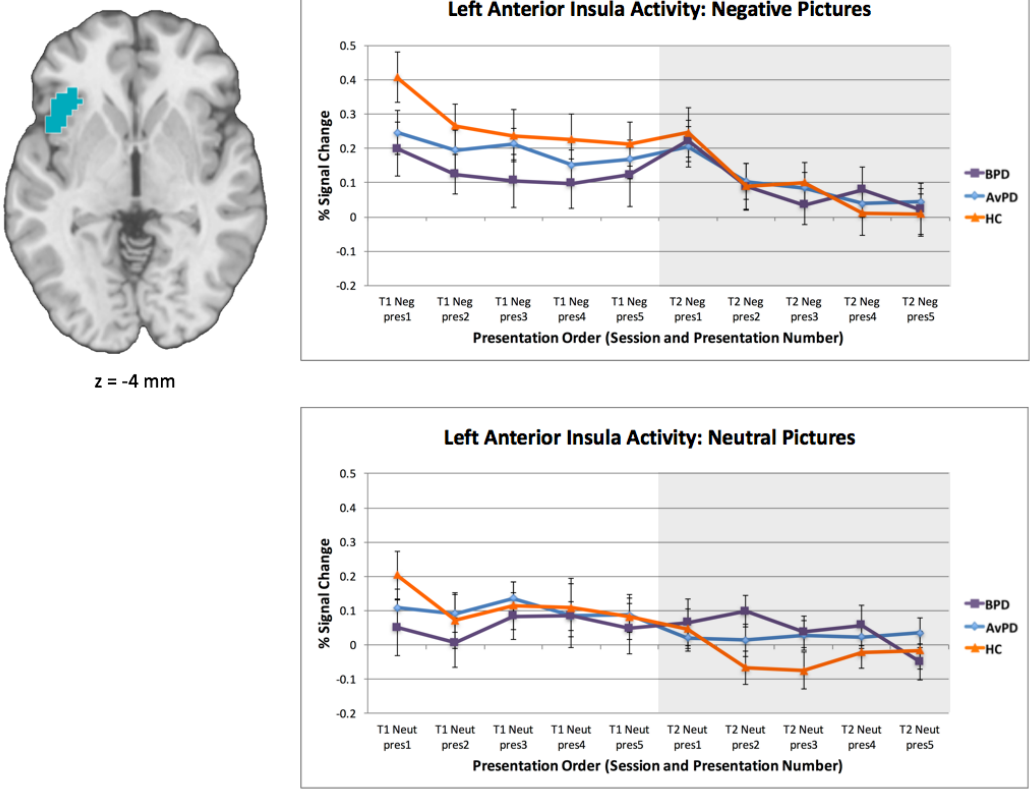

Figure S5. Left anterior insula activity during the longitudinal habituation task. T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.

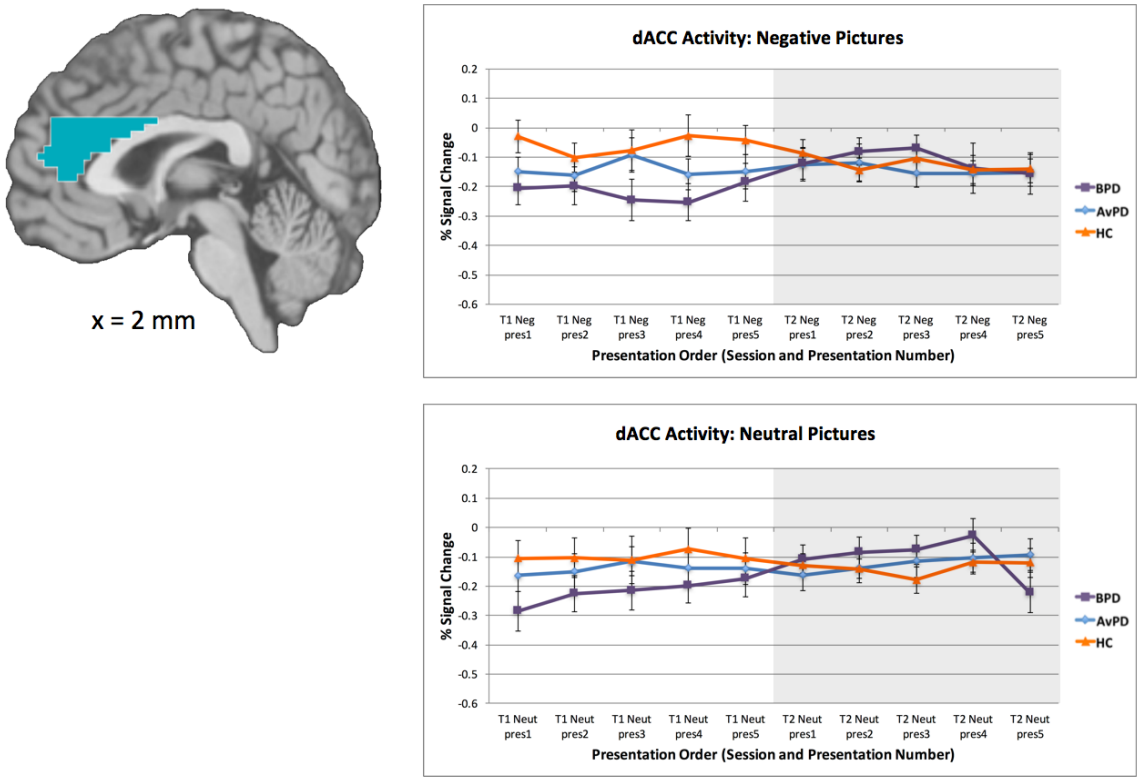

Figure S6. dACC during the longitudinal habituation task. T1 refers to Session 1 and T2 refers to Session 2. Pres refers to Presentation Order.