**Behavioral and emotional dysregulation trajectories marked by prefrontal–amygdala function in symptomatic youth**

**M. A. Bertocci *et al.***

*Exclusion criteria*

Exclusion criteria were: systemic medical illnesses, neurological disorders, history of trauma with loss of consciousness, use of central nervous system effecting medications, IQ<70 assessed by the Wechsler Abbreviated Scale of Intelligence (WASI), positive drug and/or alcohol screen on the day of MR scan, alcohol/substance abuse in the past 3 months (determined by the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version;K-SADS-PL-W) (Kaufman *et al.*, 1997), significant visual disturbance, non-English speaker, history of physical/sexual abuse, autistic spectrum disorders/developmental delays, pregnancy, claustrophobia, and metal in the body.

*Protocol*

We used an emotional face *n*-back (EFNBACK) task to examine the ability to recruit prefrontal cortical areas involved in “executive control” systems in the context of simultaneously-presented emotionally-salient distracting stimuli during a working memory task (Ladouceur *et al.*, 2009, Ochsner and Gross, 2005) which reliably activates DLPFC, dACC, VLPFC and amygdala and has been used to examine ER neural circuitry in bipolar adults (Bertocci *et al.*, 2011, Mullin *et al.*, 2012), adults with major depressive disorder (Kerestes *et al.*, 2012) The EFNBACK task is a modified version of the *n*-back working memory task (Ladouceur *et al.*, 2009). The EFNBACK task consists of visually presenting on the computer screen a pseudorandom sequence of letters with participants responding to a pre-specified letter. The *n*-back task included two memory load conditions: a no-memory load (0-back-e.g., press the button to “M”) and high memory load (2-back-e.g., press the button whenever the current letter is identical to the letter present two trials back (L-X-L)). The emotional *n*-back task comprised the original *n*-back task flanked by two emotional or neutral face distracters (Tottenhan *et al.*, 2009). A no-face condition controlled for the interference related to presentation of a face distracter on either side of the letter in 2- and 0-back task conditions. There were eight stimulus blocks: two memory-load conditions (0-back and 2-back), each with one of four emotional face distracter conditions (fearful, happy, neutral or no face distracter). The task comprised three, 7- min 4-sec runs, for a total of 24 blocks- presented in a pseudorandomized order. Each block included 12 trials. Each trial comprised a letter flanked with either no pictures, or identical pictures of an actor’s facial expression (fearful, happy, or neutral). Trial duration was 500ms. The inter-trial interval comprised a fixation cross (flanked with faces) and was jittered (mean duration=3500ms). Participants responded as quickly as possible with their index finger to the target letter. Brief instructions were presented on the screen for 4000ms at the beginning of each block. Detailed instructions were provided during task practice prior to the scanning session. Our analysis focused on the 2-back with emotional face distracters to stress working memory in a more complicated activity.

*Neuroimaging Data Acquisition*

fMRI data were collected on a 1) 3T Siemens Verio MRI scanner at Case Western Reserve University, 2) 3T Philips Achieva X-series MRI scanner at Cincinnati Children’s Hospital, and 3) 3T Siemens Trio MRI scanner at University of Pittsburgh Medical Center. An axial 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (192 axial slices; flip angle=9°; field of view=256 mm; TR=2300 msec; TE=3.93 msec; matrix=256x192) acquired T1-weighted volumetric anatomical images covering the whole brain. A reverse interleaved gradient echo planar imaging (EPI) sequence (178 axial slices; flip angle=90°; field of view=205 mm; TR=2000 msec; TE=28 msec; matrix=64x64) acquired T2-weighted BOLD images covering the whole cerebrum and most of the cerebellum.

Statistical Parametric Mapping software SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) was used to preprocess and analyze fMRI data. Preprocessing involved realignment and unwarping, coregistration, normalization into a standard stereotactic space (Montreal Neurologic Institute, MNI; <http://www.bic.mni.mcgill.ca>), and spatial smoothing using an 8 mm FWHM Gaussian kernel.

*Accuracy data for Entire Imaging sample*

Performance for the entire imaging sample on the 2-back with emotional faces task showed the same pattern of similarities as the subsample who were able to complete the task (mean accuracy=85%). Performance differed by group, with HC (accuracy=92%) and LowD (accuracy=87%) performing more accurately than HighD (accuracy=78%) (F(2,133)=11.22, p<.001). LowD and HC did not differ significantly on task performance.

*Post hoc full factorial results: 3 groups (LowD, HighD, HC) X 2 cognitive loads (0back and 2back) X 3 emotional conditions (fear, happy, neutral).*

*BOLD activity*

Main effect of group is reported in the main text.  Group comparisons show greater activity for LowD than HC across both cognitive loads and all emotional conditions, using a Bonferroni-corrected voxelwise threshold of p<0.003 (0.01/3) to control for three pairwise between-group comparisons (t(487) = 4.17, p<.001, corrected, 80 voxels mni 34 26 42).

There was no group X cognitive load X emotional condition interaction.

*PPI connectivity*

There was no group X cognitive load X emotional condition interaction for functional connectivity.

Between group comparisons revealed increased functional connectivity for LowD relative to both HighD and HC across all cognitive loads and emotional conditions in the following ways. LowD relative to HighD showed greater connectivity between amygdala and left VLPFC (BA47; t(487) = 4.69, p<.001, corrected, 76 voxels, mni -34 32 -14), and between amygdala and bilateral dACC (BA 24; left: t(487) = 4.08, p<.001, corrected, 161 voxels, mni -2 6 40; right: 2 clusters: t(487) = 4.03, p<.001, corrected, 170 voxels, mni 4 8 38 and t(487) = 3.40, p<.001, corrected, 38 voxels, mni 4 32 14). LowD relative to HC across all cognitive loads and emotional conditions showed greater connectivity between amygdala and left VLPFC (BA47; t(487) = 3.30, p<.001, corrected, 32 voxels, mni -36 30 -16) and between amygdala and bilateral dACC (BA 24; left: t(487) = 3.05, p<.001, corrected, 27 voxels, mni -2 6 40; right: t(487) = 3.50, p<.001, corrected, 61 voxels, mni 4 -4 42).

*Exploratory analysis*

There were no significant relationships between extracted BOLD signal for the main effect of group in bilateral DLPFC and any demographic variables (age, IQ, gender, SES, site), for HighD, LowD, and HC. There were no relationships between extracted BOLD signal for the main effect of group in bilateral DLPFC and clinical variables (KMRS, KDRS, SCARED, diagnosis of BPSD, anxiety disorder, depressive disorder, ADHD, disruptive disorder), or taking, versus not taking, any of the five classes of medication examined (antidepressants, antipsychotics, mood stabilizers, stimulants, or non-stimulant ADHD medications) for MSDB and LSDB (Supplementary Table S1).

There were no other significant relationships between bilateral amygdala-left VLPFC connectivity and any other clinical, demographic or medication variables in LAMS youth.

*Follow-up analysis with significant covariates*

*Covarying for Accuracy*

Covarying for accuracy largely confirmed the main effect of group on activity findings, with a main effect of group in right DLPFC (F(2,240)=9.84,p<.001, mni:36,28,42,corrected. There was no significant main effect of emotion or group x emotion interaction. Post-hoc analyses with accuracy as a covariate revealed that LowD showed greater bilateral DLPFC activity than HC (right:t(240)=4.18,p<.001, mni:36,28,42; left:t(240)=3.41,p<.001, mni:-22,42,40, corrected) and greater left DLPFC activity than HighD (t(240)=3.29,p<.001, mni:-32,24,38, corrected).

Covarying for accuracy also confirmed main PPI findings, with a significant main effect of group on functional connectivity between bilateral amygdala and left VLPFC (F(2,240)=7.14, p=.001, mni:-42,30,-14) and between bilateral amygdala and left dACC(F(2,240)=6.60, p=.002, mni:-2,6,40); and a significant main effect of emotion on functional connectivity between bilateral amygdala and bilateral DLPFC (right:F(2,240)=8.10, p<.001, mni:40,38,38; left: F(2,240)=8.06, p<.001, mni:-40,36,36, corrected). Post-hoc tests showed that LowD had greater functional connectivity than HighD between bilateral amygdala and left VLPFC (t(240)=3.73,p<.001, mni:-42,30,-14) and between bilateral amygdala and left dACC (t(240)=3.60,p<.001, mni:-2,6,40). Post-hoc tests covarying for accuracy also showed that all youth showed greater functional connectivity between bilateral amygdala and bilateral DLPFC to fear than the neutral condition (right: t(240)=4.01,p<.001, mni:40,38,38, left: t(240)=3.98,p<.001, mni:-38,36,38, corrected).

*Covarying for BPSD diagnosis and Mood stabilizer use*

Given the relationships between PPI findings and both mood stabilizer medication and BPSD diagnosis in LAMS, PPI analyses were re-run, comparing functional connectivity between the bilateral amygdala seed region and bilateral ROI mask in HighD and LowD over all three conditions, now including mood stabilizer medication and BPSD diagnosis, age, sex, IQ, and scanning site, as covariates. Using these two factors as additional covariates in PPI analyses did not alter main between-group differences in functional connectivity in LowD and HighD described in the main text. LowD continued to have significantly greater bilateral amygdala-left VLPFC connectivity (t(174)=2.74,p=.003,corrected mni:-42,30,-14) and greater bilateral amygdala-bilateral dACC connectivity (right:t(174)=3.38, p<.001, corrected mni:12,-8,48; left:t(174)=2.94,p=.002, mni:-4,-8,50), than HighD.

*Wholebrain Exploratory Analyses*

These analyses largely confirmed *a priori* ROI analyses. For wholebrain analyses of activity, there was a significant main effect of group in left DLPFC (k=95, F(2,241)=6.40,p<.001,corrected mni:-30,30,38), where LowD showed significantly greater activity than HighD (k=96, t(241)=3.46,p<.001, corrected mni:-30,30,38) and HC (k=91, t(2,241)=3.46,p<.001, corrected mni:-22,42,40) in this region to all three conditions.

For wholebrain PPI analyses using a bilateral amygdala seed region, there was a significant main effect of group on bilateral amygdala-left VLPFC functional connectivity (k=86, F(2,241)=7.58,p<.001, corrected mni: -42,30,-14), with LowD showing significantly greater bilateral amygdala-left VLPFC functional connectivity than HighD (k=156, t(241)=3.87,p<.001, corrected mni: -42,30,-14). In addition, a main effect of emotion was observed upon bilateral amygdala-bilateral DLPFC functional connectivity (right:k=60, F(2,241)=8.70,p<.001 corrected mni: 40,38,38; left:k=39, F(2,241)=8.42,p<.001, corrected mni: -40,36,36), with greater functional connectivity to fear than neutral distracter in this region over all participants (right:k=117, t(241)=4.14,p<.001, corrected mni:40,38,38; left:k=71, t(241)=4.08,p<.001, corrected mni:-40,36,36) (Supplementary Tables S5 and S6).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Completed EFNBACKn=85 | Did not complete EFNBACKn=78 | Statistic | p |
| **Demographic Information** |  |  |  |
| Age | 13.9 (2.02) | 12.8(2.16) | t(162) = 3.40 | .001 |
| Gender (females) | 39 | 27 | χ2=2.14 | .143 |
| IQ | 104(14.9) | 98.9(14.43) | t(161) =2.08 |  . 039 |
| SES (primary caregiver education) | χ2= 2.69 | .611 |
|  | No/some HS | 3 | 5 |  |  |
|  | GED or HS Diploma | 16 | 21 |  |  |
|  | Some post HS | 22 | 16 |  |  |
|  | Associate’s Degree | 22 | 19 |  |  |
|  | Bachelor’s Degree or higher | 17 | 22 |  |  |
| **Clinical Measures** | n=61 | n=67 |  |  |
| Lams1 baseline assessment |  |  |
| PGBIM10  | 12.2(7.2) | 11.7(7.0) | t(124) = -.401 | .689 |
| Biyearly assessment closest to scan |  |  |  |
| PGBIM10 | 5.7(6.2) | 6.7(6.2) | t(124) = .908 | .366 |
| Scan day assessments |  |  |
| KDRS | 3.1(4.44) | 3.2(4.43) | t(159) = .309 | .868 |
| KMRS | 3.38(6.7) | 3.68(5.8) | t(159) = .166 | .758 |
| SCARED | 9.85(9.5) | 12.55(12.2) | t(159) = 1.56 | .121 |
| Diagnosis |  |  |  |  |
| Major Depressive Disorder | 20/61 | 18/67 | χ2= .536 | .464 |
| Bipolar spectrum disorder | 20/61 | 23/67 | χ2=.034 | .854 |
| ADHD | 47/61 | 55/67 | χ2= .501 | .479 |
| Disruptive Disorder | 42/61 | 42/67 | χ2= .538 | .463 |
| Anxiety Disorder | 21/67 | 17/67 | χ2= 1.25 | .263 |
| **Site** |  | χ2= 3.16 | .207 |
| University of Pittsburgh Medical Center | 30 | 35 |  |  |
| Case Western Reserve University | 18 | 27 |  |  |
| Cincinnati Children’s Hospital | 31 | 23 |  |  |

Supplementary Table S1. Comparison of participants who did and did not complete both runs of the EFNBACK neuroimaging task.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | LowDCompleted EFNBACKn=39 | LowDDid not complete EFNBACKn=39 | Statistic | p |
| **Demographic Information** |  |  |  |
| Age | 14.3 (1.87) | 13.3(2.04) | t(76) = -2.44 | .017 |
| Gender (females) | 14 | 11 | χ2=.530 | .467 |
| IQ | 105(15.2) | 99.4(15.3) | t(76) =-1.55 |  .126 |
| SES (primary caregiver education) | χ2= .608 | .962 |
|  | No/some HS | 2 | 1 |  |  |
|  | GED or HS Diploma | 11 | 11 |  |  |
|  | Some post HS | 8 | 8 |  |  |
|  | Associate’s Degree | 10 | 9 |  |  |
|  | Bachelor’s Degree or higher | 8 | 10 |  |  |
| **Clinical Measures** |  |  |  |  |
| Lams1 baseline assessment |  |  |
| PGBIM10  | 8.6(5.4) | 8.4(5.9) | t(74) = -.148 | .883 |
| Biyearly assessment closest to scan |  |  |  |
| PGBIM10 | 3.0(3.6) | 3.0(3.1) | t(76) = -.007 | .994 |
| Scan day assessments |  |  |
| KDRS | 3.9(5.1) | 1.7(2.4) | t(75) = -2.5 | .015 |
| KMRS | 2.9(5.3) | 1.8(3.8) | t(75) = -1.06 | .294 |
| SCARED | 9.8(10.1) | 10.4(11.6) | t(75) = .219 | .827 |
| Diagnosis |  |  |  |  |
| Major Depressive Disorder | 11/39 | 11/39 | χ2= .000 | 1.0 |
| Bipolar spectrum disorder | 6/39 | 6/39 | χ2= .000 | 1.0 |
| ADHD | 29/39 | 31/39 | χ2= .289 | .591 |
| Disruptive Disorder | 24/39 | 26/39 | χ2= .223 | .637 |
| Anxiety Disorder | 11/39 | 8/39 | χ2= .626 | .429 |
| **Site** |  | χ2= 1.46 | .483 |
| University of Pittsburgh Medical Center | 16 | 11 |  |  |
| Case Western Reserve University | 8 | 9 |  |  |
| Cincinnati Children’s Hospital | 15 | 19 |  |  |
|  | HighDCompleted EFNBACKn=22 | HighDDid not complete EFNBACKn=28 | Statistic | p |
| **Demographic Information** |  |  |  |
| Age | 13.7 (2.02) | 12.6(1.86) | t(48) = -2.01 | .05 |
| Gender (females) | 12 | 11 | χ2=1.16 | .283 |
| IQ | 101.4(17.0) | 93.7(15.9) | t(48) =-1.65 |  .106 |
| SES (primary caregiver education) | χ2= 5.82 | .213 |
|  | No/some HS | 1 | 4 |  |  |
|  | GED or HS Diploma | 4 | 9 |  |  |
|  | Some post HS | 7 | 5 |  |  |
|  | Associate’s Degree | 6 | 9 |  |  |
|  | Bachelor’s Degree or higher | 4 | 1 |  |  |
| **Clinical Measures** |  |  |  |  |
| Lams1 baseline assessment |  |  |
| PGBIM10  | 18.4(5.4) | 16.1(5.7) | t(48) = -1.42 | .163 |
| Biyearly assessment closest to scan |  |  |  |
| PGBIM10 | 10.5(6.9) | 11.9(5.5) | t(48) = .748 | .458 |
| Scan day assessments |  |  |
| KDRS | 4.9(4.2) | 5.9(5.7) | t(47) = .675 | .503 |
| KMRS | 8.0(9.7) | 7.6(7.2) | t(47) = -.150 | .881 |
| SCARED | 11.5(10.3) | 16.3(13.5) | t(46) = 1.35 | .185 |
| Diagnosis |  |  |  |  |
| Major Depressive Disorder | 9/22 | 7/28 | χ2= 1.43 | .231 |
| Bipolar spectrum disorder | 14/22 | 17/28 | χ2=.045 | .833 |
| ADHD | 18/22 | 24/28 | χ2= .139 | .709 |
| Disruptive Disorder | 16/22 | 18/28 | χ2= .403 | .525 |
| Anxiety Disorder | 10/22 | 9/28 | χ2= .927 | .336 |
| **Site** |  | χ2= .545 | .761 |
| University of Pittsburgh Medical Center | 8 | 13 |  |  |
| Case Western Reserve University | 7 | 8 |  |  |
|  | HCCompleted EFNBACKn=24 | HCDid not complete EFNBACKn=8 | Statistic | p |
| **Demographic Information** |  |  |  |
| Age | 13.4(2.21) | 11.2(2.66) | t(31) = -2.46 | .020 |
| Gender (females) | 13 | 5 | χ2= .005 | .943 |
| IQ | 105.2(12.5) | 106.1(15.2) | t(31) = .175 |  .862 |
| SES (primary caregiver education) | χ2= 1.51 | .680 |
|  | No/some HS | 0 | 0 |  |  |
|  | GED or HS Diploma | 1 | 1 |  |  |
|  | Some post HS | 7 | 2 |  |  |
|  | Associate’s Degree | 1 | 1 |  |  |
|  | Bachelor’s Degree or higher | 10 | 5 |  |  |
| **Clinical Measures** |  |  |  |  |
| Scan day assessments |  |  |
| KDRS | .13(.34) | 1.2(2.0) | t(31) = 1.599 | .148 |
| KMRS | 0(0) | .22(.44) | t(31) = 1.512 | .169 |
| SCARED | 8.1(7.8) | 11.4(9.5) | t(31) = 1.04 | .306 |
| **Site** |  | χ2= 9.52 | .009 |
| University of Pittsburgh Medical Center | 11 | 4 |  |  |
| Case Western Reserve University | 12 | 1 |  |  |
| Cincinnati Children’s Hospital | 1 | 4 |  |  |

Supplementary Table S2. Comparison of LowR, HighR, and HC participants who did and did not complete both runs of the EFNBACK neuroimaging task.

Supplementary Figure S1. Signal to Noise Ratios for each site from October 2011 to December 2012. Anova comparing the three sites F(2, 39)=.870, p = .43.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | HighDn=50 | LowDn=78 | Statistic | p = |
| Major Depressive Disorder | 16 | 22 | χ2= .210 | .647 |
| Bipolar Spectrum Disorder | 31 | 12 | χ2= 29.68 | .000 |
| Anxiety Disorder | 19 | 19 | χ2= 2.72 | .093 |
| ADHD | 42 | 60 | χ2= .943 | .332 |
| Disruptive Disorder | 34 | 50 | χ2= .205 | .651 |

Supplementary Table S3. Diagnostic table of 128 LAMS2 youth by Latent class growth analysis subgroups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | BOLD Main effect of group bilateral DLPFC | PPI Main effect of group left VLPFC | PPI Main effect of emotion bilateral DLPFC |
| Group Variable |  | Statistic pvalue | Statistic pvalue | Statistic pvalue |
| HighD, LowD, and Healthy Control |  |  |
|  | Age | r=.014 .90 | r=-.003 .98 | r=.028 .80 |
|  | IQ | r=-.191 .08 | r=.043 .70 | r=-.178 .10 |
|  | Gender | t(83)=-.025 .98 | t(83)= 1.08 .28 | t(83)=-.008 .99 |
|  | SES | χ2= 340 .43 | χ2= 340 .43 | χ2= 340 .43 |
|  | Site | χ2=170 .44 | χ2=170 .44 | χ2=170 .44 |
| LowD and HighD |  |  |  |
| Medication |  |  |  |  |
|  | Antidepressant | t(59)=.321 .75 | t(59)=1.6 .12 | t(59)=.338 .74 |
|  | Mood stabilizer | t(59)=.686 .50 | t(59)=2.23 .03\* | t(59)=.124 .90 |
|  | Antipsychotic | t(59)=-.147 .88 | t(59)=1.45 .17 | t(59)=.362 .72 |
|  | Benzodiazepine | t(59)=-.072 .94 | t(59)=1.7 .10 | t(59)=.821 .42 |
|  | Stimulant | t(59)=.580 .56 | t(59)=.707 .48 | t(59)=.443 .66 |
|  | Non-stimulant ADHD medication | t(59)=1.08 .28 | t(59)=-1.22 .23 | t(59)=-.224 .82 |
| Diagnosis |  |  |  |
|  | BPSD | t(59)=1.70 .10 | t(59)=2.25 .03\* | t(59)=.879 .38 |
|  | Depression | t(59)=-.289 .77 | t(59)=.239 .81 | t(59)=-1.04 .31 |
|  | ADHD | t(59)=1.39 .17 | t(59)=.770 .44 | t(59)=.390 .70 |
|  | Disruptive disorder | t(59)=-.775 .44 | t(59)=-.049 .96 | t(59)=.112 .91 |
|  | Anxiety disorder | t(59)=-.019 .99 | t(59)=-.186 .85 | t(59)=.307 .76 |
|  | Substance use disorder | t(59)=..089 .93 | t(59)=-1.13 .26 | t(59)=-.764 .45 |

Supplementary Table S4. Exploratory relationships between mean extracted main effect of group and emotion for both BOLD response and PPI and demographic and clinical variables. p= pvalue of statistic, \* = significant at < .01

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Whole brain activation** |  |  |  |  |  |  |
|  | **Region** |  | **BA** | **Cluster** | **MNI** | **statistic** | **p** |
|  | **Comparison** |  |  |  |  |  |
| **Whole Brain analysis**Voxelwise threshold p<.005, clusterwise threshold p<.01 |  |  |  |  |  |
|  |  | Peak Voxel |  |  |
| Main effect of Group |  |  |  |  |  |
|  | Right Superior frontal cortex | 8 | 157 | 34 28, 44 | F(2,241) =10.74 | .001 |
|  | Left parietal lobe |  | 113 | -12 -70 44 | F(2,241) =9.56 | .001 |
|  | Right parietal lobe | 7 | 29 | 16 -74 44 | F(2,241) =7.91 | .001 |
|  | Left DLPFC | 9 | 95 | -30 30 38 | F(2,241) =6.40 | .001 |
| LowD>HC |  |  |  |  |  |
|  | Right Superior frontal cortex | 8 | 193 | 34 28, 44 | t(241) =4.43 | .001 |
|  | Right frontal lobe | 6 | 33 | 36 12 44 | t(241) =3.68 | .001 |
|  | Left DLPFC | 9 | 91 | -22 42 40 | t(241) =3.46 | .001 |
| LowD>HighD |  |  |  |  |  |
|  | Left frontal lobe | 6 | 61 | -24 8 58 | t(241) =3.65 | .001 |
|  | Left DLPFC | 9 | 96 | -30 30 38 | t(241) =3.46 | .001 |
| HC>HighD |  |  |  |  |  |
|  | Left parietal lobe |  | 151 | -10 -70 44 | t(2,241) =4.12 | .001 |
|  | Left limbic lobe | 23 | 44 | -6 -34 28 | t(241) =3.89 | .001 |
|  | Left parietal lobe |  | 71 | -30 -62 34 | t(241) =3.41 | .001 |
| HC>HighD |  |  |  |  |  |
|  | Right parietal lobe | 7 | 40 | 16 -74 54 | t(241) =3.95 | .001 |
|  | Left parietal lobe |  | 51 | -12 -72 44 | t(241) =3.67 | .001 |
| Main effect of emotion |  |  |  |  |  |
|  | Left parietal lobe | 7 | 216 | -4 -58, 58 | F(2,241) =10.91 | .001 |
|  | Left caudate |  | 334 | -6 10 -4 | F(2,241) =9.05 | .001 |
|  | right temporal lobe |  | 59 | 46 -56 -12 | F(2,241) =7.88 | .001 |
|  | right parietal lobe |  | 29 | 62 -38 34 | F(2,241) =7.26 | .002 |
|  | Right frontal lobe |  | 34 | 40 24 32 | F(2,241) =6.78 | .002 |
| Fear > Happy |  |  |  |  |  |
|  | Left parietal lobe |  | 310 | -4 -58, 58 | t(241) =4.67 | .001 |
|  | Right parietal lobe |  | 49 | 62 -38 34 | t(241) =3.69 | .001 |
|  | Right frontal lobe |  | 136 | 30 24 32 | t(241) =3.59 | .001 |
|  | Right frontal lobe |  | 50 | 32 44 24 | t(241) =3.35 | .001 |
| Happy>Neutral |  |  |  |  |  |
|  | Right temporal lobe |  | 95 | 46 -54 -12 | t(241) =3.90 | .001 |
|  | Left caudate |  | 81 | -4 6 -4 | t(241) =3.46 | .001 |
| Fear>Neutral |  |  |  |  |  |
|  | Left parietal lobe |  | 27 | -26 -82 38 | t(241) =3.37 | .001 |
| Happy>Fear |  |  |  |  |  |
|  | Left caudate head |  | 326 | -8 12 -6 | t(241) =4.07 | .001 |
| Neutral>Fear |  |  |  |  |  |
|  | Left putamen |  | 33 | -20 8 -10 | t(241) =3.43 | .001 |
| Group X Emotion interaction |  |  |  |  |  |
|  | Left temporal lobe |  | 385 | -36 -76 20 | F(2,241) =6.62 | .001 |
|  | Right temporal lobe |  | 312 | 54 -44 0 | F(2,241) =6.40 | .001 |
|  | Right frontal lobe |  | 30 | 44 -20 -10 | F(2,241) =5.77 | .001 |
|  | Right parietal lobe | 19 | 95 | 36 -80 34 | F(2,241) =5.09 | .001 |
|  | Posterior cingulate |  | 31 | 0 -68 12 | F(2,241) =4.58 | .002 |
|  | Right putamen |  | 68 | 30 -10 -10 | F(2,241) =5.74 | .001 |
|  | Left parahippocampal gyrus | 27 | 30 | -22 -36 -6 | F(2,241) =5.21 | .001 |
|  | Right posterior cingulate | 31 | 27 | 10 -58 18 | F(2,241) =4.33 | .001 |

Supplementary Table S5. Whole brain activity. Voxelwise threshold p<.005, clusterwise threshold p<.01

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PPI Connectivity Amygdala seed region** |  |  |  |  |  |  |
|  | **Region** |  | **BA** | **Cluster** | **MNI** | **statistic** | **p** |
|  | **Comparison** |  |  |  |  |  |
| **Whole Brain analysis**Voxelwise threshold p<.005, clusterwise threshold p<.01 |  |  |  |  |  |
|  |  | Peak Voxel |  |  |
| Main effect of Group |  |  |  |  |  |
|  | Left VLPFC | 47 | 86 | -42 30 -14 | F(2,241) =7.58 | .002 |
|  | Right posterior cingulate |  | 84 | 2 -50 8 | F(2,241) =6.99 | .002 |
|  | Left DLPFC | 9 | 43 | -16 54 36 | F(2,241) =7.67 | .002 |
|  | Left frontal lobe | 5 | 36 | -8 -34 52 | F(2,241) =7.24 | .002 |
|  | Left medial prefrontal cortex | 10 | 27 | -2 60 28 | F(2,241) =7.17 | .002 |
|  | Right cerebellum |  | 31 | 34 -60 -16 | F(2,241) =6.19 | .002 |
| LowD>HighD |  |  |  |  |  |
|  | Left DLPFC | 9 | 199 | -18 54 34 | t(241) =3.89 | .001 |
|  | Left VLPFC | 47 | 156 | -42 30 -14 | t(241) =3.87 | .001 |
|  | Right insula |  | 55 | -38 2 14 | t(241) =3.64 | .001 |
|  | Left temporal lobe | 21 | 37 | -64 -20 -2 | t(241) =3.63 | .001 |
|  | Left medial prefrontal cortex | 10 | 142 | -8 64 4 | t(241) =3.51 | .001 |
|  | Left dacc | 24 | 79 | -2 6 40 | t(241) =3.49 | .001 |
|  | Right occipital lobe |  | 52 | 36 -62 -16 | t(241) =3.38 | .001 |
|  | Left temporal lobe | 22 | 51 | -50 8 -4 | t(241) =3.28 | .001 |
| HC>HighD |  |  |  |  |  |
|  | Left frontal lobe |  | 55 | -8 -34 50 | t(241) =3.73 | .001 |
|  | Posterior cingulate |  | 175 | 0 -52 10 | t(241) =3.70 | .001 |
|  | Right cerebellum |  | 50 | 4 -62 -16 | t(241) =3.33 | .001 |
|  | Left VLPFC | 47 | 156 | -42 30 -14 | t(241) =3.87 | .001 |
| Main effect of emotion |  |  |  |  |  |
|  | Right parietal lobe | 40 | 262 | 46 -50 52 | F(2,241) =11.76 | .001 |
|  | Right DLPFC | 9 | 60 | 40 38 38 | F(2,241) =8.70 | .001 |
|  | Left DLPFC | 9 | 39 | -40 36 36 | F(2,241) =8.42 | .001 |
|  | Left frontal lobe | 8 | 120 | -2 28 44 | F(2,241) =7.95 | .001 |
|  | Right frontal lobe | 6 | 54 | 26 0 52 | F(2,241) =7.93 | .001 |
| Fear>Neutral |  |  |  |  |  |
|  | Right parietal lobe | 40 | 369 | 46 -50 52 | t(241) =4.85 | .001 |
|  | Right DLPFC | 9 | 117 | 40 38 38 | t(241) =4.14 | .001 |
|  | Left DLPFC | 9 | 71 | -40 36 36 | t(241) =4.08 | .001 |
|  | Left frontal lobe | 8 | 189 | -2 28 44 | t(241) =3.98 | .001 |
|  | Right frontal lobe | 6 | 124 | 26 0 52 | t(241) =3.97 | .001 |
|  | Right medial prefrontal cortex | 10 | 63 | 30 46 18 | t(241) =3.47 | .001 |
|  | Left temporal lobe | 21 | 43 | -62 -40 -4 | t(241) =3.38 | .001 |

Supplementary Table S6. Whole brain PPI connectivity with Amygdala seed. Voxelwise threshold p<.005, clusterwise threshold p<.01

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