**Supplementary Section**

Reappraisal-Related Neural Predictors of Treatment Response to

Cognitive Behavior Therapy for Posttraumatic Stress Disorder

**Table of Contents**

**Supplementary Methods**

**Supplementary Results**

**Table S1.** Summary of voxel-wise whole brain activation analyses for cognitive reappraisal and emotional reactivity for each group and for group comparisons.

**Table S2.** Summary of voxel-wise whole brain connectivity analyses for cognitive reappraisal and emotional reactivity.

**Table S3.** Summary of voxel-wise cognitive reappraisal single sample and group comparison activation analyses in our hypothesized ROIs.

**Table S4.** Summary of voxel-wise emotional reactivity single sample and group comparison activation analyses in our hypothesized ROIs.

**Table S5.** Summary of voxel-wise cognitive reappraisal single sample and group comparison connectivity analyses in our hypothesized ROIs

**Table S6.** Summary of voxel-wise emotional reactivity single sample and group comparison connectivity analyses in our hypothesized ROIs

**Table S7.** Cross-validated linear regressions using averaged coefficients from bootstrapped datasets, for cognitive reappraisal and emotional reactivity with change in CAPS.

**Table S8.** Cross-validated binary logistic regressions using averaged coefficients from bootstrapped datasets, for cognitive reappraisal and emotional reactivity comparing responders and non-responders.

**Table S9.** Cross-validated binary logistic regression for best predictive model of treatment response.

**Table S10.** Bivariate correlation analyses for cognitive reappraisal and emotional reactivity activation and connectivity with change in CAPS in unmedicated PTSD patients.

**Table S11.** Partial correlations controlling for antidepressant use with cognitive reappraisal and emotional reactivity activation and connectivity and change in CAPS.

**Supplementary Methods**

**fMRI connectivity analyses using generalized psychophysiological interactions (gPPI)**

Generalized context-dependent PPI models identify how task-specific changes in the BOLD signal, of different regions across the brain, interact over time. The model generates a regressor of the onset times of each condition in the task, for reappraising a negative image (THINK), watching a negative image (WATCH), or watching a neutral image (NEUTRAL), and individually convolves this with the hemodynamic response function to form a psychological interaction term. The physiological regressor (the estimated neural activity of a specified seed region, derived from the deconvolved blood-oxygen level dependent [BOLD] signal of this seed) is then multiplied by the psychological interaction term, and other relevant covariates i.e. motion regressors, to create the generalized psychophysiological interaction. This differs from a standard psychophysiological interaction, where the psychological regressor is created by producing the production of each condition onset times and a weighted contrast vector, before being multiplied with the physiological term. Using the gPPI model therefore creates a more accurate model of the interaction, when there are more than two conditions. We can then explore correlation of BOLD response in various ROIs throughout the brain and neural activity in the seed region, during any of the task conditions, providing an effective measure of task-related connectivity. In our analyses, the ROIs chosen as the seed were those that were found to be significantly correlated with symptom improvement in the activation analyses. Second level analyses were performed evaluating the correlation of CAPS improvement with connectivity maps of these contrasts, as described in the main text.

**Train and test data cross-validation analyses using bootstrapping in R**

Cross-validation analyses with binary outcomes (i.e. to predict treatment responders vs. non-responders) were done using R. The data (n=37) was randomly split into an approximately 50% training dataset and 50% testing dataset (n=19, and n=18, respectively). The training dataset was then bootstrapped two hundred times, and binary logistic regressions were performed on each bootstrapped dataset. The binary logistic regressions were run using the extracted beta values from all the ROIs (outlined in the main text) in the cognitive reappraisal and emotional reactivity networks as predictors. This was done to avoid any ‘double dipping’ and so that the model included all our hypothesized ROIs and was independent of the findings from the main analyses. Model coefficients from each predictor were extracted and averaged across all results. These averaged coefficients were then used in a binary logistic regression model on the test data to determine the model’s cross-validated accuracy statistics. This training dataset bootstrapping, with its averaged coefficients being used in a binary logistic regression for the test data for cross-validation was the method used for all cross-validation methods listed in the supplementary.

**Supplementary Results**

**Interpretation of the correlation of symptom improvement with left amygdala activation for THINK vs WATCH and WATCH vs NEUTRAL contrasts:**

As treatment success was associated with both a capacity to engage the amygdala (emotional reactivity – WATCH vs NEUTRAL) as well as a capacity to regulate/inhibit the amygdala (appraisal contrast – THINK vs WATCH), we unpacked this further to evaluate if these correlations (i.e., between treatment response and each of THINK > WATCH and WATCH > NEUTRAL) are dissociable.

We evaluated association of amygdala activation for each condition separately relatively to the implicit baseline (i.e. THINK vs baseline; WATCH vs baseline and NEUTRAL vs baseline) with symptom change. However, amygdala activation for neither of these contrasts was significantly associated with symptom improvement (for the left amygdala cluster associated with cognitive reappraisal: the Pearson correlation coefficient for THINK vs baseline was -0.077, p=0.650; for WATCH vs baseline was -0.185, p=0.273; for NEUTRAL vs baseline was 0.143, p=0.399; and for the left amygdala cluster associated with emotional reactivity: the Pearson correlation coefficient for THINK vs baseline was -0.010, p=0.953; for WATCH vs baseline was -0.178, p=0.291; and for NEUTRAL vs baseline was 0.095, p=0.575) , which suggests that the significant correlations for the THINK>WATCH and WATCH>NEUTRAL contrasts are dissociated and are evident only for the difference between conditions.

**Exploratory whole brain activation and connectivity analyses.**

Exploratory whole brain activation and connectivity analyses were conducted to evaluate brain regions recruited for cognitive reappraisal (THINK vs WATCH) and emotional reactivity (WATCH vs NEUTRAL) contrasts. These were run as single sample t-tests for the healthy control & PTSD groups and as a two-sample group comparison between healthy controls and PTSD, with a familywise error (*pFWE*<0.05) correction threshold and significant effects are summarized in Tables S1. Exploratory whole brain voxel-wise correlations between activation and percentage improvement in clinical administered PTSD severity scores were also conducted for both cognitive reappraisal and emotional reactivity contrasts. However no significant results were found at a familywise correction threshold of 0.05.

**Table S1.** Summary of voxel-wise whole brain activation analyses for cognitive reappraisal and emotional reactivity. Significant clusters (*pFWE*<0.05) for one sample-tests for the control group, and PTSD vs control group comparisons are reported below. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Cluster size in voxels** | **Peak MNI**  **Coordinates** | **Peak z-score** | ***p*-value (FWE**  **corrected)** |
| **(X, Y, Z)** |
| ***Cognitive Reappraisal*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| Left Inferior Occipital | Increase | 2620 | -26 - 90 - 8 | 6.1 | <0.001 |
| Left Lingual Gyrus | Increase |  | -12 -94 -12 | 6.09 | <0.001 |
| Right Inferior Occipital | Increase |  | 28 -92 -10 | 6.03 | <0.001 |
| Left Inferior Frontal Gyrus, Pars Orbitalis | Increase | 516 | -44 36 -6 | 5.68 | 0.001 |
| Left Inferior Frontal Gyrus, Pars Triangularis | Increase |  | -42 24 0 | 5.6 | 0.001 |
| Right Middle Frontal Gyrus | Increase | 124 | 42 40 24 | 5.32 | 0.001 |
| Left Anterior Cingulate Gyrus | Increase | 378 | -8 20 32 | 5.23 | 0.006 |
| Right Midcingulate Area | Increase |  | 8 26 40 | 4.98 | 0.017 |
| Left Supplementary Motor Area | Increase | 33 | -2 8 54 | 4.98 | 0.017 |
| Left Precentral Gyrus | Increase | 29 | -44 0 48 | 4.96 | 0.045 |
| *One sample t-test in PTSD* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| Left Inferior Occipital  Cortex | PTSD < HC | 6696 | 14 -94 -8 | 7.12 | <0.001 |
| Left Crus I of Cerebellar Hemisphere | PTSD < HC |  | -28 -82 -24 | 7.1 | <0.001 |
| Left Precentral Gyrus | PTSD < HC | 234 | -46 0 -48 | 5.83 | 0.012 |
| Left Insula | PTSD < HC | 297 | -46 16 -2 | 5.62 | 0.03 |
| Right Middle Frontal Gyrus | PTSD < HC | 164 | 44 40 30 | 5.57 | 0.001 |
| Right Superior Temporal Pole | PTSD < HC | 426 | 42 26 -20 | 5.55 | 0.001 |
| Left Olfactory Cortex | PTSD < HC | 1174 | -6 18 36 | 5.47 | 0.001 |
| Left Supplementary Motor Area | PTSD < HC |  | -2 6 56 | 5.44 | 0.001 |
| Right Midcingulate Area | PTSD < HC | 449 | 8 -10 6 | 5.32 | 0.002 |
| Left Thalamus | PTSD < HC |  | -14 -10 2 | 4.94 | 0.012 |
| Left Middle Frontal Gyrus | PTSD < HC | 105 | -28 50 24 | 5.16 | 0.004 |
| Left Inferior Frontal Gyrus, Pars Orbitalis | PTSD < HC | 62 | -44 40 -12 | 4.96 | 0.011 |
| ***Emotional Reactivity*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| Right Cerebellum Posterior Lobe | Increase | 2899 | 42, -70, -26 | 5.65 | 0.003 |
| Right Cerebellum Posterior Lobe | Increase |  | 46, -54, -34 | 5.55 | 0.003 |
| Right Lingual Gyrus | Increase |  | 18, -94, -16 | 5.37 | 0.003 |
| Left Postcentral Gyrus | Increase | 1464 | -44, -20, 58 | 5.6 | 0.003 |
| Left Parietal Inferior Gyrus | Increase |  | -26, -20, 50 | 4.97 | 0.005 |
| Left Postcentral Gyrus | Increase |  | -50, -30, 58 | 4.67 | 0.01 |
| Left Lingual Gyrus | Increase | 2019 | -34, -90, -18 | 5.54 | 0.003 |
| Left Lingual Gyrus | Increase |  | -12, -98, -14 | 5.46 | 0.003 |
| Left Fusiform | Increase |  | -38, -82, -18 | 5.19 | 0.004 |
| Right Precentral Gyrus | Decrease | 2224 | 38, -20, 42 | 2.77 | 0.031 |
| *One sample t-test in PTSD* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

**Table S2.** Summary of voxel-wise whole brain connectivity analyses for cognitive reappraisal and emotional reactivity. Significant clusters (*pFWE*<0.05) for one sample-tests for the control group, and PTSD vs control group comparisons are reported below. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Cluster size in voxels** | **Peak MNI**  **Coordinates** | **Peak z-score** | ***p*-value (FWE**  **corrected)** |
| **(X, Y, Z)** |
| ***Cognitive Reappraisal*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| *One sample t-test in PTSD* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| ***Emotional Reactivity*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| R Amygdala <> Frontal Superior Medial Lobe | Increase | 4 | -8, 50, 36 | 4.82 | 0.032 |
| *One sample t-test in PTSD* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

**Exploratory uncorrected single sample and group comparison analyses for the selected ROIs.**

We conducted single sample t-tests for healthy controls, and between group (PTSD vs Healthy Controls) comparisons for cognitive reappraisal (THINK vs WATCH; Table S3 & S5) and emotional reactivity (WATCH vs NEUTRAL; Table S4 & S6) for the selected ROIs, for both activation (Table S3 & S4) and connectivity (Table S5 & S6). To observe directional trends, these are reported at an exploratory p<0.05 uncorrected threshold here. The results that survive at a familywise error (*pFWE*<0.05) correction threshold are marked and are also reported in the main text.

**Table S3.** Summary of voxel-wise cognitive reappraisal single sample and group comparison activation analyses in our hypothesized ROIs. Clusters significantly activated at an uncorrected threshold (*punc*<0.05) for single sample t-tests for healthy controls, PTSD patients, and between the groups are reported below for the Think vs Watch contrast. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant, L – left, R – Right, dmPFC – dorsomedial prefrontal cortex, dlPFC – dorsolateral prefrontal cortex. \* denotes significant at p*FWE*<0.05 correction level)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Peak MNI Coordinates**  **(X, Y, Z)** | **Cluster size in voxels** | **Peak z-score** | ***p*-value**  **(uncorrected)** |
| ***Cognitive Reappraisal*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| dmPFC | Increase | -8, 18, 36 | 513 | 5.11 | <0.001\* |
| L dlPFC | Increase | -50, 14, 12 | 515 | 4.57 | <0.001\* |
|  |  | -40, 8, 52 | 13 | 3.79 | <0.001\* |
| R dlPFC | Increase | 42, 34, 30 | 413 | 5.08 | <0.001\* |
|  |  | 52, 18, 40 | 165 | 4.29 | <0.001\* |
| L Amygdala | Decrease | -16, 2, -16 | 2 | 1.98 | 0.024 |
| R Amygdala | Decrease | 32, 2, -30 | 14 | 1.84 | 0.033 |
| *One sample t-test in PTSD patients* | | | | | |
| dmPFC | Decrease | 0, 18, 48 | 320 | 2.57 | 0.005 |
| L dlPFC | Decrease | -42, 14, 24 | 181 | 2.13 | 0.017 |
| R dlPFC | Decrease | 50, 22, 52 | 284 | 2.96 | 0.002 |
|  |  | 38, 30, 48 | 58 | 2.43 | 0.008 |
| L Amygdala | Decrease | -30, -4, -16 | 96 | 2.27 | 0.011 |
| R Amygdala | Decrease | 22, -4, -18 | 32 | 1.97 | 0.024 |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| dmPFC | PTSD < HC | 0, 18, 46 | 511 | 5.4 | <0.001\* |
| L dlPFC | PTSD < HC | -46, 8, 28 | 502 | 4.30 | <0.001\* |
|  |  | -40, 8, 52 | 24 | 3.96 | <0.001\* |
| R dlPFC | PTSD < HC | 44, 38, 34 | 425 | 4.83 | <0.001\* |
|  |  | 54, 16, 40 | 226 | 4.16 | <0.001\* |
| L Amygdala | PTSD < HC | -30, -4, -16 | 4 | 1.99 | 0.023 |
| R Amygdala | PTSD > HC | 32, 0, -30 | 17 | 2.32 | 0.01 |

**Table S4.** Summary of voxel-wise emotional reactivity single sample and group comparison activation analyses in our hypothesized ROIs. Clusters significantly activated at an uncorrected threshold (*punc*<0.05) for single sample t-tests for healthy controls, PTSD patients, and between the groups are reported below for the Watch vs Neutral contrast. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant, sgACC – subgenual anterior cingulate cortices, pgACC – pregenual anterior cingulate cortices, L – left, R – Right. \* denotes significant at p*FWE*<0.05 correction level)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Peak MNI Coordinates**  **(X, Y, Z)** | **Cluster size in voxels** | **Peak z-score** | ***p*-value**  **(uncorrected)** |
| ***Emotional reactivity*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala | Increase | -30, 0, -26 | 2 | 1.81 | 0.041 |
| R Amygdala | Increase | 30, 4, -28 | 5 | 2.22 | 0.013 |
| L Insula | Decrease | -30, 8, 16 | 281 | 2.99 | 0.001 |
| R Insula | Decrease | 36, -22, 14 | 69 | 3.83 | <0.001\* |
|  | Increase | 34, 28, 0 | 25 | 1.92 | 0.028 |
| L Hippocampus | Increase | -20 -28, -12 | 125 | 2.63 | 0.004 |
| R Hippocampus | Increase | 24, -32, -4 | 22 | 1.82 | 0.034 |
| *One sample t-test in PTSD patients* | | | | | |
| sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala | Increase | -28, -6, -18 | 49 | 2.44 | 0.007 |
| R Amygdala | Increase | 34, -2, -24 | 18 | 2.34 | 0.01 |
| L Insula | Increase | -32, 26, -2 | 691 | 2.9 | 0.002 |
|  | Decrease | -32, -6, 18 | 18 | 2.07 | 0.019 |
| R Insula | Increase | 34, 30, -2 | 347 | 3.59 | <0.001\* |
|  | Decrease | 42, -16, 14 | 675 | 3.68 | <0.001\* |
| L Hippocampus | Increase | -22, -34, -6 | 514 | 4.46 | <0.001\* |
| R Hippocampus | Increase | 20, -30, -10 | 285 | 4.44 | <0.001\* |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| sgACC | PTSD vs HC | n.s. | n.s. | n.s. | n.s. |
| pgACC | PTSD vs HC | n.s. | n.s. | n.s. | n.s. |
| L Amygdala | PTSD vs HC | n.s. | n.s. | n.s. | n.s. |
| R Amygdala | PTSD vs HC | n.s. | n.s. | n.s. | n.s. |
| L Insula | PTSD > HC | -30, 10, 16 | 309 | 2.38 | 0.009 |
| R Insula | PTSD > HC | 40, -10, 8 | 44 | 1.92 | 0.027 |
| R Insula | PTSD > HC | 46, -2, -6 | 24 | 1.89 | 0.029 |
| L Hippocampus | PTSD > HC | -38, -24, -12 | 61 | 2.09 | 0.018 |
| R Hippocampus | PTSD vs HC | n.s. | n.s. | n.s. | n.s. |

**Table S5.** Summary of voxel-wise cognitive reappraisal single sample and group comparison connectivity analyses in our hypothesized ROIs. Clusters significantly activated at an uncorrected threshold (*punc*<0.05) for single sample t-tests for healthy controls, PTSD patients, and between the groups are reported below for the Think vs Watch contrast. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant, L – left, R – Right, dmPFC – dorsomedial prefrontal cortex, dlPFC – dorsolateral prefrontal cortex. \* denotes significant at p*FWE*<0.05 correction level)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Peak MNI Coordinates**  **(X, Y, Z)** | **Cluster size in voxels** | **Peak z-score** | ***p*-value**  **(uncorrected)** |
| ***Cognitive Reappraisal*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| L Amygdala <> dmPFC | Decrease | 8, 14, 38 | 38 | 2.28 | 0.011 |
| L Amygdala <> L dlPFC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> R dlPFC | Increase | 56, 18, 52 | 81 | 2.26 | 0.012 |
| *One sample t-test in PTSD patients* | | | | | |
| L Amygdala <> dmPFC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> L dlPFC | Increase | -36, 10, 58 | 261 | 2.49 | 0.006 |
|  |  | -48, 20, 24 | 21 | 2.12 | 0.017 |
|  |  | -60, 14, 18 | 14 | 2.09 | 0.018 |
|  |  | -48, 14, 30 | 3 | 1.82 | 0.034 |
| L Amygdala <> R dlPFC | Increase | 48, 14, 52 | 34 | 1.79 | 0.037 |
|  |  | 50, 18, 40 | 2 | 1.70 | 0.044 |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| L Amygdala <> dmPFC | PTSD > HC | 8, 18, 38 | 23 | 2.10 | 0.018 |
| L Amygdala <> L dlPFC | PTSD > HC | -30, 22, 58 | 11 | 1.90 | 0.028 |
| L Amygdala <> R dlPFC | n.s. | n.s. | n.s. | n.s. | n.s. |

**Table S6.** Summary of voxel-wise emotional reactivity single sample and group comparison connectivity analyses in our hypothesized ROIs. Clusters significantly activated at an uncorrected threshold (*punc*<0.05) for single sample t-tests for healthy controls, PTSD patients, and between the groups are reported below for the Watch vs Neutral contrast. (PTSD – post traumatic stress disorder, HC – healthy controls, n.s. – not significant, sgACC – subgenual anterior cingulate cortices, pgACC – pregenual anterior cingulate cortices, L – left, R – Right. \* denotes significant at p*FWE*<0.05 correction level)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain region** | **Direction** | **Peak MNI Coordinates**  **(X, Y, Z)** | **Cluster size in voxels** | **Peak z-score** | ***p*-value**  **(uncorrected)** |
| ***Emotional reactivity*** | | | | | |
| *One sample t-test in Healthy Controls* | | | | | |
| L Amygdala <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> pgACC | Decrease | -6, 40, 8 | 27 | 1.97 | 0.024 |
| L Amygdala <> L Insula | Increase | -40, 12, -12 | 63 | 1.95 | 0.025 |
|  | Decrease | -38, 6, 14 | 79 | 2.55 | 0.005 |
|  |  | -26, 30, 12 | 19 | 2.09 | 0.018 |
| L Amygdala <> R Insula | Increase | 32, 20, -20 | 99 | 2.68 | 0.004 |
|  |  | 46, 20, -10 | 5 | 1.85 | 0.032 |
|  | Decrease | 48, 2, 4 | 29 | 2.20 | 0.014 |
|  |  | 34, -8, 12 | 1 | 1.76 | 0.039 |
| L Amygdala <> L Hippocampus | Increase | -20, -20, -14 | 290 | 3.11 | 0.001 |
|  |  | -18, -40, 6 | 11 | 1.85 | 0.032 |
| L Amygdala <> R Hippocampus | Increase | 20, -30, -10 | 13 | 2.08 | 0.019 |
|  | Decrease | 38, -20, -12 | 9 | 1.82 | 0.034 |
| R Amygdala <> sgACC | Increase | 6, 22, -4 | 6 | 1.84 | 0.033 |
|  |  | -4, 22, -4 | 4 | 1.79 | 0.037 |
| R Amygdala <> pgACC | Increase | -2, 40, 10 | 31 | 1.92 | 0.027 |
| R Amygdala <> L Insula | Increase | -40, 22, 2 | 46 | 2.81 | 0.003 |
|  | Decrease | -36, 2, 10 | 49 | 2.19 | 0.014 |
| R Amygdala <> R Insula | Increase | 28, 18, -18 | 71 | 2.25 | 0.012 |
|  |  | 46, 20, -10 | 1 | 1.71 | 0.044 |
|  | Decrease | 36, -8, 18 | 30 | 2.08 | 0.019 |
| R Amygdala <> L Hippocampus | Increase | -26, -20, -12 | 50 | 2.54 | 0.006 |
|  |  | -24, -36, -4 | 6 | 1.92 | 0.028 |
| R Amygdala <> R Hippocampus | Increase | 40, -32, -10 | 2 | 1.82 | 0.034 |
|  |  | 18, -14, -18 | 3 | 1.79 | 0.037 |
|  | Decrease | 22, -36, 10 | 22 | 2.59 | 0.005 |
| L Hippocampus <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> pgACC | Decrease | -4, 36, 6 | 14 | 1.99 | 0.024 |
| L Hippocampus <> L Insula | Decrease | -34, 10, 16 | 44 | 2.41 | 0.008 |
|  |  | -28, 28, 14 | 15 | 2.01 | 0.022 |
|  |  | -44, 6, 8 | 1 | 1.82 | 0.034 |
| L Hippocampus <> R Insula | Increase | 36, 20, -10 | 48 | 1.83 | 0.034 |
| L Hippocampus <> L Amygdala | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> R Amygdala | n.s. | n.s. | n.s. | n.s. | n.s. |
| *One sample t-test in PTSD patients* | | | | | |
| L Amygdala <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> L Insula | Decrease | -38, -22, 14 | 11 | 2.20 | 0.014 |
|  |  | -34, 6, -14 | 6 | 1.90 | 0.028 |
|  |  | -34, 10, -16 | 1 | 1.86 | 0.031 |
|  |  | -36, -32, 22 | 3 | 1.85 | 0.032 |
| L Amygdala <> R Insula | Decrease | 32, 24, -20 | 7 | 2.00 | 0.022 |
|  |  | 46, -12, 6 | 4 | 1.83 | 0.034 |
| L Amygdala <> L Hippocampus | Decrease | -24, -14, -12 | 33 | 2.04 | 0.020 |
| L Amygdala <> R Hippocampus | Decrease | 24, -22, -16 | 70 | 2.58 | 0.005 |
|  |  | 38, -10, -20 | 30 | 2.28 | 0.011 |
| R Amygdala <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| R Amygdala <> pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| R Amygdala <> L Insula | Increase | -26, 16, -14 | 5 | 1.76 | 0.040 |
|  |  | -26, 10, -14 | 1 | 1.66 | 0.049 |
|  | Decrease | -34, -20, 20 | 18 | 1.83 | 0.034 |
| R Amygdala <> R Insula | Decrease | 38, 8, 8 | 50 | 2.18 | 0.015 |
| R Amygdala <> L Hippocampus | Increase | -26, -40, -2 | 7 | 2.15 | 0.016 |
| R Amygdala <> R Hippocampus | Increase | 28, -28, -10 | 8 | 1.84 | 0.033 |
|  |  | 16, -36, 10 | 9 | 1.82 | 0.038 |
| L Hippocampus <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> pgACC | Increase | 2, 36, 2 | 37 | 2.09 | 0.018 |
| L Hippocampus <> L Insula | Decrease | -40, -16, 14 | 3 | 1.81 | 0.035 |
|  |  | -42, 8, -14 | 2 | 1.75 | 0.040 |
| L Hippocampus <> R Insula | Decrease | 48, 10, -10 | 38 | 2.60 | 0.005 |
|  |  | 40, 20, 6 | 63 | 2.44 | 0.007 |
|  |  | 42, -6, -12 | 2 | 1.87 | 0.031 |
|  |  | 34, 24, -18 | 1 | 1.68 | 0.046 |
| L Hippocampus <> L Amygdala | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> R Amygdala | Decrease | 28, -2, -16 | 155 | 2.82 | 0.002\* |
| *Group comparison (PTSD vs Healthy Controls)* | | | | | |
| L Amygdala <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Amygdala <> L Insula | PTSD > HC | -26, 30, 12 | 25 | 2.55 | 0.005 |
|  |  | -32, 4, 14 | 72 | 2.37 | 0.009 |
|  | PTSD < HC | -34, 10, -16 | 30 | 2.51 | 0.006 |
|  |  | -42, 18, -2 | 2 | 1.66 | 0.048 |
| L Amygdala <> R Insula | PTSD > HC | 48, 2, 4 | 37 | 2.36 | 0.009 |
|  |  | 32, 20, 14 | 18 | 1.96 | 0.025 |
|  | PTSD < HC | 34, 20, -20 | 57 | 3.03 | 0.001 |
|  |  | 46, 20, -10 | 9 | 1.84 | 0.033 |
| L Amygdala <> L Hippocampus | PTSD < HC | -24, -20, -12 | 267 | 3.31 | <0.001\* |
| L Amygdala <> R Hippocampus | PTSD < HC | 22, -26, -12 | 51 | 2.76 | 0.003 |
|  |  | 30, -8, -16 | 7 | 1.95 | 0.025 |
|  |  | 40, -12, -22 | 3 | 1.89 | 0.029 |
|  |  | 40, -32, -12 | 1 | 1.76 | 0.039 |
| R Amygdala <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| R Amygdala <> pgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| R Amygdala <> L Insula | PTSD < HC | -38, 22, 4 | 50 | 2.16 | 0.016 |
| R Amygdala <> R Insula | PTSD > HC | 38, -8, 18 | 26 | 2.46 | 0.007 |
|  |  | 40, 2, -10 | 16 | 1.85 | 0.032 |
|  |  | 46, 4, 0 | 8 | 1.83 | 0.034 |
|  | PTSD < HC | 34, 22, 0 | 14 | 1.81 | 0.035 |
| R Amygdala <> L Hippocampus | PTSD < HC | -24, -16, 12 | 34 | 2.55 | 0.005 |
| R Amygdala <> R Hippocampus | PTSD > HC | 22, -36, 10 | 49 | 2.90 | 0.002 |
|  |  | 36, -14, -18 | 7 | 1.72 | 0.043 |
| L Hippocampus <> sgACC | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> pgACC | PTSD > HC | 0, 34, 4 | 57 | 2.57 | 0.005 |
| L Hippocampus <> L Insula | PTSD > HC | -32, 8, 16 | 37 | 2.20 | 0.014 |
|  |  | -26, 30, 12 | 5 | 1.84 | 0.033 |
| L Hippocampus <> R Insula | PTSD < HC | 36, 20, -14 | 173 | 2.28 | 0.011 |
| L Hippocampus <> L Amygdala | n.s. | n.s. | n.s. | n.s. | n.s. |
| L Hippocampus <> R Amygdala | PTSD < HC | 28, 2, -18 | 90 | 2.35 | 0.010 |

**Evaluation of predictive value for neural measures relative to easy to obtain demographic and clinical measures in prediction of treatment response**

We ran correlations of demographic and clinical variables with treatment response and found no significant correlations. We then wanted to identify whether the significant brain measures improved the predictive power of a model containing clinical measures that traditionally predict treatment response. We performed a backward step-wise logistic regression analysis: block 1 – entering all demographic/clinical measures, block 2 – entering the significant neural measures identified in the main analyses (in a backward step-wise method, using the Wald statistic). Block 2 was entered in a backward step-wise fashion as we also wanted to retain only the neural measures most significantly contributed to the model.

In Block 1, the model, including only clinical and demographic variables, did not significantly predict treatment response (p=0.190, χ2=11.22, *r2*=26.2%). In Block 2, when significant neural measures were added, and at step 11 (where the most significant/best neural measures were retained), the block (p<0.001, χ2=35.41) and model (p<0.001, χ2=46.63, *r2*=71.6%) were significantly improved over the inclusion of demographic/clinical measures alone. The neural measures that were retained in the last step were left hippocampal activation, and left amygdala to right insula connectivity (relative to the emotional reactivity contrast).

**Estimation of prediction accuracy and cross validation analyses of neural measures to predict response to treatment.**

For both cognitive reappraisal (THINK vs WATCH) and emotional reactivity (WATCH vs NEUTRAL) contrasts, we ran linear and binary logistic cross-validation regression analyses, to determine the prediction validity of all our hypothesized ROI measures in predicting change in symptom from pretreatment to posttreatment, and to classify PTSD patients based on treatment outcome (responders and non-responders groups were characterized using 50% reduction in symptoms as threshold).

The overall model after cross-validated linear regression explained less than 1% of the variance for the cognitive reappraisal measures in predicting symptom improvement, whereas that for emotional reactivity explained 14.41% of the variance. The model coefficients for each predictor measure are listed in table S7. For cognitive reappraisal, the most significant contributor to the model was the left amygdala, which replicates the finding from our main analysis i.e. left amygdala activation significantly negatively correlated with PTSD symptom improvement. For emotional reactivity, the most significant contributor to the model correlated with symptom improvement was the right hippocampus, which also replicates the significant result from the main analysis where right hippocampus activation was significantly positively correlated with symptom improvement.

The cross-validated binary logistic regression analysis to classify responders and non-responders of treatment had an overall cross-validated accuracy of 66.7% for the cognitive reappraisal contrast and 50.0% for emotional reactivity. The model coefficients for each predictor measure are listed in table S8. For cognitive reappraisal, the most significant contributor to the model predicting treatment response was found to be the right dlPFC which was not found significant in the main results. For emotional reactivity, the most significant contributor to the model in predicting treatment response was the right hippocampus which replicates a significant result from the main analyses, where a positive increase in hippocampal activation was correlated with symptom improvement.

**Table S7.** Cross-validated linear regressions using averaged coefficients from bootstrapped datasets, for cognitive reappraisal and emotional reactivity. Extracted betas for the relevant ROIs for each contrast are included in their respective linear regression models. The table lists the overall goodness of fit of the training and cross-validated models, and the coefficient beta values of the cross-validated model, to determine which variable most contributes to the test model. (L-left, R- Right, dmPFC – dorsomedial prefrontal cortex, dlPFC – dorsolateral prefrontal cortex, HPC – hippocampus, sgACC – subgenual anterior cingulate cortex, pgACC – pregenual anterior cingulate cortex. \* denotes the most weighted coefficient value).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Variable** | **Coefficient β values** | **Overall model**  ***r2*** |
| ***Cognitive Reappraisal*** | | | |
| *Training model* |  |  | 41.62% |
| *Cross-validated model* |  |  | 0.078% |
|  | L Amygdala | -115.15\* |  |
|  | R Amygdala | 97.13 |  |
|  | dmPFC | 3.53 |  |
|  | L dlPFC | 10.14 |  |
|  |  | 16.33 |  |
|  | R dlPFC | -12.49 |  |
|  |  | -8.34 |  |
| ***Emotional Reactivity*** | | | |
| *Training model* |  |  | 23.69% |
| *Cross-validated model* |  |  | 14.41% |
|  | sgACC | 15.61 |  |
|  | pgACC | -1.64 |  |
|  | L Amygdala | 42.49 |  |
|  | R Amygdala | -53.56 |  |
|  | L Insula | -14.29 |  |
|  | R Insula | 30.53 |  |
|  | L Hippocampus | -6.77 |  |
|  | R Hippocampus | 72.63\* |  |

**Table S8.** Cross-validated binary logistic regressions using averaged coefficients from bootstrapped datasets, for cognitive reappraisal and emotional reactivity. Extracted betas for the relevant ROIs for each contrast are included in their respective binary logistic regression models. The table lists the overall model accuracy, confidence interval, specificity, sensitivity of the training and cross-validated models, and the coefficient beta values of the cross-validated model, to determine which variable most contributes to the test model. (L-left, R- Right, dmPFC – dorsomedial prefrontal cortex, dlPFC – dorsolateral prefrontal cortex, HPC – hippocampus, sgACC – subgenual anterior cingulate cortex, pgACC – pregenual anterior cingulate cortex. \* denotes the most weighted coefficient value).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Variable** | **Coefficient β values** | **% accuracy**  **(95% CI)** | **% specificity** | **%**  **sensitivity** | **Positive/Negative Predictive Value** |
| ***Cognitive Reappraisal*** | | | | | |  |
| *Training model* |  |  | 73.6%  (48%, 90%) | 84.6% | 50.0% | 60.0%/78.5% |
| *Cross-validated model* |  |  | 66.7%  (41%, 86%) | 67% | 67% | 50.0%/80.0% |
|  | L Amygdala | 3.65e13 |  |  |  |  |
|  | R Amygdala | 1.08e14 |  |  |  |  |
|  | dmPFC | 1.07e14 |  |  |  |  |
|  | L dlPFC | -9.75e13 |  |  |  |  |
|  |  | -8.39e13 |  |  |  |  |
|  | R dlPFC | 3.36e14\* |  |  |  |  |
|  |  | -1.59e14 |  |  |  |  |
| ***Emotional Reactivity*** | | | | | |  |
| *Training model* |  |  | 89.4%  (66%, 98%) | 92.0% | 83.3% | 83.3%/92.3% |
| *Cross-validated model* |  |  | 50.0%  (26%, 74%) | 75.0% | 0% | 0%/60.0% |
|  | sgACC | 2.18e13 |  |  |  |  |
|  | pgACC | -1.21e13 |  |  |  |  |
|  | L Amygdala | -1.26e13 |  |  |  |  |
|  | R Amygdala | -5.18e13 |  |  |  |  |
|  | L Insula | -1.53e13 |  |  |  |  |
|  | R Insula | 1.43e13 |  |  |  |  |
|  | L Hippocampus | -1.67e13 |  |  |  |  |
|  | R Hippocampus | 5.99e13\* |  |  |  |  |

**Identification and cross-validation of best neural measures model in predicting treatment response.**

For determining the best predictive model, we ran a backwards stepwise binary logistic regression inputting all clinical variables and all significant neural measures for both cognitive reappraisal (THINK vs WATCH) and emotional reactivity (WATCH vs NEUTRAL) contrasts. The best predictive model significantly predicted treatment response (p<0.001, χ2=20.22, accuracy = 89.2%, specificity = 83.3%, sensitivity = 92.0%), and retained left hippocampal activation (p=0.017) and left amygdala to right insula connectivity (p=0.014) (related to the emotional reactivity contrast) as the significant features in a model that best predicted treatment response. These two variables were then included in a cross-validation regression analysis, to determine the prediction accuracy of this “best predictive model” in predicting treatment outcome.

The model coefficient values for each predictor are listed in Table S9. The most significant contributor to the model best predicting treatment response was found to be left amygdala to right insula connectivity, which replicates the above noted whole-sample best predictive model results. This cross-validated binary logistic regression analysis had an overall cross-validated accuracy of 88.9%. However, this estimate could be inflated due to an internal validation in the same dataset and should be tested for replication in an independent cohort.

**Table S9.** Cross-validated binary logistic regression for best predictive model of treatment response. Extracted betas for the ROIs identified as the significant features of the best predictive model were included in a binary logistic regression model that was cross-validated after bootstrapping. The table lists the overall model accuracy, confidence interval, specificity, sensitivity of the training and cross-validated models, and the coefficient beta values of the cross-validated model, to determine which variable most contributes to the test model. (L-left, R- Right. \* denotes the most weighted coefficient value).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Contrast** | **Variable** | **Coefficient β values** | **% accuracy**  **(95% CI)** | **% specificity** | **%**  **sensitivity** | **Positive/Negative Predictive Value** |
|  | | | | | | | |
| *Training model* |  |  |  | 73.7%  (48%, 91%) | 92.3% | 33.3% | 66.7%/75.0% |
| *Cross-validated model* |  |  |  | 88.9%  (65%, 98%) | 100% | 66.7% | 100%/85.7% |
|  | Watch vs Neutral | L Hippocampus | 125.1 |  |  |  |  |
|  | Watch vs Neutral | L Amygdala <> R Insula | -187.9\* |  |  |  |  |

**Testing effects of current antidepressant medication use on findings**

To examine if the current associations between symptom change and pretreatment neural activations and connectivity were not confounded by use of antidepressant medications, we re-ran the significant activation and connectivity correlations of both cognitive reappraisal (THINK vs WATCH) and emotional reactivity (WATCH vs NEUTRAL) including only the 26 patients not on any current antidepressants at time of TF-CBT treatment (Table S10). Furthermore, we also re-ran correlations of symptom change with neural measures controlling for anti-depressant use (Table S11).

All identified significant associations between symptom change and pre-treatment neural measures were not confounded by antidepressant use based on both analyses.

**Table S10.** Bivariate correlation analyses for cognitive reappraisal and emotional reactivity activation and connectivity with unmedicated patients. Extracted betas for significant activation and connectivity results for each contrast are included, and each is correlated with symptom change, including only 26 currently unmedicated patients, to determine whether results hold with unmedicated patients. (L-left, R- Right, HPC – hippocampus, sgACC – subgenual anterior cingulate cortex, pgACC – pregenual anterior cingulate cortex).

|  |  |  |
| --- | --- | --- |
| **Brain Region** | **Pearson**  **Correlation** | **P-value** |
| ***Cognitive Reappraisal*** |  |  |
| *Correlation between reduction in PTSD severity and activation or connectivity* | | |
| L Amygdala | -0.484 | 0.012 |
| ***Emotional Reactivity*** |  |  |
| *Correlation between reduction in PTSD severity and activation or connectivity* | | |
| L Amygdala | 0.585 | 0.002 |
| R Amygdala | 0.448 | 0.022 |
| L Hippocampus | 0.574 | 0.002 |
| R Hippocampus | 0.543 | 0.004 |
| L Amygdala <> sgACC | -0.596 | 0.001 |
| L Amygdala <> pgACC | -0.464 | 0.017 |
| L Amygdala <> R Insula | -0.455 | 0.02 |
| R Amygdala <> R Hippocampus | 0.636 | <0.001 |
| L Hippocampus <> R Amygdala | -0.458 | 0.019 |

**Table S11.** Partial correlations controlling for antidepressant use with cognitive reappraisal and emotional reactivity activation and connectivity and PTSD symptom change. Extracted betas for significant activation and connectivity results for each contrast are included in partial correlations, with each correlated with symptom change whilst controlling for anti-depressant use. (L-left, R- Right, HPC – hippocampus, sgACC – subgenual anterior cingulate cortex, pgACC – pregenual anterior cingulate cortex).

|  |  |  |
| --- | --- | --- |
| **Brain Region** | **Pearson**  **Correlation** | **P-value** |
| ***Cognitive Reappraisal*** |  |  |
| *Correlation between reduction in PTSD severity and activation or connectivity* | | |
| L Amygdala | -0.483 | 0.003 |
| ***Emotional Reactivity*** |  |  |
| *Correlation between reduction in PTSD severity and activation or connectivity* | | |
| L Amygdala | 0.479 | 0.004 |
| R Amygdala | 0.441 | 0.008 |
| L Hippocampus | 0.549 | 0.001 |
| R Hippocampus | 0.511 | 0.002 |
| L Amygdala <> sgACC | -0.468 | 0.005 |
| L Amygdala <> pgACC | -0.508 | 0.002 |
| L Amygdala <> R Insula | -0.562 | <0.001 |
| R Amygdala <> R Hippocampus | 0.532 | 0.001 |
| L Hippocampus <> R Amygdala | -0.454 | 0.006 |