**Supplementary Online Content**

**Increased Amygdala-Visual Cortex Connectivity in Youth with Persecutory Ideation. DeCross SN, Farabaugh AH, Holmes AJ, Ward M, Boeke EA, Wolthusen RPF, Coombs G, Nyer M, Fava M, Buckner RL and Holt DJ.**

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**MRI data acquisition and scan parameters:** The neuroimaging session included 9 scans: one T1, one T2, one DTI, two resting-state blood oxygenation level-dependent (BOLD) scans, and four task-based BOLD scans(Holt *et al*., 2014, Holmes *et al*., 2015). Functional imaging data were acquired using a gradient-echo echo-planar imaging (EPI) sequence sensitive to BOLD contrast. The current analyses were conducted using the following scans: 1) one high-resolution multiecho T1-weighted magnetization-prepared gradient-echo image (MPRAGE) with 1.2 mm isotropic voxels, repetition time (TR) = 2200 ms, inversion time (TI) = 1100 ms, echo time (TE) = 1.54 ms for image 1 to 7.01 ms for image 4, flip angle (FA) = 7º, and field of view (FOV) = 230 and 2) two 6.2-min resting-state BOLD scans with 124 time points, 3 mm isotropic voxels, TR = 3000 ms, TE = 30 ms, FA = 85º, FOV = 216, and 47 axial slices collected with interleaved acquisition and no gap between slices, during which subjects were instructed to keep their eyes open and blink normally.

**Quality control procedures and exclusion criteria:** All scans were initially visually checked for adequate brain coverage and registration. Only resting-state scans with an SNR ≥ 125 were included in the analyses. In addition, since subtle differences in head motion across groups can give rise to spurious findings that mimic neural effects(Van Dijk *et al*., 2012), runs with a relative head motion value of ≥ 1 mm between one or more pairs of consecutive TRs and/or runs with a mean relative net displacement of ≥ 0.1 mm across all TRs of the run were excluded from the analyses.

The data of 1 subject was excluded from all analyses due to a structural abnormality detected in the anatomical scan; the resting-state data of 7 subjects were excluded due to excessive head motion based on the above criteria; and the data of 1 subject was excluded due to an incomplete PDI. Thus, a total of 122 subjects were included in the analyses; of these subjects, 114 had two usable resting-state runs, whereas 2 subjects had one run each excluded due to a low SNR, and 6 subjects had one run each excluded due to excessive head motion.

**Analyses of resting-state BOLD data**

*Preprocessing****:*** Preprocessing of the resting state data (averaged across both resting-state scans) was conducted using an in-house script to measure low-frequency (< 0.08 Hz) fluctuations in the BOLD signal (Buckner *et al*., 2009). Nuisance regressors, including the six parameters computed from the rigid-body motion correction procedure, the averaged signal within a ventricular region-of-interest (ROI), a region within the deep white matter, and the signal averaged over the whole brain were used to remove systematic variance associated with these variables. The first temporal derivative of each regressor was also included to account for temporal shifts in the BOLD signal.

*Voxel-wise analysis****:*** After computing Pearson correlations between 1) the averaged time series across all voxels within the amygdala seed and 2) the time series of each voxel in the brain, a Fisher’s r-to-z transformation was applied. Group-level functional connectivity maps (one- and two-sample t-tests, random effects) were constructed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Voxel-wise whole-brain regression analyses were also conducted using 1) the PDI total score and 2) the PDI distress score (adjusted for total number of items endorsed) as the regressor of interest. The primary voxel-wise analyses were performed at a voxel-wise p-value threshold of p < 0.01; secondary analyses that included multiple covariates were performed at a voxel-wise p-value threshold of p < 0.05. In all analyses, only clusters which met a cluster-level False Discovery Rate (FDR)-corrected level of significance across the whole brain (p < 0.05) were considered significant. FDR-corrected p-values are reported in all tables. To determine whether symptoms other than delusional beliefs contributed to the main findings, the primary analyses were repeated with levels of depressive symptoms, anxiety, and hallucinatory experiences as covariates. For all analyses, each individual subject’s mean value for relative net head displacement was used as a covariate.

*Region-of-interest (ROI) analysis:*AnROI analysis was conducted to investigate the contribution of the data of individuals with persecutory beliefs to the main findings by first extracting the average signal at each time point of the two averaged resting-state scans from the bilateral (combined right and left) amygdala ROI and the Jülich Atlas V1 ROI from FSL (<https://fsl.fmrib.ox.ac.uk/fsl>), and then computing the correlation between the two time courses within each subject. By convention, a Fisher’s r-to-z transformation was performed to obtain a z-score corresponding to a value for amygdala-V1 connectivity for each subject. We chose to examine the connectivity of the amygdala to V1 in these analyses, because V1 (unlike other visual cortical areas) can be reliably identified in individual subjects based on anatomical landmarks. These z-scores then served as the dependent variable in the subsequent ANOVA and multiple regression analysis. First, one-way ANOVAs were conducted to test for a difference in mean z-scores among the H+P, H-P, and L groups, and in mean z-scores among the PH+P, PH-P, and PL groups. Second, to determine the relative contributions of different aspects of delusional beliefs to the increase in connectivity between the amygdala and V1 in this cohort, multiple linear regression analyses were performed including the following factors: the total number of delusional beliefs endorsed, the amount of distress associated with those beliefs, and the endorsement of persecutory beliefs. To determine whether results were specific to persecutory thinking, the multiple regression analysis was then repeated with two other categories of delusional thinking (the religiosity and thought disturbances factors, see **Methods S2** for additional details) included as additional regressors.

*Localization and visualization of effects:*All analysis and localization procedures took place in MNI152 space. For each analysis, the Harvard-Oxford Atlas within FSL was used to identify the location of the peak effects, with the exception of peaks found within the visual cortex. Since the Harvard-Oxford Atlas does not include a delineation of the borders of V1, the Jülich Histological Atlas within FSL was used to localize effects observed within visual cortical areas. The Jülich Histological Atlas’s probabilistic representation of V1 was thresholded at 50%, and peaks within this thresholded region were categorized as falling within striate cortex (V1), while peaks outside of V1, within other visual areas, were categorized as falling within extrastriate cortex. This thresholded Jülich V1 ROI was also used as the V1 seed for the ROI analysis.

For the purposes of visualization, maps displaying only the clusters which reached significance (unless otherwise noted) were transformed into Talairach space and projected to the cortical surface using FreeSurfer. A cortical surface-based, thresholded V1 label from FreeSurfer(Hinds *et al*., 2009) is shown on the FreeSurfer-generated cortical surfaces for reference.

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**Methods S2. Peters et al. Delusions Inventory (PDI) factors**

**The “persecutory factor” of the PDI:** In a prior study, a principal components analysis identified PDI item 4 (“Do you ever feel as if you are being persecuted in some way?”) and item 5 (“Do you ever feel as if there is a conspiracy against you?”) as the “persecutory factor” of the PDI(Peters *et al*., 1999, 2004). In the current study, participants who endorsed one or both of these items at baseline and/or at the one-year follow-up time point were identified as having persecutory thinking (+P). Since a paranoid individual may report symptoms inconsistently, we included those individuals who reported these symptoms at either time point to identify all individuals who were vulnerable to experiencing persecutory beliefs. To confirm that our findings remained if the analyses were limited only to those endorsing these beliefs at the time of the scan (baseline), we repeated the analyses excluding 3 participants who endorsed persecutory thinking at follow-up, but not at baseline; all main ANOVA and regression results remain significant.

The groups which were compared in the initial analyses of this study, the High (H) and Low (L) groups, and the Persistently High (PH) and Persistently Low (PL) groups, differed with respect to the numbers of participants who endorsed persecutory thinking, as expected. The High (H) group included a significantly higher number of subjects with persecutory thinking than the Low (L) group (19 in the H group vs. 1 in the L group; X2 (1, n = 87) = 21.58, p < 0.001). The Persistently High (PH) group included a significantly higher number of subjects with persecutory thinking than the Persistently Low (PL) group (10 in the PH group vs. 0 in the PL group; X2 (1, n = 39) = 10.40, p = 0.001). Due to these differences, and because a primary goal of the study was to examine the effects of persecutory thinking on amygdala connectivity, ROI analyses were then conducted which examined the role of persecutory thinking on amygdala-V1 connectivity using well-matched subgroups of participants (see **Figure 3** and **Table S2**).

**Control factors:** In order to further assess the specificity of our main findings, we also examined the contributions of two of the other PDI factors identified by principal components analyses(Peters *et al*., 1999, 2004), the “religiosity factor” and the “thought disturbances factor,” to the magnitude of amygdala-V1 connectivity. We chose these two factors because, like persecutory ideation, they represent established categories of delusional beliefs commonly observed in patients with psychotic disorders(Kimhy *et al*., 2005). The “religiosity factor” includes PDI items 8 (“Do you ever feel that you are especially close to God?”) and 11 (“Do you ever feel as if you have been chosen by God in some way?”). The “thought disturbances” factor includes PDI items 18 (“Do your thoughts ever feel alien to you in some way?”) and 20 (“Do you ever feel as if your own thoughts were being echoed back to you?”). Participants who endorsed one or both items at baseline and/or at the one-year follow-up time point were characterized as exhibiting religiosity or thought disturbances, respectively.

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**Table S1. Current psychotropic medication use of the High (H) and Low (L), and Persistently High (PH) and Persistently Low (PL), groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **H**  **(n = 43)** | **L**  **(n = 44)** | **PH**  **(n = 22)** | **PL**  **(n = 17)** |
| **Antidepressant (SSRI)** | 1 | 2 | 1 | 0 |
| **Antidepressant (SNRI)** | 1 | 0 | 0 | 0 |
| **Anxiolytic (benzodiazepine)** | 1 | 0 | 0 | 0 |
| **Anxiolytic (non-benzodiazepine)** | 1 | 0 | 0 | 0 |
| **Stimulant** | 2 | 1 | 0 | 0 |
| **Total number of subjects** | **5** | **2** | **1** | **0** |

There were no significant differences between the High (H) and Low (L), and between the Persistently High (PH) and Persistently Low (PL), groups in the number of subjects taking psychotropic medications. No subjects reported taking antipsychotic medications. In the High (H) group, one subject was taking fluoxetine, one subject was taking duloxetine, one subject was taking buspirone, one subject was taking amphetamine/dextroamphetamine, and one subject was taking clonazepam and amphetamine/dextroamphetamine. In the Low (L) group, one subject was taking sertraline, and one subject was taking citalopram and amphetamine/dextroamphetamine. In the Persistently High (PH) group, one subject was taking citalopram. No subjects in the Persistently Low (PL) group were taking psychotropic medications. The findings of the primary analyses (see **Table 2**) remained significant when the analyses were repeated excluding the subjects taking psychotropic medications (p = 0.01, FDR-corrected across the whole brain).

**Table S2. Characteristics of the groups with (+P) and without (-P) persecutory beliefs**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **H+P**  **(n = 19)** | **H-P**  **(n = 24)** | **P-value** | **PH+P**  **(n = 10)** | **PH-P**  **(n = 12)** | **P-value** |
| **Gender** | 11 F, 8 M | 17 F, 7 M | 0.521 | 5 F, 5 M | 9 F, 3 M | 0.378 |
| **Age (years)** | 19.68 ± 1.11 | 19.17 ± 1.52 | 0.221 | 19.80 ± 0.79 | 18.75 ± 1.06 | 0.017\* |
| **Relative head motion (mm)** | 0.05 ± 0.01 | 0.05 ± 0.02 | 0.680 | 0.04 ± 0.01 | 0.04 ± 0.01 | 0.875 |
| **PDI total score** | 10.63 ± 2.56 | 9.71 ± 1.65 | 0.160 | 8.40 ± 2.07 | 8.17 ± 2.62 | 0.822 |
| **PDI distress score** | 2.93 ± 0.59 | 2.73 ± 0.76 | 0.381 | 2.75 ± 0.60 | 2.26 ± 1.01 | 0.206 |
| **BDI score** | 13.72 ± 8.98 | 10.75 ± 6.13 | 0.210 | 8.33 ± 8.11 | 12.08 ± 9.77 | 0.362 |
| **STAI score** | 50.06 ± 10.53 | 45.32 ± 9.00 | 0.144 | 45.00 ± 6.53 | 44.75 ± 10.82 | 0.950 |
| **LSHS-R score** | 24.54 ± 16.88 | 22.67 ± 8.10 | 0.684 | 15.50 ± 11.86 | 17.22 ± 8.76 | 0.736 |
| **Cannabis use (past 30 days)** | 0.77 ± 1.54 | 1.58 ± 3.61 | 0.453 | 1.75 ± 2.87 | 5.43 ± 10.95 | 0.535 |

There were no significant differences between the subgroup of the High group with persecutory beliefs (H+P) and the subgroup of the High group without persecutory beliefs (H-P) in gender, mean age, relative head motion, ethnicity, or race; or in mean number of delusional beliefs endorsed, mean levels of distress associated with delusional beliefs, mean levels of symptoms of depression, anxiety, hallucinatory experiences, or cannabis use in the past month. There were no significant differences between the subgroup of the Persistently High group with persecutory beliefs (PH+P) and the subgroup of the Persistently High group without persecutory beliefs (PH-P) in gender, relative head motion, race, or ethnicity; or in any symptom measure or cannabis use in the past month. The mean age of the PH+P group was significantly higher than that of the PH-P group; however, the findings of the analyses remained significant after covarying for age (see text). +P, endorsement of persecutory thinking; -P, no endorsement of persecutory thinking; PDI, Peters et al. Delusions Inventory; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; LSHS-R, Launay-Slade Hallucinations Scale – Revised; \* significant between-group difference (independent t-test, p < 0.05).

**Figure S1. Inclusion criteria and sample sizes of subject groups of the primary analyses**

Schematic chart describing the inclusion criteria and sample sizes of the cohorts studied in the primary analyses. After 9 subjects were excluded from all analyses following the quality control procedures,three primary analyses were conducted: 1) a categorical analysis comparing the two groups representing the two extremes of severity of psychotic experiences, with high (the High group) and low (the Low group) levels of delusional beliefs, 2) a second categorical analysis conducted within the subsample with longitudinal follow-up data who met PDI score criteria for inclusion in the Persistently High (n = 22) and Persistently Low (n = 17) groups, and 3) dimensional regression analyses, for which the full cohort of subjects with usable MRI data (n = 122) were included.

**Figure S2. Average amygdala connectivity across all subjects**

An average amygdala functional connectivity map for all subjects (n = 122) revealed the expected pattern of amygdala connectivity (Roy *et al*., 2009), with strong positive correlations between the resting BOLD activity of the amygdala and medial frontal, medial and lateral temporal, and mid-cingulate cortices, and negative correlations with lateral frontal, parietal, and occipital cortices (also see **Figure S3**). Positive correlations are represented by warm colors, and negative correlations are represented by cool colors.

**References**

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**Figure S3. Within-group maps: effects of global signal regression**

The within-group amygdala connectivity maps for the High and Low groups when global signal regression (GSR) is excluded (A) or included (B) in the preprocessing pipeline. When GSR is excluded, the amygdala-visual cortex within-group correlations are positive, whereas when GSR is included, the correlations are negative.

GSR remains a controversial issue in the field; based on evidence that motion artifact is a confound that can account for a large portion of the globally shared variance in resting-state data and can mimic neuronal signals, resulting in spurious findings (Power *et al*., 2012, Van Dijk *et al*., 2012), we opted to include GSR, because it is an effective tool for removing motion artifact (Buckner *et al*., 2008, 2009, Van Dijk *et al*., 2010, Power *et al*., 2011, 2015, Yeo *et al*., 2011, Satterthwaite *et al*., 2012). However, standard GSR procedures result in an approximately zero-meaned distribution of correlation constants, thus artificially inducing “negative correlations” (or “anti-correlations”) for half of the constants (Buckner *et al*., 2008, Fox *et al*., 2009, Murphy *et al*., 2009).

The maps above suggest that the correlations between the resting BOLD activity of the amygdala and visual cortex are weakly positive correlations, and not true negative correlations.

When comparing the groups directly (see **Figure 1**), the maps reflect the relative differences in amygdala connectivity strength; the High group shows *relatively greater* amygdala-visual cortex connectivity than the Low group, and the Persistently High group shows *relatively greater* amygdala-visual cortex connectivity than the Persistently Low group.

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**Figure S4. Results at a lower threshold (p < 0.05, FDR whole-brain-corrected) than in the primary analyses**

Inflated (top rows) and flattened (bottom rows) voxel-wise maps of clusters that met FDR whole-brain correction at p < 0.05, for the comparisons of the High (H) vs. Low (L) groups (A) and Persistently High (PH) vs. Persistently Low (PL) groups (B), and for the whole-brain regression analyses with PDI total score (C) or PDI distress score (D) as regressors. Multiple views (inflated and flattened) of the cortical surface show that the results reported in the primary analyses (**Figures 1-2**) are robust and remain relatively specific to visual cortex at a lower threshold.

In addition, at a more stringent threshold of p < 0.001, FDR whole-brain-corrected, the findings for the PH vs. PL group comparison remain significant (MNI coordinates of peak in striate cortex [x, y, z] = 16, -90, 4, z = 4.2, p = 0.001, 188 voxels), whereas the other findings do not.

The border of V1 is shown in green. Several anatomical landmarks are labeled on the flattened map in A for orientation purposes. The p-values of the clusters showing significant between-group differences in A and B are represented by warm colors (H > L in A; PH > PL in B; the reverse contrasts, L > H and PL > PH, showed no significant differences) and the p-values of the clusters in C and D are represented by warm (positive correlations) and cool (negative correlations) colors.**Figure S5. Increased amygdala-V1 connectivity in delusional youth may be limited to a pathway involving primarily the basolateral amygdala**

To localize the area of the amygdala most closely associated with the effects of delusional thinking on amygdala-visual cortex connectivity, a 3 mm sphere centered on the most significant peak of the primary analyses (see **Figure 1B**: Persistently High > Persistently Low group, amygdala connectivity map; MNI coordinates of peak in striate cortex (V1) [x, y, z] = 16, -90, 4) was used as a seed in a voxel-wise functional connectivity analysis. The connectivity of this seed in the High (H) and the Low (L) groups (A) and in the Persistently High (PH) and the Persistently Low (PL) groups (B) was then compared. Bilateral peaks in the amygdala were observed (see white arrows) in each of the two uncorrected maps shown above (p < 0.01); one of these four peaks, in the right amygdala in panel B, was significant at a threshold of p < 0.01, FDR whole-brain-corrected. Two peaks (in the right amygdala in A and the left amygdala in B) were contained within larger clusters; the peaks of those clusters, in the putamen and temporal pole, respectively, were significant at a threshold of p < 0.01, FDR whole-brain-corrected. P-values of the clusters in these maps are represented by warm (H > L in A; PH > PL in B) and cool (L > H in A; PL > PH in B) colors.

The anatomical segmentations of the centromedial, superficial, and basolateral amygdala nuclei, as delineated by the Jülich Histological Atlas within FSL, were used to determine the location of these peaks within the amygdala. All four were located in the basolateral nucleus. The MNI coordinates of these peaks are listed here: for A, the MNI coordinates of the peak in right basolateral amygdala are [x, y, z] = 28, 0, -24; and the MNI coordinates of the peak in left basolateral/superficial amygdala are [x, y, z] = -30, 0, -18. For B, the MNI coordinates of the peak in the right basolateral amygdala are [x, y, z] = 28, -8, -18; and MNI coordinates of the peak in the left basolateral amygdala are [x, y, z] = -26, -8, -22.

This evidence for an alteration of the functional pathway between the basolateral nucleus of the amygdala and primary visual cortex in youth with subclinical delusional beliefs is consistent with the known topographical distribution of amygdala-visual cortical projections in primate cortex, as described by Amaral *et al*., 2003. In the monkey, these projections are rostrocaudally organized such that caudal portions of the visual cortex (e.g., striate cortex/V1) receive input from the most dorsal portion of the basal nucleus of the amygdala (see Figure 9 of Amaral *et al*., 2003). However, due to the limited spatial resolution of our scans (relative to the size of these amygdala nuclei) and the group averaging required to generate these maps, these findings must be considered preliminary, requiring further replication in an independent sample.

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**Figure S6. A voxel-wise, between-group comparison of hippocampal connectivity**

The between-group comparisons conducted using the amygdala seed (see **Figure 1**) were also performed using a bilateral (combined left and right) hippocampus seed, also derived from the Harvard-Oxford Atlas and thresholded at 50%. Uncorrected flattened maps demonstrate that the patterns of hippocampus-visual cortex connectivity for the High (H) vs. Low (L) group comparison (A) and Persistently High (PH) vs. Persistently Low (PL) group comparison (B) were similar to the amygdala-visual cortex connectivity patterns, but did not reach significance at a p < 0.01, FDR whole-brain-corrected threshold. The border of V1 is shown in green. P-values of the clusters in these maps are represented by warm (H > L in A; PH > PL in B) and cool (L > H in A; PL > PH in B) colors.

Repeated measures ANOVAs comparing amygdala-V1 and hippocampus-V1 extracted connectivity values for the H vs. L groups and PH vs. PL groups revealed a significant seed by group interaction for the PH vs. PL comparison (p = 0.018), driven by a greater difference between the PH and PL groups in amygdala-V1 connectivity than in hippocampus-V1 connectivity. The seed by group interaction was not significant in the H vs. L analysis. The hippocampus and amygdala are spatially close to one another, yet functionally distinct; the differences in extent and magnitude of findings using these two seeds suggest that the effects of delusional thinking on connectivity reported here are relatively specific to the amygdala.