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Increased amygdala-visual cortex connectivity in youth with persecutory ideation

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Abstract

Background. Subclinical delusional ideas, including persecutory beliefs, in otherwise healthy individuals are heritable symptoms associated with increased risk for psychotic illness, possibly representing an expression of one end of a continuum of psychosis severity. The identification of variation in brain function associated with these symptoms may provide insights about the neurobiology of delusions in clinical psychosis.

Methods. A resting-state functional magnetic resonance imaging scan was collected from 131 young adults with a wide range of severity of subclinical delusional beliefs, including persecutory ideas. Because of evidence for a key role of the amygdala in fear and paranoia, resting-state functional connectivity of the amygdala was measured.

Results. Connectivity between the amygdala and early visual cortical areas, including striate cortex (V1), was found to be significantly greater in participants with high ($n = 43$) *v.* low ($n = 44$) numbers of delusional beliefs, particularly in those who showed persistence of those beliefs. Similarly, across the full sample, the number of and distress associated with delusional beliefs were positively correlated with the strength of amygdala-visual cortex connectivity. Moreover, further analyses revealed that these effects were driven by those who endorsed persecutory beliefs.

Conclusions. These findings are consistent with the hypothesis that aberrant assignments of threat to sensory stimuli may lead to the downstream development of delusional ideas. Taken together with prior findings of disrupted sensory-limbic coupling in psychosis, these results suggest that altered amygdala-visual cortex connectivity could represent a marker of psychosis-related pathophysiology across a continuum of symptom severity.

Introduction

Schizophrenia has been frequently referred to as a 'dysconnectivity syndrome' (Friston and Frith, 1995; Liang *et al*., 2006; Stephan *et al*., 2009), since neuroimaging studies have identified a range of abnormalities in the connections among regions of the brain in schizophrenia (Karlsgodt *et al*., 2010; Whitfield-Gabrieli and Ford, 2012). However, it remains unclear whether the reported connectivity abnormalities observed in psychotic illness are related to the underlying biology of the disease, or if some are attributable to secondary effects of having the illness, including effects of its treatment (Stephan *et al*., 2001; Schmidt *et al*., 2013; Sarpal *et al*., 2015). This unresolved question has contributed to a recent increased interest in earlier, more broadly-defined 'psychosis spectrum' states (Calkins *et al*., 2014), including 'psychotic experiences' (PEs) (Linscott and van Os, 2013), that are unaffected by these confounds.

PEs are subclinical expressions of psychotic symptoms that are reported commonly (5–35% prevalence) in the general population (Poulton *et al*., 2000; van Os *et al*., 2009; Kelleher *et al*., 2012; Calkins *et al*., 2014). Although the majority of individuals reporting PEs do not develop clinical psychosis (Dominguez *et al*., 2011; Linscott and van Os, 2013), several lines of evidence suggest that PEs and clinical psychosis represent distinct stages of a symptomatic and biological continuum of severity. Severe and persistent PEs are associated with a greater than 10-fold increase in risk for the development of clinical psychosis (Poulton *et al*., 2000; Dominguez *et al*., 2011), and similar to clinical psychosis, PEs are familial and heritable (Kelleher and Cannon, 2011). Many of the same epidemiological risk factors that increase risk for schizophrenia (e.g. cannabis use, childhood adversity) also increase risk for PEs

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(Cougnard *et al.*, 2007; Kelleher and Cannon, 2011; Linscott and van Os, 2013). Thus, shared etiological mechanisms may underlie these common associations.

In addition, recent neuroimaging studies have provided evidence for biological overlap between PEs and psychosis, identifying changes in brain structure (Kelleher and Cannon, 2011) and function (Fusar-Poli *et al.*, 2012; Satterthwaite *et al.*, 2015) in individuals with PEs that are similar to those observed in patients with psychotic disorders. However, few studies thus far have investigated the neurobiological basis of the clinically apparent heterogeneity of PEs. Like clinical psychosis, PEs comprise a range of seemingly distinct symptoms, such as delusional beliefs and hallucinatory experiences (Yung *et al.*, 2009; Capra *et al.*, 2013; Ronald *et al.*, 2014). Of the subclinical psychotic phenomena, paranoia is the most heritable (Zavos *et al.*, 2014) and prevalent (Wigman *et al.*, 2011) symptom, with a 10–15% prevalence within the general population (Freeman, 2007). Suspiciousness (one manifestation of paranoia) is associated with an increased risk for developing clinical psychosis in at-risk populations (Tarbox *et al.*, 2013; Cannon *et al.*, 2016), suggesting that a phenomenological continuum of severity, spanning suspiciousness and paranoia to frank persecutory delusions, may be associated with a common underlying mechanism.

Paranoia or persecutory ideation has been proposed to involve misattributions of threat to non-threatening events, objects, or experiences (Freeman *et al.*, 2002) and is associated with elevated levels of negative affect (Bentall *et al.*, 2009). Because of these findings, prior neuroimaging studies of paranoia have focused on the amygdala, due to its well-established role in fear, threat perception, and negative affect (LeDoux, 2003; Phelps, 2006; Delgado *et al.*, 2008; Coombs *et al.*, 2014; Cullen *et al.*, 2014). For example, one recent study found significantly elevated amygdala perfusion in paranoid compared to non-paranoid patients with schizophrenia (Pinkham *et al.*, 2015). Changes in the connectivity of the amygdala have been observed previously in schizophrenia (Anticevic *et al.*, 2014; Ford *et al.*, 2015); however, it is not known whether these findings were related to the presence of paranoia. Recent evidence for symptom-specific changes in brain function in psychotic illness (Menon *et al.*, 2001; Shaffer *et al.*, 2015) highlights the importance of investigating the specific neural correlates of individual psychotic symptoms, which are associated with different antecedents (Cannon *et al.*, 1990), levels of risk (Yung *et al.*, 2003; Demjaha *et al.*, 2010; Ruhrmann *et al.*, 2010), and outcomes (Ho *et al.*, 1998; Marshall *et al.*, 2005).

Thus, in the current study, we sought to determine whether amygdala connectivity in non-help-seeking youth is altered in association with delusional thinking, particularly persecutory beliefs.

Methods and materials

Study design and participants

Subjects were recruited from a larger pool of participants of a study of psychopathology in college students (Farabaugh *et al.*, 2012; Nyer *et al.*, 2013), in which college students were assessed at four Boston-area universities during on-campus, in-person mental health screenings. In these screenings, two questionnaires [the Beck Depression Inventory (BDI) (Beck *et al.*, 1961) and the 21-item Peters *et al.* Delusions Inventory (PDI) (Peters *et al.*, 2004)] were used to identify young adults with a range of severity of depressive and/or psychotic-like symptoms, in order to characterize young adults currently enrolled in college who are at risk for depression, psychosis, and other types of psychopathology. Students with elevated scores [BDI total score >5, representing approximately the top half of the distribution for this population (Farabaugh *et al.*, 2012), and/or PDI total score >7, scores that are typical of individuals with clinical psychosis (Preti *et al.*, 2007*b*)], or students who endorsed the suicidal ideation item of the BDI (BDI item #9 > 0), as well as a small number of low-scoring students (BDI total score = 0, included to increase variance in the measures), were invited to participate in: (1) a brief clinical assessment (to identify those who were in immediate need of treatment) (Farabaugh *et al.*, 2012), (2) a baseline neuroimaging session, and (3) longitudinal follow-up assessments, conducted via self-report questionnaires administered online. Levels of anxiety and hallucinatory experiences [measured using the State-Trait Anxiety Inventory (Spielberger *et al.*, 1970) and the Launay–Slade Hallucinations Scale-Revised (Bentall and Slade, 1985), respectively] were also assessed, among other symptoms (Farabaugh *et al.*, 2012). Written informed consent was obtained from all subjects in accordance with the guidelines of the Partners Institutional Review Board (IRB), and those completing the neuroimaging session provided additional written informed consent in accordance with the guidelines of the Harvard University IRB. Subjects with neurological disorders, a history of substance abuse or dependence, serious medical illness, or contraindications to magnetic resonance imaging (MRI) scanning were excluded from the neuroimaging session.

One hundred and thirty-one subjects completed the neuroimaging portion of the study; the analyses reported here included the 122 subjects (mean age = 19.5 ± 1.3 years; 87 females; 47.5% Caucasian, 30.3% African-American, 7.4% Asian, 8.2% Other; 12.3% Hispanic) whose data passed quality control procedures (see online Supplementary Methods S1). In this sample, 9.8% reported taking psychotropic medications (antidepressants, anxiolytics, and stimulants; no antipsychotic medications). Of the 122 subjects, 56 completed an online follow-up assessment that was conducted 1 year following the baseline assessment.

Analyses

The 21-item PDI (Peters *et al.*, 2004), a validated self-report scale widely used to assess unusual thinking within the general population (Verdoux *et al.*, 1998*a*, 1998*b*; Scott *et al.*, 2008, 2009; Varghese *et al.*, 2008), was used to measure subclinical delusions and persecutory thinking. The PDI measures the total number of delusional beliefs endorsed by the participant (PDI total score) as well as the levels of distress, preoccupation, and conviction associated with these beliefs (the distress, preoccupation, and conviction subscales). Given that: (1) the overall total number and degree of persistence of PEs are established risk factors for the development of clinical psychosis (Poulton *et al.*, 2000; Dominguez *et al.*, 2011; Kaymaz *et al.*, 2012; van Os and Linscott, 2012) and (2) higher distress levels associated with delusional beliefs have been linked to both clinical severity (Freeman, 2006; Sisti *et al.*, 2012) and persecutory ideation (Cutting, 1997; Yung *et al.*, 2009; Wigman *et al.*, 2011), we examined the contribution of each of these factors, as well as the presence of persecutory beliefs, to amygdala connectivity variation in this cohort. We adjusted the distress subscale score for the total number of items endorsed on the PDI by dividing each subject's distress subscale score by their total score. We measured persecutory beliefs

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using the 'persecutory factor' of the PDI [defined in a prior factor analysis (Peters *et al*., 1999; Peters *et al*., 2004)]. Also, to assess the specificity of our findings with the persecutory factor, we examined two other PDI factors ('religiosity' and 'thought disturbances') in control analyses (see online Supplementary Methods S2 for additional details).

To test our hypotheses regarding changes in amygdala connectivity associated with subclinical delusions and persecutory thinking, we conducted two sets of categorical analyses (between-group comparisons). First, we compared participants with markedly elevated scores on the PDI [the high (H) group, $n = 43$, PDI total score >7] to those with low scores [the low (L) group, $n = 44$, PDI total score <5]. These PDI scores were chosen based on prior evidence showing that PDI scores above 7 are typical of patients with clinical psychosis (Preti *et al*., 2007*b*) and PDI scores below 5 are typical of healthy subjects (van Os *et al*., 1999; Kim *et al*., 2013). In a second set of analyses, we compared subjects who had at least moderately elevated PDI total scores both at baseline and at 1-year follow-up [the persistently high (PH) group, $n = 22$, PDI total scores $\geqslant 5$ at both time points] to those with persistently low (PL) PDI total scores [the PL group, $n = 17$, PDI total scores <5 at both time points]. In addition, to determine whether our findings in the between-group comparisons would also be observed using a dimensional approach, we conducted whole brain regressions in the full sample ($n = 122$), in order to examine the dimensional relationship between amygdala connectivity and (1) PDI total score and (2) PDI distress score. Demographic information about these groups of participants is provided in Table 1; also see online Supplementary Fig. S1 for a schematic summary of the design of the analyses and online Supplementary Table S1 for details on subjects' current psychotropic medication use.

Also, because previous studies have observed correlations between delusional severity and measures of symptoms of depression, anxiety, and hallucinatory experiences (Verdoux *et al*., 1999; Preti *et al*., 2007*a*; Cella *et al*., 2008; Scott *et al*., 2008; Varghese *et al*., 2008), we repeated the analyses while covarying for these symptoms, to determine the specificity of our findings to delusional beliefs. Lastly, we measured the contribution of the participants who endorsed persecutory beliefs (+P) and those who did not (−P), using a regions-of-interest (ROI) approach.

MRI data acquisition

All MRI data were collected on a 3T Siemens Tim Trio scanner using a 12-channel head coil at the Harvard Center for Brain Science. The scans collected during the scan session (Holmes *et al*., 2015) included one T1 anatomical scan and two 6.2-min resting-state scans. See online Supplementary Methods S1 for scan parameters and quality control procedures.

Seed-based functional connectivity: voxel-wise and ROI-based analyses

A seed-based functional connectivity analysis was conducted using a bilateral amygdala seed, using standard preprocessing techniques for resting-state functional connectivity analyses (Buckner *et al*., 2009; Van Dijk *et al*., 2009; Yeo *et al*., 2011; Van Dijk *et al*., 2012). The seed was defined by thresholding the Harvard-Oxford Atlas amygdala ROI within FSL (https://fsl.fmrib.ox.ac.uk/fsl) at 50%; each voxel included in the seed had a greater than or equal to 50% chance of falling within the amygdala. Pearson correlations between the averaged time series across all voxels within the amygdala seed and the time series corresponding to each voxel across the brain were computed and group-level functional connectivity maps were constructed. The primary voxel-wise analyses were performed at a voxel-wise p-value threshold of $p < 0.01$; 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. The average amygdala connectivity map for all subjects ($n = 122$) showed the expected pattern of amygdala connectivity (Roy *et al*., 2009) (online Supplementary Fig. S2).

An ROI analysis was conducted to investigate the contribution of the data of individuals with persecutory beliefs to the findings of the categorical analyses. The average signal at each time point of the two averaged resting-state scans was extracted from the bilateral amygdala ROI and the Jülich Atlas V1 ROI. The Pearson's correlation between the two time courses within each subject was then computed, followed by a Fisher's r-to-z transformation. The z-scores for each subject were then used as dependent variables in subsequent analysis of variance (ANOVA) and multiple regression analyses. See online Supplementary Methods S1 for additional details.

Results

Amygdala connectivity in youth with delusional beliefs: relationship to number, persistence, and associated distress

Categorical analyses

Youth with high levels of delusional beliefs (the H group, $n = 43$) exhibited significantly greater connectivity between the amygdala and visual cortex compared to those with low levels of delusional beliefs (the L group, $n = 44$) [Fig. 1*a*, Table 2*a*; MNI (Montreal Neurological Institute) coordinates of peak in extrastriate visual cortex (x, y, z) = −34, −80, 10, $z = 3.62$, $p = 0.034$, 325 voxels; MNI coordinates of peak in striate cortex (x, y, z) = 20, −88, 10, $z = 3.31$, $p = 0.034$, 345 voxels; see online Supplementary Fig. S3 for the effects of global signal regression]. No other clusters met whole-brain-corrected level of significance.

Next, the magnitude of amygdala connectivity of youth who exhibited persistently high levels of subclinical delusional thinking (the PH group, $n = 22$) was compared to those with persistently low levels (the PL group, $n = 17$). Compared to the PL group, the PH group exhibited significantly elevated amygdala connectivity with visual cortex (Fig. 1*b*, Table 2*b*; MNI coordinates of peak in striate cortex (x, y, z) = 16, −90, 4, $z = 4.20$, $p < 0.001$, 2390 voxels). No other clusters met whole-brain-corrected level of significance.

Regression analyses

A whole-brain regression in the full sample ($n = 122$) was conducted to determine whether a continuous relationship was present between amygdala-visual cortex connectivity and (1) levels of delusional beliefs (PDI total score) and/or (2) the degree of distress associated with these beliefs (PDI distress score, corrected for the total number of beliefs). Both outcome measures (total number of beliefs and associated distress) were significantly positively correlated with the strength of functional connectivity between the amygdala and a widely distributed area of visual cortex, including both striate and extrastriate areas (Fig. 2, Table 2*c* and *d*).

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Table 1. Characteristics of the High (H) and Low (L), and Persistently High (PH) and Persistently Low (PL), groups

	H ($n = 43$)	L ($n = 44$)	*p*-value	PH ($n = 22$)	PL ($n = 17$)	*p*-value
Gender	28 F, 15 M	33 F, 11 M	0.355	14 F, 8 M	14 F, 3 M	0.288
Age (years)	19.40 ± 1.37	19.66 ± 1.31	0.361	19.23 ± 1.07	19.71 ± 1.45	0.242
Relative head motion (mm)	0.05 ± 0.02	0.05 ± 0.02	0.451	0.04 ± 0.01	0.04 ± 0.02	0.957
PDI total score	10.12 ± 2.13	2.55 ± 1.36	<0.001*	8.27 ± 2.33	2.82 ± 1.29	<0.001*
PDI distress score	2.83 ± 0.68	1.92 ± 1.10	<0.001*	2.50 ± 0.84	2.11 ± 1.14	0.240
BDI score	12.02 ± 7.53	7.00 ± 5.73	<0.001*	10.48 ± 9.08	6.29 ± 5.98	0.111
STAI score	47.32 ± 9.83	39.32 ± 12.15	<0.001*	44.86 ± 8.93	38.38 ± 11.47	0.057
LSHS-R score	23.45 ± 12.33	7.60 ± 5.03	0.002*	16.41 ± 10.03	6.50 ± 4.93	0.008*
Cannabis use (past 30 days)	1.25 ± 2.94	2.56 ± 4.36	0.160	4.09 ± 8.83	2.00 ± 4.58	0.494

As expected, the H and L groups showed significant differences ($p < 0.05$) in measures of total number of delusional beliefs and the degree of distress associated with their delusional beliefs, as well as in levels of symptoms of depression, anxiety, and hallucinatory experiences, with significantly higher values in the H compared to the L group. The PH and PL groups showed significant differences ($p < 0.05$) in measures of total number of delusional beliefs and levels of hallucinatory experiences, but not in other measures. The findings of the analyses remained significant when controlling for these between-group differences in depression, anxiety, and hallucinatory experiences (see the text). There were no significant differences in gender, mean age, relative head motion, cannabis use in the past month, race, or ethnicity between the comparison groups. Race and ethnicity for each group were as follows: for the H group, 39.5% Caucasian, 34.9% African-American, 4.7% Asian, 11.6% Other, and 16.3% Hispanic; for the L group, 54.5% Caucasian, 25.0% African-American, 9.1% Asian, 4.6% Other, and 9.1% Hispanic; for the PH group, 36.4% Caucasian, 50.0% African-American, 0.0% Asian, 9.1% Other, and 4.6% Hispanic; and for the PL group, 52.9% Caucasian, 29.4% African-American, 5.9% Asian, 0.0% Other, and 11.8% Hispanic. F, female, M, male, PDI, Peters *et al.* Delusions Inventory; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory (state); LSHS-R, Launay–Slade Hallucinations Scale-Revised;
*Significant between-group difference (independent *t* test, $p < 0.05$).

Specificity of findings

In the full sample ($n = 122$), levels of symptoms of depression, anxiety, and hallucinatory experiences were found to be significantly correlated with levels of subclinical delusional thinking ($r = 0.38$, $p < 0.001$; $r = 0.31$, $p = 0.001$; $r = 0.64$, $p < 0.001$, respectively), as expected (Cella *et al.*, 2008; Varghese *et al.*, 2008). Given these relationships, we repeated the categorical analyses above with levels of depression, anxiety, and hallucinatory experiences included as covariates; the findings remained significant [$p < 0.05$, FDR whole-brain-corrected; MNI coordinates of peak of the H *v.* L group comparison (x, y, z) = −24, −84, −2, $z = 4.69$, $p = 0.020$, 1523 voxels; MNI coordinates of peak of the PH *v.* PL group comparison (x, y, z) = −28, −78, 2, $z = 5.83$, $p = 0.003$, 1756 voxels]. Additionally, findings in all primary comparisons remained significant when excluding those currently taking psychotropic medication ($p < 0.01$, FDR whole-brain-corrected). Moreover, lowering the significance thresholds used in the analyses did not alter the pattern of findings, which remained primarily limited to visual cortex (online Supplementary Fig. S4).

Next, to explore whether the origins of the amygdala-visual cortex pathway affected by delusional thinking could be further localized within the amygdala, we created a 3-mm spherical seed centered on the strongest peak in the primary analyses [MNI (x, y, z) = 16, −90, 4; see Table 2] and repeated the categorical analyses above using this visual cortex seed. Significant differences in visual cortex-amygdala connectivity were observed in both analyses ($p < 0.01$, FDR whole-brain-corrected), with significant clusters found within the basolateral nucleus of the amygdala (online Supplementary Fig. S5), consistent with the known topography of the projection of the amygdala to the visual cortex in non-human primates (Amaral *et al.*, 2003).

Lastly, in light of the close anatomical proximity and functional relationship between the amygdala and hippocampus, we repeated the two categorical analyses using a bilateral hippocampus (rather than amygdala) seed. The analyses using the hippocampal ROI revealed a similar but weaker pattern of results compared to those observed using the amygdala ROI, suggesting some specificity of our results to the amygdala (online Supplementary Fig. S6).

Persecutory beliefs

In the full sample ($n = 122$), the subjects who endorsed persecutory beliefs ($n = 28$) had a significantly greater overall number of delusional beliefs ($t_{(120)} = 5.00$, $p < 0.001$) and associated distress ($t_{(114)} = 2.65$, $p = 0.009$), and also showed a higher rate of persistence of high levels of delusional beliefs [χ^2 (1, $n = 56$) = 10.06, $p = 0.002$], compared to those without persecutory beliefs ($n = 94$). Thus, based on these data and our *a priori* hypothesis, additional analyses were conducted to determine the specific contribution of persecutory ideation to the above findings.

First, an anatomical ROI analysis was conducted. Amygdala-V1 connectivity values were extracted for all subjects and mean amygdala-V1 connectivity values were compared among the following groups: (1) members of the high group with persecutory beliefs (H + P, $n = 19$), (2) members of the high group without persecutory beliefs (H − P, $n = 24$), and (3) the members of the low group (L, $n = 43$; excluding one L subject who endorsed persecutory beliefs). These groups were well-matched on all demographic and symptom variables (see online Supplementary Table S2), with the exception of a small but significant difference in age between the H + P and H − P groups; however, all reported effects (see below) remained significant after controlling for age.

A one-way ANOVA revealed a significant effect ($F_{(2,83)} = 3.80$, $p = 0.026$) that arose from greater amygdala-V1 connectivity of the H + P group compared to both the H − P ($p = 0.043$) and L ($p = 0.006$) groups, with no difference observed between the H − P and L groups ($p = 0.760$) (Fig. 3*a*). Similar findings were observed for the PH + P, PH − P, and PL groups in the cohort with 1-year follow-up data ($F_{(2,36)} = 7.42$, $p = 0.002$; Fig. 3*b*).

To determine the relative contribution of the number, associated distress, and persecutory nature of participants' delusional beliefs to the above findings, a multiple regression analysis was then conducted. A statistically significant effect of persecutory

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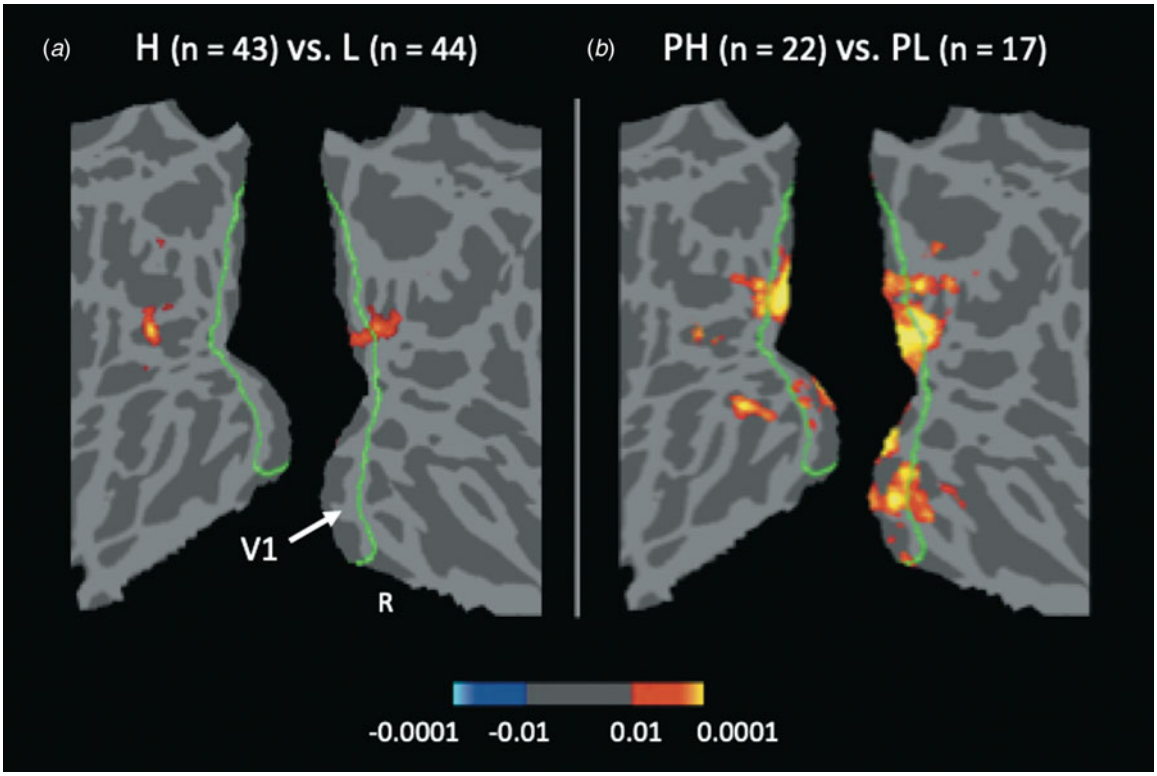


Fig. 1. Amygdala-visual cortex connectivity is elevated in youth with high levels of delusional beliefs. Flattened voxel-wise maps of parietal and occipital cortex showing clusters that met FDR whole-brain correction in the comparisons of amygdala connectivity of the H *v.* L groups (*a*); and PH *v.* PL groups (*b*). The border of V1 is shown in green. The *p*-values of the clusters showing significant between-group differences in these maps [H > L in (*a*); PH > PL in (*b*); the reverse contrasts, L > H and PL > PH, showed no significant differences] are represented by warm colors. All significant clusters are shown.

thinking on amygdala-V1 connectivity ($\beta = 0.29$, $p = 0.032$, $n = 86$) was found; no other factors were significant in the model. An analysis of the sample with 1-year follow-up data yielded similar results; persecutory thinking was again the only significant factor ($\beta = 0.40$, $p = 0.027$, $n = 39$). Lastly, to explore whether the findings were specific to persecutory thinking, these two regression analyses were repeated including two other PDI factors [religiosity and thought disturbances (Peters *et al.*, 1999; Peters *et al.*, 2004)] as additional regressors; persecutory thinking remained the only significant predictor ($p = 0.034$ and $p = 0.025$, respectively).

Discussion

Summary of main findings

In this study, young adults with high levels of delusional beliefs showed greater functional connectivity between the amygdala and visual cortex than young adults with low levels of delusional beliefs. This pattern of results was even stronger in those with delusional beliefs that persisted over the course of 1 year. Subsequent analyses revealed that this effect was primarily driven by participants who endorsed persecutory beliefs, suggesting that excessive functional coupling between the amygdala and visual cortex may represent a vulnerability marker or a consequence of persecutory thinking.

Relationship to prior work

Prior studies of amygdala responses or connectivity in psychosis have demonstrated somewhat inconsistent findings; some of these discrepancies may be attributable to differences in experimental paradigms, stage of illness effects, or treatment effects. For example, studies have detected significant elevations (Kosaka *et al.*, 2002; Holt *et al.*, 2006), no differences (Anticevic *et al.*, 2011), or significant reductions (Schneider *et al.*, 1998; Gur *et al.*, 2002; Anticevic *et al.*, 2012) in task-elicited responses of the amygdala in schizophrenia patients compared to demographically-matched healthy controls. Reductions in amygdala responses have also been reported in paranoid compared to non-paranoid schizophrenia patients (Williams *et al.*, 2004; Russell *et al.*, 2007). However, studies conducted in first-degree relatives of schizophrenia patients (Rasetti *et al.*, 2009; Cao *et al.*, 2016) have suggested that the reported reductions in amygdala responses in schizophrenia may represent a consequence of antipsychotic treatment. Consistent with this interpretation is a recent finding of significantly elevated amygdala responses to negatively-valenced faces in unmedicated, non-help-seeking adolescents with subclinical psychotic symptoms, in comparison to typical adolescents (Wolf *et al.*, 2015). Reports of increased task-elicited amygdala responses in schizophrenia (Kosaka *et al.*, 2002; Holt *et al.*, 2006) and increased baseline amygdala cerebral blood flow in schizophrenia patients compared to healthy controls (Taylor *et al.*, 2005) and in paranoid compared to non-paranoid schizophrenia patients (Pinkham *et al.*, 2015) also suggest that the amygdala is overactive during psychotic states. In addition, two resting-state functional connectivity studies of patients with schizophrenia have observed overconnectivity of the amygdala with downstream projection sites, such as the brainstem (Anticevic *et al.*, 2014) and visual cortex (Ford *et al.*, 2015). Consistent with these prior findings and the continuum model

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Table 2. Results of between-group comparisons of amygdala connectivity and regressions of amygdala connectivity *v.* total number of delusional beliefs and associated distress

Analysis	Location of peak	MNI (*x*, *y*, *z*)	*z*	*p*-value	Size (vox)	Distribution of effects
(*a*) Amygdala connectivity in youth with high (H) *v.* low (L) levels of subclinical delusional beliefs						
H > L	Extrastriate cortex	−34, −80, 10	3.62	0.034	325	7.1% in striate cortex (V1), 49.5% in extrastriate cortex
	Striate cortex (V1)	20, −88, 10	3.31	0.034	345	29.0% in striate cortex (V1), 0.9% in extrastriate cortex
(*b*) Amygdala connectivity in youth with PH *v.* PL levels of subclinical delusional beliefs						
PH > PL	Striate cortex (V1)	16, −90, 4	4.20	<0.001	2390	51.0% in striate cortex (V1), 34.7% in extrastriate cortex
(*c*) Amygdala connectivity *v.* PDI total score						
Positive correlations	Temporal occipital fusiform cortex	36, −50, −10	3.84	0.001	681	0.1% in striate cortex (V1), 49.2% in extrastriate cortex
(*d*) Amygdala connectivity *v.* PDI distress score						
Positive correlations	Precuneus cortex	−8, −78, 48	3.95	0.006	445	47.6% in precuneus cortex, 48.1% in lateral occipital cortex
	Extrastriate cortex	10, −54, 2	3.60	<0.001	795	81.3% in striate cortex, 18.2% in extrastriate cortex
Negative correlations	Putamen	26, −8, 8	4.00	<0.001	1009	38.8% in putamen, 5.1% in pallidum
	Putamen	−32, −8, 2	3.69	<0.001	815	55.7% in putamen, 5.2% in pallidum

Peaks that survived FDR whole-brain correction. (*a*) and (*b*) describe findings of the comparisons between the H and L groups, and the PH and the PL groups, respectively. There were no areas that showed greater connectivity in the L compared to the H group, or the PL compared to the PH group. (*c*) and (*d*) describe the dimensional relationships found between amygdala connectivity and: (1) the number of subclinical delusions (PDI total score) and (2) the degree of associated distress (PDI distress score), respectively. For (*c*), there were no significant negative correlations. The proportion of the significant cluster that was located in striate *v.* extrastriate cortex and other regions is listed in the column furthest to the right ('Distribution of effects').

of psychosis, the current study shows that amygdala overconnectivity is present in non-help-seeking youth with subthreshold persecutory beliefs.

Potential functional implications of findings

The increase in connectivity observed in the delusional compared to the non-delusional youth in the current study resulted from a statistically significant difference between the magnitude of negative correlations between the amygdala and visual cortex in each group. Although the source of negative correlations (or 'anti-correlations') may vary across studies (Buckner *et al.*, 2008; Fox *et al.*, 2009; Murphy *et al.*, 2009), here the negative correlations in our data were attributable to the regression of the global mean during preprocessing. Thus, these results suggest that resting blood oxygenation level dependent activity of the amygdala and visual cortex is *weakly positively* correlated in humans, which is consistent with the established presence of excitatory projections from the amygdala to the visual cortex (Amaral *et al.*, 2003). Work in non-human primates has shown that fibers originating primarily in the basal nucleus of the amygdala project to all levels of the ventral visual stream [the object processing, or 'what,' pathway of the visual system (Ungerleider and Haxby, 1994)], terminating in synaptic connections (Tigges *et al.*, 1983; Iwai and Yukie, 1987; Amaral *et al.*, 2003). Referred to as the 'temporal-occipital amygdalo-cortical pathway,' these projections are distributed continuously across both striate and extrastriate cortices in a primarily unidirectional, nonreciprocal manner, with a point-to-point, non-diffuse organization (Freese and Amaral, 2005). For example, projections from dorsal portions of the basal nucleus of the amygdala terminate in the posterior visual cortical areas, i.e. striate cortex/V1, whereas neurons in the ventral portion of the basal nucleus of the amygdala terminate in more anterior visual cortical areas (Amaral *et al.*, 2003). Our data suggest that the dorsal basal nucleus-V1 pathway is altered in youth with elevated delusional thinking. Follow-up studies conducted

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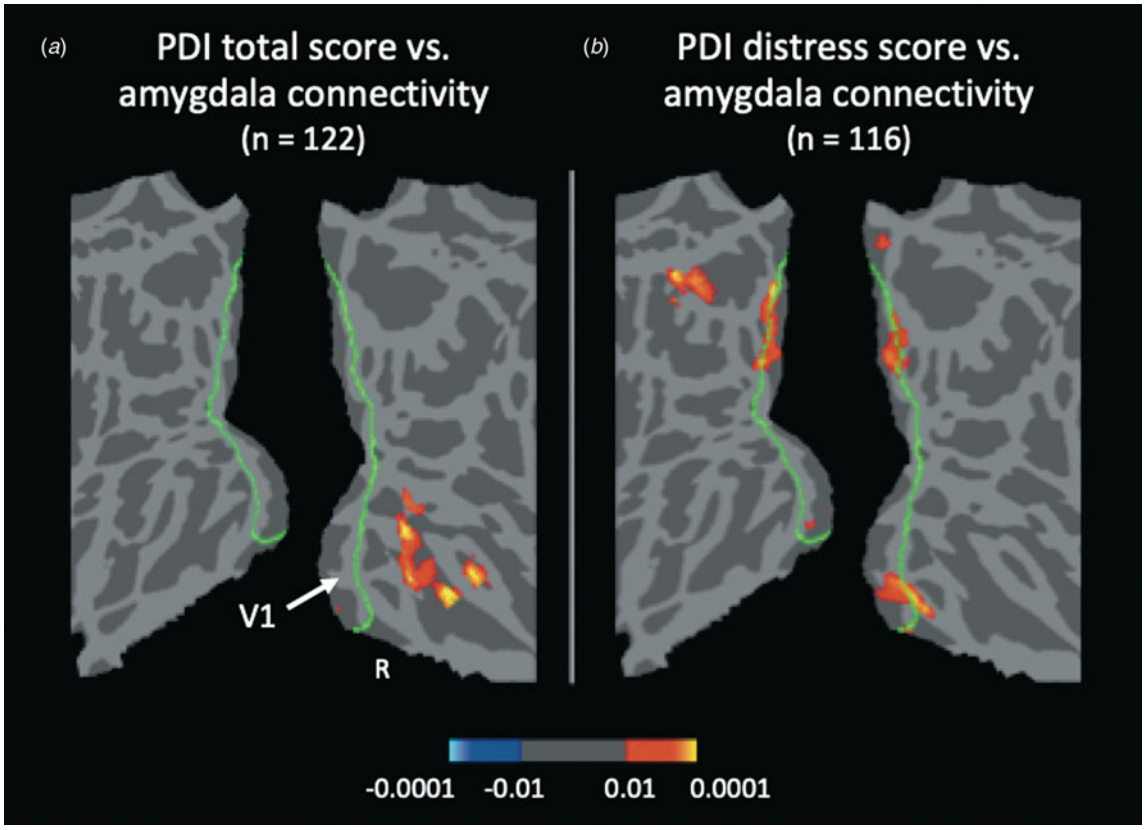


Fig. 2. The number of delusional beliefs and degree of associated distress correlate with amygdala-visual cortex connectivity. Flattened voxel-wise maps of parietal and occipital cortex showing clusters that met FDR whole-brain correction following whole-brain regression of amygdala connectivity with PDI total score (*a*) or PDI distress score (*b*) as regressors. These maps reveal similar patterns of correlations between these measures and amygdala-visual cortex connectivity [in (*a*), MNI coordinates of peak in temporal occipital fusiform cortex (*x*, *y*, *z*) = 36, −50, −10, *z* = 3.84, *p* = 0.001, 681 voxels; in (*b*), MNI coordinates of peak in extrastriate cortex (*x*, *y*, *z*) = 10, −54, 2, *z* = 3.60, *p* < 0.001, 795 voxels]. The border of V1 is shown in green. The *p*-values of the clusters are represented by warm (positive correlations) and cool (negative correlations) colors. Two clusters (negative correlations) in (*b*) are not shown; see Table 2*d* for details.

using high field strength MRI in independent samples will be necessary to confirm these observations.

Functional neuroimaging work in humans has suggested that these feedback-like projections to visual cortex from the amygdala modulate lower-level visual processing. One study showed that both healthy controls and patients with hippocampal lesions (but an intact amygdala) exhibit greater activation of visual cortex in response to fearful faces compared to neutral faces, whereas patients with amygdala lesions fail to show this response (Vuilleumier *et al.*, 2004). These findings are consistent with single-unit recordings conducted in non-human primates that suggest that top-down processes bias early perception (Lee, 2002). Therefore, projections from the amygdala to the primary visual cortex may influence sensory processing, particularly in the context of environmental threats.

Abnormal sensory-limbic coupling in psychosis

Prior evidence for increased amygdala-visual cortex connectivity in schizophrenia patients with visual hallucinations suggests that coupling between perceptual and affective processing is altered in psychotic illness (Ford *et al.*, 2015). These findings are generally consistent with evidence for abnormalities in early sensory processing in schizophrenia (Javitt, 2009), as well as with the 'aberrant salience' model of psychosis (Kapur, 2003). This model suggests that perceptual processing is disrupted by changes in dopaminergic neurotransmission during pre-illness or subthreshold psychotic states, leading to misattributions of motivational salience to neutral or irrelevant stimuli in the environment. Abnormal function of the amygdala-visual cortical pathway in psychosis may contribute to this putative cycle of misattribution of threat to incoming sensory signals (Das *et al.*, 2007). It has been proposed that delusional thinking may represent a consequence of these misattributions, reflecting a compensatory effort to make sense of inappropriately labeled perceptual experiences (Maher, 2005).

Limitations and future directions

In this study, we enrolled a large sample of young adults, the majority (90.2%) of whom were medication-naïve, yet displayed a wide range of subthreshold psychotic symptoms. Although all subjects initially underwent a brief, in-person assessment by a clinician, we relied primarily on self-report measures, in order to reduce subject burden and facilitate recruitment. Also, we did not formally assess whether our participants had, or later developed, clinical psychosis. However, the unmedicated status of the majority of our subjects and their concurrent enrollment in college suggest that the symptoms endorsed by this cohort were generally not severe enough to merit clinical intervention or cause substantial functional impairment and were likely predominantly subthreshold in nature. An additional limitation was that

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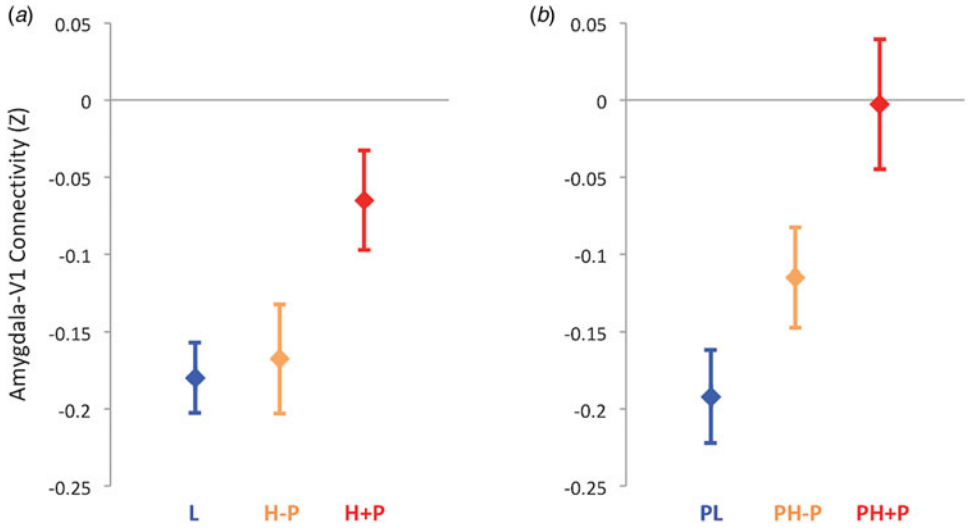


Fig. 3. Amygdala-V1 connectivity is elevated in individuals with, compared to those without, persecutory beliefs. In an ROI analysis, average amygdala-V1 connectivity values (*z* scores) were extracted. The mean values are plotted here for the following groups: members of the H group with persecutory beliefs (H + P, $n = 19$), the H group without persecutory beliefs (H − P, $n = 24$), and the L group (L, $n = 43$) in (*a*); and members of the PH group with persecutory beliefs (PH + P, $n = 10$), the PH group without persecutory beliefs (PH − P, $n = 12$), and the PL group (PL, $n = 17$) in (*b*). In (*a*), post-hoc *t* tests showed that amygdala-V1 connectivity of the H + P group was significantly greater in magnitude than that of both the H − P and L groups ($p = 0.043$ and $p = 0.006$, respectively), while there was no significant difference between the H − P and L groups ($p = 0.760$) in amygdala-V1 connectivity. Similarly, the PH + P group showed significantly greater amygdala-V1 connectivity compared to both the PH − P and PL groups ($p = 0.045$ and $p = 0.001$, respectively), while the difference between the PH − P and PL groups did not reach significance ($p = 0.099$). Note that the majority of the extracted *z*-scores are negative in value because of the effects of the global mean regression (see online Supplementary Fig. S3). Error bars represent standard errors of the mean.

persecutory ideation was measured by responses to only two items on a self-report scale; although paranoia is somewhat categorical in nature, future investigations could also assess paranoia in a dimensional manner.

Lastly, it is unclear whether the identified changes in amygdala-visual cortex connectivity represent a vulnerability to or a consequence (which could be either maladaptive or compensatory) of persecutory ideation. Studies that perturb this neural system may shed further light on the role of this pathway in persecutory thinking. For example, pharmacological interventions with compounds such as psilocybin that are known to inhibit threat-induced increases in amygdala-striate cortex connectivity (Kraehenmann *et al.*, 2016), or psychosocial interventions that decrease threat attributions, could be tested for potential effects on this circuitry and paranoia.

Conclusions

The demonstration of a robust association, using both categorical and dimensional analyses between a quantitative imaging phenotype (amygdala-visual cortex functional connectivity) and a symptom (delusional beliefs and persecutory ideation) that has been linked to increased risk for clinical psychosis (Cannon *et al.*, 2016) and functional disability (Yung *et al.*, 2009; Pinkham *et al.*, 2016) may represent a novel biomarker of psychosis. Following further validation, such a marker could serve as a target for interventions that could slow or interrupt progression of psychosis-related changes in this pathway, or be used to identify individuals who merit further monitoring.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718004221.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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