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Correlation Between Levels of Delusional Beliefs and Perfusion of the Hippocampus and an Associated Network in a Non–Help-Seeking Population

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Abstract

BACKGROUND—Delusions are a defining and common symptom of psychotic disorders. Recent evidence suggests that subclinical and clinical delusions may represent distinct stages on a phenomenological and biological continuum. However, few studies have tested whether subclinical psychotic experiences are associated with neural changes that are similar to those observed in clinical psychosis. For example, it is unclear if overactivity of the hippocampus, a replicated finding of neuroimaging studies of schizophrenia, is also present in individuals with subclinical psychotic symptoms.

METHODS—To investigate this question, structural and pulsed arterial spin labeling scans were collected in 77 adult participants with no psychiatric history. An anatomical region of interest approach was used to extract resting perfusion of the hippocampus, and 15 other regions, from each individual. A self-report measure of delusional ideation was collected on the day of scanning.

RESULTS—The level of delusional thinking (number of beliefs [$r = .27$, $p = .02$]), as well as the associated level of distress ($r = .29$, $p = .02$), was significantly correlated with hippocampal perfusion (averaged over right and left hemispheres). The correlations remained significant after controlling for age, hippocampal volume, symptoms of depression and anxiety, and image signal-to-noise ratio, and they were confirmed in a voxelwise regression analysis. The same association was observed in the thalamus and parahippocampal, lateral temporal, and cingulate cortices.

CONCLUSIONS—Similar to patients with schizophrenia, non–help-seeking individuals show elevated perfusion of a network of limbic regions in association with delusional beliefs.

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DISCLOSURES

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Keywords

Arterial spin labeling; Delusion; fMRI; Hippocampus; Perfusion; Psychosis

Abnormally elevated resting neural activity (as reflected by blood flow) of the hippocampus or medial temporal lobe has been demonstrated repeatedly in schizophrenia (1–3) using a range of methods (1,4–8). Some of these previous studies have linked this finding to the presence or severity of positive symptoms (6,9,10) or delusions specifically (7). Despite the repeated replication of this finding, it is unclear whether hippocampal overactivity is linked to the presence of psychotic symptoms (independent of diagnosis) or to the illness of schizophrenia. Although there is some evidence that elevations in hippocampal perfusion are present during the prodromal period preceding the onset of frank psychotic illness (7,11), it is unknown whether such changes are also associated with even milder, subthreshold forms of psychosis.

Recently there has been increased interest in these types of subthreshold psychotic phenomena, sometimes referred to as psychotic experiences (PEs) (12–14), because they are associated with some impairment in cognition and daily functioning (12,15–18) and a small but significant increase in risk for developing psychotic disorders (19–22). PEs have reported prevalence rates ranging from 5% to 35% (19,23–26), depending on the population studied and the instrument used to measure them. Although individuals with PEs typically do not experience distress or seek help for their symptoms, some evidence suggests that there may be biological mechanisms that are common across PEs and clinical psychotic symptoms. For example, epidemiological studies have demonstrated that PEs and clinical psychosis share some environmental risk factors, such as cannabis use, urban living, and adverse events during prenatal development (13,27,28). In addition, findings of elevated PE levels in relatives of schizophrenia patients (29,30) further support the possibility that, although most individuals with PEs do not develop frank psychosis, they may carry milder forms of the neurobiological abnormalities associated with psychosis. Consistent with this model, recent studies conducted in adolescents with PEs have detected changes in the brain in this population that are similar to those observed in psychotic illness (31,32), including smaller hippocampal volumes (33). However, although overactivity of the hippocampus has been observed in schizophrenia and linked to changes in glutamate neurotransmission in animal models (11), consistent with evidence for abnormalities in glutamatergic neurotransmission in schizophrenia (34,35), it is not yet known whether similar changes in hippocampal function occur in individuals with PEs.

To examine this question, in the current study we measured hippocampal perfusion using pulsed arterial spin labeling (PASL) in healthy people who varied with respect to the quantity and intensity of self-reported subclinical delusional beliefs, the most common type of PE (23,36). Delusional beliefs were measured using the Peters *et al.* Delusions Inventory (PDI), which has been used previously to measure delusional beliefs in both nonclinical and clinical populations (37–39). In this study, we focused on delusional beliefs, rather than on other PEs, because of evidence for a specific relationship between overactivity of the hippocampus and delusions (5). Because the hippocampus plays a central role in retrieving

contextual information about incoming sensory input (40–42), disinhibition of the hippocampus may interfere with the retrieval of contextual information, leading to misinterpretations of the personal relevance of incoming stimuli and, in some cases, to the formation of delusional ideas. In addition, delusion formation may be facilitated by disruption of other hippocampal-dependent processes that support accurate memory retrieval, such as pattern separation and completion (43).

PASL, the method used here to measure resting neural activity, has been validated as a reliable measure of regional cerebral blood flow at rest (44) and is particularly useful for the quantitative measurement of baseline “resting” neural activity, since it is comparatively free of the slow drift associated with blood oxygen level–dependent imaging (44,45). In the current study, we used PASL and individually based anatomical segmentations of the hippocampus to conduct a hypothesis-driven, region of interest (ROI) analysis, testing whether hippocampal perfusion is correlated with levels of subclinical delusional thinking. In addition, because evidence from animal and computational models of psychosis, as well as human imaging studies, suggest that a network of limbic regions [including the hippocampus, medial prefrontal cortex/cingulate gyrus, thalamus, and striatum (46–48)] and regions that are adjacent and densely connected to the hippocampus in the temporal lobe [such as the amygdala (49), parahippocampal gyrus (50–53), and lateral temporal cortex (54–56)] may represent important nodes of a larger circuitry underlying the pathophysiology of psychosis, we also tested for associations between delusional beliefs and perfusion of these regions in a secondary analysis.

METHODS AND MATERIALS

Participants

Healthy subjects were recruited via online advertisements for a project focused on understanding the neurobiological basis of delusions and associated affect or fear processing abnormalities. These subjects participated in several task-based functional magnetic resonance imaging (fMRI) paradigms (57–59); however, the PASL sequence used in all subjects was identical. Potential subjects were excluded if they had any contraindications for MRI scanning (e.g., metal implants, claustrophobia), a history of a neurologic disorder or head trauma with neurologic sequelae, or a history of a psychiatric disorder (including a lifetime history of substance dependence, or a history of substance abuse within the previous 3 months) as determined by the Structured Clinical Interview for DSM-IV. No subject was using any drugs of abuse at the time of scanning, per self-report. Also, potential participants were excluded if they had ever been treated with a psychotropic medication.

Written informed consent was obtained from all subjects before enrollment, in accordance with the guidelines of the Partners HealthCare Institutional Review Board. Data from 9 subjects were excluded based on quality control criteria (see below). Thus, the final cohort included in the analyses was composed of 48 males and 29 females ($N = 77$; mean age [$\pm$ SD] 31.08 ± 10.04 years, age range 19–60 years). A portion of these data ($n = 30$) was included in an unrelated, prior analysis (60).

Assessments

Self-report measures of delusional ideation, depression, and anxiety were collected from all subjects on the day of the scanning session using the 21-item version of the PDI (38), the Beck Depression Inventory (61), and the Spielberger State and Trait Anxiety Inventory (62).

The 21 questions of the PDI (e.g., “Do you ever feel as if you are a robot or zombie without a will of your own?”; “Do you ever feel as if there is a conspiracy against you?”) each capture different components of delusional thinking, such as suspiciousness/paranoid ideation/feelings of persecution, religiosity, grandiosity, paranormal beliefs, thought disturbances, depersonalization, thought broadcasting, and ideas of reference and influence (37). The subject answers “yes” or “no” to each question. In addition, if the subject endorses a belief with a “yes” answer, he or she is then asked to rate the level of distress, preoccupation, and conviction associated with that belief on a five-point Likert scale. The total number of beliefs endorsed comprises the total PDI score. Scores on the distress, preoccupation, and conviction subscales of the PDI are calculated by summing those respective ratings over all of the questions.

We used the total score on the PDI as our main outcome measure, as in previous studies (63–71). Thus, in our primary analysis, we tested the prediction that the perfusion of the hippocampus is positively correlated with the number of delusional beliefs. In addition, because the degree of distress associated with delusional beliefs has been linked to clinical severity (69,72,73), in a secondary analysis we tested for associations between hippocampal perfusion and scores on the distress subscale of the PDI (as well as the other two subscales). We normalized the subscale scores by correcting for the number of delusional beliefs endorsed [i.e., dividing the individual’s score on each subscale by the total number of endorsed beliefs (74,75)]. For the mean scores on these measures and the relationships among them, see Supplemental Tables S1 and S2.

Image Acquisition

Imaging data were acquired using a 3T Siemens TIM Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) using either a 12-channel head coil (12-ch coil; $n = 41$) or a 32-channel head coil (32-ch coil; $n = 36$). One or two conventional high-resolution three-dimensional structural T1 magnetization prepared rapid acquisition gradient-echo scans and one 6:02 PASL scan were collected (see the Supplement for the scan parameters). For the PASL scan, the PICORE-Q2TIPS MRI labeling method (76) was used; “Tag” images were acquired by labeling a thick inversion slab (110 mm) proximal to the imaging slices (gap 21.2 mm). Fifty-seven “control” images were also acquired, interleaved with 57 Tag images, by applying an off-resonance inversion pulse without any spatial encoding gradient.

At the beginning of each PASL scan, an M_0 scan (i.e., the longitudinal magnetization of fully relaxed tissue) was acquired for quantification purposes (77). A delay time of 1 second was inserted between the end of labeling pulses and image acquisition to reduce transit-related effects. During the PASL scan, subjects were instructed to keep as still as possible and to keep their eyes open and blink normally.

PASL fMRI Analysis and Quality Control

Analyses of the PASL data were performed using FMRIB's Software Library (www.fmrib.ox.ac.uk/fsl) (78) and FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>) tools. The Tag, Control, and M_0 scans were first motion-corrected using MCFLIRT (79) and registered to the high-resolution anatomical images using FreeSurfer's bbgregister tool (80). Image and segmentation quality of the anatomical and PASL scans were assessed by visual inspection in three planes.

Scans were excluded if there was >2 mm of absolute head motion during the scan (one 12-ch coil subject was excluded), registration was poor (no subject was excluded), or the signal-to-noise ratio was below 1.5 SDs from the group average (for the 12-ch and 32-ch coil datasets, 5 and 3 subjects were excluded, respectively).

Tag and control scans were surround subtracted to generate perfusion-weighted images (81). All of the perfusion-weighted maps were then averaged and scaled by a factor proportional to the M_0 scan, to obtain perfusion maps of absolute perfusion values (mL/100 g of tissue/min) (77). Group-level analyses were conducted. Smoothing with a three-dimensional isotropic, 7.02-mm full width half maximum Gaussian kernel (2*voxel size) was performed on individual subject perfusion maps before the group-level regression.

Regions of Interest

An automated segmentation method (<http://surfer.nmr.mgh.harvard.edu>) was used to generate a left and right hippocampal ROI from each T1 scan for each subject (Supplemental Figure S1).

Using these individual hippocampal ROIs, regional cerebral blood flow (perfusion) levels of the hippocampus were extracted from each subject. Also, perfusion was extracted from 15 additional ROIs (generated automatically during the FreeSurfer segmentation procedure) for a secondary analysis. In addition, a secondary (uncorrected) voxelwise analysis using the total PDI score as a regressor was conducted to localize any effects observed in the primary, hippocampal ROI analysis (see Supplement for additional details).

Statistical Analyses

We tested our main prediction of a significant correlation between levels of delusional thinking and hippocampal perfusion using Spearman's rho ($\alpha = .05$). Because we did not have a prediction regarding laterality of this effect, we combined the perfusion data from the left and right hippocampus to afford additional power. Also, we conducted follow-up analyses in which we controlled for potential confounds, such as head coil, age, gender, hippocampal volume, levels of depressive and anxiety symptoms, and signal-to-noise ratio using both partial correlations and linear regression.

RESULTS

Symptoms

Total PDI scores for the sample ranged from 0 to 13, with a mean of 2.33 (SD 2.90) (means of all symptom scales are shown in Supplemental Table S1). Levels of delusional beliefs did not correlate with state anxiety levels ($r = .15$, $p = .20$) but showed weak associations with trait anxiety ($r = .23$, $p = .05$) and depressive symptoms ($r = .21$, $p = .06$), similar to previous studies (59,82).

Primary ROI Analysis

Confirming our prediction, hippocampal perfusion (average of left and right hippocampi, as well as the left and right separately) (Figure 1) was significantly correlated with PDI total score (for average hippocampal perfusion: $r = .27$, $p = .02$). In contrast, there were no correlations between hippocampal perfusion and levels of depressive ($r = .01$, $p = .98$) or anxiety ($r = .04$, $p = .75$) symptoms. Also, when controlling for age, hippocampal volume, depression, anxiety levels, and signal-to-noise ratio, the association between hippocampal perfusion and total PDI score remained significant ($r = .27$, $p = .02$). A linear regression model showed that head coil type had no effect on hippocampal perfusion ($p = .13$), and there were no significant differences in hippocampal perfusion or symptom levels (p values $> .16$) between the subjects scanned with the two coil types.

We next examined whether hippocampal perfusion was predicted by dimensions of delusional thinking as reflected by the PDI subscale scores. Average hippocampal perfusion (as well as perfusion of the left hippocampus alone) was significantly correlated with the levels of distress associated with delusional beliefs ($r = .29$, $p = .02$) but was not correlated with levels of conviction ($r = .20$, $p = .09$), or preoccupation ($r = .16$, $p = .18$) (see Figure 2 and Table 1).

Confirmatory Voxelwise Regression

Consistent with the results of the ROI analysis, we found evidence, using voxelwise regression, for significant correlations between total PDI score and perfusion of the hippocampus bilaterally (Talairach coordinates $[x, y, z]$ of peak with the left hippocampus = $-22, -31, -10$, $p = .004$; peak with the right hippocampus = $32, -29, -4$, $p = .01$) (Figure 3).

Regions With Hippocampal Connections

In a secondary ROI analysis, we tested for associations between delusional thinking and perfusion of 13 brain regions with close connections to the hippocampus, some of which have been previously linked to delusions or psychosis (83–87), including the medial prefrontal cortex/cingulate gyrus, thalamus, and striatum and regions of the medial and lateral temporal lobe (the amygdala, parahippocampal gyrus, and lateral temporal cortex). This analysis revealed significant correlations between total PDI score and perfusion of the thalamus and caudal anterior and posterior cingulate cortices, as well as the middle and superior temporal cortices and parahippocampal gyrus (Table 2 and Supplemental Table S3). In contrast, the amygdala, the regions of the striatum (the caudate nucleus, putamen, and

nucleus accumbens), and two control regions (the fusiform gyrus and lateral occipital cortex) failed to show this association.

DISCUSSION

We tested the hypothesis that subclinical delusions are associated with elevated perfusion of the hippocampus. This hypothesis was based on evidence for elevations in activity of the hippocampus in schizophrenia patients (7,11,88) and in individuals in the clinical high-risk state (7,89), which has been linked to the severity of psychotic symptoms (6) or specifically delusions (7). We confirmed this hypothesis using an anatomical ROI analysis; the number of delusion-like beliefs and the level of distress associated with them were each positively correlated with perfusion of the hippocampus in a non-help-seeking, healthy cohort. This relationship was not accounted for by other subthreshold symptoms (depression or anxiety) or other potential confounds. In addition, secondary analyses revealed that in addition to the hippocampus, regions with strong anatomical connections with the hippocampus, such as the thalamus, caudal anterior cingulate and posterior cingulate cortices, parahippocampal gyrus, and lateral temporal cortex, showed a similar association, whereas the amygdala, striatum, and two control regions in the visual cortex did not.

Although inferences regarding the sequence or direction of effects cannot be derived from these data, we speculate that the absence of an association between perfusion of striatal regions and delusional beliefs is consistent with the possibility that the striatum is at least one synapse downstream from where the pathological process originates or is most prominent initially, consistent with data derived from animal models of psychosis (47,90,91). These animal models suggest that after a loss or malfunctioning of parvalbumin-expressing interneurons of the hippocampus, disinhibition of pyramidal neurons of the hippocampus leads to abnormal dopamine neurotransmission in the striatum (via dysfunction of hippocampal-striatal projections) and the ventral tegmental area, which then gives rise to conditions (potentially related to inappropriate responses of dopamine neurons to irrelevant, nonsalient stimuli and impairments in context-dependent retrieval of stored information by the hippocampus) that favor the development of prepsychotic symptoms, including delusional beliefs. After some degree of persistence of these abnormalities, elevated perfusion of the striatum may develop at a later stage in the evolution of the illness, at the time when more clinically apparent and distressing psychotic symptoms emerge (89).

In light of the previous evidence for overactivity of the amygdala in psychosis (32,92)—particularly in association with persecutory beliefs (93)—it was surprising that no association was found here between levels of delusional beliefs and amygdala perfusion. However, given that amygdala overactivity may be more closely linked to the presence of delusional beliefs with a negative affective valence (such as persecutory/paranoid ideas), the fact that only a small number ($n = 11$) of our participants endorsed persecutory beliefs could account for this negative result.

Although the exact mechanisms and sequence of cellular events underlying hippocampal overactivity in psychosis remain incompletely understood, some recent studies have found evidence that overactivity of the hippocampus in schizophrenia is initially limited to the

CA1 subfield of the hippocampus (3,7), which is then followed by CA1 atrophy (11). This localized hypermetabolism and atrophy of CA1 appears to begin before the first episode of psychosis (7). Moreover, recent evidence suggests that following the first psychotic episode, these abnormalities may gradually spread to involve the remaining subfields of the hippocampus (11,94). This dynamic pattern of changes is consistent with findings in the literature; previous studies of psychotic patients have found evidence for overactivity of the medial temporal lobe overall (6,9), the hippocampus (1,89,95–97), or only the CA1 subfield of the hippocampus (3,7,11). Although the PASL scans of the current study did not have the necessary spatial resolution to measure the perfusion of the individual hippocampal subfields separately, our results suggest that the changes in hippocampal perfusion observed during the psychosis prodrome and first episode of psychosis in previous studies are also present in those with subclinical psychotic experiences. Subsequent studies can determine whether the association observed in the present study is limited to particular subregions of the hippocampus.

Although the hippocampus may play a central role in the pathophysiology of psychotic illness, it has become increasingly clear that psychosis is associated with a disruption of the coordinated functioning of a distributed network of regions, rather than affecting a single brain area (98–100). This model is consistent with our findings of associations between delusional beliefs and perfusion of a network of limbic, highly interconnected regions that have been previously linked to psychotic symptoms, including the thalamus (101,102), anterior (103,104) and posterior (105,106) cingulate gyri, parahippocampal gyrus (50,51,53), and lateral temporal cortices (56,107–109). These findings also suggest that a range of severity of prepsychotic and psychotic states is associated with elevated activity of the hippocampus and a closely connected thalamocortical network.

Previous studies using the PDI have shown that elevated scores on this measure are associated with risk (19,110) and/or genetic liability (111–113) for psychosis. For example, one study found that first-degree relatives of schizophrenia and bipolar patients with prominent psychotic symptoms had significantly higher PDI scores than first-degree relatives of patients without psychotic symptoms (30). Also, in several studies, total PDI score has been found to correlate strongly with levels of self-reported hallucinatory experiences (36,114,115), which is consistent with the continuum model of psychosis (13).

The subscales of the PDI may be particularly useful for distinguishing impairing versus more benign expressions of delusional beliefs; patients with psychotic disorders have higher scores on the PDI distress subscale compared to healthy individuals with subclinical delusions (37,38,73). This is consistent with the larger literature on PEs, which has shown that the majority of individuals with PEs are not distressed by them, but the presence of distress is a risk factor for clinical progression and high risk status (116). Thus, the correlation found in the current study between the degree of distress associated with delusional ideas and hippocampal perfusion further supports the possibility that this association in healthy individuals is linked to neurobiological mechanism(s) underlying psychotic symptoms across healthy and clinical populations.

The results of this study must be interpreted in light of the specific characteristics of the cohort—that only non-help-seeking, relatively healthy participants were enrolled, with low scores on the measure of interest on average, compared to previous studies (38,39,115,117). However, despite the limited range of symptom severity, the predicted association was easily detected, suggesting that this association is present at many levels of severity. Future studies can further assess whether perceptual aberrations, which were not comprehensively examined here (the three PDI items that assess perceptual abnormalities were infrequently endorsed), are also associated with overactivity of the limbic network linked to delusional beliefs, or an overlapping but distinct network.

The observation of hippocampal overactivity in association with psychotic experiences in non-help-seeking, relatively healthy individuals indicates that at least some aspects of this neural phenotype can be studied in populations that are not affected by the typical confounds associated with having a serious mental illness. Given the overall consistency of findings across studies using a wide range of methods, hippocampal overactivity may also represent a useful target for testing potential novel interventions, both in animal models of psychosis and clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Scatter plots displaying correlations between hippocampal perfusion and total Peters *et al.* Delusions Inventory (PDI) score. Significant correlations were found between total PDI score and perfusion of the (A) left ($r = .26$, $p = .03$) and (B) right ($r = .25$, $p = .03$) hippocampus, and with the (C) average of both hemispheres ($r = .27$, $p = .02$), in this non-help-seeking healthy cohort ($n = 77$). The r and p values listed here are corrected for effects of potential confounds (age, hippocampal volume, levels of depressive and anxiety symptoms, and signal-to-noise ratio).

Figure 2.

Perfusion of the hippocampus is correlated with the degree of distress associated with subthreshold delusional beliefs. A significant correlation was found between perfusion of the hippocampus (averaged over the left and right hemispheres) and scores on the Peters *et al.* Delusions Inventory subscale measuring (A) distress ($r = .29$, $p = .02$) but not (B) conviction ($r = .20$, $p = .09$), or (C) preoccupation ($r = .16$, $p = .18$). The r and p values listed here are corrected for effects of potential confounds (age, hippocampal volume, levels of depressive and anxiety symptoms, and signal-to-noise ratio).

Figure 3.

Voxelwise regression confirms correlations detected between total Peters *et al.* Delusions Inventory score and perfusion of the right (R) and left hippocampus (Hipp). The findings of the region of interest analysis were confirmed in a voxelwise regression analysis in which total Peters *et al.* Delusions Inventory score was used as a regressor (also see Supplement). (A) Sagittal view, $x = -27$. (B) Coronal view, $y = -18$. (C) Coronal view, $y = -31$. The display threshold is $p = .01$. PHG, parahippocampal gyrus.

Table 1**Correlations Between PDI Scores and Hippocampal Perfusion**

	Left Hippocampus	Right Hippocampus	Average Hippocampus
PDI Total	.26/.03 ^a	.25/.03 ^a	.27/.02 ^a
PDI Distress	.30/.01 ^a	.24/.05	.29/.02 ^a
PDI Conviction	.22/.07	.18/.13	.20/.09
PDI Preoccupation	.18/.14	.13/.27	.16/.18

Spearman's ρ and p values are listed for the correlations between hippocampal perfusion (for the left hemisphere, right hemisphere, and averaged across hemispheres) and scores on the Peters *et al.* Delusions Inventory (the total score and normalized scores on the subscales distress, conviction, and preoccupation) for this healthy sample ($n = 77$). Age, hippocampal volume, levels of depressive and anxiety symptoms, and image signal-to-noise ratio were included as covariates in these analyses.

PDI, Peters *et al.* Delusions Inventory.

^aCorrelations with $p < .05$.

Table 2

Correlations Between PDI Total Score and Psychosis-Linked and/or Temporal Lobe Regions

	Correlation Coefficient	<i>p</i> Value
Psychosis-linked Circuitry		
Medial prefrontal/cingulate cortices		
Medial orbitofrontal cortex	-.004	.98
Rostral anterior cingulate cortex	.09	.44
Caudal anterior cingulate cortex	.27 ^a	.02 ^a
Posterior cingulate cortex	.35 ^a	.003 ^a
Thalamus	.26 ^a	.03 ^a
Striatum		
Caudate nucleus	.20	.09
Putamen	.18	.12
Nucleus accumbens	-.09	.45
Temporal Lobe Regions		
Amygdala	.10	.40
Parahippocampal gyrus	.26 ^a	.03 ^a
Lateral temporal cortex		
Inferior temporal gyrus	.10	.40
Middle temporal gyrus	.27 ^a	.02 ^a
Superior temporal gyrus	.29 ^a	.01 ^a
Control Regions		
Fusiform cortex	-.01	.93
Lateral occipital cortex	-.07	.55

Spearman's ρ and *p* values for correlations between perfusion of selected regions of interest and total Peters *et al.* Delusions Inventory (PDI) score are listed. Age, structural measures (volume or cortical thickness), levels of depressive symptoms, anxiety levels, and image signal-to-noise ratio were included as covariates in these analyses.

^a $p < .05$ and the accompanying p values.