Differential Targeting of the CA1 Subfield of the Hippocampal Formation by Schizophrenia and Related Psychotic Disorders

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Context: Because schizophrenia and related disorders have a chronic time course and subtle histopathology, it is difficult to identify which brain regions are differentially targeted.

Objective: To identify brain sites differentially targeted by schizophrenia, we applied a high-resolution variant of functional magnetic resonance imaging to clinically characterized patients and matched healthy controls and to a cohort of prodromal subjects who were prospectively followed up. Additionally, to explore the potential confound of medication use, the fMRI variant was applied to rodents receiving an antipsychotic agent.

Design: Cross-sectional and prospective cohort designs.

Setting: Hospital clinic and magnetic resonance imaging laboratory.

Participants: Eighteen patients with schizophrenia, 18 controls comparable in age and sex, and 18 prodromal patients followed up prospectively for 2 years. Ten C57-B mice received an antipsychotic agent or vehicle control.

Main Outcome Measures: Regional cerebral blood volume (CBV), as measured with magnetic resonance imaging, and symptom severity, as measured with clinical rating scales.

Results: In a first between-group analysis that compared patients with schizophrenia with controls, results revealed abnormal CBV increases in the CA1 subfield and the orbitofrontal cortex and abnormal CBV decreases in the dorsolateral prefrontal cortex. In a second longitudinal analysis, baseline CBV abnormalities in the CA1 subfield differentially predicted clinical progression to psychosis from a prodromal state. In a third correlational analysis, CBV levels in the CA1 subfield differentially correlated with clinical symptoms of psychosis. Finally, additional analyses of the human data set and imaging studies in mice suggested that antipsychotic agents were not confounding the primary findings.

Conclusions: Taken as a whole, the results suggest that the CA1 subfield of the hippocampal subregion is differentially targeted by schizophrenia and related psychotic disorders. Interpreted in the context of previous studies, these findings inform underlying mechanisms of illness progression.

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The frontal cortex, basal ganglia, amygdala, and hippocampal formation—all brain areas implicated in schizophrenia—are subdivided into functionally distinct subregions (Figure 1). Each subregion is unique in its molecular expression profile so that select regions are differentially vulnerable to mechanisms of disease. Nevertheless, pinpointing regions differentially targeted by schizophrenia is difficult. By the time patients are clinically diagnosed with schizophrenia, multiple brain sites are affected, making the task of dissociating primary from secondary sites of dysfunction challenging. Further confounding the problem is the absence of pathognomonic histological markers or florid neurodegeneration. Thus, because schizophrenia is primarily a disease of neuronal dysfunction, not neuronal cell death, cross-sectional comparisons of postmortem samples do not necessarily reveal patterns of anatomical progression.

Two recent developments can be exploited to overcome these challenges. First, clinical criteria have been established that identify a high-risk prodromal group that, although clinically heterogeneous, is enriched with subjects in the earliest stages of the disease. Approximately 35% of prodromal patients progress clinically within a few years; therefore, a relatively short prospective study can provide a snapshot of brain regions differentially targeted during early stages of the disease.

Second, variants of functional magnetic resonance imaging are now available...
that possess sufficient anatomic resolution to detect dysfunction in small subregions of the brain, including the hippocampal formation, the amygdala, and other implicated areas. Functional imaging relies on correlates of energy metabolism through either glucose uptake as an indicator of glucose metabolism or cerebral blood flow, cerebral blood volume, or deoxyhemoglobin as indicators of oxygen metabolism.9-12 Although an external sensory or cognitive stimulant can induce a transient change in brain metabolism, the internal stimulus of a disease state typically affects basal metabolic rates. There are many advantages to imaging disease-associated abnormalities in the basal state,13 in particular, the ability to slow image acquisition time, thereby significantly enhancing spatial resolution. As previously reviewed,14 the use of the contrast agent gadolinium to map basal cerebral blood volume (CBV) with magnetic resonance imaging is a functional imaging approach that provides high spatial resolution. Previous studies have shown that disease-associated basal defects in glucose uptake, as measured with positron emission tomography, tightly correlate with basal defects in CBV, as measured with magnetic resonance imaging.15 Intravenous injections of gadolinium can generate CBV maps using either a dynamic contrast enhancement approach or the steady state approach.14 For our purposes, the steady state approach is superior because it generates CBV with higher spatial resolution and because it relies on T1-weighted rather than T2*-weighted images. Both features are advantageous for imaging small subregions in the medial temporal lobe and the orbitofrontal cortex. In previous studies we have successfully used this approach to pinpoint dysfunction to individual hippocampal subregions in humans16 and nonhuman primates.17 Additionally, CBV mapping can be now used to generate high-resolution maps of the rodent hippocampal formation18,19 so questions that emerge from human studies can be explored in mouse models of disease.

To identify brain regions differentially targeted in schizophrenia, we completed 4 studies using high-resolution basal CBV mapping. First, because this imaging approach has not yet been applied to the disease, we compared patients with schizophrenia with matched controls. Second, using the findings from the first study as a guide, we tested which brain subregions predicted progression to psychosis from an ultra–high-risk state. Third, we performed regression analyses that tested the association of CBV with clinical symptoms of psychosis. Fourth, to address the potential medication use confound, we performed additional analyses in human subjects and generated longitudinal CBV maps in mice exposed to an antipsychotic agent. Taken together, the results suggest a hippocampal subregion differentially targeted by schizophrenia and related disorders.

**METHODS**

**HUMAN IMAGING**

**Subject Groups**

We studied a total of 54 subjects (Table 1). The schizophrenia group met DSM-IV criteria for schizophrenia (n=14) or schizoaffective disorder (n=4) and were recruited from the inpatient and outpatient Lieber schizophrenia research clinics at the New York State Psychiatric Institute. The control group comprised healthy subjects comparable in age and sex with the patient group and were recruited within Columbia University Medical Center. The prodromal group was recruited from the Center of Prevention and Evaluation Clinic and met ultra–high-risk criteria for psychosis.5 All ultra–high-risk subjects were followed up longitudinally from the time of clinic enrollment and were typically evaluated every 3 months up to 2 years; none were lost to follow-up.
Clinical Assessment

Subjects in the schizophrenia and prodromal groups older than 18 years received the Diagnostic Interview for Genetic Studies to confirm diagnosis, while subjects in the prodromal group received the Structured Interview for Prodromal Symptoms for clinical inclusion as well as the Kiddie Schedule for Affective Disorders and Schizophrenia interview if subjects were aged between 12 and 18 years. Symptom severity in the schizophrenia group was evaluated with the Positive and Negative Symptom Scale (PANSS) positive and negative symptom items and with the Scale of Prodromal Symptoms (SOPS) in the prodromal group.

CBV Mapping

As previously described, CBV maps were generated with a 1.5-T Philips Intera scanner (Andover, Massachusetts) using gadolinium pentate (Omniscan, 0.1 mmol/kg; GE Healthcare, Chalfont St Giles, England). Briefly, a set of oblique coronal, 3-dimensional, T1-weighted, high-resolution (0.86 × 0.86 mm pixel size) images were acquired perpendicular to the hippocampal long axis before and 4 minutes after intravenous administration of the contrast agent. Subtracted images were then divided by the contrast-induced difference in signal measured from the superior sagittal sinus. Investigators blind to subject grouping (N.M.L. and S.A.S.) performed all image processing. The imaging protocol was approved through the Columbia University institutional review board.

Identifying Regions of Interest

Because of coregistration challenges when evaluating small brain regions in clinical populations, whole-brain voxel-based analyses are problematic; instead, we used a region-of-interest approach that relies on strict anatomical criteria to identify regions in areas previously implicated in schizophrenia (Figure 1).

Hippocampal Subregions. As previously described by identifying the external morphology and internal architecture of the hippocampal formation, we can reliably parse the hippocampal subregions. As shown in Figure 1, this slice is invariably anterior in the hippocampal long axis, so we also demarcated a region of interest in a slice taken from the posterior hippocampus. In posterior slices, however, the entorhinal cortex no longer exists, and there is typically insufficient anatomical information to parse the individual hippocampal subregions.

Basal Ganglia. The ventral striatum CBV measurements were completed in a coronal section where the septum was best visualized. The anterior ventral portion of the head of the caudate, nucleus accumbens, and putamen were analyzed.

Frontal Lobes. The gyrus rectus, medial orbitofrontal gyrus, and dorsolateral prefrontal cortex were completed in the slice in which all 3 regions were best visualized. The dorsolateral prefrontal cortex was defined according to the criteria of Rajkowska and Goldman-Rakic. Within this same slice, the gyrus rectus was identified and the medial orbital gyrus was selected as the gyrus immediately lateral to the gyrus rectus. Of note, signal artifact from braces excluded 1 prodromal subject from this analysis.

Amygdala. The dorsal and basolateral nuclei of the amygdala were measured according to the atlas by and colleagues as well as according to the methodology of Etkin et al.

MOUSE IMAGING

Generation of longitudinal CBV mapping in mice has been previously described. After a baseline image, C57/B6 mice were given 2 doses daily of risperidone (0.75 mg/kg/dose or 1.5 mg/kg/d) or its tartrate vehicle via oral gavage, and then reimaged following 3 weeks of treatment. Dosage was determined by previous binding and behavioral studies. All experiments were approved by and conducted according to the guidelines of the Institutional Animal Care and Use Committees of Columbia University Medical Center and The New York State Psychiatric Institute.

STATISTICAL ANALYSIS

The statistical models used for data analysis will be described according to the 4 studies. All statistical tests were 2-sided, and α = .05.

Identifying Brain Regions Differentially Affected in Schizophrenia

A multivariate analysis of variance (ANOVA) model was constructed in which CBV values measured from the brain subregions were included as the dependent variables, diagnosis (schizophrenia vs controls) was included as the fixed factor, and demographics (age and sex) were included as covariates.
Identifying Brain Regions That Differentially Predict Clinical Progression of Prodromal Subjects

A multivariate ANOVA model was constructed in which CBV values identified in the first study were included as dependent variables, outcome (psychosis vs nonpsychosis) was included as the fixed factor, and demographics (age and sex) were included as covariates. Based on results of the first analysis, we dichotomized CA1 subfield metabolism at the overall mean value of the data set into high-CBV and low-CBV groups and constructed a $2 \times 2$ analysis with CA1 CBV as the categorical exposure variable and outcome to psychosis as the categorical disease variable. We then applied the Fischer exact test to the resultant $2 \times 2$ table.

Identifying Brain Regions Differentially Linked to Clinical Symptoms

The statistical reliability of any correlational analysis is strengthened by using a large number of subjects and by minimizing type I error incurred by multiple comparisons. Sensitive to these issues, we tried when possible to collapse symptom measures accumulated across schizophrenia and prodromal subjects. However, because of concerns that the 2 clinical constructs are not necessarily on a continuum, secondary analyses were performed for each group individually.

Positive Symptoms. Because the 5 positive items in the SOPS were directly developed from the PANSS, it was justifiable to collapse positive symptoms across subjects. Though the dynamic range of each scale is weighted differently, one toward a prepsychotic stage (SOPS) and the other toward frank psychosis (PANSS), the 2 scales test identical items. Thus, the 2 scales were unified into a single scale of positive symptom for each of those 5 psychotic items: PANSS 1=SOPS 0; PANSS 2=SOPS 3; PANSS 3=SOPS 4; PANSS 4 or 5=SOPS 6; PANSS 6 or 7=SOPS 7. For each of the positive items, PANSS ratings at the PANSS 3, or mild level, include the ability to reality-test or organize thought and are thus considered to be of prepsychotic severity. With progression to PANSS 4, or moderate level, this flexibility of thought form and content is lost and is thus equivalent to the SOPS 6 cutoff for psychosis. Finally, the PANSS contains levels of severe or extreme psychosis not reflected in the SOPS. Thus, the additional 7 designation was created to include PANSS items rated at a level of 6 or 7. The 5 items were added together to derive a total positive symptom summary score. All rating scale mean values by group are shown in Table 1.

A single linear regression model was constructed in which the total positive symptom score and the CBV values measured from regions identified in the first analysis were included as predictor variables and demographics were included as covariates.

Negative Symptoms. Because the negative symptom measurements in the PANSS and the SOPS are different, we could not generate a unified total negative symptom summary score between subject groups. Therefore, the linear regression analysis was performed individually for each summary score. A single linear regression model was constructed in which the total negative symptom score from each subscale (SOPS or PANSS) was the dependent variable and the CBV values measured from regions identified in the first analysis (CA1, orbitofrontal cortex, and dorsolateral prefrontal cortex) were included as predictor variables, and demographics were included as covariates.

Investigating the Potential Medication Use Confound

In addition to t tests between subjects treated with antidepressants or antipsychotics vs not, a categorical data analysis was also conducted to test whether antidepressant or antipsychotic exposure was associated with conversion status to psychosis and the Fischer exact test was applied. For the rodent treatment study, a repeated-measures ANOVA model was constructed in which CBV values from the hippocampal subregions before and after treatment were included as dependent variables and treatment (risperidone vs vehicle) was included as the fixed factor.
DISEASE-ASSOCIATED DYSFUNCTION DIFFERENTIALLY OBSERVED IN THE CA1 SUBFIELD, ORBITOFRONTAL CORTEX, AND DORSOLATERAL CORTEX

The multivariate component of the ANOVA model comparing the schizophrenia group with the control subjects revealed a significant group effect ($F = 3.8; P = .004$), and univariate components of the model revealed that this group effect was selectively driven by CBV increases in the schizophrenia group in the CA1 subfield ($F_{1,34} = 14.7; P = .001$) and orbitofrontal cortex ($F_{1,34} = 10.3; P = .003$) and CBV decreases in the dorsolateral cortex ($F_{1,34} = 4.5; P = .04$) (Figure 1B; Table 2). A trend was observed for the subiculum ($F_{1,34} = 3.5; P = .07$). Of note, mean areas of the regions of interest taken for CBV measurements did not differ across subjects in any brain subregion.

DIFFERENTIAL CA1 DYSFUNCTION OBSERVED IN EARLY STAGES OF DISEASE

After an average of 2 years of follow-up, 7 of the 18 (39%) prodromal subjects clinically progressed. Six subjects met formal criteria for schizophrenia spectrum disorders (3 with schizophrenia, 2 with schizoaffective disorder, bipolar type, 1 with schizophreniaiform disorder), and 1 patient now meets the criteria for major depression with psychotic features.

In a primary analysis guided by the first study, we compared CBV values measured from the CA1 subfield, orbitofrontal cortex, and dorsolateral cortex between subjects who progressed with those who did not. The only between-group difference was observed in the CA1 subregion, where subjects who progressed were found to have significantly higher CBV values ($F_{1,17} = 6.8; P = .02$) (Figure 3A). In a secondary analysis, we expanded the focus to include all regions in which CBV was measured, and none were found to significantly distinguish between the groups.

Categorical analysis of baseline CBV data revealed that CA1 dysfunction predicted clinical progression with a positive predictive value of 71% and a negative predictive value of 82% from analysis of the resultant $2 \times 2$ table (Fisher exact $P = .05$).

DIFFERENTIAL CORRELATION OF CA1 DYSFUNCTION WITH CLINICAL SYMPTOMS

To minimize type I error, a multivariate regression model was used in primary analyses that included CBV values from the 3 regions identified in the first study: the CA1 subfield, the orbitofrontal cortex, and the dorsolateral prefrontal cortex. Additionally, to increase statistical reliability, we collapsed symptom scores when possible, thereby increasing the number of subjects included in the model. Then, in secondary analyses we performed additional simple correlations to better understand the source of the primary findings.

For positive symptoms, the combined positive rating scale was found to differentially correlate with CBV in the CA1 subfield and was associated with total positive symptoms ($\beta = .53; P = .01$). No association was observed between CBV in the orbitofrontal cortex or dorsolateral prefrontal cortex and positive symptoms (Figure 3C). Of the specific items, delusional severity was the positive symptom that had the strongest association with CA1 CBV ($\beta = .54; P = .003$). Because the 2 clinical groups might not be on a continuum, additional analyses were performed within each group. An association was found between CA1 CBV and delusions in both the schizophrenia ($\beta = .57; P = .01$) and the prodromal patient groups ($\beta = .58; P = .01$).

In contrast to positive symptoms, the scales for negative symptoms used for prodromal subjects and those with schizophrenia are incompatible, so we used summary scores of negative symptoms separately for each group. Of the patients with schizophrenia, no significant association was found with the summary of negative symptoms, although a trend was noted only for the CA1 subfield ($\beta = .61; P = .09$). Within the prodromal group, CBV in the CA1 subfield was significantly associated with total negative symptoms ($\beta = .59; P = .03$) as well as with the social dysfunction ($\beta = .58; P = .01$) and avolition items ($\beta = .6; P = .03$). Within this same regression model, dorsolateral prefrontal cortex CBV was also negatively associated with total negative symptoms in the prodromal group at a trend level ($\beta = -.47; P = .09$) and was negatively associated with the social withdrawal subscale ($\beta = -.73; P = .005$).

Table 2. Cerebral Blood Volumes by Subregion

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Control Mean (SD)</th>
<th>Ultra-High-Risk Mean (SD)</th>
<th>Schizophrenia Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior hippocampus</td>
<td>1.56 (0.84)</td>
<td>1.41 (0.92)</td>
<td>1.29 (1.03)</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>1.76 (0.88)</td>
<td>1.60 (0.98)</td>
<td>2.50 (1.38)</td>
</tr>
<tr>
<td>Subiculum</td>
<td>1.26 (0.47)</td>
<td>1.48 (0.49)</td>
<td>1.99 (0.82)</td>
</tr>
<tr>
<td>CA1 subfield</td>
<td>1.86 (1.18)</td>
<td>1.69 (0.82)</td>
<td>1.93 (1.48)</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>1.51 (1.02)</td>
<td>0.78 (0.88)</td>
<td>1.47 (1.00)</td>
</tr>
<tr>
<td>Posterior hippocampus</td>
<td>1.98 (0.52)</td>
<td>2.08 (0.51)</td>
<td>1.88 (1.10)</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyrus rectus</td>
<td>2.13 (0.96)</td>
<td>2.08 (0.60)</td>
<td>1.92 (0.96)</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>1.36 (1.06)</td>
<td>2.03 (0.84)</td>
<td>2.51 (1.00)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>2.35 (0.56)</td>
<td>2.09 (0.60)</td>
<td>1.79 (0.84)</td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>1.78 (0.43)</td>
<td>1.70 (0.63)</td>
<td>2.05 (1.16)</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>1.88 (0.52)</td>
<td>2.16 (0.71)</td>
<td>2.04 (1.16)</td>
</tr>
<tr>
<td>Putamen</td>
<td>2.32 (0.51)</td>
<td>1.98 (0.64)</td>
<td>2.07 (0.84)</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.30 (1.02)</td>
<td>1.41 (1.61)</td>
<td>1.22 (1.59)</td>
</tr>
<tr>
<td>Dorsal nucleus</td>
<td>1.04 (1.03)</td>
<td>1.49 (0.55)</td>
<td>1.50 (1.03)</td>
</tr>
<tr>
<td>Basolateral nucleus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a P < .10$ for controls vs patients with schizophrenia by analysis of variance.  
$^b P < .01$ for controls vs patients with schizophrenia by analysis of variance.  
$^c P < .05$ for controls vs patients with schizophrenia by analysis of variance.
NO ASSOCIATION BETWEEN CA1 DYSFUNCTION AND MEDICATION USE

Only 1 of 7 subjects who clinically progressed received antipsychotic medications at baseline, suggesting that our CA1 CBV findings were not confounded by antidopaminergic agents. Supporting this interpretation, comparing mean CBV values of the 3 prodromal subjects who were taking antipsychotic medications with those of the 13 subjects who were not revealed no significant difference in CA1 CBV ($t = -0.68$; $P = .51$) (Figure 4). Four of the 7 subjects who clinically progressed received antidepressant medications at baseline. Antidepressant use (Fisher exact $P = .67$) and antipsychotic use (Fisher exact $P = .67$) were not associated with conversion status. Finally, an analysis comparing the mean CBV values of the 10 prodromal subjects who were taking antidepressant medications with those of the 8 who were not revealed no significant difference in CA1 CBV ($t = -0.47$; $P = .65$) (Figure 4).

To further explore this issue in an experimental setting, we performed an experiment in which 5 C57/B6 mice received the antipsychotic agent risperidone (0.75 mg/kg, twice per day by oral gavage) for 3 weeks and 5 mice received vehicle control. Hippocampal CBV maps (Figure 5) were generated before and after drug administration and a repeated-measures ANOVA revealed no drug effect in any hippocampal subregion, including the CA1 subfield ($F = 0.50$; $P = .50$) (Figure 5).

Figure 3. The CA1 subfield is a site of dysfunction selectively associated with clinical features. A, Cerebral blood volume (CBV) measured in the CA1 subfield, but not the orbitofrontal cortex (OFC) or dorsolateral prefrontal cortex (DLPFC), was significantly elevated at baseline, comparing the prodromal subjects who clinically progressed to psychosis with those who did not. B, Individual CBV maps of the hippocampal formation are shown for a healthy control, a prodromal subject, and a patient with schizophrenia. The CBV maps are color coded such that warmer colors reflect higher CBV values. Higher CBV was observed in the CA1 subfield of the prodromal subject, and higher CBV was observed in the CA1 and subiculum in the patient with schizophrenia. C, CA1 CBV, but not OFC or DLPFC CBV correlated with positive symptoms, in particular, delusional severity. PANSS indicates Positive and Negative Symptom Scale.
Our main finding is that dysfunction in the CA1 subfield of the hippocampal formation best fulfilled the clinical criteria for a brain site differentially targeted by schizophrenia and related psychotic disorders: (1) it is present in the established diagnosis of schizophrenia; (2) it selectively predicts clinical progression; and (3) it is differentially associated with both positive and negative symptoms of psychosis. The observed pattern of dysfunction found in our study, characterized by abnormal elevations of CBV, is suggestive of a basal hypermetabolic state in the hippocampus in schizophrenia. Basal metabolic increases in the medial temporal lobe or hippocampal formation that are associated with symptoms of psychosis have been shown in most published single-photon emission computed tomography and positron emission tomography-based studies of schizophrenia using basal cerebral blood flow, a correlate of CBV, consistent with our findings. Nevertheless, because of suboptimal spatial resolution, imaging approaches using cerebral blood flow have shown global medial temporal or hippocampal hypermetabolism but cannot pinpoint defects to specific hippocampal subregions.

In prodromal research, baseline predictors of transition to psychosis have not yet been shown convincingly with existing methodologies. Although the volume of the hippocampus appears to be decreased compared with controls at baseline, it has not predicted transition to psychosis in 3 of 5 published studies. In one study that originally predicted transition, voxel-based morphometry methodology was used, and a study of this expanded sample using region-of-interest methodology did not replicate the earlier finding. By contrast, longitudinal study of high-risk patients has shown progressive reduction of medial temporal lobe volumes in patients whose psychosis became exacerbated over time. N-acetyl-aspartate levels in the hippocampus, as assessed by magnetic resonance spectroscopy, are equivalent to those of controls and are not known to predict psychosis.43 Prefrontal volume contraction has been associated with the onset of psychosis but has not predicted psychosis at baseline in a large clinical high-risk sample. Among patients at genetically high risk from the Edinburgh sample (eg, with a first-degree relative with a psychotic disorder), predictors of transition to psychosis have been found in prefrontal regions and have included increased prefrontal gyrification. Less inferior frontal gray matter at baseline was shown in ultra-high-risk individuals who transitioned to psychosis in one sample, while decreased right prefrontal gray matter from baseline to transition to psychosis has been shown in a separate sample using longitudinal methods.

Previous studies have suggested that the CA1 subfield of the hippocampal formation might be involved in psychotic illness. In particular, studies by Benes and colleagues have relied on observed postmortem changes in interneurons to predict increased excitation in the hippocampal formation and, based on properties of the hippocampal trisynaptic circuit, have hypothesized that the CA1 subfield might exhibit the greatest increase in excitation. However, as described, establishing the precise location and functional alterations in the hippocampal formation must be empirically determined.

Further studies rely on the observation that N-methyl-D-aspartate antagonists phenocopy many key clinical features of schizophrenia. Several models of N-methyl-D-aspartate receptor hypofunction predict that the locus of this effect should occur predominately in the CA1 subfield of the hippocampal formation as well as affect interneuron function. Nonetheless, these models have not excluded the importance of other hippocampal subregions. More importantly, whereas one model predicts that N-methyl-D-aspartate antagonists would reduce activity of inhibitory interneurons, leading to increased excitation, other models predict that N-methyl-D-aspartate antagonists act on primary neurons, leading to...
decreased CA1 excitation. Thus, there is disagreement as to whether this subfield exhibits an increase or decrease in activity and whether other hippocampal subregions might also be involved.

Brambilla et al\(^{14}\) and Loeb et al\(^{15}\) have performed CBV estimates of the hemisphere and cerebellum in patients with established schizophrenia and found evidence of hemispheric decreases in CBV and cerebellum increases in CBV. Because they used different methods to obtain their estimates of CBV, normalized their results using differing methodologies, and chose differing regions of interest, it is difficult to draw direct comparisons of how the present study relates to the prior CBV studies.

Our study is the first to apply high-resolution functional imaging to prodromal subjects, a newly developed clinical category that, although etiologically heterogeneous, is enriched with subjects in the early stages of schizophrenia and related psychotic disorders. The results demonstrate that CA1 dysfunction is an early and selective defect that predicts progression to psychosis, which, by virtue of the characteristics of the prodromal patient sample, is not confounded by illness duration or antipsychotic treatment effects. As noted, subjects who clinically progressed had schizophrenia, but also schizoaffective disorder and major depression with psychotic features. Future studies imaging a larger group of prodromal subjects are required to clarify the question of the diagnostic utility of CA1 subfield CBV, despite its remarkably high predictive power in this small sample. At the same time, the selectivity and statistical strength of the findings indicate that CA1 dysfunction is at least 1 primary defect in schizophrenia. This interpretation is supported by the associational analyses showing that the CA1 subfield consistency correlates with clinical symptoms in patients with documented schizophrenia as well as in prodromal subjects. Although each of the 3 imaging analyses—mapping disease-selective dysfunction, predicting progression, and associating dysfunction with symptoms—has limitations, as a composite they provide strong evidence that the CA1 subfield is a brain site differentially targeted in schizophrenia and related disorders.

Our findings support the hypothesis that psychosis is characterized by abnormal excitation of hippocampal afferents linked to increases in synaptic glutamate. Besides evidence from spectroscopy studies investigating patients with schizophrenia,\(^{56}\) this view is supported by animal models showing how stimulation of hippocampal afferents results in elevated cell population dopamine activity.\(^{57-59}\) Moreover, a recent drug study has shown clinical efficacy in patients using an agonist of the metabotropic glutamate 2/3 receptors, which causes a decrease in glutamate release.\(^{60}\) Future animal or postmortem studies are required to isolate the molecular and cellular mechanisms that underlie CA1 subfield dysfunction, perhaps by affecting mechanisms of glutamate regulation in the hippocampal circuit. Our study has important limitations. First, although large for an functional magnetic resonance imaging study, the sample size could be larger, particularly to assess the diagnostic utility of the findings. Second, though we are confident that inclusion of a prodromal group and an animal treatment study provides evidence that antipsychotic treatment did not confound our results (Medoff et al\(^{43}\) shows normalization of hippocampal hypermetabolism with treatment), we recognize that testing medication-free subjects with first-episode psychosis is a priority for future research to more definitively establish our subregional findings. Third, we recognize that user-guided region-of-interest techniques are imperfect; however, there are presently no automated methods available to investigate hippocampal subregions.

At a phenomenological level, our findings raise questions regarding why CA1 hypermetabolism would be so tightly linked to symptoms of the disease. In this regard, it is interesting to note that the anterior CA1 subfield and the subiculum monosynaptically connect with a number of outflow sites implicated in schizophrenia,\(^{61}\) including the orbitofrontal cortex. Thus, it is interesting to postulate that CA1 hypermetabolism may be driving dysfunction in other brain regions in the established illness. By combining functional magnetic resonance imaging techniques with other imaging modalities such as positron emission tomography that can assess dopamine release, and by applying these techniques to a large number of prodromal subjects followed up longitudinally, it is now possible to test these circuit-based hypotheses in living subjects.

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