Published in final edited form as:

Psychiatry Res. 2016 October 30; 256: 21–25. doi:10.1016/j.psychres.2016.09.002.

Hippocampal arterial cerebral blood volume in early psychosis

Pratik Talati^{a,*}, Swati Rane^{b,d}, Manus J. Donahue^{a,b,c}, and Stephan Heckers^a

^aVanderbilt Brain Institute, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN 37212, USA

^bInstitute of Imaging Science, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^cDepartment of Neurology, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^dDepartment of Radiology, University of Washington, Seattle, WA 98195, USA

Abstract

Recent studies of patients in the early stage of psychosis have revealed increased cerebral blood volume (CBV) in specific subfields of the anterior hippocampus. These studies required injection of a contrast agent to measure steady state CBV. Here we used a novel, non-invasive method, inflow-based-vascular-space-occupancy with dynamic subtraction (iVASO-DS), to measure the arterial component of CBV (aCBV) in a single slice of the hippocampus. Based on evidence from contrast-enhanced CBV studies, we hypothesized increased aCBV in the anterior hippocampus in early psychosis. We used 3T MRI to generate iVASO-derived aCBV maps in 17 medicated patients (average duration of illness = 7.6 months) and 25 matched controls. We did not find hemispheric or regional group differences in hippocampal aCBV. The limited spatial resolution of the iVASO-DS method did not allow us to test for aCBV differences in specific subfields of the hippocampus. Future studies should investigate venous and arterial CBV changes in the hippocampus of early psychosis patients.

Keywords

hippocampus; inflow-based-vascular-space-occupancy; iVASO; arterial cerebral blood volume; aCBV; early psychosis

*Corresponding author: Pratik Talati, PhD, Vanderbilt University Department of Psychiatry and Behavioral Sciences 3057 VPH 1601 23rd Ave South Nashville, TN 37212. +615-875-5897. pratik.talati@vanderbilt.edu.

Conflict of interest

The authors disclose no conflict of interest.

Contributors

Pratik Talati and Swati Rane were both involved in data collection, analysis, and manuscript preparation. Stephan Heckers and Manus Donahue helped with project inception, funding, data interpretation, and manuscript revisions.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. INTRODUCTION

Recent evidence implicates hippocampal excitation-inhibition imbalances in schizophrenia (Heckers and Konradi, 2014). While neurovascular coupling has allowed for the examination of hippocampal cerebral blood flow (CBF) and blood volume (CBV) as proxies for neural activity, CBF may not be a good surrogate in medicated patients because antipsychotic medications can ‘normalize’ blood flow in the hippocampus (Lahti et al., 2006; Lahti et al., 2009; Medoff et al., 2001). Some initial studies suggest that CBV is not affected by antipsychotic medications (Schobel et al., 2009; Talati et al., 2014), which may explain uncoupling between these two hemodynamic parameters in schizophrenia (Talati et al., 2015).

Anterior hippocampal CBV is increased in schizophrenia. Contrast-enhanced steady state CBV mapping has revealed increased anterior hippocampal CBV in chronic (Schobel et al., 2009; Talati et al., 2014) and early psychosis (Schobel et al., 2013) patients. A preliminary study suggests that increased CBV *precedes* volumetric changes in the anterior hippocampus in early psychosis (Schobel et al., 2013), which may serve as a biomarker for schizophrenia (Tregellas, 2014). Therefore, we were interested in a non-invasive method to study hippocampal CBV changes in psychotic disorder patients.

One such method is inflow-based-vascular-space-occupancy with dynamic subtraction (iVASO-DS), which measures arterial CBV (aCBV). Arterial CBV comprises approximately 20–30% of total CBV (Ito et al., 2001; Kim et al., 2007) and is under direct regulation of precapillary sphincters that adjust blood flow into capillary beds. The arterial compartment experiences the most changes after neural stimulation (Chen et al., 2011; Hillman et al., 2007; Kim et al., 2007), with the venous compartment experiencing slower, less specific changes after neural activity. Arterial CBV is therefore more sensitive to neural activity than total CBV.

We recently demonstrated good reproducibility of the iVASO-DS method in a group of young, healthy individuals (Rane et al., 2015). This single-slice method acquires a series of paired (label & control) images in a brain region of interest, such as the hippocampus. The control image contains signal from blood and tissue while the label image is acquired precisely when the inflowing arterial blood water magnetization is zero (hence also called the nulled image) and contains only tissue signal. The difference between the images (control – null) contains signal from arterial blood. We have shown recently that the hippocampal aCBV values have higher reproducibility at shorter inversion times (ie, $TI < 1000$ ms) (Rane et al., 2015).

In this study, we used iVASO-DS to study hippocampal aCBV in 17 patients who were in the early stage of psychosis and 25 group-matched controls with $TI = 725$ ms. Based on the existing literature of increased total (i.e., arterial and venous) CBV in the anterior parts of hippocampal subfield CA1 (Schobel et al., 2013; Schobel et al., 2009; Small et al., 2011; Talati et al., 2014; Talati et al., 2015), we hypothesized increased anterior hippocampal aCBV in the patient group.

2. METHODS

2.1 Participants

17 patients in the early stage of psychosis (age range: 18–29 years) and 25 matched healthy controls (age range: 19–27 years) provided informed consent in a manner approved by the Vanderbilt Institutional Review Board. The early stage of psychosis was defined as the first two years of psychotic illness. The average duration of psychotic illness in our sample was 7.6 months. Both groups were matched across several demographics, including age, race, and gender (Table 1). Subjects were recruited from the Vanderbilt Psychotic Disorders Program or the local community and were paid for their participation. We used the Structural Clinical Interview for DSM-IV Axis I disorders (SCID, (First, 2002)) to establish all diagnoses and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to assess patient clinical status. Ten of the 17 (59%) patients were diagnosed with schizophreniform disorder, 3 (18%) with bipolar with psychotic features, 1 (6%) with schizoaffective disorder, and 3 (18%) with schizophrenia. Thirteen patients were treated with antipsychotic medication (for chlorpromazine equivalent dosages (Gardner et al., 2010) see Table 1). Subjects were excluded from the study for any history of major neurological or medical illness or a pre-morbid IQ < 70 assessed by the Wechsler Test of Adult Reading (WTAR).

2.2 Structural and Functional Imaging

2.2.1 iVASO acquisition—A Philips 3T MRI Achieva scanner (Best, The Netherlands) with a 32 channel SENSE head coil was used for imaging. The high-resolution T1-weighted (FFE) structural scan was acquired as part of a larger imaging protocol and comprised of 170 sagittal slices with the following scan parameters: spatial resolution = 1.0 mm^3 isotropic, TR/TE = 8.0/3.7 ms. For the single slice structural image, the data were resliced in an oblique angle along the long axis of both hippocampus with the same thickness as the iVASO image slice (resolution = $1 \times 1 \times 4 \text{ mm}^3$). The iVASO sequence was a single-shot gradient-echo, echo-planar imaging acquisition with the following parameters: spatial resolution = $2.5 \times 2.5 \times 4 \text{ mm}^3$, TE = 15 ms, TR = 500, 1000, 1492, 2000, 5000 ms corresponding to TI = 429, 725, 914, 1034, 1191 ms, respectively. Alternating control and null images (30 each) were acquired for a total of 60 dynamics. Slice placement was determined from the angulations of the oblique anatomical slice. No parallel acceleration was used. Five averages of an equilibrium magnetization (TR = 6000 ms) image with the same slice geometry and acquisition scheme but in the absence of iVASO preparation pulses were also acquired. For the null image, the inversion volume, along the slice-select direction for non-selective inversion, extended above the imaging slice, similar to Seq IIa, in (Hua et al., 2011a; Rane et al., 2015). For the control image acquisition, two slice-selective inversion pulses were used, as proposed by Donahue et al. (Donahue et al., 2010). The shim volume was extended well-below the imaging slice to improve homogenous labeling of incoming blood water magnetization through the carotid and basilar arteries.

2.2.2 iVASO pre-processing and analysis—iVASO images at each TR/TI were motion corrected using FSL's MCFLIRT and registered to the equilibrium magnetization

image (Jenkinson et al., 2002). aCBV was calculated using the following equation (Donahue et al., 2010),

$$aCBV \approx \frac{\Delta S}{AC_b \left(\frac{TI}{\tau}\right) M_b^0 E1 E2} \quad [1]$$

where ΔS is the difference signal between the control and the null image, A is a constant dependent on the scanner gain, C_b is the blood water density (0.87ml/ml) (Herscovitch and Raichle, 1985), TI is the inversion time, τ is the arterial arrival time (time for inverted blood water to reach the capillary exchange site), M_b^0 is the steady state magnetization of blood water, $E1 = 1 - e^{(-TR/T1b)}$, and $E2 = e^{(-TE/R2^*b)}$ where $R2^*b$ is the $R2^*$ of blood water. Note that $E1$ accounts for the effect of excitation pulse, which was omitted in (Donahue et al., 2010). $T1b = T1$ of blood water 1.627s, $\tau = 500$ ms for the hippocampus, $R2^*$ of arterial blood water = $16s^{-1}$ and of venous blood water = $21s^{-1}$. The product AM_b^0 was calculated from the first control image for each TR/TI combination using a sagittal sinus region of interest (ROI) and a correction for differences between arterial and venous $R2^*$ as outlined by Petersen et al. (Petersen et al., 2006). Signal in the sagittal sinus was calculated from the control image as follows:

$$S_c = S_{venous\ blood} \quad [2]$$

$$S_c = AM_b^0 C_b E1 E2 \quad [3]$$

$$AM_b^0 = \frac{S_c}{C_b E1 E2} \quad [4]$$

For each subject, the bilateral two regions (anterior, posterior) were manually segmented on a high spatial resolution anatomical image to generate four ROIs. The anatomical image was then skull-stripped and co-registered (downsampled) to the equilibrium magnetization image. The transformation matrix was then applied to the four ROIs to bring them into the iVASO space. Mean aCBV values were recorded for each region at each TI. Macrovascular aCBV contributions from the middle hippocampal artery (Duvernoy, 2013) were minimized by excluding voxels with aCBV > 5 ml/100g.

2.3 Analysis

The primary analysis was conducted at TI = 725 ms based on our previously published work (Rane et al., 2015) that optimized this parameter for the hippocampus in healthy controls. The same time point was chosen for the schizophrenia patients, since recent evidence suggests no differences in hippocampal blood flow or mean transit time in schizophrenia (Talati et al., 2015). To account for individual differences in arterial arrival time in the hippocampus, a secondary analysis was performed that determined the best inversion time

for each subject based on the maximum difference signal between the control and null images. Using this criterion, 14 out of 25 controls and 10 out of 17 patients had the maximum difference signal at $TI = 725$ ms. Mean aCBV values for that inversion time were then used for group analyses, with the individual inversion times as covariates of no interest. Matlab (version 7.13.0.564, The MathWorks Inc, Natick, Massachusetts) was used to generate an in-house script to obtain aCBV values.

The primary analysis was a repeated-measures ANOVA to investigate between group regional differences, with region (anterior, posterior) and hemisphere as repeated measures. Effects of clinical status were tested with two-sided t-tests and chi-square tests. Because groups were well matched, age, gender, and race were not included as covariates in the analysis. Statistical analyses were performed using The Statistical Package for Social Sciences software (SPSS version 20, Armonk, NY: IBM Corp <http://www.spss.com>).

3. RESULTS

Figure 1 illustrates the single slice structural image (Figures 1A, 1D), iVASO image (Figures 1B, 1E), and arterial CBV map (Figure 1C, 1F) of the long axis of right and left hippocampus. Figures 1D–F show the right anterior and posterior hippocampal ROIs.

We quantified aCBV values at $TI = 725$ ms for the right anterior (RA), right posterior (RP), left anterior (LA), and left posterior (LP) hippocampus. Healthy controls had aCBV values (mean $\pm$ st deviation) of 2.00 ± 0.55 ml/100g in the anterior and 2.30 ± 0.29 ml/100g in the posterior hippocampus. These values are comparable with reported values in the literature for hippocampal arterial CBV with some inclusion of capillary CBV (due to uncertainties in arterial arrival time) (Hua et al., 2011a; Rane et al., 2015).

A repeated measures ANOVA showed no main effects of diagnosis ($F_{1,33} = 0.66$, $p = 0.42$), hemisphere ($F_{1,33} = 0.82$, $p = 0.37$), or region ($F_{1,33} = 2.14$, $p = 0.15$) and no significant interactions (all $p > 0.10$). Healthy controls had significantly higher aCBV in the posterior region than the anterior region of the right hippocampus (2.24 ± 0.61 ml/100g vs 1.90 ± 0.49 ml/100g, t-test, $p = 0.039$), which was not seen in early psychosis patients (t-test, $p > 0.10$, Figure 2); however, there was no region by diagnosis interaction for the right hippocampus ($F_{1,36} = 1.12$, $p = 0.30$). A secondary analysis of male only subjects confirmed the finding that there was no main effect of diagnosis and no interactions with hemisphere or region.

To account for individual physiological differences in arterial arrival time, we also generated aCBV values at an inversion time that was optimized for each subject. There was no main effect of diagnosis ($F_{1,23} = 2.63$, $p = 0.12$), region ($F_{1,23} = 3.13$, $p = 0.09$) or hemisphere ($F_{1,23} = 0.037$, $p = 0.85$). Furthermore, there were no significant interactions (all $p > 0.10$), confirming the primary analysis (Supplementary Figure 1).

4. DISCUSSION

We employed the inflow-based-vascular-space-occupancy with dynamic subtraction (iVASO-DS) method to test the hypothesis of increased arterial CBV in the hippocampus of psychotic patients. This is, to the best of our knowledge, the first application of the iVASO-

DS method for the study of CBV changes in psychotic disorders. Contrary to our hypothesis, derived from studies of psychotic disorders using total CBV methods (Schobel et al., 2013; Schobel et al., 2009; Talati et al., 2014; Talati et al., 2015), we did not find any differences in arterial CBV in the hippocampus of patients who were in the early stage of psychosis.

There is great interest in neuroimaging biomarkers for neuropsychiatric disorders (Tregellas, 2014). Increased hippocampal CBV has been proposed as such a biomarker (Schobel et al., 2013; Schobel et al., 2009), but the method used previously requires intravenous access and contrast administration, two significant limitations. Furthermore, gadolinium-based contrast has been shown to accumulate in brain regions such as the globus pallidus and the dentate nucleus of the cerebellum, although the significance of this finding in the context of an intact blood-brain barrier and normal renal function is still unclear (Ramalho et al., 2015). Due to these concerns, we were interested in establishing a less invasive method for the study of increased hippocampal CBV as a biomarker of psychosis.

Our current study failed to find group differences in aCBV, even though the arterial compartment experiences robust changes in response to neural stimulation (Chen et al., 2011; Hillman et al., 2007; Kim et al., 2007). Our findings of normal aCBV in the context of previous findings of increased total CBV in prodromal (Schobel et al., 2013; Schobel et al., 2009), early psychosis (Schobel et al., 2013), and chronic schizophrenia patients (Schobel et al., 2013; Schobel et al., 2009; Talati et al., 2014; Talati et al., 2015) can be interpreted in a new working model: acute excitation-inhibition imbalances lead to robust aCBV changes, while chronic imbalances result in minimal aCBV differences, due to precapillary sphincter desensitization and higher venous CBV differences due to its slower response (eg venous pooling). This is consistent with studies that have shown gradual venous CBV changes after neural stimulation (Kim et al., 2007; Kim and Kim, 2011). Currently, a few sequences exist to test this hypothesis directly, including a hyperoxic gas challenge (Bulte et al., 2007), venous refocusing for volume estimation (VERVE (Stefanovic and Pike, 2005)), and subtraction of contrast-enhanced total CBV from aCBV (Kim and Kim, 2011). While we were not able to collect such data in the current cohort, this should be an area of exploration in future studies.

The mechanism of hippocampal hyperactivity in psychotic disorders remains unknown (Lisman et al., 2008). Current hypotheses focus on excitation-inhibition imbalance due to N-methyl-D-aspartate (NMDA) receptor hypofunction (Greene, 2001) or parvalbumin- and somatostatin-containing interneuron dysfunction (Heckers and Konradi, 2014). Current human imaging methods do not have sufficient spatial and temporal resolution to parse out the underlying mechanism. Several animal studies have provided intriguing data in support of the NMDA-receptor hypofunction model (Schobel et al., 2013) or the GABAergic interneuron model. Acute administration of ketamine has been shown to increase CA1 and subiculum CBV, while chronic administration has been shown to recapitulate hippocampal hyperactivity and subsequent atrophy (Schobel et al., 2013). Meanwhile, the methylazoxymethanol acetate (MAM) G17 model has been shown to affect the density of parvalbumin-containing GABAergic interneurons in the ventral (anterior) hippocampus and disrupt gamma oscillations between the hippocampus and prefrontal cortex (Lodge et al., 2009). Future animal studies need to directly test NMDA receptor hypofunction vs

interneuron dysfunction. One possible way is to generate animal models that selectively suppress a subpopulation of interneurons (Brown et al., 2015). Hippocampal CBV maps from these models before and after ketamine administration can then be compared with results from human studies to draw stronger inferences about underlying mechanisms of psychosis.

We have to acknowledge several limitations of the iVASO-DS method, which could have contributed to our inability to find increased aCBV in psychotic patients. First, the limited spatial resolution of the iVASO-DS data did not allow us to test for subfield-specific aCBV changes in psychosis. All previous studies of hippocampal CBV in psychosis have found CBV increases in hippocampal sector CA1, but not other subfields of the hippocampal formation (Schobel et al., 2013; Schobel et al., 2009; Small et al., 2011; Talati et al., 2014). The greater resolution of gadolinium-enhanced imaging methods (Small et al., 2011) might be necessary to test the hypothesis of subfield-specific CBV changes in the hippocampus.

Second, the 4 mm thick imaging slice included not only the hippocampal formation but also surrounding white matter, which confounds our aCBV results. Efforts can be focused on reducing the macrovascular contribution relative to the microvascular contribution through a combination of bipolar crusher gradients and/or different TIs (Hua et al., 2011b; Lorenz, 2013). This would reduce flow signal from the macrovascular component, although it may be technically difficult with this sequence because the arteries are in the plane of the imaging slice.

Third, we assumed that the consecutive inversion pulses in both the control and null images were identical, in line with previous studies (Hua et al., 2011a; Hua et al., 2011b). Our previous work has shown that this assumption does not significantly alter aCBV values and is not likely to have affected the outcome of our study (Donahue et al., 2010; Rane et al., 2015). Fourth, advanced models can be used for multi-TI iVASO data, which will likely improve the result (Hua et al., 2011b). However, insufficient data points collected in the present study prevent us from applying this method. Finally, our limited finding could be due to partial volume effects. However, this is very unlikely as our previously published work (Rane et al., 2015) shows that partial volume effects do not significantly affect aCBV values derived from manually-segmented hippocampal ROIs.

In conclusion, we could not confirm our hypothesis of increased hippocampal aCBV in the early stage of psychosis using the iVASO-DS method. Further studies are needed to better understand changes in both arterial and venous CBV in the hippocampus of psychotic disorder patients.

Acknowledgments

The authors thank S. Kristan Armstrong for help with subject recruitment. The study was supported by the following grants: R01 MH070560 awarded to SH; Vanderbilt Office of Clinical and Translational Scientist Development awarded to SR; R01 NS078828 supported SR and MJD (PI); R01 NS097763 supported MJD; F30 MH102846 and T32 GM07347 provided support to PT.

References

- Brown JA, Ramikie TS, Schmidt MJ, Baldi R, Garbett K, Everheart MG, Warren LE, Gellert L, Horvath S, Patel S, Mirnics K. Inhibition of parvalbumin-expressing interneurons results in complex behavioral changes. *Mol Psychiatry*. 2015; 20:1499–1507. [PubMed: 25623945]
- Bulte D, Chiarelli P, Wise R, Jezzard P. Measurement of cerebral blood volume in humans using hyperoxic MRI contrast. *J Magn Reson Imaging*. 2007; 26:894–899. [PubMed: 17896390]
- Chen BR, Bouchard MB, McCaslin AF, Burgess SA, Hillman EM. High-speed vascular dynamics of the hemodynamic response. *Neuroimage*. 2011; 54:1021–1030. [PubMed: 20858545]
- Donahue MJ, Sideso E, MacIntosh BJ, Kennedy J, Handa A, Jezzard P. Absolute arterial cerebral blood volume quantification using inflow vascular-space-occupancy with dynamic subtraction magnetic resonance imaging. *J Cereb Blood Flow Metab*. 2010; 30:1329–1342. [PubMed: 20145656]
- Duvernoy, HM.; Cattin, Françoise; Risold, Pierre-Yves. The human hippocampus: functional anatomy, vascularization and serial sections with MRI. 4. Springer; 2013.
- First, MB.; Spitzer, Robert L.; Miriam, Gibbon; Williams, Janet BW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/PSY SCREEN). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
- Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010; 167:686–693. [PubMed: 20360319]
- Greene R. Circuit analysis of NMDAR hypofunction in the hippocampus, in vitro, and psychosis of schizophrenia. *Hippocampus*. 2001; 11:569–577. [PubMed: 11732709]
- Heckers S, Konradi C. GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. *Schizophr Res*. 2014
- Herscovitch P, Raichle ME. What is the correct value for the brain–blood partition coefficient for water? *J Cereb Blood Flow Metab*. 1985; 5:65–69. [PubMed: 3871783]
- Hillman EM, Devor A, Bouchard MB, Dunn AK, Krauss GW, Skoch J, Bacsikai BJ, Dale AM, Boas DA. Depth-resolved optical imaging and microscopy of vascular compartment dynamics during somatosensory stimulation. *Neuroimage*. 2007; 35:89–104. [PubMed: 17222567]
- Hua J, Qin Q, Donahue MJ, Zhou J, Pekar JJ, van Zijl PC. Inflow-based vascular-space-occupancy (iVASO) MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2011a; 66:40–56.
- Hua J, Qin Q, Pekar JJ, van Zijl PC. Measurement of absolute arterial cerebral blood volume in human brain without using a contrast agent. *NMR Biomed*. 2011b; 24:1313–1325. [PubMed: 21608057]
- Ito H, Kanno I, Iida H, Hatazawa J, Shimosegawa E, Tamura H, Okudera T. Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Ann Nucl Med*. 2001; 15:111–116. [PubMed: 11448068]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17:825–841. [PubMed: 12377157]
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987; 13:261–276. [PubMed: 3616518]
- Kim T, Hendrich KS, Masamoto K, Kim SG. Arterial versus total blood volume changes during neural activity-induced cerebral blood flow change: implication for BOLD fMRI. *J Cereb Blood Flow Metab*. 2007; 27:1235–1247. [PubMed: 17180136]
- Kim T, Kim SG. Temporal dynamics and spatial specificity of arterial and venous blood volume changes during visual stimulation: implication for BOLD quantification. *J Cereb Blood Flow Metab*. 2011; 31:1211–1222. [PubMed: 21179068]
- Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Carpenter WT, McMahon R. Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. *Neuropsychopharmacology*. 2006; 31:221–230. [PubMed: 16123774]
- Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Cropsey KL. Modulation of limbic circuitry predicts treatment response to antipsychotic medication: a functional imaging study in schizophrenia. *Neuropsychopharmacology*. 2009; 34:2675–2690. [PubMed: 19675535]

- Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci.* 2008; 31:234–242. [PubMed: 18395805]
- Lodge DJ, Behrens MM, Grace AA. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J Neurosci.* 2009; 29:2344–2354. [PubMed: 19244511]
- Lorenz, K.; Mildner, T.; Pampel, A.; Möller, HE. Transient effects in arterial CBV Quantification; ISMRM 21st Annual Meeting and Exposition; Salt Lake City, UT, USA. 2013.
- Medoff DR, Holcomb HH, Lahti AC, Tamminga CA. Probing the human hippocampus using rCBF: contrasts in schizophrenia. *Hippocampus.* 2001; 11:543–550. [PubMed: 11732707]
- Petersen ET, Lim T, Golay X. Model-free arterial spin labeling quantification approach for perfusion MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine.* 2006; 55:219–232.
- Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M. Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update. *AJNR Am J Neuroradiol.* 2015
- Rane S, Talati P, Donahue MJ, Heckers S. Inflow-vascular space occupancy (iVASO) reproducibility in the hippocampus and cortex at different blood water nulling times. *Magn Reson Med.* 2015
- Schobel SA, Chaudhury NH, Khan UA, Paniagua B, Styner MA, Asllani I, Inbar BP, Corcoran CM, Lieberman JA, Moore H, Small SA. Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron.* 2013; 78:81–93. [PubMed: 23583108]
- Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, Small SA. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Arch Gen Psychiatry.* 2009; 66:938–946. [PubMed: 19736350]
- Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat Rev Neurosci.* 2011; 12:585–601. [PubMed: 21897434]
- Stefanovic B, Pike GB. Venous refocusing for volume estimation: VERVE functional magnetic resonance imaging. *Magn Reson Med.* 2005; 53:339–347. [PubMed: 15678548]
- Talati P, Rane S, Kose S, Blackford JU, Gore J, Donahue MJ, Heckers S. Increased hippocampal CA1 cerebral blood volume in schizophrenia. *Neuroimage Clin.* 2014; 5:359–364. [PubMed: 25161901]
- Talati P, Rane S, Skinner J, Gore J, Heckers S. Increased hippocampal blood volume and normal blood flow in schizophrenia. *Psychiatry Res.* 2015; 232:219–225. [PubMed: 25896442]
- Tregellas JR. Neuroimaging biomarkers for early drug development in schizophrenia. *Biol Psychiatry.* 2014; 76:111–119. [PubMed: 24094513]

Highlights

- Anterior hippocampal cerebral blood volume (CBV) is increased in early psychosis
- Methods used to report this finding require a contrast agent
- We used a novel, non-invasive iVASO-DS method to study hippocampal arterial CBV
- We did not find hemispheric or regional hippocampal differences
- Future studies should measure both hippocampal arterial and venous CBV

Figure 1. iVASO slice planning

The top panel shows a representative structural (A), iVASO image at TI = 725 ms (B), and arterial CBV (aCBV) map (C). Figures D–F show the respective figures with a right anterior and posterior hippocampal ROI overlay. Note that the macrovasculature is white with aCBV values > 25 on the nonlinear aCBV colormap. L denotes left and R denotes right side of the image.

Figure 2. aCBV values in hippocampal ROIs at TI = 725 ms

Figure 2 illustrates aCBV values in patients and healthy controls at TI = 725 ms for the left and right anterior and posterior regions (LA, LP, RA, RP). A repeated measures ANOVA illustrated no main effect of diagnosis, hemisphere, region, or significant interactions with diagnosis. Error bars denote standard deviation.

Table 1

Subject Demographics

	Controls (n = 25)	First Episode Psychosis (n = 17)	Statistic	p-value
Age (yrs)	22.7±2.4	21.9±3.4	t(40) = 0.82	0.42
Males/Females	22/3	13/4	X(1) = 0.97	0.33
Race (W/B/O)	21/3/1	11/5/1	X(2) = 2.18	0.34
Subject edu. (yrs)	15.0±1.83	13.4±2.1	t(40) = 2.70	0.01
Avg. parental edu. (yrs)	14.5±1.8	15.1±2.0	t(40) = 1.06	0.30
WTAR	112.6±11.0	105.7±12.6	t(40) = 1.88	0.07
Duration of Illness (mo)		7.6±6.1		
CPZ equivalent (mg/day) ^a		339.7±235.3		
PANSS		Pos: 13.6±6.7 Neg: 15.5±8.7 Gen: 28.1±6.7		

Healthy control and early psychosis subject demographics. Groups are matched on age, gender, race. Values are reported as mean ± st dev.

^a 13 out of 17 patients had CPZ equivalents