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Hippocampal arterial cerebral blood volume in early psychosis

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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 3 T 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.

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, 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

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parts of hippocampal subfield CA1 (Schobel et al., 2013, 2009; Small et al., 2011; Talati et al., 2014, 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 3 T MRI Achieva scanner (Best, The Netherlands) with a 32 channel SENSE head coil was used for imaging. The high-resolution T1-weighted gradient echo 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 = $1 \times 1 \times 4\ mm^3$). 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 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. (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),

$$aCBV \approx \frac{\Delta S}{AC_b\left(\frac{TI}{\tau}\right)M_b^0 E1E2} \quad (1)$$

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 (0.87 ml/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). $T1_b$ = $T1$ of blood water 1.627 s, τ = 500 ms for the hippocampus, R2* of arterial blood water = 16 s^{-1} and of venous blood water = 21 s^{-1}. The product AM^0_b 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. (2006). Signal in the sagittal sinus was calculated from the control image as follows:

$$S_c = S_{venousblood} \quad (2)$$

$$S_c = AM_b^0 C_b E1E2 \quad (3)$$

$$AM_b^0 = \frac{S_c}{C_b E1E2} \quad (4)$$

For each subject, the bilateral two regions (anterior, posterior)

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	$X^2(1)$ = 0.97	0.33
Race (W/B/O)	21/3/1	11/5/1	$X^2(2)$ = 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.