Reduced Grey Matter Arteriolar Cerebral Blood Volume in Schizophrenia

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PURPOSE: Microvascular abnormality in the brain has been reported in schizophrenia patients (1), which has been linked to the neuropathology of the disease (2). This has previously been studied measuring changes in *total* cerebral blood volume (CBV) and flow (CBF) (including arterial, capillary and venous vessels) in schizophrenia using various techniques such as MRI and PET. Neurophysiology studies have shown that small arteries and arterioles are most responsive to changes in metabolism. Therefore, the measurement of changes in arteriolar blood vessels separately may furnish information that is not obtainable from total CBV and CBF measures. In this study, we applied the inflow-based vascular-space-occupancy (iVASO) MRI technique (3-5), to investigate potential arteriolar CBV (CBVa) abnormality in the grey matter (GM) of the brain in schizophrenia patients, and compare it with matched control subjects.

METHODS: *Participants:* twelve schizophrenia patients and twelve age and sex matched normal controls with informed consent were scanned. None of the subjects had other neurologic history or signs on exam, or history of vascular diseases. *MRI:* All scans were performed on a 7T Philips MRI scanner. A 32-channel phased-array head coil (Nova Medical) was used for RF reception and a head-only quadrature coil for transmit. Anatomical images were acquired with a 3D MPRAGE scan (TR/TE/TI=4.7/2.1/446ms, voxel=0.6mm isotropic). GM CBVa was measured using 3D iVASO MRI with whole brain coverage. iVASO parameters: TR/TI=10000/1383, 5000/1093, 3800/884, 3100/714, 2500/533, and 2000/356ms; 3D TFE readout, TR_{TFE}/TE_{TFE}=4.2/2.2ms; voxel=3.5x3.5x5mm^3, 20 slices; SENSE=2x2; crusher gradients of b=0.3s/mm^2 and V_{enc}=10cm/s on z-direction. A reference scan (TR=20s, other parameters identical) was obtained to determine the scaling factor M0 in iVASO images so that absolute CBVa values can be calculated. *Image analysis:* SPM8, AIR and other in-house code programmed in Matlab 6.0 (Mathworks, USA) were used for image analysis. Partial volume effects of WM and CSF on the iVASO signals in GM were corrected. CBVa maps were generated using the iVASO theory (3). *Statistical analysis:* Second-level t-tests were performed to examine group difference (thresholded at a voxel-level of p<.001 and multiple-comparisons corrected at a cluster-level threshold of p<.05). Effect size was estimated with Cohen's *d*. The IBASPM116 atlas (PickAtlas, WFU) was used to identify anatomical regions within the significant clusters.

Table 1: CBVa abnormality in the brain.

Region	Hemis-phere	Size (#voxels)	GM CBVa (ml/100ml) SCZ mean	SCZ std	Control mean	Control std	Relative Change (%)	Effect size	Peak (mm, MNI) x	y	z	T score max	mean	std	Adjusted P value
Angular	R	390	0.81	0.17	1.15	0.19	-29.2	-1.96	48	-64	38	3.52	1.80	0.37	0.002
Angular	L	462	0.73	0.24	1.18	0.28	-38.1	-1.81	-44	-72	38	4.21	2.12	0.57	0.004
Cingulum_Mid	R	248	0.87	0.14	1.06	0.06	-17.7	-1.87	6	-14	44	2.47	1.58	0.23	0.007
Cuneus	L	506	0.79	0.16	1.12	0.26	-29.9	-1.66	-2	-86	32	3.54	1.78	0.40	0.008
Frontal_Mid	L	489	0.80	0.19	1.23	0.27	-34.7	-1.94	-46	6	54	3.76	1.76	0.37	0.003
Frontal_Sup	L	573	0.79	0.22	2.02	0.94	-60.7	-1.86	-18	-2	76	3.08	1.78	0.36	0.007
Frontal_Sup_Medial	R	236	0.99	0.31	1.86	0.67	-46.5	-1.72	14	38	58	3.14	1.77	0.37	0.008
Parietal_Inf	R	267	0.75	0.24	1.11	0.21	-32.0	-1.68	44	-46	54	3.05	1.74	0.34	0.007
Parietal_Inf	L	644	0.71	0.26	1.14	0.31	-37.5	-1.59	-30	-74	48	3.79	1.91	0.44	0.010
Parietal_Sup	R	872	0.56	0.30	1.13	0.42	-50.8	-1.65	16	-78	56	4.51	2.00	0.55	0.008
Parietal_Sup	L	698	0.58	0.31	1.17	0.36	-50.3	-1.85	-36	-44	68	4.44	2.08	0.56	0.004
Precuneus	R	791	0.73	0.19	1.18	0.19	-38.0	-2.49	8	-48	66	3.73	1.81	0.41	0.000
Precuneus	L	816	0.67	0.26	1.17	0.28	-42.9	-1.99	-2	-78	52	3.62	1.87	0.48	0.002
Supp_Motor_Area	R	520	0.93	0.24	1.69	0.61	-44.9	-1.71	6	4	70	4.00	1.76	0.40	0.009

RESULTS: Representative CBVa maps are shown in Fig. 1. Table 1 summarizes the main findings in the group comparison. The average GM CBVa values in controls were all in normal range (3), providing validation for our measurements. Significant reduction of GM CBVa values was detected in several cortical regions in schizophrenia patients compared to controls (n=12) with relative changes of 17-60% and effect sizes of 1.5-2.5. No substantial GM CBVa increase in schizophrenia patients was found in any brain regions.

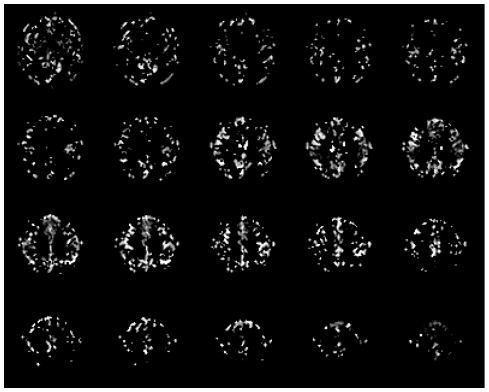

Figure 1: Representative 3D iVASO CBVa maps from one control subject.

DISCUSSION: Hypoperfusion in the brain has been documented in schizophrenia. Using methods including ASL MRI, DSC MRI, PET and SPECT, reduced CBF was found in the frontal lobe, parietal region, precuneus, and cingulate cortex (1,6-9). Decrease in total CBV (including arterial, capillary and venous vessels) was also observed in the frontal lobe (6,9). These literature data are all consistent with our finding of smaller GM CBVa in schizophrenia patients. The iVASO MRI approach used in this study allows the assessment of arteriolar CBV changes separately, which is the most actively regulated compartment in the microvasculature. In addition to the areas with abnormal total CBV and CBF values reported in the literature, decreased GM CBVa was also detected in our data in the angular gyrus, cuneus and the motor region, all of which have been implicated in schizophrenia (10). A similar study from our group using iVASO MRI at 7T found *increased* (instead of decreased) GM CBVa in various brain regions in Huntington's disease (11), which provides evidence that the measured CBVa effects are not likely due to some systemic bias. An important caveat is that the patients, not controls, in this study were all receiving antipsychotic medicines. Whether the same findings would be seen in younger or unmedicated patients remains to be determined.

CONCLUSION: We report widespread GM CBVa reduction in the brain of schizophrenia patients. Our results indicate that neurovascular abnormality may serve as a surrogate marker of schizophrenia, and such changes may be a fundamental aspect of disease pathogenesis.

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