Alterations in Cardiac-Correlated Brain BOLD Signal in Children with Chronic Kidney Disease

Hua-Shan Liu[1], Abbas F. Jawad[2], Nina Laney[2], Stephen Hooper[3], Jerilynn Radcliffe[2], Divya Moodalbail[2], Christos Davatzikos[1], Robert Schultz[2], Susan Furth[2], and John Detre[1]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, United States, [3]University of North Carolina School of Medicine, Chapel Hill, NC, United States

Target audience: Researchers interested in ASL/ BOLD fMRI methods and clinical applications

Introduction and purpose: Chronic kidney disease (CKD) is characterized by a progressive loss in kidney function over a period of months or years and is associated with systemic complications such as hypertension and anemia. Brain function may be affected in CKD by a variety of factors including developmental alterations and vascular injury to disorders of metabolism [1]. Blood-oxygen-level dependent (BOLD) contrast provides an indirect measure of changes in cerebral metabolism [2] that represents a complex interaction between blood flow, blood volume, and blood oxygenation. It has been suggested that systemic cardiovascular fluctuations can cause changes in cerebral blood flow (CBF), accounting for the some of the information carried in the cerebral hemodynamics [2]. Accounting for these cardiovascular fluctuation-induced modulations in BOLD signals can therefore be used to make comparisons across populations with different degrees of cardiovascular integrity [3]. In the present study, the cardiac-correlated resting BOLD response was used to investigate group differences between children with CKD and healthy controls. We hypothesized that CKD-induced alterations in cardiovascular function may be manifested by alterations in physiology-related BOLD response.

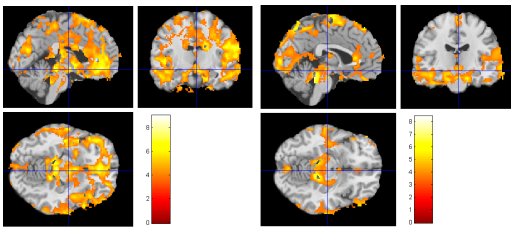

Fig. 1. Group maps of cardiac-related activity on the BOLD signal for CKD (left) and control (right)groups. P_{uncorr}<0.001, K> 100 voxels; FDR cluster-level P_{corr}<0.05.

Methods: Twenty-seven patients with any stage of CKD I to V (defined as estimated glomerular filtration rate, eGFR <90 ml/min/1.73m^2 using modified Schwartz formula, on dialysis, and post-transplant) and 21 age-matched healthy control subjects were included in this study (see Table 1 for group differences in renal function). Data acquisition was performed on a Siemens 3T Verio whole body MRI scanner using a 32-channel head coil. A single block of 120 BOLD resting functional images was acquired using a gradient-echo echo-planar (GE EPI) pulse sequence with: TR/ TE= 3000/ 30 ms, flip angle = 90°, FOV = 192 mm, bandwidth= 2441 Hz/ pixel, matrix size = 64 × 64 and slice thickness=3 mm with 46 slices. High-resolution whole brain anatomic images were collected using 3-dimensional magnetization-prepared rapid gradient echo with: inversion time = 1050 msec, TR/ TE = 1790 /3.06 msec and 160 axial slices with 1 mm isotropic resolution. During BOLD imaging scanning, physiological signals were recorded using the product physiological monitoring unit (PMU) [3]. CBF was also measured using pCASL with 2D GE EPI. The labeling and control RF duration was 1.5 sec with post-labeling delay of 1.2 sec. Multi-slice perfusion maps with 40 label/ control pairs were acquired with: TR/TE = 4000/17 ms, flip angle=90^0, bandwidth = 1532 Hz/pixel, slice thickness = 4mm with 25% distance factor, matrix size = 64×64, FOV = 240×240 mm^2, slice number = 20, and GRAPPA factor = 2. Absolute CBF maps were calculated using ASLtbx [4]. Cardiac fluctuations were derived from PMU pulse oximetry. Cardiac signals were extracted from the high frequency covariate in the raw pulse arrays [3]. In the first level analysis, cardiac phase regressors calculated using RETROICOR [5] were fitted to the BOLD signal. Estimates of cardiac-induced modulation of the BOLD signal were performed using a regression with hematocrit (Hct) as a covariate variable. Within -group analysis used a one-sample t-test. Voxel-wise differences in cardiac influence maps between CKD patients and controls were then assessed using two-sample t-test. To explore how cardiac-induced fluctuation results related to physiological scores, we performed a series of Spearman correlation analyses of BOLD fMRI outcome (beta values) with CBF, heart rate (HR) derived from RETROICOR, blood pressure (BP, total systolic load) and Hct. Region of interest analyses with signals extracted from the cluster in the group effect were conducted to examine associations between those measurements. Multiple stepwise regression was used to model BOLD fMRI outcomes using group, age, CBF, BP and Hct.

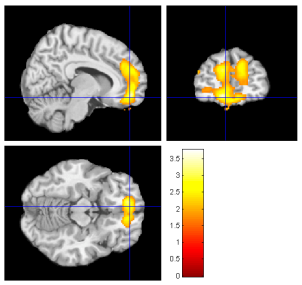

Fig. 2. Group difference. CKD group showed greater cardiac-induced modulations in the ACC as compared with control group. P_{uncorr}<0.05, K> 500 voxels; FDR cluster-level P_{corr}<0.0005.

Roh P-value	CBF (ml/100 g/min)	Heart Rate	BP (Total systolic load)	Hct (%)
Beta (CKD)	-0.301 0.198	0.015 0.942	0.187 0.351	0.064 0.751
Beta (Control)	0.092 0.65	-0.323 0.153	0.099 0.669	0.275 0.227

Table2. Spearman correlations between BOLD beta and other physiological measures in CKD and control subjects. Data are presented as correlation coefficients and P values. No significant association was found (P>0.05).

Results: Figure 1 shows group maps of cardiac-related activity on the BOLD signal. Regions showing the largest cardiac-induced variance in the BOLD signal are close to the major vessels and their main branches, as has previously been reported [5,6]. Most of this cardiac-correlated BOLD signal showed no difference between CKD and controls in the group comparison. However, CKD showed significantly larger cardiac-correlated BOLD effects in the anterior cingulate cortex (ACC, Fig.2). Corresponding beta and CBF values extracted from the ACC cluster and other physiological measurements were presented in Table 1. Post hoc paired-sample t-test confirmed significantly higher cardiac phase beta in CKD subjects. Lower and non-significant (P>0.05) Spearman correlations were found between beta and other physiological measures (Table 2) and there was no significant effect in the prediction of BOLD beta outcome in a multiple regression analysis using these parameters.

Table 1. Data presented as mean±std

Group	BOLD beta	CBF (ml/100g/min)	Heart rate	BP (total systolic load)	Hematocrit (%)	Creatinine (mg/dl)	eGFR (ml/min/1.73 m^2)	Age	Gender (M/ F)
CKD (n=27)	0.33±0.22	56.37±8.74	72.9±11.3	0.22±0.24	38.06±4.73	2.93±2.60	43.16±25.38	15.0±3.1	17/ 10
Controls (n=21)	0.19±0.11	51.81±9.25	70.9±10.8	0.16±0.18	41.08±5.23	0.69±0.2	96.43±16.52	15.14±3.44	9 /12
p-value	0.01	0.2	0.53	0.4	0.03	0.002	<0.0001	0.92	0.14

Discussion and conclusion: Cardiac-related modulation is widely recognized in BOLD fMRI. Our within-group data replicate previous findings that cardiac-induced variance in BOLD signal is concentrated near major cerebral arteries including the middle cerebral artery near the anterior temporal lobes and insula, the anterior cerebral artery in the anterior interhemispheric fissure in the medial frontal lobes, and the vertebrobasilar system near the brainstem [5,6]. However, patients with CKD demonstrated a focal increase of cardiac modulation of resting BOLD signal in the ACC, which cannot be fully explained by CBF, BP, HR and Hct as revealed in the univariate correlation and multiple regression analyses. The mechanism for the observed changes in cardiac-correlated BOLD in the ACC in CKD is unknown. It may reflect a focal disturbance of cerebrovascular autoregulation or alternatively may represent a neural correlate of altered cardiovascular function, though group differences in RETROICOR-derived HR were not observed. Alterations in the ACC may also contribute to cognitive dysfunction observed in CKD [7]. Future work will focus on correlating alterations in cardiac-correlated BOLD with cognitive function and more detailed assessments of cardiovascular variability.

References: 1. Moodalbail et al., Clin J Am Soc Nephrol. 2013; 8:1429-48. **2.** Chang et al., Neuroimage 2013; 68:93-104. **3.** Verstynen et al., Neuroimage 2011; 55: 1633-44. **4.** Wang et al., MRI 2008; 26:261-9. **5.** Glover et al., MRM 2000; 44: 162-7. **6.** Dagli et al., Neuroimage.1999; 9:407-15. **7.** Tsai et al., Kidney Int. 2010 ;78:605-10.

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