Test-retest reproducibility of BOLD-CVR measures in children using a computer-controlled CO_2 challenge

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Introduction: Cerebrovascular reactivity (CVR), which quantifies the cerebral blood flow response to a vasoactive stimulus, is the equivalent of a cerebrovascular 'stress test' and offers insight into the function of the cerebrovasculature. In particular, CVR measurements have shown applicability in the assessment cerebrovascular disease [1-4]. A key parameter for evaluating the efficacy and utility of CVR imaging is the reproducibility of the measurements. Various factors may influence reproducibility, including physiological fluctuations in CBF or metabolism as well as physical factors such as variability in the stimulus, subject positioning and the uniformity of the main magnetic field. Good reproducibility has previously been shown in adults using blood-oxygen level-dependent (BOLD) MRI measures in combination with a model-free prospective end-tidal targeting (MPET) system to deliver precise concentrations of a CO_2 stimulus [5]. However, reproducibility in children using this method has not yet been established and needs to be evaluated to facilitate routine CVR measurements in the pediatric population with this approach. The purpose of this study was to perform test-retest reproducibility of BOLD-CVR measures in children using the MPET system. We hypothesize that CVR measures using this system will have reproducibility comparable to the published adult values.

Materials and Methods: Eight healthy volunteers (4 males and 4 females) between 15 and 17 years old were imaged on a clinical 3T MRI scanner (MAGNETOM Tim Trio; Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. CVR was measured twice (10 minutes apart) on two separate days (2-8 weeks apart). The BOLD data was acquired in synchrony with the MPET system (RespirAct™; Thornhill Research Inc., Toronto, Canada), which enabled simultaneous and accurate targeting of end-tidal partial pressures of CO_2 ($PETCO_2$) and O_2 ($PETO_2$). The stimulus consisted of an 8 minute alternating step-function cycling between normocapnia ($PETCO_2$ = 40mmHg) and hypercapnia ($PETCO_2$ = 45mmHg), while maintaining normoxia ($PETO_2$ = 100mmHg). The BOLD sequence parameters were as follows: TR/TE = 2000/40ms, FOV = 220mm, matrix size = 64×64, slices = 25, slice thickness = 4.5mm, volumes = 240, time = 8min. CVR maps for each subject were computed by correlating the voxel-wise BOLD signal change to the sampled $PETCO_2$ waveform using FSL v4.1 (http://www.fmrib.ox.ac.uk/fsl/), then normalizing to the temporal mean BOLD signal to express CVR in units of %ΔMR / mmHg(CO_2). To separate grey matter (GM) and white matter (WM) regions, we segmented each subject's T1-weighted anatomical images. The CVR maps were then coregistered to these images to extract mean GM and WM values. Reproducibility was assessed using SPSS v22.0 to compute the within-day and between-day intraclass coefficients (ICC) within a 95% confidence interval (CI) and the coefficient of variation (CV).

Results: Figure 1 shows a box graph of the within-day and between-day variation of our pediatric CVR measurements. All statistical results are included in Table 1, showing significant reproducibility ($p \leq 0.02$). The within-day ICC was 0.871 and 0.919 for GM and WM, respectively. The between-day ICC was a little lower at 0.701 and 0.667 for GM and WM.

Discussion: BOLD-CVR reproducibility was comparable to adult data for within-day measures, but lower for between-day measures [5]. This may be due to our smaller sample size compared to the adult reference. Nonetheless, our study suggests that BOLD measurements with the MPET system is a reliable method for the assessment of CVR in children and supports its application in the clinic.

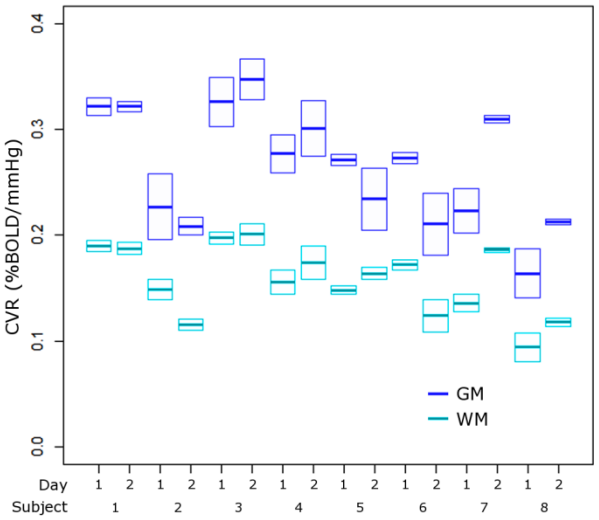

Figure 1. Box plot showing CVR variations within-day and between-day for all subjects.

References:

1. Fierstra J, et al. *Stroke* 2011; 42(6):1631-7; **2.** Mandell DM, et al. *Stroke* 2008; 29(7):2021-8; **3.** Ziyeh S, et al. *Stroke* 2005; 26(4):751-6; **4.** Han JS, et al. *Stroke* 2011; 42(5)1261-9; **5.** Kassner A, et al. *JMRI* 2010; 31(2):298-304.

	Mean CVR (%ΔMR / mmHg)		Within-Day				Between-Day			
	Day 1	**Day 2**	**ICC**	**95% CI**	***p*-value**	**CV (%)**	**ICC**	**95% CI**	***p*-value**	**CV (%)**
GM	0.260±0.020	0.268±0.021	0.871	[0.630, 0.955]	< 0.001	9.4±2.4	0.701	[0.144, 0.891]	0.013	12.4±3.5
WM	0.155±0.012	0.159±0.012	0.919	[0.768, 0.972]	< 0.001	13.1±3.4	0.667	[0.048, 0.896]	0.020	7.8±1.8

Table 1: Mean CVR ± SEM and within-day / between-day ICC, 95% CI, *p*-value, and %CV ± SEM.