# Alterations in Cerebrovascular Reactivity across the Adult Lifespan: a 4-year Follow-up

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**Introduction:** Age is the single most important risk factor for stroke and associated cerebrovascular diseases. Therefore, it is of critical importance to characterize age-related changes in brain vascular integrity. To date, the most direct vascular marker *in vivo* has been shown to be cerebrovascular reactivity (CVR), which reflects the ability of the vessel to dilate when challenged. CVR can be measured by brief inhalation of CO2 while simultaneously acquiring perfusion-sensitive MR data such as the BOLD image. Recently, in one of the most comprehensive vascular imaging studies to date, we examined CVR in a lifespan sample of 207 healthy subjects ranging from 20 to 89 years old. Compared to resting cerebral blood flow (CBF) measure, CVR was found to decline at an earlier age and at a faster rate [1], suggesting a superiority of CVR in detecting vascular alterations. A limitation of that study is its cross-sectional nature, which is known to be susceptible to recruitment bias. For example, a cross-sectional aging study is effectively comparing typical 20 years old to "super-normal" 80 years old, which may under-estimate the extent of age-changes. Therefore, although excessively challenging, the cognitive aging community usually considers longitudinal studies to be the true gold-standard in characterizing age-related changes in cognitive and brain markers. In this work, we present four-year longitudinal follow-up CVR data in 80 healthy individuals ranging from 20 to 85 years old. The findings from the longitudinal data were compared to those from the cross-sectional data. Regional differences were also investigated.

**Methods:** Experiment: The data for this study were collected from the cohort of a large-scale aging study, the Dallas Lifespan Brain Study. Of 207 subjects (aged 20-88) who had participated in the CVR scan successfully during 2008-2010, 98 (aged 24-85) completed the follow-up CVR scan from 2012 till now. Within the 98 subjects, 18 were excluded from the data analyses because their data during CO2 challenge failed to meet our quality control criteria thus not suitable for longitudinal analysis. CVR measurement was performed on a Philips 3T system, following protocols established in our previous studies [2]. Briefly, the CVR was assessed using hypercapnia induced by 5% CO2 breathing (mixed with 21%O2 and 74%N2). The subject with sealed nose breathed through a mouth piece that connected to a 5% CO2 gas bag or room air. The type of air inhaled was switched via a valve in a 1min interleaved manner while BOLD images and physiologic parameters (end-tidal CO2, breathing rate, heart rate, and arterial oxygenation) were continuously collected for 7min. Data Analysis: CVR maps were obtained by general linear regression using BOLD signal as dependent variable and end-tidal CO2 (EtCO2) time course as independent variable [2]. For cross-sectional data, age-related decline in CVR were examined through the slope of linear regression of CVR as a function of age. For longitudinal data, CVR decline rate was examined through the subtraction of the two time-points and then dividing by the time gap. Regional differences in decline rate were investigated using paired t tests for longitudinal data and confidence interval tests for cross-sectional data. A time-course of decline rate was calculated to allow the assessment of age-dependence of the CVR decline. A sliding window with two decades in width and one year in step was used for both cross-sectional and longitudinal calculations.

**Results and Discussions:** The average time gap between Wave 1 and Wave 2 was 4.09±0.17 years. Decade-by-decade CVR maps are shown in Fig. 1, demonstrating a general decreasing trend. Quantitative CVR values for the cross-sectional (N=207) and longitudinal results (N=80) are plotted in Figs. 2a and 2b, respectively. Shown here are whole-brain averaged values, but regional results exhibit same patterns. Across the adult lifespan, cross-sectional data showed an annual CVR decline rate of 0.58±0.07%. On the other hand, longitudinal data revealed a significantly greater ($p<0.05$, one-tail t test) decay rate, 1.23±0.51% annually. That is, cross-sectional data may have under-estimated the decline rate by about 50%. This observation is consistent with the notion that, as the age of the cohort becomes older, there is an increasing selection bias toward more subjects with better cognitive and physical health. Fig. 3 shows region-by-region decline rates. Again, longitudinal data generally exhibit a faster rate. Across brain regions, the longitudinal data revealed a clear regional heterogeneity in CVR decline rates (Fig. 3). For example, occipital lobe has the slowest CVR decline among all brain regions, consistent with the notion that occipital lobe is relatively preserved in aging [3]. On the other hand, temporal lobe revealed the fastest CVR decline with age, which may be because it contains some of the most age-sensitive regions such as hippocampus. For the cross-sectional data, they were not able to show any significant differences across regions. The sensitivity in detecting regional differences is actually one of the advantages of the longitudinal studies, as it allows paired tests in statistical comparison. Temporal patterns of CVR were also examined using both the cross-sectional and longitudinal data (Fig. 4). Interestingly, cross-sectional and longitudinal patterns are drastically different. Cross-sectional time course (blue in Fig. 4) showed that CVR declines more rapid in the 30's and 70's, compared to middle-age. In contrast, longitudinal time course (red in Fig. 4) revealed that CVR decline is more rapid in the middle-age but became plateaued in the older age.

In summary, this study presented 4-year follow-up data on age-related changes in cerebrovascular reactivity. It was found that the rate of CVR decline estimated from the longitudinal data was twice that from the cross-sectional data, confirming that cross-sectional aging studies may be susceptible to recruitment biases. The longitudinal data allowed us to clearly identify regional differences in CVR decline rate, the spatial pattern of which is similar to pattern of longitudinal structural changes [3]. Temporal patterns of longitudinal and cross-sectional changes also manifested substantial differences. To our knowledge, the present report is the first longitudinal study on CVR changes across the adult lifespan.

**Referenes:** [1] Lu et al. Cer. Cor. 21, 1426 (2010); [2] Yezhuvath et al. NMR in Biom. 22, 779 (2009); [3] Raz et al. Cer. Cor. 15, 1676 (2005).

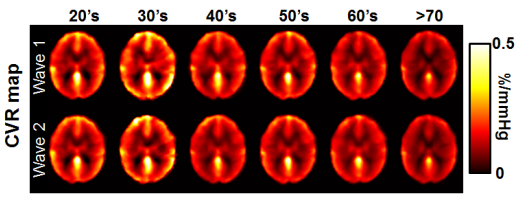


**Fig. 1.** Decade-by-decade maps of averaged CVR from the longitudinal data.

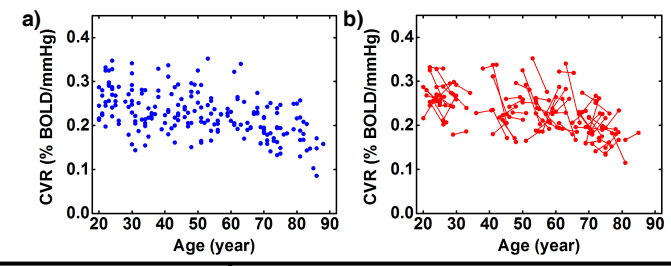


**Fig. 2.** Whole-brain CVR as a function of age. **(a)** cross-sectional scatter plot (N=207), **(b)** longitudinal spaghetti plot (N=80)

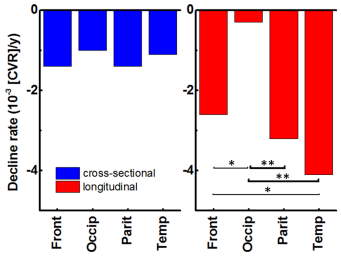


**Fig. 3.** Regional CVR annual decline in the unit of $10^{-3}$ %BOLD /mmHgCO2/year: frontal cortex (Front), occipital cortex (Occip), parietal cortex (Parit), and temporal cotex (Temp). The * corresponds to P<0.05 (uncorrected); the ** corresponds to P<0.001 (corrected).

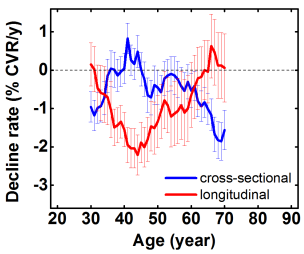


**Fig. 4.** Time-course of the CVR decline rate in the unit of percent CVR change per year. Errorbar stands for the standard error of the data in each age-select window.