S1. Cerebral Blood Flow (CBF) and Cerebrovascular Reactivity (CVR)

The absolute CBF was estimated by using Alsop and Detre's (1996) equation in the units of mL blood/min/100g of brain tissue, represented by the following equation:

$$f_{pCASL}(x,y,z) = \frac{\lambda \cdot e^{(\frac{\delta}{T_{1a}})}}{-2\alpha \cdot M_b^0 \cdot T_1 \cdot \left[e^{(\frac{\min(\delta - w_z),0}{T_1})} - e^{(\frac{-w_z}{T_1})(1-\frac{T_{1RF}}{T_1})} \right]} \times \Delta M(x,y,z)$$

where f_{pCASL} is the blood flow value at voxel (x,y,z) obtained from pCASL in ml blood/min/100g brain; α is the labeling efficiency (0.86); λ is the blood-brain partition coefficient (0.98 ml/gram); δ is the arterial transit time of blood from the tagging plane to the imaging slice (2 seconds); w is the delay between the end of labeling and the start of acquisition (1.525 seconds); T_1 is the brain tissue T_1 (1.165 seconds); T_{1a} is the T_1 of arterial blood (1.624 seconds); T_{1RF} is the T_1 in the presence of off-resonance irradiation (0.75 seconds); M_b^0 M_b^0 is the value of equilibrium magnetization of brain tissue, which was obtained from manual ROI drawing of mid axial slice of the control image and accounting for the saturation recovery of the magnetization (T_1 = 1.165 seconds, recovery time = labeling time + post labeling delay of this slice). The whole brain blood flow values were calculated by averaging all the voxels in the brain. In voxel based analyses (VBA), the individual CBF maps were spatially smoothed (with full-width half-maximum [FWHM] of 4 mm) to account for small differences in sulci/gyri location across subjects.

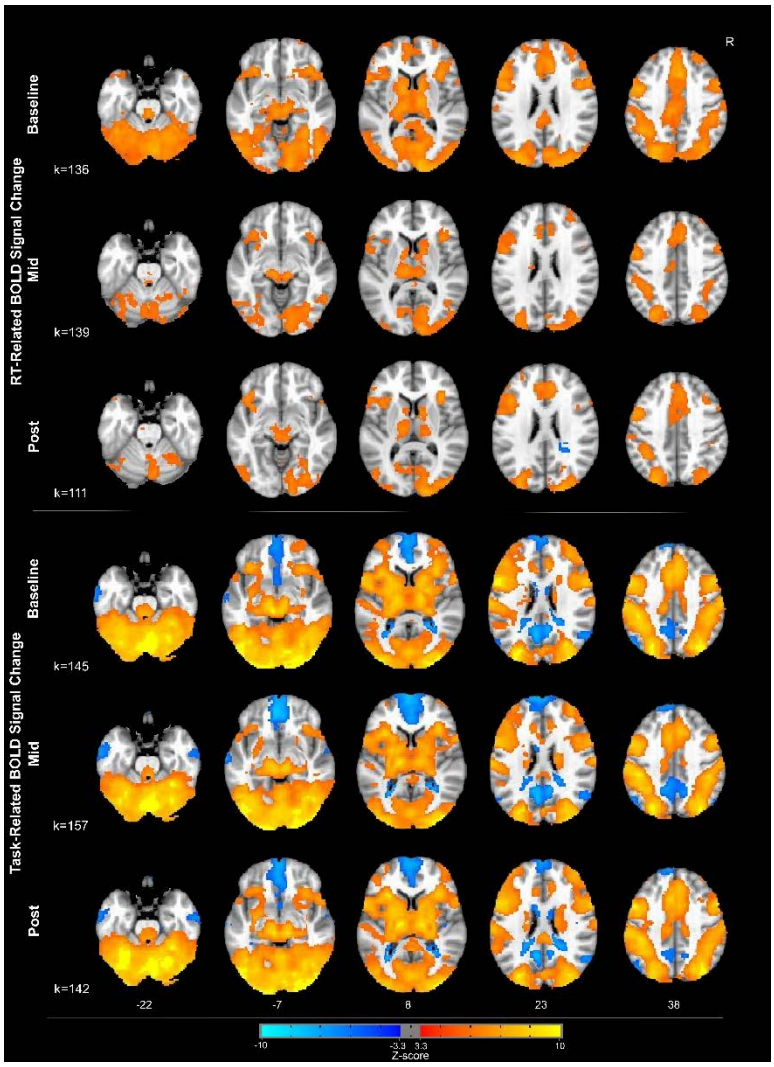
In the hypercapnia fMRI scan, participants were fitted with a nose clip, and breathed room air and 5% CO2 gas (mixed with 74% N2 and 21% O2) through a mouthpiece. The CO2 gas was contained in a Douglas bag with a valve to switch between room air and CO2 air. The type of air breathed in was switched every minute in an interleaved fashion (similar to a block design fMRI experiment), while BOLD MR images were acquired. Physiologic parameters including EtCO2 were recorded simultaneously during the scan.

Hypercapnia fMRI data was preprocessed using Statistical Parametric Mapping (SPM, University College, London, UK). Preprocessing steps included realignment and smoothing (6 mm FWHM). Since the hypercapnia-induced vasodilation is mediated through CO2 level changes, EtCO2 time-course provides the input function to the vascular system and the BOLD time-course is the measured output. So, during postprocessing, a general linear model (GLM) was used to deconvolve the BOLD response to EtCO2 on a per-voxel basis. The EtCO2 trace for this analysis was extracted using in-house scripts. Importantly, the time lag between the EtCO2 time-course and global BOLD response was calculated by shifting the EtCO2 time-course in steps of 1 second until maximum cross-correlation to BOLD was obtained. This was done because the BOLD signal lags behind the EtCO2: this is due to the time taken for the blood in the lungs (where the EtCO2 was measured) to travel to the heart, be pumped to the brain and for the brain vessels to react to the higher CO2 level (when the BOLD change occurs). Following GLM analysis, absolute CVR maps with units of %BOLD signal change per mmHg of EtCO2 change (%BOLD/mmHg CO2) were generated. These maps were finally normalized to MNI space using HAMMER software.

Given that (a) BOLD fMRI signal changes depend upon the dilation of blood vessels and (b) this vasodilatory capacity is known to decline with age (Lu et al. 2011), studying any underlying vascular alterations was a critical aspect of this study. CVR is typically measured by either using a CO2 inhalation paradigm (Lu et al. 2011, Yezhuvath et al. 2009) or breath-holding (Kannurpatti et al. 2011). Unlike breath-holding, CO2 inhalation allows for measuring the end tidal CO2 change in real-time, which helps with more accurate quantification of CVR.

S2. Digit Symbol Verification Task-Related and RT-Related BOLD Signal-Change

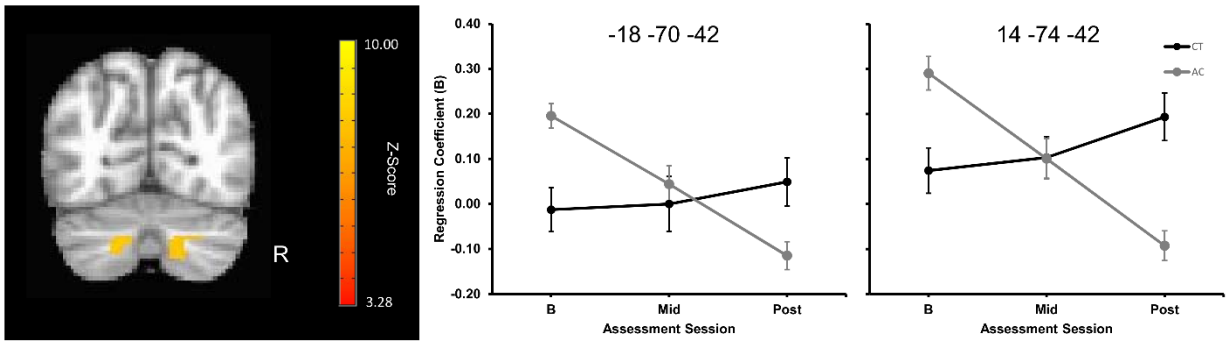
Task-related signal-change and RT-related signal-change at each assessment session were consistent with previously reported findings (see Supplemental Figure S2.1; Biswal, et al., 2010; Motes et al., 2011; Rao et al., 2014; Rypma, et al., 2006).



Supplemental Figure S2.1. Cluster showing significant RT-related (upper three panels) and Task-Related (lower three panels) BOLD signal-change averaging over the cognitive training, wait-listed control, and active control groups for each assessment session. MNI slice coordinates are shown below the images (image orientation in neurological convention indicated with R=right). Results from voxel-wise one-sample *z*-tests comparing mean regression coefficients for RT-related and Task-related BOLD signal-change estimates to zero, conducted separately for each assessment session. Analyses per assessment session were FWE corrected to a cluster-wise α=0.05 with minimum voxels (*k*) shown and with a voxel-wise *Z*=3.30 at α=0.001. Red to yellow color-scaled *z*-score indicates mean parameter estimate was significantly greater than zero, and blue to cyan indicates mean parameter estimate was significantly less than zero.

S3. Digit Symbol Verification RT-Related BOLD Signal-Change Cerebellum Differences between the Cognitive Training (CT) and Active Control (AC) Groups

Group x Assessment Session linear interaction contrasts on the RT-related regression coefficients comparing the CT and AC groups revealed significant clusters bilaterally within cerebellum (Left: Peak Voxel t[24]=4.89, p<0.001, at MNI Coordinates -18, -70, -42, k=250 cluster-wise α=.05 requiring k=126, voxels at a voxel-wise Z=3.28 and α=.001; Right: Peak Voxel t[24]=4.72, p<0.001 at MNI Coordinates -18, -70, -42, k=250 cluster-wise α=.05 requiring k=126 voxels at a voxel-wise Z=3.28 and α=.001; see Supplemental Figure S3.1). Similar to the finding within left PFC, the increase in the correlation between RT and BOLD signal-change for the CT group significantly differed from the decrease in the correlation for the AC group.



Supplemental Figure S3.1. Cerebellum clusters showing significant Group (CT versus AC) x Assessment Session interaction contrast of RT-related parameter estimates and mean RT-related parameter estimates as a function of assessment session and group extracted from the peak voxel within the cluster (peak voxel MNI coordinates shown below above line graphs). Significant clusters were observed bilaterally (Left: peak voxel t[24]=4.89, p<0.001, k=250 cluster-wise α=.05 requiring k=126 voxels at a voxel-wise Z=3.28 and α=.001; Right: peak voxel t[24]=4.72, p<0.001, k=250 cluster-wise α=.05 requiring k=126 voxels at a voxel-wise Z=3.28 and α=.001). Image orientations are in neurological convention indicated with R=Right. Red to yellow indicates increasing strength of the Group x Assessment Session interaction contrast. For assessment session, BL=baseline, Mid=6 weeks into training, and Post=post-training. Black=cognitive training (CT) group, gray=Active Control (AC) group. Errors bars show SEM.