Cerebral blood flow, vascular reactivity and oxygen consumption in healthy aging.

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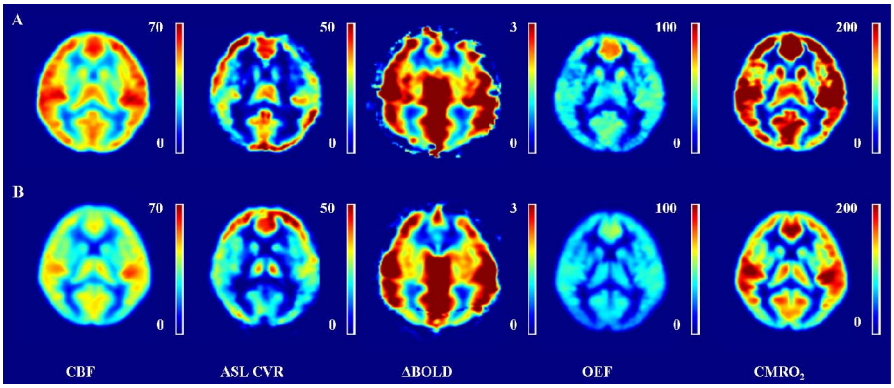
Purpose: Age-related changes in brain metabolism have been extensively studied using various imaging modalities such as oxygen-15 positron emission tomography (O15-PET) and TRUST-MRI[1]. However, results have been conflicting. Some studies demonstrated regional decreases in brain metabolism with age[2] while others have shown an overall increase[3]. In addition, conclusions have been hampered due to the unclear influence of partial volume effects on the measurements. Therefore, we set out to evaluate changes in brain metabolism with age using calibrated MRI. For this purpose we compared quantitative hemodynamic parameters of two groups; healthy young subjects and healthy elderly subjects.

Methods: Approval of the institutional ethical review board was obtained. For this study 65 subjects were included; 20 young healthy subjects (age = 28 ± 3 yrs) and 45 elderly healthy subjects (age = 66 ± 4 yrs). MP-RAGE and respiratory calibrated MRI acquisitions were performed (3T, Philips, Best, The Netherlands). During calibrated MRI normocapnia was alternated with 2 hypercapnia blocks (lasting 105 s each) which were delivered using a prospective end-tidal gas targeting system (Respiract^{TM}, Thornhill Research Inc., Toronto, Canada). Acquisition was performed using a multi-slice single shot EPI dual-echo pseudocontinuous arterial spin labeling (pCASL) sequence; TR/TE1/TE2: 4000/13.8/36.3, label duration 1650 ms, postlabel delay 1550 ms, spatial resolution 3x3x7 mm, and total scan time 18:30 min. Quantitative[3] ASL data was obtained from the first echo and T_2^* signal changes (ΔBOLD) from the second echo. Oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$) were measured voxelwise[4,5]. The resulting CBF, CVR (ASL reactivity), ΔBOLD, OEF, and $CMRO_2$ maps were coregistered to the Montreal Neurological Institute standard brain (MNI152) using flirt[6] (linear registration) and fnirt (nonlinear registration, fsl fmrib software). Regions of interest (frontal lobe, parietal lobe, occipital lobe, temporal lobe, and basal ganglia) were extracted for each individual and were defined from the 50% threshold of the MNI structural atlas probabilistic map[7]. These ROIs were subsequently combined with a gray matter mask to obtain regional gray matter values. For statistical analysis student's t-tests were used.

Results: Calibrated MRI could not be performed in 16 of the 65 subjects due to anxiety during hypercapnia breathing (n = 7) or due to technical problems (n = 9). Two subjects were excluded from further analysis as a result of post processing errors and one subject was, in retrospect, considered unhealthy. Therefore, analysis were performed on the results of 16 young volunteers and 30 elderly volunteers. Grouped CBF, ASL CVR, ΔBOLD, OEF, and $CMRO_2$ maps of both the young and elderly subjects are shown in Figure 1. Whole brain CBF, OEF and $CMRO_2$ were significantly lower in elderly compared to young ($p < 0.05$, < 0.05, and < 0.01 respectively, Table 1). Results from regional measurements and intersubject comparisons are shown in Table 1. The occipital region showed no age-related changes. CBF and $CMRO_2$ in elderly subjects showed decreases in all other regions. BOLD CVR was significantly lower in the temporal region and in the basal ganglia while the OEF decreased in the frontal region and in the basal ganglia.



	CBF (ml/100g/min)		ASL CVR (%)		ΔBOLD		OEF (%)		$CMRO_2$ (μmol/100g/min)	
	Young	Elderly	Young	Elderly	Young	Elderly	Young	Elderly	Young	Elderly
Wb	47 ± 13 *	40 ± 9	21 ± 9	17 ± 10	2.6 ± 0.7	2.3 ± 0.5	36 ± 9 *	30 ± 7	153 ± 52 **	109 ± 38
Frontal	49 ± 14 **	40 ± 9	23 ± 10	21 ± 13	2.3 ± 0.6	2.1 ± 0.8	37 ± 10 ***	28 ± 7	170 ± 72 ***	103 ± 32
Tempor	49 ± 13 **	40 ± 10	26 ± 11	21 ± 15	2.5 ± 0.7 **	2.1 ± 0.4	43 ± 15	36 ± 10	183 ± 72 **	127 ± 46
Pariet	49 ± 14 *	41 ± 9	20 ± 11	17 ± 10	2.5 ± 0.7	2.3 ± 0.4	32 ± 9	29 ± 8	140 ± 50 *	109 ± 37
Occip	48 ± 14	40 ± 11	21 ± 15	17 ± 9	2.7 ± 0.8	2.5 ± 0.5	34 ± 12	31 ± 11	141 ± 48	118 ± 60
BG	41 ± 10 *	34 ± 9	21 ± 10	16 ± 13	2.5 ± 0.7 *	2.1 ± 0.4	49 ± 15 **	36 ± 10	175 ± 59 ***	113 ± 49

Figure 1: Upper row (A) shows results of all young healthy subjects, lower row shows results of the elderly group, for CBF in ml/100g/min, ASL CVR in %, OEF in %, and $CMRO_2$ in μmol/100g/min. Table 1: Wb, whole brain; BG, basal ganglia. CBF, ASL CVR, ΔBOLD, OEF, and $CMRO_2$ results of the young and elderly group are compared. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Discussion: Calibrated MRI has the ability to overcome some of the limitations related to O15-PET. Due to the intrinsic nature of the OEF measurement, which is based on relative changes in ASL and BOLD signal from baseline to hypercapnia, partial volume effects are eliminated. In this study we find significant lower OEF in elderly subjects which can only be explained by decreased neuronal activity in this population. When interpreting $CMRO_2$ results one should be careful as this measurement is based on both the OEF and the CBF measurement. The latter, which was also significantly lower in our elderly subjects, may have been affected by partial volume effects. However, even partial volume insensitive techniques such as xenon studies[8] or flow studies which corrected for brain volumes[2] have demonstrated a decrease in CBF with age. Therefore, even though our CBF decrease may have been overestimated and this may have propagated into our $CMRO_2$ measurements, we believe that CBF decreases or remains equal at most with advancing age. Hence, taking into account that OEF decreases with age, $CMRO_2$ should decrease as well which is in agreement with O15-PET studies[1]. Furthermore, our regional analysis demonstrated significant lower OEF in the frontal region and the basal ganglia of the elderly subjects, but not in the temporal, parietal or occipital cortex. This corresponds to the regional-dependence of age-related neuronal loss[9].

References: [1] Lu H et al. Cereb Cortex 2011. [2] Marchal G et al. Arch Neurol 1992. [3] Buxton RB et al. MRM 1998. [4] Davis TL et al. Proc Natl Acad Sci USA 1998. [5] Hoge RD et al. MRM 1999. [6] Jenkinson M et al. Neuroimage 2001. [7] Collins et al. Human brain mapping 1995. [8] Naritomi H et al. Arch Neurol 1979. [9] Pu F et al. J Neuroradiol 2013.

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