Increased Metabolic Stress with Aging

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INTRODUCTION: The aging brain faces multiple domains of challenges (1). An important category is the metabolic stress, meaning that the balance of oxygen delivery and consumption in the brain is disturbed. This is usually quantified by the term Oxygen Extraction Fraction, OEF. A higher OEF usually indicates the delivery cannot keep up with the consumption and the neuron has to take extra fraction of oxygen from the blood. OEF is not easy to measure directly and often requires extensive mathematical modeling and the use of radiotracers (2). Alternatively, one can measure the venous oxygenation, Y_v, because OEF and Y_v have straightforward relationship (Y_v=1-OEF) when assuming fully oxygenated arterial blood. This study aims to assess baseline venous oxygenation in the brain as a function age. Global venous oxygenation was measured using a recently developed T2-relaxation-under–spin-tagging (TRUST) MRI technique (3) in 116 healthy subjects. Furthermore, to elucidate the mechanism of the metabolic stress, we also assessed the oxygen delivery (via cerebral blood flow, CBF) and oxygen consumption (via cerebral metabolic rate of oxygen, CMRO2) in a subset (n=60) of these subjects.

METHODS: MRI experiments were performed on a 3T Philips System. TRUST MRI (3) was applied on 116 healthy subjects (age 47±29 years old, 65 female, 51 male) and was performed at the level of sagittal sinus, providing a global assessment of venous oxygenation of the whole brain. The TRUST sequence parameters were: voxel size 3.44x3.44x5mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms, duration 4.5 min. In addition, global CBF and CMRO2 were determined in a subset of 60 subjects (age 51±21 y, 30 female, 30 male). CBF was measured with phase-contrast (PC) MRI at the level of internal carotid and vertebral arteries, yielding whole brain CBF in units of ml blood/min. The position of the PC MRI was based on a neck angiogram (TR/TE/flip angle=23ms/3.45ms/18°, FOV=160x70x160mm^3, voxel size 1.0x1.0x1.5mm^3, number of slices =47, one saturation slab of 60mm positioned above the imaging slab, duration 1 min 26 sec), which allows to visualize the internal carotid and vertebra arteries. The PC MRI used the following parameters: voxel size 0.45x0.45x5 mm^3, maximum velocity 80cm/s, duration 30 sec. The whole brain CBF was further normalized by the brain volume obtained from a high-resolution T1W MPRAGE (voxel size 1x1x1mm^3). Thus the final CBF is in unit of ml/min/100g. Global CMRO2 (4) in unit of µmol/min/100g was calculated from the two measures above using Fick principle $CMRO_2 = CBF \cdot (1 - Y_v) \cdot C_a$, where C_a is the amount of oxygen molecules that a unit volume of blood can carry, assumed to be 833.7 µmol O_2/100ml blood based on physiology literature (5). For data analysis, the brain volume estimation used the software FSL (FMRIB Software Library, Oxford University) and the other data were processed with in-house MATLAB scripts.

RESULTS and DISCUSSION: Over 116 subjects, Y_v was found to be 60.5±7.2% (mean±std). Fig 1 shows a significant reduction of Y_v with age (p=0.005, one tail). On average, Y_v decreases by 0.9% every decade. We note that this is a very small change compared to inter-subject variations in Y_v, the normal range of which is between 50-75% (6). It is also interesting to note that the spread of Y_v seems to increase with age (Fig. 1). The standard deviation of Y_v across subjects increased from 5.4% at 20's to 8.7% at 70's.

Reduced Y_v only indicates that oxygen delivery is not able to match the consumption, but may have multiple possible scenarios. For example, it could be that delivery is unchanged but consumption is increased, delivery is reduced but consumption is unchanged, or consumption is reduced but delivery decreased more. Assessment of CBF and CMRO2 can differentiate these possible mechanisms. Fig. 2 shows CBF as a function of age. A significant age-dependent reduction is observed (p=0.045). On average, CBF decreases by 1.0ml/min/100g every decade, again a very small change. The CMRO2 dependence on age is shown in Fig. 3. Despite a slightly negative trend, the CMRO2 did not show a significant correlation with age (p=0.48), suggesting that the whole brain CMRO2 does not change much with age and the reduced Y_v in our data may be attributed to decreased oxygen delivery in the face of unchanged consumption rate.

We would like to emphasize that our calculation of CBF and CMRO2 have used the brain parenchyma volume (i.e. gray matter + white matter) instead of the intracranial volume, because the aging brain is accompanied by atrophy and enlarged ventricles. This is illustrated in Fig. 4 by assessing the ratio of parenchyma volume and intracranial volume as a function of age. The ratio shows a gradual (but not linear) decay with age. This is important because, if we had used the intracranial volume for the calculation, we would have observed a significant reduction in CMRO2, as noted in several previous reports (7, 8). However, such a reduction is attributed to CSF partial volume effect, rather than metabolism in the actual tissue.

In summary, our data suggest that the venous oxygenation shows a small but significant decrease with age. The CBF shows a decrease at a similar rate, but the whole brain oxygen metabolic rate did not show a reduction (in the tissue that has been corrected for atrophy). A caveat of the present study is that the measurements were made for the whole brain only and no spatial information was obtained. It may be that some brain regions have reduced metabolism while other regions have a compensatory increase, which after summation showed no changes in the whole brain value.

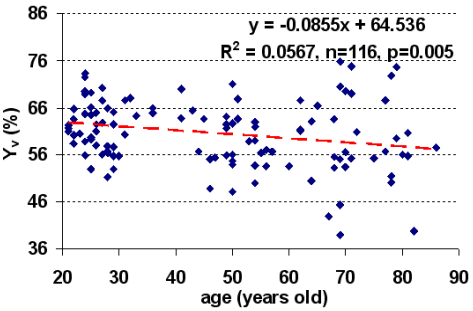

Fig 1: Y_v as a function of age. Each point in the plot represents data from one subject. The red line is the fitted curve.

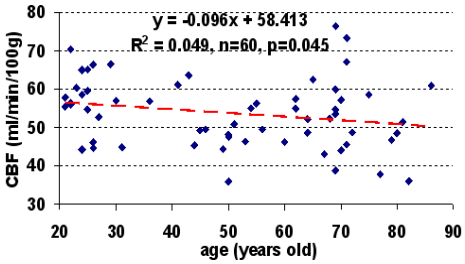

Fig 2: CBF as a function of age.

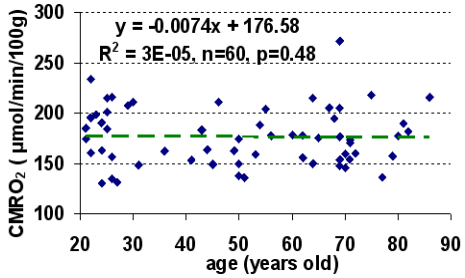

Fig 3: $CMRO_2$ as a function of age.

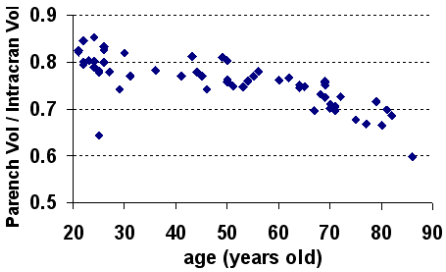

Fig 4: Ratio between parenchyma volume and intracranial volume as function of age. A reduction in the value suggests brain atrophy. n=60.

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