# Age-related hypermetabolism in the human brain

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**INTRODUCTION:** With age, many aspects of the brain structure undergo a pronounced decline, yet individuals generally function well until advanced old age. There appear to be several compensatory mechanisms in brain aging, but their precise nature is not well characterized. Here we aim to provide evidence that the brain of older adults works "harder" when compared to younger adults, as manifested by an age-related increase in cerebral metabolic rate of oxygen ($CMRO_2$). We took advantage of a novel MRI-based technique that can correct for brain atrophy up to a spatial resolution of 1×1×1 $mm^3$. The present study also elucidated gender differences in the age-pattern. Females are known to have a greater prevalence rate of Alzheimer's Disease compared to males, even after accounting for longevity. Thus, it is reasonable to expect that the age-pattern of oxygen consumption may also be sex dependent in older adults. In addition, potential dependence of brain metabolic rate on circadian phase and ethnicity was examined.

**METHODS:** The study population consisted of 118 healthy subjects (62 female and 56 male). The age range was 18-74 years. All experiments were conducted on a 3T MR system (Philips Medical System, Best, The Netherlands). Global $CMRO_2$ was measured using a recently described method (1). Briefly, $CMRO_2$ (in unit of umol $O_2$/min/100g brain tissue) was quantified based on the Fick principle as the following equation: $CMRO_2=CBF\times(Y_a-Y_v)\times C_a$, where CBF was measured by phase-contrast MRI at the four feeding arteries of the brain (Fig. 1a), $Y_a$ is the arterial blood oxygenation which alters minimally with age (2), $Y_v$ is the venous oxygenation and was determined by a novel TRUST MRI technique (Fig. 1b), and $C_a$ is a constant representing the capacity of blood to carry $O_2$. The total scan duration for a complete $CMRO_2$ data set was less than 5 minutes. To examine the dependence of $CMRO_2$ on age and sex, a linear regression analysis was performed, in which $CMRO_2$ was assigned as the dependent variable while age and sex were used as the independent variables. To evaluate the sex differences in the age pattern, we conducted further analysis by including an age×sex interaction term in the regression model. If a significant interaction effect was observed, we then divided the data into female and male subgroups and conducted separate linear regression analysis as a function of age in each sex. We also tested the possibility of $CMRO_2$ dependence on circadian phase by classifying the data into three categories according to the time of data collection: 7:00~10:00 (morning), 10:00~14:00 (noon), and 14:00~18:00 (afternoon). The data were then analyzed by one-way ANOVA for a categorical effect. A P value of 0.05 or less was considered statistically significant.

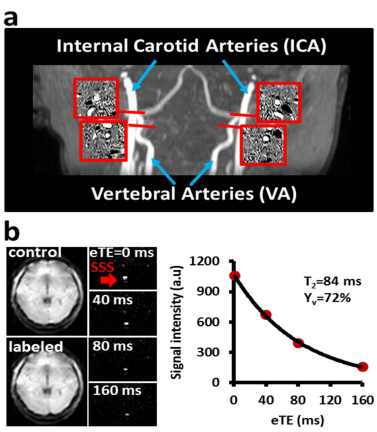


**Fig. 1**. $CMRO_2$ technique. (a) Phase contrast MRI for the measurement of global CBF. (b) TRUST MRI for the measurement of global $Y_v$. Red arrow indicates the superior sagittal sinus (SSS).

**RESULTS and DISCUSSION:** Figure 2a shows the scatter plot between $CMRO_2$ and age for all subjects. Regression analysis revealed that global $CMRO_2$ increased with age ($R^2$=0.09, P=0.02) and females had a greater $CMRO_2$ than male (P=0.02). When adding the age×sex interaction term in the regression model and reanalyzing the data, all three variables, age (P<0.001), sex (P<0.001), and their interaction (P<0.001), had a significant effect on $CMRO_2$. Therefore, the data were divided into female (Fig. 2b) and male (Fig. 2c) subgroups and regression analysis were performed separately for each subgroup. It was found that the age-increase pattern in the whole group was primarily attributed to an age-related increase in $CMRO_2$ in male ($R^2$=0.28, P<0.001), while age had little effect on $CMRO_2$ in females ($R^2$=0.01, P=0.62).

To test our hypothesis that the gender difference of the age effect mainly occurs after menopause, we conducted additional regression analysis in which only subjects equal or less than 51 years old (the average menopause age according to reports from National Institute on Aging) were used. It was found that the age-dependence of $CMRO_2$ in this age range was comparable for male and female groups. There was a significant age effect (P=0.003), but not the interaction effect (P=0.43). We further analyzed female subjects only by dividing them into two sub-groups, those younger and older than 51 years old. Figure 2d shows the fitting results for these sub-groups. It can be seen that, for females before menopause age, there was a trend (P=0.12) of age-related increase in $CMRO_2$, similar to the male results in Fig. 2c. On the other hand, there was no such trend (P=0.8) in females after the menopause age (Fig. 2d). We note that none of our female subjects were under estrogen replacement therapy per our inclusion criteria.

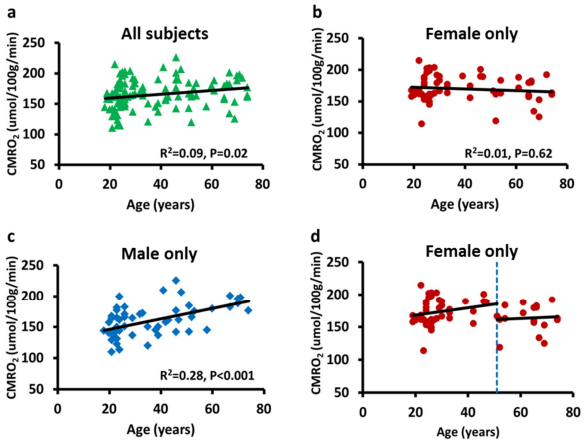


**Fig. 2.** Scatter plots between $CMRO_2$ and age. (a) Data from all subjects. $CMRO_2$ showed a significant increase with age. (b) Data from female subjects only. There was not a significant age effect on $CMRO_2$. (c) Data from male subjects only. $CMRO_2$ increases significantly with age. (d) Same female data as those in (b) but were divided into subgroups younger and older than 51 years old.

We also examined whether $CMRO_2$ at rest is dependent on other factors such as circadian phase and ethnicity, in addition to age and gender. We first corrected for the age and gender effects by calculating the residual value using the regression equation. ANOVA analysis revealed that there was a significant difference (P=0.042) among $CMRO_2$ measured during the three time blocks, 7:00~10:00 (morning, N=29), 10:00~14:00 (noon, N=52), and 14:00~18:00 (afternoon, N=37). Post-hoc Scheffe test showed that there was a significant difference in $CMRO_2$ comparing morning to noon (P=0.039). ANOVA analysis on ethnicity did not find a significant $CMRO_2$ difference among Caucasian (N=63), Asian (N=37), and African American (N=18) subjects.

In summary, the present study provides strong evidence that age-related changes of the brain are characterized by an increase in energy consumption and hypermetabolism. The following possible mechanisms may have contributed to this age-pattern. First, age-related hypermetabolism in brain tissue may be compensatory to a loss of tissue volume with age. Second, the computational efficiency of the neural activity in elderly may be reduced and the brain has to engage greater neural activity to achieve the same behavioral outcome. Finally, the cellular machineries that are responsible for generating neural activity may decline themselves with age, thus more oxygen consumption is needed in order to produce the same amount of neural activity. Furthermore, we showed that, prior to the menopausal age, female and male groups have similar rates of increase. However, females older than menopausal age have a significantly slower rate of $CMRO_2$ change, when compared to elderly men. This gender difference may be attributed to a decrease in estrogen level following menopause. This reduced ability to increase metabolism and perform compensatory neural processing may be one of the reasons for a higher prevalence of Alzheimer's disease in elderly females. Our data also revealed a possible circadian rhythm of $CMRO_2$ in that brain metabolic rate is greater at noon than in the morning.

**REFERENCES:** 1. Liu et al, MRM 69: 675; 2013. 2. Lu et al, Cereb Cortex, 21:1426, 2011.