Age-related increase of resting metabolic rate in the human brain

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ABSTRACT

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 provide evidence that the brain of older adults expends more energy when compared to younger adults, as manifested by an age-related increase (P = 0.03) in cerebral metabolic rate of oxygen ($CMRO_2$) (N = 118, men = 56, ages 18 to 74). We further showed that, before the mean menopausal age of 51 years old, female and male groups have similar rates of $CMRO_2$ increase (P = 0.015) and there was no interaction between age and sex effects (P = 0.85). However, when using data from the entire age range, women have a slower rate of $CMRO_2$ change when compared to men (P < 0.001 for age × sex interaction term). Thus, menopause and estrogen level may have played a role in this sex difference. Our data also revealed a possible circadian rhythm of $CMRO_2$ in that brain metabolic rate is greater at noon than in the morning (P = 0.02). This study reveals a potential neurobiological mechanism for age-related compensation in brain function and also suggests a sex-difference in its temporal pattern.

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Introduction

The human brain consumes about 20% of the total energy, although it only accounts for 2% of the total body weight (Attwell and Laughlin, 2001). In addition, most of the oxygen that brain consumes is used for neural activity (Buxton, 2002). Thus, the rate of oxygen consumption by the brain, referred to as cerebral metabolic rate of oxygen ($CMRO_2$), is an important index for neural activity. Regulation of brain metabolism is critical for the maintenance of normal cognitive function. In the context of brain aging, earlier studies showed that resting $CMRO_2$ were lower in older subjects (Aanerud et al., 2012; Eustache et al., 1995; Ibaraki et al., 2010; Yamaguchi et al., 1986), whereas activation data usually show that task-evoked fMRI signal (presumably reflecting task-evoked $CMRO_2$ changes) increases with age (Cabeza et al., 2004; Cappell et al., 2010; Daselaar et al., 2003; Park et al., 2003). Therefore,

the exact relationship between $CMRO_2$ and age requires further examination.

Most of the prior studies on resting $CMRO_2$ were conducted using Positron Emission Tomography (PET) (Aanerud et al., 2012; Eustache et al., 1995; Ibaraki et al., 2010; Yamaguchi et al., 1986), which until recently was the only method to measure $CMRO_2$ in humans. Only a few of these had accompanying high-resolution (e.g. 1 mm³) MRI image to allow careful delineation of regions of interest (Aanerud et al., 2012), and none had corrected partial volume effect at high-resolution. A potential limitation of low-resolution images in the study of aging is that, as brain atrophy occurs, cerebral spinal fluid (CSF) volume fraction in the voxel increases and tissue fraction decreases, which could result in a $CMRO_2$ reduction in the absence of any real tissue metabolic change. Recently, using a novel, MRI-based $CMRO_2$ technique (Xu et al., 2009), we presented preliminary evidence that $CMRO_2$ may, in fact, increase in older individuals (Lu et al., 2011). A limitation of that study is that it did not account for a possible age-related decline in hemoglobin concentration (Aanerud et al., 2012), which is important for accurate estimation of $CMRO_2$. Indeed, when re-analyzing the data by including hematocrit changes, the age effect on $CMRO_2$ now becomes a trend only. Additionally, $CMRO_2$ measured in that study was based on blood flow determined

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at the level of cervical spine (Lu et al., 2011; Xu et al., 2009), which is not as accurate as that determined at a more proximal (relative to the brain) location of foramen magnum (Liu et al., 2013).

Another unexplored aspect in the prior study is that sex differences in the age-pattern. Sex differences in brain metabolism have yet to be characterized. Previous work by Baxter et al.(1987) showed that young women (age 28–39 years) have a higher cerebral metabolic rate of glucose (CMR_{glu}) compared to young men (Baxter et al., 1987), which is consistent with animal research findings that estrogen injection enhances brain glucose metabolism (Namba and Sokoloff, 1984). On the other hand, estrogen levels in females are known to change with age, thus this enhancing effect, if present, may dissipate with age. Therefore, it is reasonable to expect that the age-pattern of oxygen metabolic rate may also be sex dependent.

In the present study, we determined global $CMRO_2$ in a healthy cohort of 118 subjects across the adult life span. Our $CMRO_2$ measure accounted for brain atrophy effect using a high-resolution ($1 \times 1 \times 1$ mm^3) anatomic image. The dependence of $CMRO_2$ on age and sex as well as the sex dependence of the age effect, i.e. the interaction between the variables, were examined. These findings were interpreted in the context of age-dependence of two constituent parameters, cerebral blood flow (CBF) and venous oxygenation (Y_v). Finally, potential dependence of $CMRO_2$ on circadian phase and ethnicity was examined.

Materials and methods

Participants

The study population consisted of 118 healthy subjects (62 female and 56 male). The age range in our inclusion criteria was 18–74 years. The Health Insurance Portability and Accountability Act (HIPAA) compliant protocol was approved by the UT Southwestern Institutional Review Board and written informed consent was obtained from all participants. The participants were carefully screened and did not report neurological or psychiatric disorders according to self-completed questionnaires. The participants did not have MR contraindications such as metal implants, pacemaker, neurostimulator, body piercings, or claustrophobia. Since our hypothesis involved the effect of estrogen on brain metabolism, the history of postmenopausal hormone replacement therapy was also used as an exclusion criterion to avoid confounding factors. Demographic information of the participants is listed in Table 1. There was no significant difference in age distribution between women and men (mean age ± SD, 38 ± 18 y for women; 36 ± 16 y for men; Chi-square test, P = 0.12). The ethnic makeup of the participants included Caucasian (53%), Asian (32%), and African American (15%).

Experimental procedures

All experiments were conducted on a 3 T MR system (Philips Medical System, Best, The Netherlands). The body coil was used for radiofrequency transmission and an eight-channel sensitivity encoding (SENSE) head coil was used for receiving. Foam padding was used to stabilize the head to minimize motion. A localizer scan was performed for slice positioning and a coil sensitivity scan was conducted for SENSE reconstruction. The $CMRO_2$ data acquisition took approximately 5 min and is detailed below. Additionally, a 3D T$_1$-weighted Magnetization-prepared-rapid-

acquisition-of-gradient-echo (MPRAGE) scan was performed for anatomical reference and the estimation of brain volume. The MPRAGE sequence used the following imaging parameters: repetition time (TR)/echo time (TE)/flip angle = 8.1 ms/3.7 ms/12°, shot interval 2100 ms, inversion time (TI) = 1100 ms, voxel size = $1 \times 1 \times 1$ mm^3, number of slices 160, sagittal slice orientation, and scan duration = 3 min 57 s. These procedures did not use any exogenous tracers.

Measurement of $CMRO_2$

The method used to quantify global $CMRO_2$ followed techniques originally developed by Xu et al. (Xu et al., 2009) and was recently improved by Liu et al. (Liu et al., 2013). It is based on the Fick principle of the arteriovenous differences in oxygen content (Kety and Schmidt, 1948):

$$tCMRO_2 = tCBF \cdot (Y_a - Y_v) \cdot C_h \qquad (1)$$

where $tCMRO_2$ and $tCBF$ are total $CMRO_2$ and cerebral blood flow, respectively; Y_a and Y_v are oxygen saturation percentage in arterial and venous blood, respectively; and C_h is a constant representing the capacity of blood to carry O_2 and is well established in physiology literature (Guyton and Hall, 2005). Here we used C_h values of 8.15 µmol O_2/ml blood for young female and 8.56 µmol O_2/ml blood for young male, based on assumed hematocrit of 0.40 and 0.42, respectively (Guyton and Hall, 2005). A recent study suggested that hematocrit may decrease with age (Aanerud et al., 2012). Thus, C_h of each individual was adjusted for this decline rate of 0.0079 µmol/ml per year in our calculation (Aanerud et al., 2012). Y_a is close to unity and our earlier study has shown that both age and sex have a small but significant effect on this parameter: $Y_a = 99.77 - 0.036 \times age - 1.235 \times sex + 0.021 \times age \times sex$ (Lu et al., 2011), where age is written in years and sex uses 0 and 1 for female and male, respectively. We therefore used this equation to estimate Y_a of each individual according to their age and sex. The two parameters that are most variable are $tCBF$ and Y_v, which are experimentally determined as described below, from which $tCMRO_2$ in units of µmol O_2/min was calculated.

Global venous oxygenation, Y_v, was noninvasively assessed from the superior sagittal sinus (SSS) using a validated approach T$_2$-relaxation-under-spin-tagging (TRUST) MRI (Lu and Ge, 2008; Lu et al., 2012; Xu et al., 2012). The imaging parameters were: voxel size $3.44 \times 3.44 \times 5$ mm^3, TR = 3000 ms, TI = 1022 ms, four effective TEs: 0, 40, 80, 160 ms, labeling thickness 100 mm, gap 22.5 mm, and scan duration 1.2 min. For processing TRUST MRI data, pairwise subtraction between control and tag images was performed, the difference of which yields pure venous blood signal (Fig. 1a). The venous blood signals were fitted to a monoexponential function to obtain T$_2$ (Fig. 1b), which was in turn converted to Y_v via a calibration plot (Lu et al., 2012).

Phase-contrast (PC) flow velocity MRI was used to measure the total CBF to the entire brain. Before the flow measurements, time-of-flight angiogram was performed to obtain the anatomical information of the feeding arteries of the brain. Imaging parameters of the angiogram were: TR/TE/flip angle = 23 ms/3.45 ms/18°, field of view (FOV) = $160 \times 160 \times 70.5$ mm^3, voxel size = $0.3 \times 0.3 \times 1.5$ mm^3, number of slices = 47, one 60-mm saturation slab positioned above the imaging slab, and scan duration = 1.4 min. Based on the maximum intensity projection reconstruction of the angiogram, four PC MRI scans were then placed on the four feeding arteries of the brain: right internal carotid artery (right ICA), left internal carotid artery (left ICA), right vertebral artery (right VA), and left vertebral artery (left VA) (Fig. 1c) (Liu et al., 2013). A region-of-interest (ROI) was then drawn on each of the 4 arteries based on the magnitude image (Aslan et al., 2010). The ROI mask was applied to the velocity map and the integration of the velocity within the ROI (i.e., velocity × area) yielded CBF in units of milliliters per minute. Scan parameters were as follows: one slice, FOV = $200 \times 200 \times 5$ mm^3, voxel size = $0.5 \times 0.5 \times 5$ mm^3, 4 averages, maximum

Table 1
Subject demographic information.

	Female subjects	Male subjects	All subjects
Number of Caucasian	36	27	63
Number of Asian	19	18	37
Number of African American	7	11	18
Subtotal	62	56	118