Age-Related Declines in Executive Function and Cerebral Oxygenation Hemodynamics

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Cerebral hemodynamics plays an important role in cognitive performance, and as such, age-related cognitive dysfunction and cerebral hypoperfusion increase the risk of dementia. However, age-related changes in cerebral oxygenation and cognitive function remain unclear. The aim of this study was to investigate age-related declines in cerebral oxygenation and executive function cross-sectionally. Ninety-eight healthy Japanese adults (age range: 23-79 years; 40 males, 58 females) participated in the present study using local advertisements. The participants were divided into 4 age groups: young (20-39 years; M15/F7), 50s (50-59 years; M10/F12), 60s (60-69 years; M9/F31), and 70s (70-79 years; M6/F8). We measured oxygenated hemoglobin (oxy-Hb) signal change in the prefrontal cortex during the Stroop task, and calculated Stroop interference time in cross-sectional design. This test is widely used to measure the ability to properly control attention and behavior in executing tasks, and to evaluate executive functions mainly associated with the prefrontal cortex. Oxy-Hb signal changes in the left prefrontal cortex in the 60s and 70s groups were significantly lower than those in the young group (both $P < 0.05$). Additionally, Stroop interference time was significantly longer in the 60s and 70s groups than in the young group (both $P < 0.05$). Furthermore, differences in oxy-Hb signal change between the left and right prefrontal cortex were evident only in the young group. These results suggest that the age-related decrease in executive function is associated with decrease in the cerebral oxygenation hemodynamics in the left prefrontal cortex.

Keywords: aging; executive function; near infrared spectroscopy; oxygenated hemoglobin; stroop task
Tohoku J. Exp. Med., 2018 August, **245** (4), 245-250.

Introduction

The increasing number of elderly patients exhibiting cognitive decline is a major public health concern in Japan. Age-related deterioration in brain structure and function decreases neurocognitive function (Park et al. 2001). Executive function—which consists of various higher-order cognitive processes related to the control of behavior, thought, and emotion (Miyake et al. 2000; Bell-McGinty et al. 2002)—is necessary for functional mobility in attention and judgment to maintain the quality of life (Forte et al. 2015). Executive functions are performed by a region in the front of the brain known as the prefrontal cortex. This region is particularly sensitive to age-related atrophy and oxygen deficiencies (Raz and Rodrigue 2006; Jurado and Rosselli 2007; Head et al. 2008). Reaction time on the Stroop test (Stroop 1935), which evaluates executive functions, decreases with age (See and Ryan 1995). Stroop reaction time was also longer in the elderly than in younger adults (Lucas et al. 2012; Laguë-Beauvais et al. 2013). However, the detailed mechanism underlying age-related deterioration in executive function is not well understood.

The brain is vulnerable to oxygen deficiency and sufficient cerebral blood flow is needed for proper brain function (Fabiani et al. 2014). Brain activation elicits neurovascular coupling, whereby the neurons and vasculature adjust their activity to meet the oxygen and metabolic demands in a specific region of the brain (Roy and Sherrington 1890). Brain activity leads to the expansion of blood vessels and increased cerebral blood flow as required to meet the brain's demand for oxygen and nutrients (Girouard and Iadecola 2006).

The increased in cerebral blood flow and oxygenated hemoglobin (oxy-Hb) by executive performance is the underlying principle in near-infrared spectroscopy (NIRS) signal measurements (Hoshi 2003). NIRS neuroimaging techniques provide a good measure of cortical activation during cognitive processing such as Stroop tasks (Dupuy et

Received June 26, 2018; revised and accepted July 27, 2018. Published online August 11, 2018; doi: 10.1620/tjem.245.245.
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al. 2015). Therefore, we evaluated the cerebral oxy-Hb by NIRS as an index of cerebral activity.

Cerebral oxygenation dynamics in the prefrontal cortex are related to the regulation of executive function. Regarding the sex differences in brain function, a previous study reported that females have greater cerebral perfusion throughout the brain including prefrontal cortex evaluated by single photon emission computed tomography (SPECT) (Amen et al. 2017). On the other hand, meta-analyses research about verbal task and NIRS could not found any sex differences in cerebral hemodynamics, and implied that brain function is susceptive to be influenced by aging (Sommer et al. 2004). Furthermore, greater cognitive function has been observed when cerebral oxygenation is higher in the left prefrontal cortex than in the right (Hyodo et al. 2016). Lack of hemispheric laterality during executive task is associated with cognitive decline in middle-aged and older adults (Reuter-Lorenz et al. 2000; Nielson et al. 2002; Colcombe et al. 2005; Zysset et al. 2007). These studies imply that cerebral oxygenation of the left hemisphere may be more important for executive function change by aging. However, the change of age category in executive function concomitant with cerebral hemodynamics remains unclear. Therefore, the aim of the present cross-sectional study was to investigate age-related declines in executive function and cerebral oxygenation dynamics in young, middle-aged, and older adults.

Methods

Participants

Ninety-eight healthy adults (40 men and 58 women, age range: 23-79 years) were recruited using local advertisements. The inclusion criteria included being a nonsmoker and using no current medications or hormone replacement therapy. The exclusion criteria included the presence of a history of neurological disorder, cerebrovascular disease, or gastroenterological surgery; treatment for hypertension, dyslipidemia, or diabetes; or use of dietary supplements influencing blood pressure. All subjects provided written informed consent to participate. All procedures were reviewed and approved by the ethical committee of the University of Tsukuba.

Experimental design

The participants were divided into the following groups: Young (20-39 years old, n = 22), 50s (50-59 years old, n = 22), 60s (60-69 years old, n = 40), and 70s (70-79 years, n = 14). All measurements were performed in the morning after a 12 h overnight fast in a quiet, temperature-controlled room (24-26°C). The participants were asked to abstain from alcohol and caffeine for at least 12 h and did not perform heavy exercise. We measured cognitive function and cerebral oxygenation dynamics. All women older than 50 years were postmenopausal, and all young women were tested with regards to their menstrual phase (3-7 days after the beginning of menstruation).

Measurements of Stroop interference

The Stroop task, which involved two experimental conditions: non-executive naming condition (EASY) and executive condition (HARD), was used to assess cognitive function (Stroop 1935). The color-word Stroop task was modified based on a previous study (Akazawa et al. 2018). In the EASY condition, a colored visual stimulus (XXXXX) (one each of red, blue, green, and yellow) was presented at the top of the monitor, and a color name was displayed in black ink on the bottom right or left side of the monitor. The participants were asked to identify the corresponding ink color for the color name. In the HARD condition, participants responded to color names displayed in incongruent colors (e.g., the word RED was presented in blue color). They were asked to identify the corresponding ink color of the word, also displayed in incongruent color, displayed on the bottom right or left side of the monitor. Each condition included 2 sets of 15 trials each with a length of 60 s and presented in a block design. Three practice sessions (1-2 weeks before, 1 h before, and immediately before the test) were completed. We used the Stroop interference time, calculated as the difference in reaction time between the EASY and HARD conditions, as an index of executive function.

Measurements of cerebral oxygenation

We used a multichannel functional near infrared spectroscopy (NIRS) optical topography system (SMARTNIRS, Shimadzu Corporation, Kyoto, Japan) to evaluate cerebral oxygenation dynamics during the Stroop task. Cerebral oxygenation is used to predict changes in local cerebral blood flow on the surface of the cortex during neural activity. Changes in concentration of oxyhemoglobin (oxy-Hb) were measured at a sampling frequency of 37 Hz. Using a custom-made head holder, two 2 × 4 multichannel probes were placed on the forehead and temple to cover the frontal cortex region. The probes consisted of 8 light source and 8 detector probes placed based on the international 10/20 system FPZ position. Twenty channels were recorded. We combined 4 neighbor channels on each site for the right (ch4, ch11, ch12, and ch18) and left (ch3, ch9, ch10, and ch17) prefrontal cortex. There were 4 tasks blocks in the block design of the cognitive task (60 s of 2 EASY and 2 HARD tasks performed alternatively) and 60 s of 5 resting blocks. Each recording lasted 9 min. To quantify activation, we calculated changes in oxy-Hb from baseline during the task. In order to minimize artifacts, we analyzed the data for 10 s immediately before each task as rest, and for 50 s during the Stroop task. We used data from the 10 s after the start of the task, as signal change peaked 10 s later than neural activity. Additionally, we used a moving average of 3 s to remove high frequency components, such as mechanical noise (Takeda et al. 2007). The oxy-Hb concentration change related to Stroop interference was calculated by subtracting the oxy-Hb concentration during the EASY task from that during the HARD task.

Statistical analysis

All data were presented as the mean ± standard error. In order to investigate age-related declines, a Dunnett's test was performed to compare older groups with the young group. Student's paired t-tests were used to compare oxy-Hb signal change in the left and right frontal cortex within each group. Statistical significance was set a priori at $P < 0.05$ for all comparisons and analyses were performed using SPSS statistical packages version 24 (SPSS, IBM, Tokyo, Chicago, IL).

Results

Participant characteristics are presented in Table 1. Significant differences in height were observed in the 50s, 60s, and 70s, and in body weight in the 60s and 70s when

Table 1. Characteristics of the participants.

	Young	50s	60s	70s
n (Males/Females)	n = 22 (15/7)	n = 22 (10/12)	n = 40 (9/31)	n = 14 (6/8)
Age, years	27 ± 1	55 ± 1**	64 ± 0**	74 ± 1**
Height, cm	169 ± 2	163 ± 1*	158 ± 1**	160 ± 2**
Weight, kg	64 ± 2	60 ± 2	55 ± 1**	52 ± 2**
BMI, kg/m^2	22 ± 1	23 ± 1	22 ± 0	20 ± 1
SBP, mmHg	116 ± 2	128 ± 4*	126 ± 2*	126 ± 4
DBP, mmHg	69 ± 1	80 ± 2**	76 ± 1**	74 ± 2
Heart rate, bpm	59 ± 2	59 ± 2	60 ± 1	63 ± 2

Data are shown as the mean ± SE.
n, number of participants; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Dunnett's test was used to compare group differences against young group.
**$P < 0.01$, *$P < 0.05$ vs. Young.

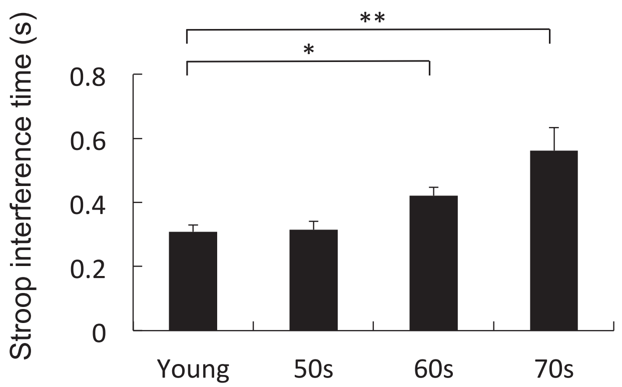

Fig. 1. Stroop interference time.
Values represented as mean ± SE. Dunnett's test was used to compare the group differences against young group.
**$P < 0.01$, *$P < 0.05$.

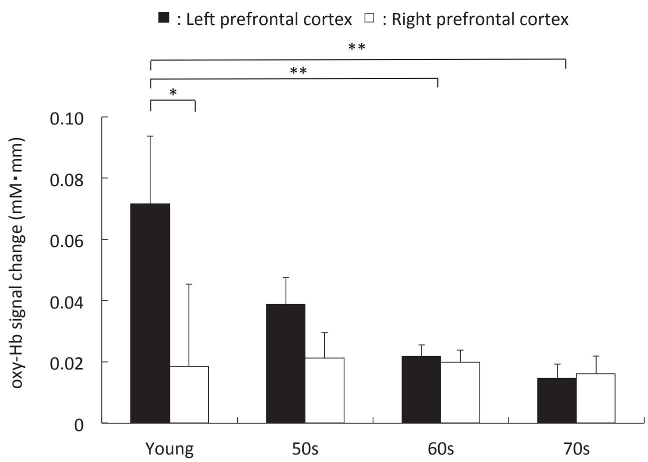

Fig. 2. Oxy-Hb signal change.
Black bar shows the left prefrontal cortex and white bar shows the right prefrontal cortex. Values represented as mean ± SE. Dunnett's test was used to compare group differences against young group and a student's paired t-test was used to compare oxy-Hb signal change in the left and right frontal cortex within each group.
**$P < 0.01$, *$P < 0.05$.

compared to the young group.

Age-related declines in Stroop interference are shown in Fig. 1. Stroop interference time was significantly longer in the 60s and 70s groups (P = 0.029, P < 0.001, respectively) than in the young group; no significant difference was found between the 50s group and the young group (P = 0.998). Fig. 2 shows the oxy-Hb signal change according to age. Similarly, the oxy-Hb signal change in the left prefrontal cortex was significantly lower in the 60s and 70s groups (P = 0.003, P = 0.009, respectively) than in the young group; no significant difference was found between the 50s group and the young group (P = 0.128). There was no difference in the oxy-Hb signal change in the right prefrontal cortex among groups. Furthermore, only the young group showed significantly greater oxy-Hb signal changes in the left prefrontal cortex than in the right (P = 0.036). The differences in oxy-Hb signal change between left and right prefrontal cortex were not observed in participants over 50 years old.

Table 2 shows the data of males and females separately. In female subjects, the Stroop interference time was longer in 70s group compared to young group (P < 0.001). The oxy-Hb signal change in the left prefrontal cortex was significantly lower in 60s groups compared to young group (P = 0.033), while no significant difference was found in the right prefrontal cortex. In male subjects, there were no significant differences in the Stroop interference time and oxy-Hb among the age groups.

Discussion

In this study, we investigated executive function and cerebral oxygenation dynamics in four age groups. Stroop interference time was significantly longer and oxy-Hb signal changes in the left prefrontal cortex were significantly

Table 2. Stroop interference time and oxy-Hb signal in the left and right prefrontal cortex in males and females.

	Young		50s		60s		70s	
	Males	Females	Males	Females	Males	Females	Males	Females
	(n = 15)	(n = 7)	(n = 10)	(n = 12)	(n = 9)	(n = 31)	(n = 6)	(n = 8)
Age, years	27 ± 1	27 ± 2	55 ± 1**	56 ± 1**	64 ± 1**	64 ± 1**	75 ± 1**	73 ± 1**
Stroop interference time, s	0.30 ± 0.03	0.32 ± 0.03	0.25 ± 0.03	0.37 ± 0.03	0.32 ± 0.02	0.45 ± 0.03	0.35 ± 0.06	0.72 ± 0.08**
oxy-Hb signal (left), mM.mm	0.080 ± 0.029#	0.053 ± 0.031	0.051 ± 0.015	0.029 ± 0.010	0.042 ± 0.010	0.016 ± 0.003*	0.016 ± 0.009	0.013 ± 0.005
oxy-Hb signal (right), mM.mm	0.011 ± 0.039	0.034 ± 0.011	0.018 ± 0.015	0.024 ± 0.009	0.037 ± 0.013	0.015 ± 0.003	0.013 ± 0.012	0.018 ± 0.006

Data are shown as the mean ± SE.
n, number of participants.
Dunnett's test was used to compare group differences against young group and a student's paired t-test was used to compare oxy-Hb signal change in the left and right frontal cortex within each group.
$^{**}P < 0.01$, $^{*}P < 0.05$ vs. Young.
$^{\#}P < 0.05$ shows the significant difference between left and right oxy-Hb signal.

lower in individuals over the age of 60 than in the young group. However, the age-related declines in oxy-Hb signal change were not observed in the right prefrontal cortex. Furthermore, there was significant laterality between the left and right prefrontal cortices of young individuals, which was not evident in middle-aged or older adults. These results suggest that cerebral oxygenation in the left prefrontal cortex may be involved in age-related cognitive decline.

Stroop interference time was gradually prolonged with advancing age, especially after the age of 60. Consistent with the present study, it was reported that Stroop interference significantly decreased in those over 60 years old (Rodríguez-Aranda and Sundet 2006). Moreover, the elderly had poorer task-switching performance than did young individuals (Vasta et al. 2018). Stroop interference and task-switching are executive functions thought to be controlled by the prefrontal cortex (Ozonoff et al. 1991; Williams et al. 1996). Therefore, prefrontal brain function may be sensitive to aging.

In previous NIRS studies, differential patterns of cerebral activation in young and older adults have been reported. Kahlaoui et al. (2012) investigated oxy-Hb signal change during a verbal fluency task and reported that older adults showed diminished oxygenation in both left and right prefrontal cortex. Similarly, Obayashi and Hara (2013) showed that the oxy-Hb signal change in the hypo-frontal anterior cortex during a verbal fluency task was significantly lower in older adults than in young adults. Additionally, Laguë-Beauvais et al. (2013) reported that there was a significant age-related difference in oxy-Hb signal change in the prefrontal cortex during both Stroop and switching tasks. In this study, we found that oxy-Hb signal change in the left prefrontal cortex decreased in conjunction with executive function. These results suggest that the age-related decrease in cerebral activation of the left prefrontal cortex, a region related to executive function, diminishes local brain activity.

In the young group, the oxy-Hb signal change was significantly greater in the left prefrontal cortex than in the right during the Stroop task, a difference that was not seen in middle-aged or older adults. This left hemisphere superiority is commonly seen during language processing related cognitive tasks, such as the Stroop task (Perret 1974; Derrfuss et al. 2005; Nee et al. 2007; Yanagisawa et al. 2010). The phenomenon of reduced laterality of cerebral neural activity during verbal cognition is conceptualized in terms of a model called "hemispheric asymmetry reduction in older adults" (HAROLD) (Cabeza 2002). It has been documented that cerebral oxy-Hb signal change in the left hemisphere, and therefore hemispheric laterality, decreases with age (Herrmann et al. 2006). In this study, the left hemispheric dominance observed in young individuals was not apparent in middle-aged or older adults. These results suggest that differential age-related patterns of cerebral activation are involved in cognitive decline.

There are several limitations to this study. First, we focused only on healthy middle-aged and older adults with normal cognitive function. It has been reported that older adults with mild cognitive impairment have decreased brain function, specifically in the dominant hemisphere (Li et al. 2009). Thus, the present study cannot be generalized to other populations, such as patients with cognitive impairment. Second, we only used the Stroop task to measure executive function, but further studies are warranted to investigate other functions such as working memory, verbal learning, processing speed, and category fluency. Third, we analyzed the data including both males and females in this study. Some studies imply that the sex differences in brain function and hemodynamics was observed, but did not find such sex differences (Sommer et al. 2004). Although the brain differences between males and females are not yet consistent, it is necessary to investigate the effect of sex on the age-related changes in cognitive function and cerebral oxygenation in the future.

In conclusion, we demonstrated that Stroop interference was longer and oxy-Hb signal change in the left prefrontal cortex was lower in individuals older than 60 years of age than in young individuals. The results of the present study suggest that age-related cognitive decline is associated with a decrease in cerebral oxygenation hemodynamics, specifically in the left prefrontal cortex. These findings imply that the attenuation of age-related decreases in cerebral oxygenation hemodynamics in the left prefrontal cortex may be important to prevent the decline in cognitive function.

Acknowledgments

This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (16K16549).

Conflict of Interest

The authors declare no conflict of interest.

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