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Research Article
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Sex Difference in Cognitive Aging for Letter Fluency and Semantic Fluency

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Abstract

This study examined the sex difference in cognitive aging for verbal abilities. To examine developmental changes on Letter Fluency (LFT) and Semantic Fluency (SFT) tests, healthy 224 women and 139 men over 40 years old participated in this study. The results showed that performance of both sex in the 40's and 50's remained at the same level, but the performance declining for the LFT and the SFT after the 70's were not parallel. For the LFT, men showed a steep decline from 50's to 70's, whereas women showed a gradual decline from 50's to 80's. For the SFT, men showed a sharp decline from 50's to 70's and remained at a similar level after the 70's, whereas women did not show a steep performance decline from their 50's to 70's and their performance level in 70's was the same as in 80's.

Keywords: Sex difference; Aging; Letter fluency test; Semantic fluency test; Sex-related hormone

Introduction

It is well known that the neuropsychological assessment on cognitive aging that addressed to community dwelling elderly people, evaluation of attention, memory and verbal function are the crucially important for screening cognitive decline [1,2]. In the case of health care examination for community dwellers, verbal function is popularly assessed by the verbal fluency test. Verbal fluency tests, which commonly consist of Letter Fluency Tests (LFT) and Semantic or category Fluency Tests (SFT), are widely used for neuropsychological assessment of language-related executive functioning [3]. For the LFT, participants are required to generate words starting with a given letter. Participants are given one minute to produce as many words as they can, with a request not to use proper nouns or repeat words. The letters used for the LFT depend on the linguistic culture. For example, F, A, S are commonly used target letters in English-speaking countries [4], while the letter F is not suitable for Indonesian; in Japanese the syllables A, Ka, Shi have been recommended [5,6]. For the SFT, participants are required to generate nouns belonging to a given semantic category (e.g., animals).

Many studies with different methodologies have attempted to clarify the underlying brain mechanisms associated with the LFT and SFT. Using behavioral approaches, for example, Martin et al. [7] employed a dual task paradigm, where healthy participant's conc were asked to engage in a second task while they did the LFT or SFT. They found that an omitant finger-tapping task disrupted performance on the LFT, while an object-decision task disrupted the SFT. Based on these findings, they postulated that the LFT reflected frontal cortex processing while the SFT is related to temporal cortex functioning. Among brain-damaged patients, several studies reported that the LFT is relatively compromised in patients with frontal/anterior damage, while the SFT performance was reduced in patients with temporal lobe/posterior damage [8-12]. Studies with patients with autopsy-confirmed Frontotemporal Dementia (FTD) and Alzheimer's Disease (AD), unique patterns of LFT and SFT deficits indicated differences in the relative contribution of frontal-lobe-mediated retrieval deficits and temporal-lobe-mediated semantic deficits in FTD and AD [13,14]. Reviewing brain imaging approaches, a meta-analysis of 22 Functional magnetic resonance imaging (fMRI) experiments indicated that the left inferior frontal gyrus is the most prominent and reliable brain region involved in verbal fluency tests, where the pars operularis is the most critical for the LFT an6d the pars triangularis is most likely implicated in performance on the SFT [15]. In a direct comparison by regional cerebral blood flow (rCBF) pattern of the LFT and SFT tasks, inferior frontal cortex and temporo-parietal cortex (hypothesized to participate in a phonologic loop for accessing word pronunciation) were activated more during LFT than SFT, whereas left temporal cortex (associated with access to semantic storage) was activated more during SFT than LFT. This study identifies differences in the neural networks underlying LFT and SFT [16]. Recent fMRI studies also are consistent with the conclusion of this meta-analysis [17]. Another new non-invasive brain imaging method (NIRS: near-infrared spectroscopy) also showed more prominent frontal cortex activation for performance on the LFT than the SFT, while more temporal cortex activation was evident for the SFT than the LFT [18,19]. Recent NIRS experiments with patients with psychoses also reported similar findings [20].

According to these different research approaches, a common finding is that performance on the LFT and the SFT reflects activity in different cortical regions. Probably the LFT involves functioning in the frontal portion of the brain, whereas the SFT involves functioning in the frontal/temporal cortex regions.

The purpose of our present study was to investigate the neural mechanisms of the verbal fluency tests from the standpoint of aging. As far as we know, no evidence has been reported concerning Japanese verbal fluency test among aging based upon large population [21]. It has been shown that verbal fluency test performances depend upon language and culture such as academic background, intelligence, sex, age, and then, culture–dependent verbal fluency tests has been

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developed such as English, Italian, Indonesian, French, German, Norwegians, Spanish, Swedish, etc. [4].

Our primary concern was the developmental changes of performance on the LFT and the SFT after middle age in healthy community-dwelling people. We addressed this issue using the data about the cognitive functioning of middle and upper-middle aged healthy people in the Yakumo Study in Japan. We were interested in determining whether the developmental changes for the LFT and the SFT are parallel over the course of aging, and to investigate neural cognitive aging mechanisms from the viewpoint of sex difference

Sex differences were not found in the process of developing the Japanese verbal fluency test [6,21]. However sex differences related to verbal functioning have been found elsewhere [22]. Kimura stressed the role of sex-related hormones on brain mechanisms to interpret why there are sex differences in verbal cognitive functions. Previously we examined differences in cognitive performance modulated by gonadal steroid hormones during the menstrual cycle of women [23]. We found evidence consistent with Kimura's proposal that sex-related hormone modulation selectively affects cognitive functions depending upon the type of task (attention and memory). A low level secretion of estradiol appears to contribute to reducing the level of attention that relates to prefrontal cortex functions. Therefore we also investigated sex differences in the performance of elderly people on the LFT and the SFT.

In sum, the purpose of this study was to examine developmental changes of healthy middle and elderly people on letter fluency (LFT) and semantic fluency (SFT) tests. Hypotheses examined in this study were that the performances on LFT and SFT show different developmental changes from middle ages to elderly because different neural networks are responsible to each test, and developmental changes from middle ages show sex differences as previous studies reported that sex-related hormone relates to the performance of verbal function [1].

Method

Participants

The participants were 365 healthy rural-community dwellers over 40 years of age; there were 226 women and 139 men. All participants voluntarily participated in the health examination organized by local government of Yakumo Town and Nagoya University. They showed no sign of physical disorders, internal disease, or of dementia at the start of the study. For signs of the internal diseases, the participants were examined by physicians in accordance with the health examination program, and for signs of dementia or other neurological defects they were evaluated by neuropsychologists using the Mini Mental State Examination (MMSE), Digit Cancellation Test for Attention (D-CAT), memory tests, the Stroop test, and the QOL (Quality of Life) questionnaire.

Using a cross-sectional design to examine developmental changes, participants were assigned into five groups based on their decade of age: 40's (*n*=26; M=44.35), 50's (*n*=62; M=54.84), 60's (*n*=128; M=64.13), 70's (*n*=95; M=73.64) and 80's (*n*=54; M=83.14). The detail of the participant's information showed the Table 1. All participants were enrolled in the Yakumo Study in Japan.

Procedures

The LFT and SFT were administered as a part of the Nagoya University Cognitive Assessment Battery (NU-CAB), which assessed individual cognitive functions, such as attention, language, memory, visuospatial and executive functions. The reliability and validity of the NU-CAB, including comparison with brain imaging methods, have been reported elsewhere [1,5,6,18,19,24-26]. The same examiner administered both the LFT and the SFT individually. Participants were asked to generate nouns belonging to named category (i.e., sports, jobs, and animals), as many as possible within 60 s for the SFT. For the LFT they were asked to generate nouns starting with a specific syllable for 60 s. They were also requested not to generate proper nouns or repeat words. The LFT and SFT took about 3 minutes each to administer.

Analysis method

The numbers of items generated for the LFT and SFT had different means and distributions, so the scores were transformed into standard scores (Z score) for the analyses. The z-scores were analyzed using an analysis of variance (ANOVA) to examine whether the developmental changes of men and women were parallel. Data of participants whose MMSE score were below 23 points (9 participants) were not included in this analysis.

Ethical approval

Ethical approval was obtained from the Nagoya University Graduate School of Medicine (#643, 2011). Each participant provided informed consent prior to data collection.

Results

The mean LFT and SFT z-scores as a function of age group and sex are shown in Table 2.

The z-scores were analyzed using an analysis of variance (ANOVA) to examine whether the developmental changes of men and women were parallel. If an interaction between the main effect of age group and the main effects of test (LFT and SFT) or sex is shown, then the developmental changes are not parallel. The results of the ANOVA (two-between and one-within mixed design) showed that the main factor of age was significant ($F_{4,353}$=27.99, p<0.001, η^2=0.241) but both main factors of sex and test did not reach significance ($F_{1,353}$=0.498, p=0.481; $F_{1,353}$=0.340, p=0.56). Both of the two-way interactions were not significant (sex x test: $F_{1,353}$=1.195, p=.275; test x age group: $F_{4,}$

	Age									
	40's		50's			60's		70's		80's
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Wome
Number of participants	7	19	17	45	52	76	39	56	24	30
M	44.86	43.84	54.18	55.49	63.81	64.45	74.18	73.09	83.58	82.70
SD	3.44	3.21	3.24	3.10	2.63	2.73	2.90	2.44	2.73	2.26
Education										
M	12.40	11.10	13.10	12.5	11.4	11.2	10.8	10.1	9.00	8.83
SD	.89	1.45	2.33	1.73	1.93	1.51	2.02	1.69	1.48	2.18

Table 1: Participants' information.

Age		40's	50's	60's	70's	80's
LFT	Women	0.653 (1.152)	0.562 (1.010)	0.124 (0.902)	-0.207 (0.734)	-0.633 (0.995)
	Men	0.605 (0.826)	0.435 (1.249)	-0.271 (0.963)	-0.148 (1.001)	-0.321 (0.767)
SFT	Women	0.335 (0.809)	0.783 (1.081)	-0.080 (0.764)	-0.361 (0.938)	-0.339 (1.113)
	Men	1.09 (0.637)	0.893 (0.745)	0.029 (0.981)	-0.439 (0.674)	-0.534 (0.836)

Table 2: Performance scores (*z* scores) on the LFT and SFT as a function of age group and sex (Numbers in the parentheses are SD).

$_{353}$=1.662, *p*=0.158). However, the three-way interaction (age group x test x sex) was marginally significant ($F_{4, 353}$=2.147, *p*=0.07,η^2=0.024). These results suggest that the four developmental changes were not parallel. Further analyses of three-way interaction, though significant level was not enough high, were conducted to get a sense of the trends in the data.

First, the performance between the age groups of the 40's and the 50's were not statistically different for the LFT and SFT (women and men: LFT of the 40's and the 50's, *p*=0.723 and 0.687, respectively; women and men: SFT of the 40's and the 50's, *p*=0.070 and 0.615, respectively).

Second, the performance of women on the LFT declined linearly from the age groups of the 50's to the 80's (50's and 60's, 60's and 70's, 70's and 80's: *p*=0.029, 0.001, 0.000, respectively). In comparison, men's performance on the LFT declined linearly from the 50's to the 70's (50's and 60's, 60's and 70's, *p*=0.021 and 0.049), but men's performance in the 70's and the 80's remained similar (*p*=0.481).

Third, the performance of women on the SFT remained at similar levels after the 60's until the 80's (60's and 70's, 70's and 80's: *p*=0.078 and 0.915). In contrast, the performance of men on the SFT declined linearly from the 50's to the70's (50's and 60's, 60's and 70's, *p*=0.001, 0.011, respectively) but their performance in the 70' and the 80's were at similar levels (*p*=0.682).

In summary, the analyses of the three-way interaction showed following suggestions; although performance declined generally with aging from middle age (50's), the declining features were not the same but depended upon the task and sex. Figure 1 shows the developmental curves after the 50's to shed light on the differences that depend upon the task and sex. Not only did the declining changes differ among the four lines, but also there was a tendency for performance on the LFT to be inferior to the SFT at the age of 50's. This suggests an earlier decline of function related to the LFT than the SFT (*t*=1.53, *df* =122).

Discussion

The purpose of this study was to examine the developmental changes in verbal fluency test performance after middle age in healthy people. We were especially interested in examining whether men and women's performance on both the LFT and the SFT would show similar developmental changes, because these tests are believed to reflect different neural patterns of activity. The LFT is regarded to reflect neural functioning in the frontal regions while the SFT is regarded to reflect functioning in the frontal and temporal regions. If performance on the LFT and the SFT reflect activity in different brain region, then these tests may show different developmental features in aging. In accord with this working hypothesis, the findings show different performance changes declining with aging, especially from age 50's to 70's.

First, for individuals in their 50s, performance on the SFT was better than on the LFT. This means that cognitive functions related to the LFT show an earlier decline. This finding coincides with findings from a variety of other cultural-linguistic backgrounds, e.g., English, Chinese, Danish, Indonesian, Norwegian, Swedish, Italian, French, German, Spanish and Portuguese [4,19,27-39].

The poorer performance on the LFT compared to the SFT in the early stages of aging could be interpreted in terms of the cognitive aging model of Hatta [18]. He proposed that cognitive functions begin to decline from around age of 50 years and the order of the cognitive decline among various cognitive facets is the reverse of the order of brain evolution in human beings. Thus prefrontal-related cognitive functioning begins to deteriorate earlier than limbic-system-related cognitive functioning. Supportive evidence for this proposition can be found in recent reviews of cognitive aging studies. This suggests that cognitive skills acquired later in life are more vulnerable than cognitive skills acquired early in development. The present findings of earlier declines on the LFT than the SFT seem to support his proposal. This might relate to the fact that category learning certainly occurs a few years before learning the alphabet and to read.

Second, men showed a steep decline from 50's to 60's, compared with women, in their performance on the LFT. Most previous studies did not find sex differences on verbal fluency tests, including the Japanese verbal fluency test [8]. However, the present findings revealed different declining changes for both sexes from the 50's. Women showed a gradual decline, while men showed a steep decline from the 50's to the 60's, although after the 60's their performance remained stable. Since verbal functions show prominent sex differences, namely women's superiority, which can be attributed to sex-related hormone differences, the present findings do not seem unusual [22,23]. Sex-related hormones enhance verbal functioning in women, however after menopause this effect tends to diminish. Hatta showed evidence that women's superiority in digit cancellation performance was evident in the 50's but diminished in the 60's, whereas women's superiority in memory performance remained same from the 40's to the 60's [24]. The menopause effect in women seems to suggest that the sex-related hormone effect is more apparent in prefrontal brain functioning than in temporal brain functioning. The influence of sex-related hormones seems to be one of the most plausible explanations for why women showed resistance against functional declines with aging, and maintained their performance level even in upper-middle age while men showed steep declines. Japanese performance on the LFT seems to be more influenced by the prefrontal brain region than their performance on the SFT. The sex differences in the declining trajectory

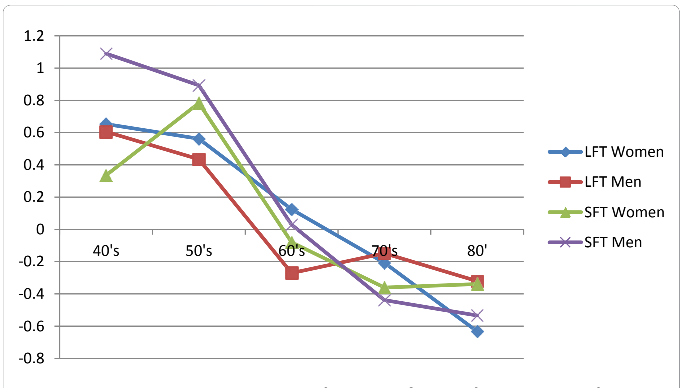

Figure 1: Developmental changes of LFT and SFT performance as a function of age and sex (vertical axis is the Z-transformed performances).

difference for performance on the LFT in this present study might be interpreted as related to biopsychosocial influences. Very recent review by Miller and Halpern suggested cultural effects on cognitive sex differences [29]. Therefore it seems reasonable that not only sex-related hormonal influence but also cultural factors such as economic prosperity and gender equity on cognitive development in men and women. These present findings suggest that the LFT is more sensitive than the SFT to age-related cognitive decline from the 50's.

In conclusion, both our working hypotheses that performance on LFT and SFT show different developmental changes from middle age to elderly and men and women show different developmental changes from middle age in verbal function were supported.

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