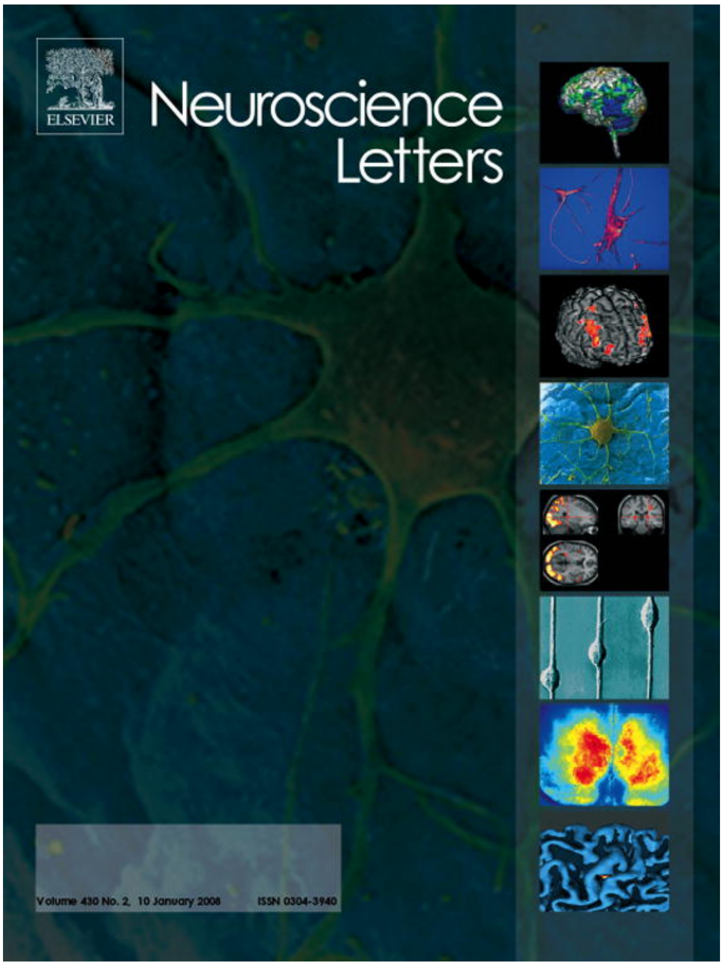
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Sex-dependent neurofunctional predictors of long-term maintenance of visual word learning

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Abstract

A previous study has revealed sex-dependent neurofunctional predictors of visual word learning [C. Chen, G. Xue, Q. Dong, Z. Jin, T. Li, F. Xue, L. Zhao, Y. Guo, Sex determines the neurofunctional predictors of visual word learning, Neuropsychologia 45 (2007) 741–747]. The present study aimed to extend that study to investigate sex-dependent neurofunctional predictors of long-term maintenance. Twenty-three Chinese college students trained in the previous study were followed up twice: immediately (T1) and 6 months after the training (T2). At both T1 and T2, subjects were tested with the simultaneously presented same-different judgment task. Compared with the T1 performance, subjects (both males and females) showed a small but significant amount of forgetting (i.e., longer reaction times) at T2. Consistent with our hypothesis, males' performance at both T1 and T2 was predicted by the pre-training left-lateralized fusiform activation, whereas females' performance was predicted by symmetrical bilateral fusiform activation.

Keywords: Asymmetry; fMRI; Language learning; Individual differences; Sex differences

Previous studies have shown significant variances in cerebral asymmetry for language processing [26,28], especially when processing a non-fluent or new language [6,29]. For example, Xue et al. [29] trained 12 Chinese college students for 2 weeks to learn the visual form of a new language (Korean Hangul). In a passive-viewing task, they found significant variances in fusiform asymmetry (from strong right-dominance to strong left-dominance) in the processing of novel characters. Furthermore, individuals who showed more left-lateralized fusiform activation learned the new script more efficiently than their right-lateralized counterparts.

Cerebral asymmetry in language processing also appears to be sex-dependent. Some researchers found that males show more left-lateralized activation and females show more bilateral activation during language processing [11,15,20]. Using Xue et al.'s [29] paradigm and a larger sample, Chen et al. further showed that the neurofunctional predictors of visual word learning efficiency varied between the two sexes [2]. Specifically, asymmetry in the fusiform cortex significantly predicted training outcomes for males (confirming Xue et al.'s results) and overall activation in bilateral fusiform predicted training outcomes for females. This suggested that males and females might recruit different optimal neural networks to learn a new script.

The present study extended these two studies [2,29] by investigating whether pre-training fusiform asymmetry would also be predictive of *long-term* retention of the learned visual words, an outcome that has more practical importance than immediate training effects. Based on previous research on the crucial involvement of the fusiform cortex in reading [3–5,14,17,30] and its sex-dependent predictive role of visual word learning [2,29], we hypothesized that fusiform asymmetry would predict the males' long-term retention of learned visual words, and bilateral fusiform activation would predict females' long-term performance.

The present study followed up the subjects who participated in Chen et al.'s study [2]. In that study, subjects went through a 2-week training program (2 h per day and 5 days per week) to learn the visual form, phonology, and semantics of a logographic

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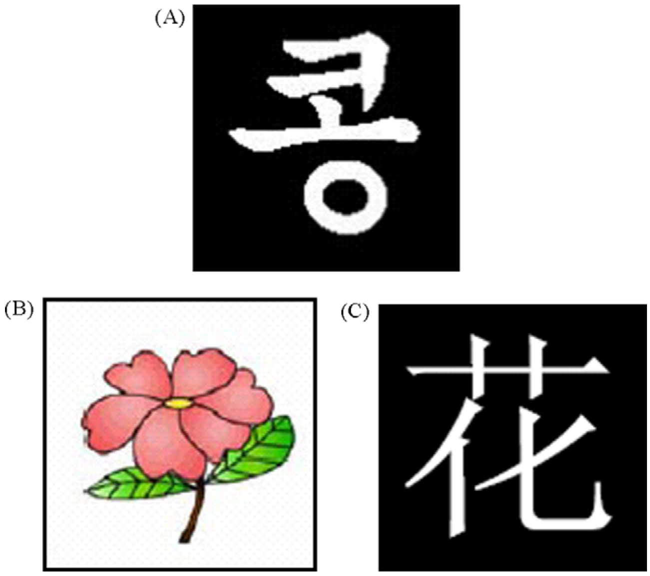

Fig. 1. An example (flower) of the materials used in this study: (A) Korean character, (B) pictorial meaning, and (C) Chinese meaning.

artificial language (LAL). The LAL was created by borrowing the writing and sounds of 60 Korean Hangul characters and was assigned arbitrary meanings (see an example in Fig. 1). For more details about the training, please refer to our previous study [2]. Of the original 24 Chinese subjects, 23 (13 males and 10 females, 19–25 years of age) were successfully located and recruited for this follow-up study. These subjects had normal or corrected-to-normal visual acuity. They were strongly right-handed as judged by Snyder and Harris's handedness inventory [22]. None of them had any formal knowledge of Korean language before the training. They gave written consent to both the original study and this follow-up study according to the guidelines set by the MRI Center at the Beijing 306 Hospital.

A simultaneously presented same-different judgment task [7,10] was adopted to examine behavioral performance for the visual word learning immediately (T1) and 6 months (T2) after the 2-week training. This task was able to reflect the efficiency in visual analysis and recognition [10]. In this task, subjects were asked to decide whether the paired characters were identical or different. Sixty learned LAL characters were used in the test. During the test, a pair of characters appeared in the center position on the screen and would stay on until subjects responded. Subjects pressed the right "Shift" key on the keyboard to indicate a "yes" response, and pressed the left "Shift" key to indicate a "no" response. If no responses were made within 3 s after stimulus presentation, the stimulus would disappear. The next stimulus would begin after an interval of 1 s. Prior to the main experiment, there were 20 pairs (10 matched and 10 non-matched pairs) of practice stimuli.

To determine the neurofunctional predictors of long-term maintenance of visual word learning, bilateral fusiform areas were selected as regions of interest (ROIs) (see [2] for detailed descriptions). The functional ROI of fusiform was defined based on the group activation (including both males and females, $p < .001$, uncorrected) within the anatomical boundary of fusiform according to the automated anatomical labelling map (AAL) [27]. Based on theoretical considerations of sex-dependent cerebral asymmetry in language processing and previous research [11,15,20], Chen et al. developed two neurofunctional predictors [2]. One was asymmetric index (AI) in this area. We used the following formula to create AI: $\mathrm{AI} = (L - R)/(L + R) \times 100\%$, where L and R represent the summed effect sizes (i.e., beta values in the general linear model) of activated voxels in the left and right ROI, respectively. A positive AI indicates left-hemispheric lateralization and a negative number indicates right-hemispheric lateralization, and a number close to zero (i.e., $-0.1 \leq \mathrm{AI} \leq 0.1$) indicates a bilateral activation. To assess the bilateral activation of the fusiform regions, Chen et al. summed the effect sizes of both left and right fusiform regions. This index was positively correlated with females' performance as predicted, but these correlations did not consistently reach statistical significance. In the present study, we continued to include this index (to be consistent with the literature), but additionally considered another index that emphasizes the symmetry of the activation, rather than the overall bilateral activation. This index was created by obtaining the absolute value of AI, thus labeled as AAI. This index represents how balanced or symmetrical the brain is using the two hemispheres (0 means completely symmetrical or balanced activation, and a large value means asymmetrical or unbalanced use of the two hemispheres).

A two-way (sex and testing sessions) repeated measure ANOVA was conducted to evaluate the retention of learned LAL characters. As shown in Fig. 2a, the reaction time in the visual judgment task increased significantly, $F(1, 21) = 11.71$, $p = .003$, suggesting a statistically significant amount of forgetting. The main effect of sex ($F(1, 21) = 1.75$, $p = .200$) and the interaction between sex and testing session ($F(1, 21) = .53$, $p = .477$) were not significant. Correct ratio was generally high for this type of tasks, thus did not differ by either sex or testing session (Fig. 2b). In terms of the neurofunctional predictors, there were no sex differences in the *means* of the two indices previously used (see [2] for detailed results). Nor were there sex differences in the means of the new index (AAI = .36 for males and .33 for females, $t(22) = .237$, n.s.).

Correlational analysis showed that pre-training (T0) AI in the fusiform cortex significantly predicted both the behavioral performance at T1 and T2 for males ($r = -.558$, $p = .024$ for T1

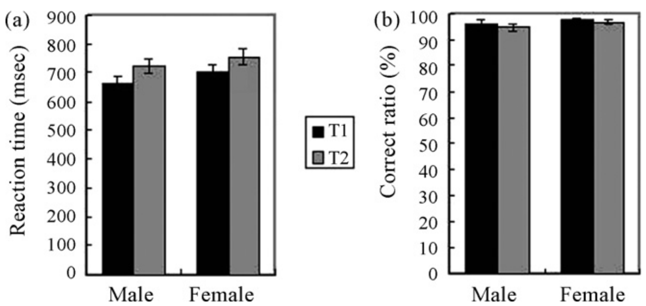

Fig. 2. Reaction time (a) and correct ratio (b) on a simultaneously presented same-different task for males and females. T1 and T2 represent tests conducted immediately and 6 months after training, respectively. Error bar represents standard error of the mean.

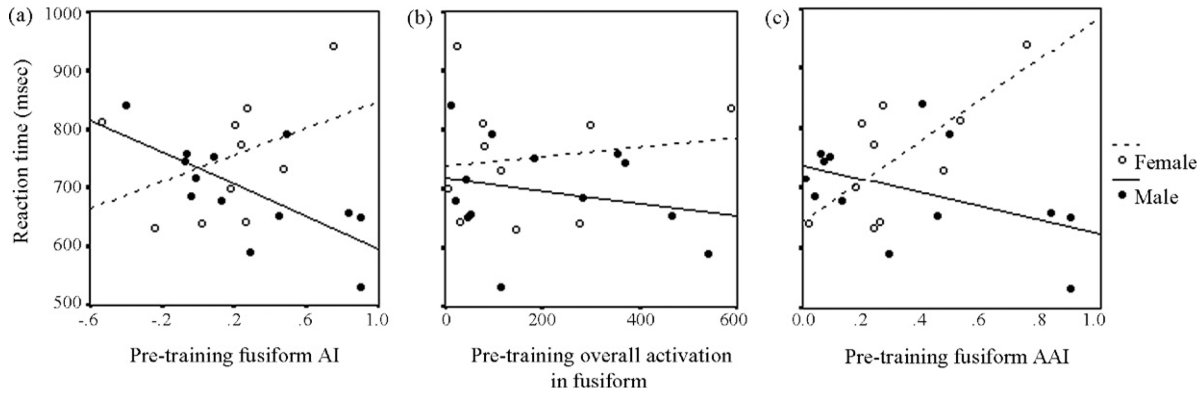

Fig. 3. Correlations between pre-training neural indices and long-term behavioral performance for males and females. The three panels were scatter diagrams for the asymmetry index (a), overall activation (b), and absolute asymmetry index (c), respectively.

and $r = -.685$, $p = .005$ for T2, one-tailed), but not for females ($r = .383$, n.s. for T1 and $r = .399$, n.s. for T2) (see Fig. 3a). The difference between the correlation coefficients for males and females was significant at $p < .05$ based on the Fisher's r-to-Z transformation test. Even after controlling for T1 performance, which was highly correlated with T2 performance ($r = .764$, $p < .01$), multiple regression showed that pre-training (T0) asymmetry index still made a unique, though only at trend level, contribution to the prediction of males' T2 performance, $\beta = -.376$, $t = -1.74$, $p = .055$, one-tailed. T1 performance also made a unique contribution, $\beta = .554$, $t = 2.57$, $p = .014$, one-tailed. In this regression analysis, the total R^2 was .680. In sum, consistent with our prediction, this result indicated that the more left-lateralized males retained more of the visual words they learned over a 6-month period than did their less left-lateralized counterparts.

As for the two indices of bilateral activation, the overall activation of the bilateral fusiform was not predictive of retention for either males ($r = -.232$, n.s.) or females ($r = .141$, n.s.) (Fig. 3b), whereas the absolute asymmetry index (AAI) predicted females' ($r = .710$, $p < .05$), but not males' ($r = -.466$, n.s.) retention (Fig. 3c). Females' correlation coefficient between AAI and T2 performance was significantly higher than that for males' based on Fisher's r-to-Z test ($Z = 2.82$, $p < .001$). Regression analysis suggested that only T1 performance made a *unique* contribution ($\beta = .673$, $t = 2.67$, $p = .016$, one-tailed) to the prediction of females' T2 performance, whereas the contribution of AAI is not significant ($\beta = .259$, $t = 1.03$, n.s.), perhaps due to the extremely high correlation between T1 and T2 performance ($r = .847$, $p = .001$, one-tailed). Together, AAI and T1 performance accounted for 75% of the variance of T2 performance.

Given the evidence of AAI's utility in predicting long-term maintenance of visual word learning, we decided to reanalyze earlier training data with this index. As shown in Fig. 4, for females, all correlations were significant ($p < .05$, one-tailed) and in the expected direction. For males, only the ninth day's was significant and in the opposite direction as in females ($r = -.535$, $p < .05$, one-tailed). Based on the Fisher's r-to-Z transformation test, females' correlation coefficients were significantly higher than males' during the last five training days (all p's < .05). These results clearly indicate that symmetrical activation was associated with better learning and less forgetting for females. It seems that AAI is a better index of symmetrical activation than the overall activation used in the original study.

These results extend the previous finding of fusiform activation pattern's prediction of short-term visual word learning [2,29] to the new finding of its prediction of long-term visual word retention. Taken together the results of these three studies, it is clear that individual differences in fusiform asymmetry play a fundamental role in individual variations in visual word learning and retention. As we have argued [2], left and bilateral fusiform may be respectively optimal for males' and females' learning of a new script because of native language tuning. That is, males show left lateralization when processing native language, whereas females show bilateral activation [11,15,20]. It should be noted that our study found similar fusiform activation pattern and similar behavioral performance for males and females at the group level in learning a new language. Thus, the two sexes may recruit different optimal neural network

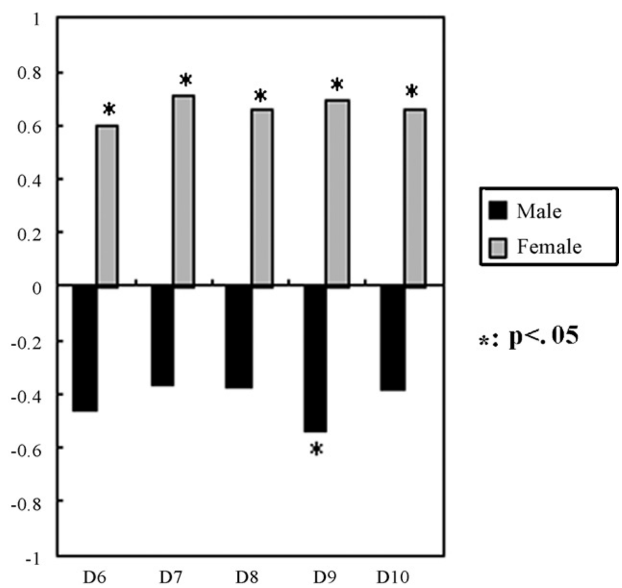

Fig. 4. Correlations between absolute asymmetry index (AAI) at the pre-training stage and reaction time on the simultaneously presented same-difference task during the last five training days for males and females. D = day.

to achieve equal learning performance. This perspective shifts attention from our traditional emphasis on mean sex differences to individual differences within and across sexes.

It has been proposed that sex-dependent neurofunctional predictors found in this study may reflect sex differences in the inter-hemispheric connectivity [11]. Previous research revealed that the isthmus of the corpus callosum is larger in females than in males [23,24]. The larger isthmus might allow females to communicate more efficiently between the two hemispheres. On the other hand, one recent animal study suggests that inter-hemispheric interactions help to inhibit the activation in one hemisphere and thus increase the laterality when processing species-specific calls [16]. Further studies are required to examine how the two hemispheres interact with each other, in terms of competition and collaboration, and how this is modulated by sex differences in neuroanatomical connection.

The results of the present study also have important implications for our understanding of the relation between hemispheric specialization and visual object learning in terms of sex differences. It has been revealed that the two hemispheres had different functional specialization [9,12,13,19]. For example, Gazzaniga has proposed that the left and right fusiform were respectively specialized for processing language and face [8]. Consistent with the laterality–bilaterality differences between males and females, one recent study found that males showed a strong right hemispheric dominance when processing human faces, whereas females showed a more bilateral trend [18]. Given our finding that the left fusiform is optimal to learn visual words for males and bilateral fusiform regions (or their symmetry) for females, it would be interesting for future studies to examine whether in learning face, the right fusiform region is better for males and bilateral fusiform regions for females.

Several lines of research might be developed to further understand the relations between functional asymmetry and language learning and retention. First, future research should experimentally examine the causality between fusiform asymmetry and visual learning. Although our studies have shown significant evidence that fusiform asymmetry predicted and likely caused the subsequent learning efficiency and retention rate. Experimental manipulation of asymmetry (via TMS or other methods) would provide more powerful evidence for causality. Such research would also provide direct insights to brain-based training and education. Second, future research should investigate whether functional asymmetry in fusiform cortex predicts language learning and retention in natural language environment. Longitudinal language development studies are needed for that purpose.

Finally, future research should also explore the role of expertise in fusiform asymmetry in word learning. Previous studies have repeatedly found evidence for the role of reading expertise in shaping the neural network of reading, including increased laterality at group level [1,21,25,29]. However, the exact mechanisms of reading expertise are not clear. Our training studies suggest that visual expertise did not seem to change the fusiform asymmetry, which was very stable across 2-week visual form training [29]. Further studies are needed to investigate the specific role of various kinds of language expertise (e.g. visual, phonological, and semantic) in shaping the fusiform asymmetry.

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