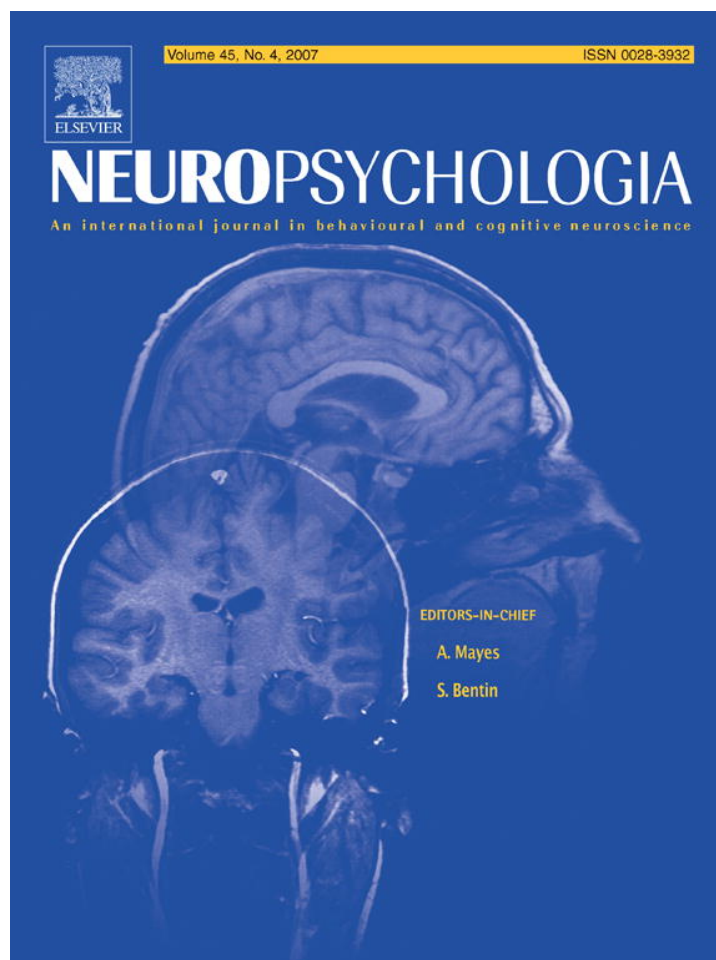


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Sex determines the neurofunctional predictors of visual word learning

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Abstract

This study used functional MRI and an artificial language training paradigm to explore sex differences in the processing of a new writing system and how sex determines the optimal neural resource recruitment for visual word learning. Results indicated that males and females achieved equal learning outcome, and their learning curve followed a similar power function. They also showed similar overall activation in the fusiform cortex, a region that has been associated with visual word processing. Despite the absence of sex differences in averaged behavioral performance and neural activation, males and females were found to have different neural predictors of visual word learning. As predicted, left-lateralized fusiform activation predicted visual word learning for males, but not for females, whereas bilateral fusiform activation predicted visual word learning for females, but not males. These results suggest that male and female brains operate differently to achieve the best performance in visual word learning. The individual-differences approach adopted in the present study provides a new and useful perspective to sex differences.

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Sex differences in the neural representation of language are an important issue in cognitive neuroscience. It has long been hypothesized that language is more strongly lateralized for males than for females. For example, it has been found that early brain damage in the left-hemisphere impairs only males' but not females' reading ability (e.g., Frith & Vargha-Khadem, 2001). Some neuroimaging studies have shown that males show more left-lateralized activation whereas females show more bilateral activation in language tasks (Kansaku, Yamaura, & Kitazawa, 2000; McGlone, 1980; Shaywitz et al., 1995), although others did not find such differences (Frost et al., 1999; Sommer, Aleman, Bouma, & Kahn, 2004). These results suggest that different neural resources may be optimal for males and females to process *native* languages. But less is known about the sex differences in the neural substrates underlying the learning of a *new* language.

In addition to the group differences between the two sexes, there are pronounced individual variations within each sex (Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004; Xiong, Rao, Gao, Woldorff, & Fox, 1998), particularly when processing a nonfluent or new language (Dehaene et al., 1997; Xue, Chen, Jin, & Dong, 2006a). For example, in a passive-viewing task, Xue et al. (2006a) found that, despite the consistent leftward fusiform activation in the processing of subjects' native language (i.e., Chinese), there was significant variance in fusiform asymmetry (from strong right-dominance to strong left-dominance) in the processing of visually matched, novel characters (i.e., Korean Hangul). This finding suggests that not all subjects show left-hemisphere dominance when processing visual words in a new language. Xue et al. further found that individuals who showed more left-lateralized fusiform activation were able to learn the new script or writing system more efficiently than those who showed more right-lateralized fusiform activation. These results suggested that some neural networks might be optimal for learning a new script and individuals may vary in their reliance on such a network. Considering the dominant leftward fusiform activation in the processing of native language

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(Bolger, Perfetti, & Schneider, 2005; Cohen et al., 2000, 2002; Xue et al., 2005, 2006a; Xue, Chen, Jin, & Dong, 2006b), it is possible that the native language network would be optimal for the learning of a new script, at least when it is similar to the native language.

However, the small sample size ($n = 12$) of the previous study (Xue et al., 2006a) did not allow us to examine possible sex differences in neural patterns for the processing of a new language and their consequences for learning outcomes. Considering the significant sex differences in neural organization for native language processing, we hypothesized that the optimal neural network for visual word learning should be different for males and females. Specifically, left-dominated fusiform activation would result in better visual word learning for males, whereas bilateral fusiform activation would predict better learning for females.

The present study aimed at testing this hypothesis of sex-specific neurofunctional predictors of visual word learning. Subjects were recruited to learn a new logographic artificial language (LAL) in 2 weeks (2 h/day and 5 days/week). Functional MRI measurements with a passive-viewing task were taken before the training. During the training stage, subjects learned the visual form, phonology, and semantics of the LAL. After each day's training, subjects were administered a simultaneously presented same-different visual judgment task that assesses their efficiency in visual word identification (Eichelman, 1970).

1. Methods

1.1. Subjects

Subjects were 24 Chinese college students (13 males and 11 females, 19–25 years of age) who had not learned any Korean language. They were strongly right-handed as judged by the Snyder and Harris's handedness inventory (Snyder & Harris, 1993). They gave written consent according to the guidelines set by the MRI Center at the Beijing 306 Hospital.

1.2. Materials

We designed a logographic artificial language (LAL) for the training (Xue et al., 2006b). The LAL was created by borrowing the writing and sounds of 60 Korean Hangul characters, but the visual forms were not paired with their original pronunciation to avoid the grapheme-phonology-correspondence (GPC) rules that are obvious in Korean Hangul characters (Taylor & Olson, 1995). These characters were assigned arbitrary meanings as concrete nouns of either man-made artifacts (e.g., "ball") or natural kinds (e.g., "sun"). Another 60 Korean Hangul characters that were matched on the visual complexity were used as the control materials.

1.3. Training

Subjects underwent a 2-week training program (2 h/day and 5 days/week) to learn the visual form, phonology, and semantics of the 60 LAL characters. It should be noted that in the previous study (Xue et al., 2006a), subjects were trained only in visual forms. To extend that work into a more realistic language-acquisition situation, we adopted for this study the simultaneous training of visual form, phonology, and semantics. In-house software was developed to administer the training. In the first 3 days, subjects started out with 20 of these characters. After that, they were trained on all 60 characters. Several types of learning tasks, including copying words by hand, visual judgment, phonological imitation, dictation, naming, semantic categorization, translation, and listening comprehension, were designed to facilitate the acquisition of visual form, phonology, and semantics and their interconnections.

1.4. Measurement of visual word learning

We adopted a simultaneously presented same-different judgment task (Eichelman, 1970) to examine the effect of training on visual word learning. Previous studies have shown that this task is capable of measuring the efficiency of word recognition (Chen, Allport, & Marshall, 1996; Eichelman, 1970). We have also shown in another study that subjects performed better on this task in their native language than in a foreign language and training of the foreign language significantly improved subjects' performance (Xue et al., 2006b). In this task, subjects were asked to decide whether the paired characters were identical or different. During the test, a pair of stimuli appeared in the central positions 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 in 3 s after stimulus presentation, the stimulus would disappear. The next stimulus would begin after an interval of 1 s. Subjects were tested everyday at the end of that day's training.

1.5. fMRI paradigm and parameters

Sixty LAL characters and 60 control characters were selected for the passive-viewing task during imaging scans. Rapid presentation event-related design was used in this experiment. The two sets of stimuli and null event (fixation) were randomly mixed. A 9 s fixation at the beginning of the scanning session allowed for stability in magnetization, and these images were excluded from analyses. Through a mirror attached to the head coil, subjects viewed stimuli that were projected onto a translucent screen. The stimuli were presented in black color on white background in the center of the screen for 1200 ms, followed by a blank of 600 ms.

fMRI scans were performed on a 2.0 T GE/Elscent Prestige whole-body MRI scanner (Elscent Ltd., Haifa, Israel) with a standard head coil. Single-shot T2*-weighted gradient-echo, EPI sequence was used for the functional imaging acquisition with the following parameters: TR/TE/θ = 3000 ms/60 ms/90°, FOV = 375 mm × 210 mm, matrix = 128 × 72, and slice thickness = 6 mm. Nineteen contiguous axial slices parallel to AC-PC line were obtained to cover the whole brain. The anatomical MRI was acquired using a T1-weighted, three-dimensional, gradient-echo pulse-sequence. The parameters for this sequence were: TR/TE/θ = 25 ms/6 ms/28°, FOV = 220 mm × 220 mm, matrix = 220 × 220, and slice thickness = 2 mm. Eighty-nine axial slices parallel to AC-PC line were acquired to provide a high-resolution image of the anatomy of the whole brain.

1.6. Analysis of imaging data

Image preprocessing and statistical analyses were performed with the Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) which is implemented in Matlab (Mathworks Inc. Sherborn, Mass., USA). Functional images were realigned, unwarped, normalized to the MNI template (Friston et al., 1995a) and smoothed with an 8 mm FWHM Gaussian filter. Global scaling was added to the time series to remove the drift of the BOLD signal. General linear model was used to estimate the condition effect for individual participants (Friston, Frith, Frackowiak, & Turner, 1995b). The SPM standard haemodynamic response function (HRF) was used to model the BOLD response of each stimulus type. The threshold for significant activation was $p < .05$ (multiple comparisons corrected). The group-averaged effects were computed with a second-level random-effects model. The group effect was computed using one-sample *t*-tests, and sex differences were examined with two-sample *t*-tests.

1.7. ROI selection and quantification of asymmetry

Due to the crucial involvement of the fusiform regions in visual language processing (Cohen et al., 2002; Xue et al., 2006b, 2005) and its predictive role in the efficiency of visual word learning (Xue et al., 2006a), we quantified the bilateral fusiform activation at the pre-training stage in terms of both overall activation and cerebral asymmetry index and used them to predict males' and females' performance in subsequent visual word learning. The functional

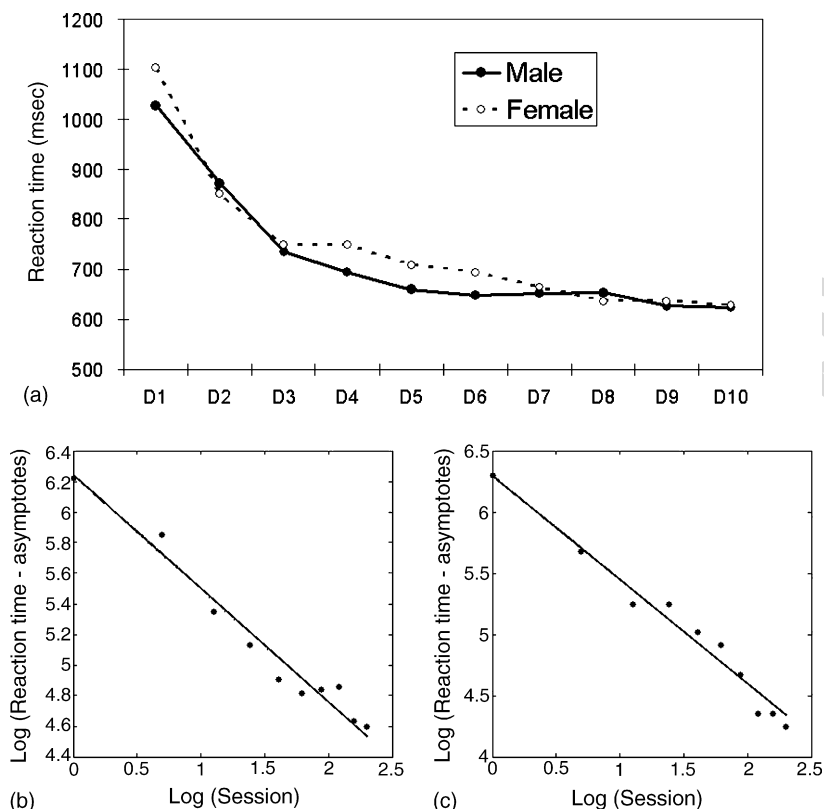


Fig. 1. Behavioral performance across training sessions. The upper panel (a) shows males' and females' reaction times on a simultaneously presented same-different judgment task as a function of training sessions, plotted in normal scale. The lower panels show this correlation in a log scale for males (b) and females (c), respectively; D=Day.

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, Tzourio-Mazoyer et al., 2002). To determine the asymmetric index (AI) in this area, we used the following formula: $AI = (L - R)/(L + R) \times 100\%$, where L and R represent the summed effect size¹ 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., $-1 \leq AI \leq 1$) indicates bilateral activation. The bilateral/overall fusiform activation was calculated by combining the fusiform activation in the two hemispheres.

2. Results

2.1. Behavioral results

Behavioral data indicated that our extensive training was effective. Fig. 1a shows that the reaction time in the visual judgment task decreased significantly over the training period, $F(9,14) = 22.62$, $p < .001$. The main effect for

sex ($F(1,22) = .367$, $p = .551$) and sex by training interaction ($F(9,14) = 1.69$, $p = .188$) were not significant.

Longitudinal studies of learning have typically found that learning curves follow a power law (Anderson, 1983; Logan, 1988), expressed in a formula form as $y = x^n + c$, where x represents the time or the number of learning sessions, y the performance (reaction time or error rates), and c an asymptote. If the empirical data fit a power function, the correlation of $\log(x)$ and $\log(y - c)$ is close to 1. We examined the fit of male and female data to the power law, and the results are shown in Fig. 1b and c. The correlations of $\log(x)$ (i.e., training sessions) and $\log(y - c)$ (i.e., reaction time) were $-.983$ and $-.986$ for males and females, respectively, suggesting a very good fit to the power law.

2.2. fMRI results

Functional MRI data indicated that, at the pre-training stage, males and females showed similar activation in the bilateral occipital and fusiform cortices, as well as in the parietal lobule (Fig. 2a). It appeared that there was more activation for females than for males in the bilateral premotor cortex, the inferior frontal cortex, and the basal ganglia. However, masked comparisons between males and females revealed no significant sex differences at the threshold of $p < .001$ (uncorrected). With a lower threshold of $p < .01$ (uncorrected), more activation was found for females than for males in left inferior frontal cortex, right

¹ It should be noted that there are other ways to quantify activation. In our previous paper (Xue et al., 2006a), we used the summed t-values as an index of activation on the basis of previous examples (e.g., Xiong et al., 1998). Both methods are able to characterize the activation in both intensity and volume, and result in very similar indices of brain activation. In our case, the correlations between them were .922 (the asymmetry index) and .933 (the overall activation). Furthermore, the pattern of sex-dependent neurofunctional predictors of visual word learning was the same no matter which method we used.

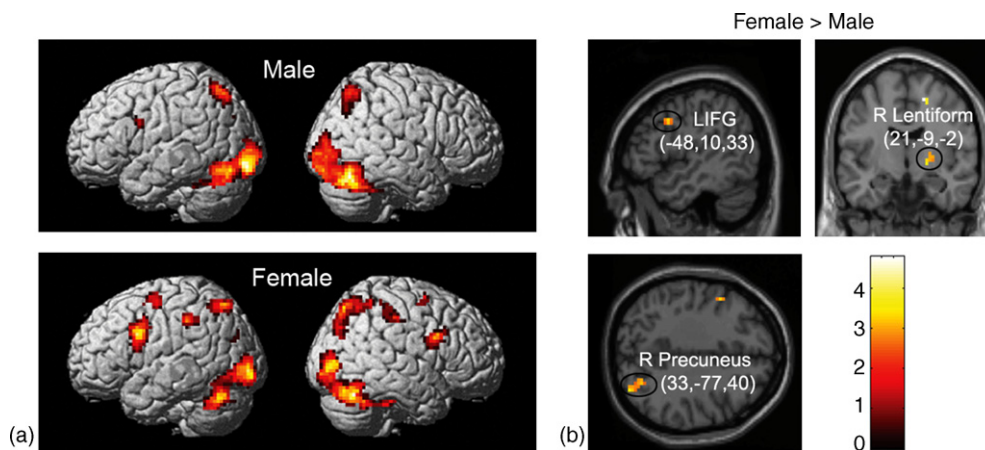


Fig. 2. Brain activation during pre-training fMRI test. (a) Group-averaged brain activation for males and females when processing LAL characters relative to fixation. The threshold for this contrast is $p < .001$, uncorrected. (b) Direct comparison between females and males. The threshold for this comparison is $p < .01$, uncorrected. IFG: inferior frontal gyrus; R: right.

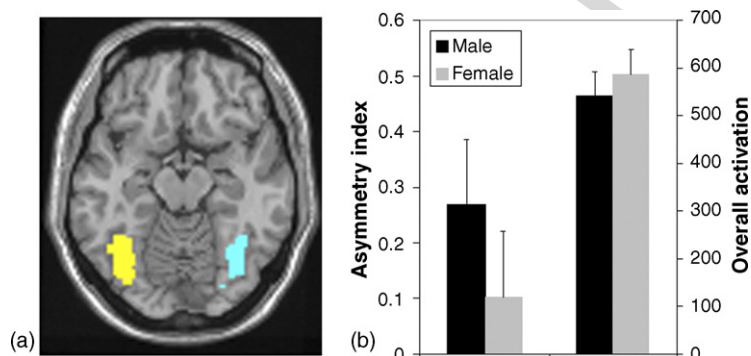


Fig. 3. ROI results: (a) schematic representation of the bilateral fusiform ROIs defined by group-averaged activation patterns, which was overlaid onto the SPM2 template. Yellow represents the left ROI and blue represents the right ROI. (b) Asymmetry index (AI) and overall activation in bilateral fusiform ROIs as a function sex. Error bar represents standardized error of the mean. L: left; R: right.

precuneus, and right lentiform (Fig. 2b). Of particular relevance to this study, no differences were found in the fusiform cortex even with the lowered threshold.

We thus defined the functional fusiform ROIs based the group activation map for the whole sample (see Section 1). Consistent with the whole-brain analysis, ROI analysis revealed no significant sex differences for either overall fusiform activation ($t(22) = .40$, $p = .69$) or asymmetry index ($t(22) = .1$, $p = .33$) (Fig. 3).

As predicted, correlational analyses showed that asymmetry in the fusiform cortex significantly predicted the post-training performance for males, but not for females. Again as predicted, the overall activation in bilateral fusiform cortex predicted to some extent the post-training performance for females, but not for males. These correlations were relatively stable across the five post-training measurements starting with Day 6, when there was no obvious behavioral improvement thereafter (Fig. 4).

Based on the Fisher's r -to- z transformation test, we examined whether the correlation coefficients between asymmetry index and reaction times for males were significantly higher (more negative) than those for females. Results showed significant sex differences at $p < .01$ (one-tailed) for all 5 days. As for the overall bilateral activation, the correlation coefficients

were significantly higher for females than for males at $p < .05$ (one-tailed) for Day 6, but not significant for other days.

3. Discussion

To our knowledge, this is the first evidence that sex may determine the neurofunctional predictors of visual word learning. It appears that, when learning a new writing system, the optimal neural resources recruitment might vary for males and females. For males, the greater reliance on the left fusiform will result in better performance, whereas for females, the use of bilateral neural network seems to facilitate the learning. This result has significant implication for our understanding of neural substrates of reading and reading acquisition, especially in terms of sex differences and individual differences.

Our results replicated and extended the previous finding on neurofunctional predictors of future learning performance (Xue et al., 2006a).² The convergent results from the two studies

² We reran our analysis with the data from our previous study (Xue et al., 2006a) just to see if there is some confirmation of sex differences. We found that the correlation between AI and post-training RT was $-.922$ for males (sig-

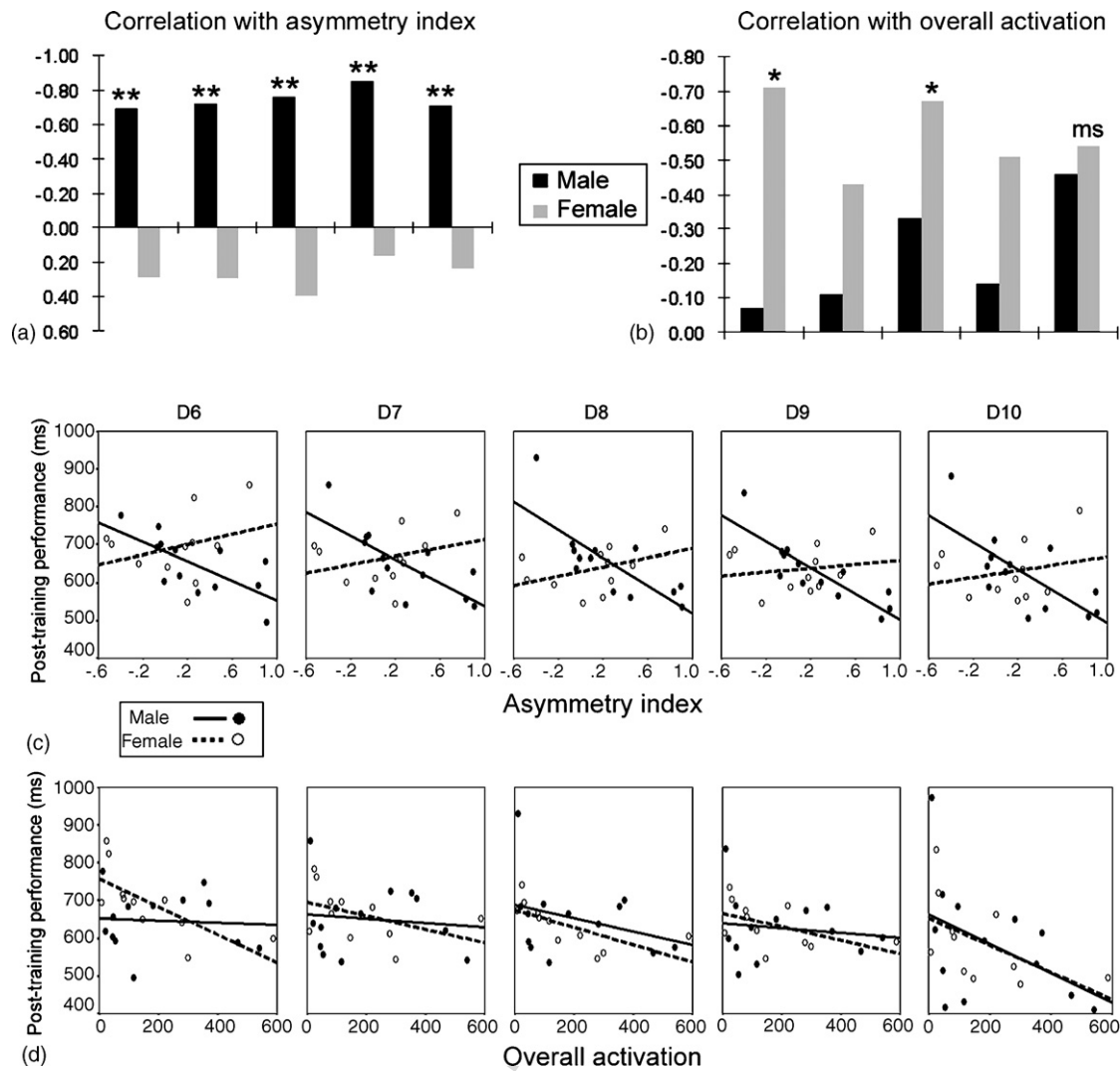


Fig. 4. Correlations and scatter plots between pre-training neural predictors (asymmetry index [a and c] and overall activation [b and d]) and post-training behavioral performance (i.e., reaction time). D = Day; ** $p < .01$; * $p < .05$; ms: marginally significant, all two-tailed.

provide compelling evidence that different neural patterns in response to novel stimuli are not random variations, but are actually linked to individuals' learning ability. Furthermore, our finding that left-hemisphere dominance predicted males' learning and bilaterality predicted females' learning paralleled the sex differences in activation patterns in native language processing (i.e., left-dominance in males and bilaterality in females). This parallel seems to suggest that the reliance on the native language network would be optimal for the learning of new languages. As we have argued (Xue et al., 2006a), this may represent the neural tuning by native language. It appears that such tuning is beneficial to the learning of a new language, especially one that is similar to the native language (e.g., LAL for Chinese subjects).

nificant at $p < .05$ even with only 6 male subjects) and $-.354$ for females. This result seems to indicate that the sex differences we found are robust and may be independent of training methods (visual form training in the previous study, but comprehensive training in the present study).

Results of this study also have significant methodological implications for future studies of sex differences in brain functions. Using the individual-differences approach, our results indicated that, males and females may show similar overall neural responses and similar behavioral performance at the group level, but there may be different neural circuitries that lead to optimal learning efficiency for the two sexes. Similar to previously reported sex differences in the associations between gray and white matters and intelligence (Haier, Jung, Yeo, Head, & Alkire, 2005), our study should help to shift the discussions on *mean* sex differences to individual differences within and across sexes and to differences in mechanisms (i.e., different mechanisms to achieve the same outcome). Such a perspective should help us to appreciate the existence of multiple "routes" (or ways of using neural resources) to the same behavioral outcome, and to avoid a simplistic examination of mean sex differences. Of course, these important implications would need much more and stronger evidence to help further our understanding of sex differences, an important area of research in neuroscience (Cahill, 2006).

Future research needs to replicate our results in other language domains (e.g., listening comprehension, production), and with subjects speaking different languages and trying to learn different new languages. Future research should also address two other questions. First, what is the origin of the sex differences in the differential patterns of neural resource recruitment for language learning and processing? One possibility is that neural optimization is constrained by the anatomical and physiological structure of the human brain. Anatomical studies have revealed that males have more overall volume of gray matter and white matter than do females (Good et al., 2001), which may mean that females might use more neural resources (e.g., in both hemispheres) to achieve the same cognitive performance. Consistent with this hypothesis, it has been revealed that females have a relatively larger isthmus segment of the callosum, perhaps reflecting a sex-specific difference in the inter-hemispheric connectivity (Steinmetz et al., 1992; Steinmetz, Staiger, Schlaug, Huang, & Jancke, 1995). Moreover, a recent study on the relations between brain structure and individual differences in general intelligence quotient (IQ) showed that, compared to men, women have more white matter and fewer gray matter relative to a given level of intelligence (Haier et al., 2005). In sum, it is likely the male and female brains are designed differently, and different operations might be implemented to achieve equal performance.

Another question is why some individuals are able to recruit the optimal neural network, whereas others are not. One explanation is that neural activities may actually reflect different cognitive strategies that correspond to different neural resources recruitment. Alternatively, brain anatomy and neurophysiology may have determined the available cognitive strategies (Breitenstein et al., 2005). Presumably, with the increase in language experience and fluency, the neural network will become more and more optimized and converge to the native language network. Long-term longitudinal studies are needed to test this hypothesis.

Taken together, our study found sex-dependent neural predictors of visual word learning, suggesting that sex may determine the optimal neural network for learning to read a new language.

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