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Research report

Gender-specific hemodynamics in prefrontal cortex during a verbal working memory task by near-infrared spectroscopy

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ABSTRACT

The presence or absence of gender differences in working memory, localized in the prefrontal cortex (PFC), has been debated in a few fMRI studies. However, the hypothesis of gender differences in PFC function has not been elaborated, and comparisons among hemodynamic parameters designed to test for gender differences are scarce. We utilized near-infrared spectroscopy during verbal *N*-back tasks on 26 male and 24 female healthy volunteers. Changes in the concentrations of oxy- (Δ[oxy-Hb]), deoxy- (Δ[deoxy-Hb]) and total hemoglobin (Δ[tot-Hb]) were recorded simultaneously. Δ[oxy-Hb] and Δ[tot-Hb] exhibited obvious gender differences, but Δ[deoxy-Hb] did not. Males showed bilateral activation with slight left-side dominance, whereas females showed left activation. The activation in males was more wide-spread and stronger than in females. Furthermore, females required a lower hemodynamic supply than males to obtain comparable performance, and only females exhibited positive correlations between hemodynamic parameters and behavioral performance. The results reinforce the existence of a gender effect in hemodynamic-based functional imaging studies. Our findings suggest that females possess more efficient hemodynamics in the PFC during working memory and emphasize the importance of studying the PFC to further a scientific understanding of gender differences.

1. Introduction

The issue of gender influences on performance has recently been highlighted in neuroscience [7]. Gender differences in performance have been recognized on various cognitive tasks [49,27]. Females outperform males on verbal tasks [49,16,2], while males outperform females on visual–spatial tasks [27].

It has been found that sex hormones may affect human prefrontal cortex (PFC) function. PFC and its neural circuitry are suggested to be chief mediators of the influence of sex hormones on cognition [26]. The replacement of estrogen or progesterone roused robust and reliable activation of PFC in females with low levels of sex hormones [5]. Use of estrogen can enhance the performance of PFC-dependent functions, such as working memory (WM) [8,10,17]. Thus, sex hormones may play an important role in maintaining certain PFC functions and, thus, PFC functions may well show sexual differentiation.

One function distinctly linked with PFC is WM. A main feature of WM is to temporarily store and maintain information while simultaneously manipulating it, for example, by reordering or actively updating the stored contents of WM [13,3]. Given that PFC may well demonstrate gender-specific functions and that WM is the most common function of PFC, it is not unreasonable to expect that PFC may be more likely to show gender differences in WM and should be a prominent brain area for intensive study of gender influences.

Gender differences in WM have been researched using *N*-back tasks with words, faces, letters and numbers [18,43,37], the auditory Q3A-INT task [14] and number recognition [4]. These studies were all based on functional magnetic resonance imaging (fMRI) observations of the blood-oxygen-level-dependent (BOLD) signal. These published gender differences in performance and activation patterns are controversial. In behavior, despite the general consensus that females and males are comparable [14,4,18,37], higher accuracy and slightly slower responses in females have also been observed [43]. In brain activation, some research has supported a greater left-lateralization for females and a greater bias toward right hemisphere for males [4,43], whereas others have reported bilateral activation in females and left-sided PFC activation in males [15] or similar lateralization patterns between the sexes [18,37].

Gender differences in brain function have been observed in signals of blood flow [8], oxygen saturation of hemoglobin [24], and concentration change of oxy-hemoglobin [25] on the basis of neurovascular coupling. The fMRI BOLD signal is altered by many hemodynamic factors, such as concentration changes in oxy-, deoxy- and total hemoglobin (Δ[oxy-Hb], Δ[deoxy-Hb], and Δ[tot-Hb], respectively), but it cannot identify which hemody-

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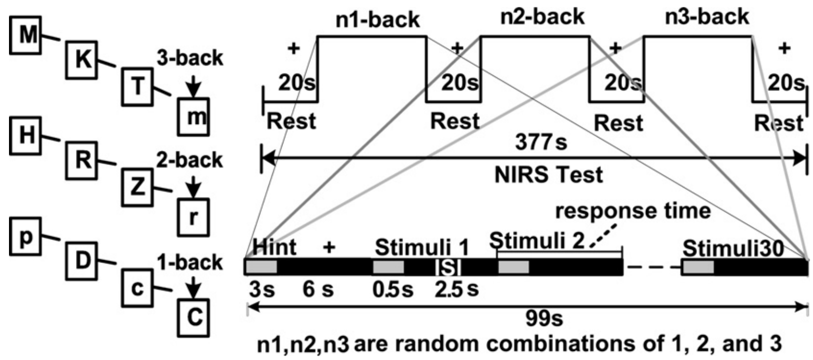

Fig. 1. Experimental design of *N*-back VWM task. (a) Protocol; (b) Timing diagram.

namic factor is altered or the quantitative contributions of each of those hemodynamic factors [9,30,12]. Accordingly, the BOLD signal cannot address gender effects on concrete hemodynamic factors. In addition, in some cases, the BOLD signal might mistakenly be interpreted as showing a gender difference in brain activation. For example, females and males alter [deoxy-Hb] equally but alter other hemodynamic factors differently (e.g., [oxy-Hb] in Ref. [25]), but since [deoxy-Hb] is the major factor determining the BOLD signal [46,22,40], the BOLD signal would merely obscure the gender difference [18,37]. Therefore, measuring multiple hemodynamic parameters is recommended for fully and precisely exploring gender effects on hemodynamics-based brain imaging studies.

Both functional near-infrared spectroscopy (fNIRS) [19,23,33,51] and fMRI measure hemodynamic responses to interpret brain activity. Compared to fMRI, fNIRS has the advantage of directly providing multiple measures, including Δ[oxy-Hb], Δ[deoxy-Hb] and Δ[tot-Hb] [46,44]. In addition, fNIRS can be measured real-life situations, improving the precision of interpreting brain activations [45].

Here, fNIRS was employed to measure hemodynamic-interpreted PFC activation under *N*-back verbal WM (VWM) tasks. Our hypothesis was that females and males might differ in PFC activation in terms of Δ[oxy-Hb] or Δ[tot-Hb], but not clearly differ in Δ[deoxy-Hb], at the same level of behavioral performance. To obtain a deeper insight into gender influences, we further attempted to investigate gender differences in the brain–behavior correlation between the hemodynamic parameters and behavioral data.

2. Materials and methods

2.1. Participants

Fifty-four right-handed healthy volunteers (26 males, 28 females) were recruited from the university community by poster advertising. Subjects with a lifetime history of neurological, psychiatric, or endocrine pathology or having first order family member with a psychotic disorder were excluded. The menstrual cycle was considered [8] as it has been reported that the levels of sex hormones affect PFC function in females [1,38]. To reduce this effect, four females with irregular menstrual cycles were excluded. Thus, at last, 24 females (who completed the experiment during the follicular phase) and 26 males were included.

The mean ages of the females and males were 21.3 years (range = 18–23 years) and 21.5 years (range = 18–23 years), respectively. The mean years of education for men and women were 15.7 (range = 15–17 years) and 15.6 (range = 15–17 years), respectively. Neither age nor education level differed significantly between the sexes. Every subject had normal or corrected-to-normal vision. Before the experiment, subjects signed an informed consent provided by the Human Subjects Institutional Review Board at Huazhong University of Science and Technology. The ethics board of the university approved this study.

2.2. VWM Task

The task (see Fig. 1) consisted of 4 fixation blocks and 3 task blocks, lasting for 377 s. Fixation blocks lasted for 20 s. In each task block, first, the task name was displayed for 3 s; then, a fixation sign was displayed for 6 s; and finally, 30 random alphabetical letters were presented (see Fig. 1(a)). Each letter was presented at the same font size for 0.5 s, followed by a 2.5-s interval during which the screen was blank. The presentation order of task blocks was random. The subjects were instructed to respond by pressing one button for yes and another for no depending on whether the current letter had the same identity (regardless of case) as the one presented just before (1-back), two before (2-back) or three before (3-back). In each task block, 10 letters were set as yes cases.

2.3. Behavioral measurements

During the experiment, response time to each stimulus was collected with ms precision, and response accuracy was recorded. After the experiment, the mean response time and accuracy of each subject for each block was recorded. The behavioral data were analyzed for differences between the sexes, as related to the task load. A series of 3 (task load: 1-back, 2-back and 3-back) × 2 (gender) ANOVA analyses were used to assess differences in response time and accuracy between groups.

2.4. fNIRS recording and data analysis

We used a 16-channel fNIRS imaging device [51,31] to measure Δ[oxy-Hb], Δ[deoxy-Hb] and Δ[tot-Hb]. The probe was fixed with a black adjustable strap over the subject's bilateral PFC. The probing area was 4.4 cm × 15 cm, covering nearly the whole forehead (Fig. 2). The separation between the light source and detector was set at 2.89 cm, which allowed hemodynamic measurement depth of 2–3 cm from the skin of the head, that is, the outer cerebral cortex [47]. The sampling rate was 4 Hz.

Δ[oxy-Hb], Δ[deoxy-Hb] and Δ[tot-Hb] were calculated as in [28,29]. A temporal high-pass filter with a cutoff frequency of .005 Hz [23,39] was used to remove the slowly drifting signal components. To correct the baseline in the rest period, we

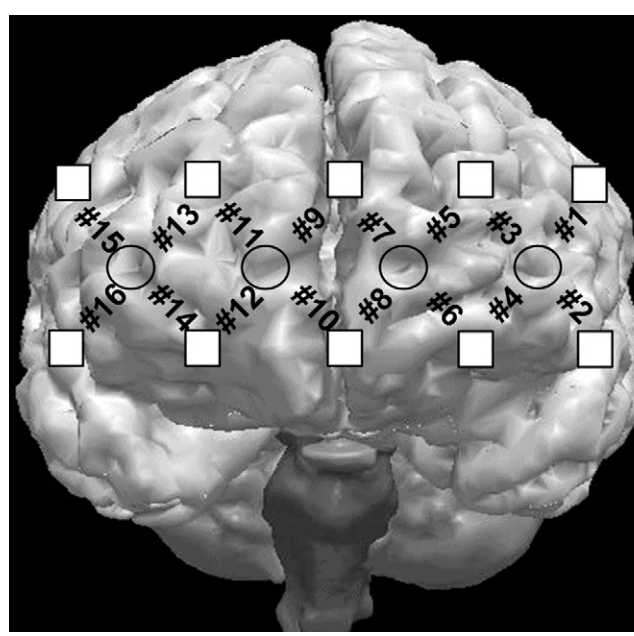

Fig. 2. fNIRS channel orientation. Light sources are shown as circles, detectors as squares. "#" denotes "channel".

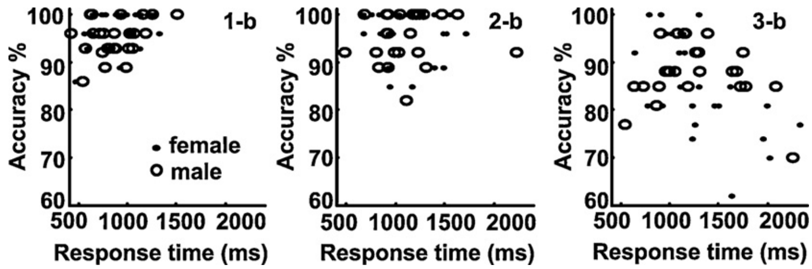

Fig. 3. Scatterplots of behavioral data for males and females.

calculated the mean values for the rest measurement and subtracted them from the mean values for the task-induced active phase. Thereby, we obtained one value for each hemodynamic parameter under each task load.

The mean Δ[oxy-Hb], Δ[deoxy-Hb] and Δ[tot-Hb] values were analyzed by separate 3 (task load) × 2 (gender) × 16 (channel) ANOVAs. These mean values were also mapped according to channel locations and then superimposed on an anatomical brain model (reconstructed from the Visible Chinese Human dataset [36]). These images were intended to illustrate the approximate coverage of fNIRS measurements over the cortex and were not meant to be exact. Other post hoc tests were subsequently performed to analyze interaction effects of gender and other factors. Finally, gender differences in the relationship between the mean values of hemodynamic parameters and the behavioral data were tested by calculating Spearman correlation coefficients. No correction for multiple comparisons was performed, and results were considered significant if $P < .05$.

3. Results

3.1. Behavioral data

Accuracy and response time did not differ significantly between the sexes for each task load (see Figs. 3 and 4). In the figures, '1-b' denotes '1-back'. The repeated measures ANOVA for accuracy showed a main effect of *task load* ($F(2,50) = 42.00$, $P < .01$), but no significant main effect of *gender* ($F(1,50) = 0.08$, $P = .78$) or *gender* × *task load* interaction ($F(2,50) = 2.21$, $P = .11$). The repeated measures ANOVA for response time also showed a main effect of *task load* ($F(2,50) = 15.88$, $P < .01$), but no significant main effect of *gender* ($F(1,50) = 0.22$, $P = .64$) or *gender* × *task load* interaction ($F(2,50) = 0.06$, $P = .94$) was found.

3.2. fNIRS data

A notable gender difference was present in PFC activation under VWM demands. The hemodynamic responses of females had significantly lower amplitudes and were more spatially focused than those of males (Figs. 5 and 6).

A 3 × 2 × 16 (task load, gender, channel) repeated measures ANOVA for each hemodynamic parameter was performed. The main effect of *gender* was not significant on Δ[deoxy-Hb] ($F(1,50) = .12$, $P = .731$), but was significant on Δ[oxy-Hb] ($F(1,50) = 179.52$, $P < .001$) and Δ[tot-Hb] ($F(1,50) = 204.02$, $P < .001$). The factors *task load* ($F(2,50) > = 25.17$, $P < .001$) and *channel* ($F(2,50) > = 3.00$, $P < .001$) also exhibited significant main effects on all hemodynamic parameters, which indicated that the activation altered with *task load* and was heterogeneous in PFC (see Figs. 5 and 6). All interaction effects on all hemodynamic parameters were not statistically significant. It is obvious in Figs. 5 and 6 that Δ[oxy-Hb] and Δ[tot-Hb] of males were always higher than females under all task loads ($F(1, 50) > 26.99$, $P < .001$). Both males and females increased Δ[oxy-Hb] and Δ[tot-Hb] when task load increased to 3-back between 1- and 2-back, $F(1,50 < .08$, $P > .780$; between 1-, 3-backs or between 2-, 3-backs, $F(1,50) > 5.49$, $P < .026$).

Here is the analysis of gender's effect on the distribution of PFC activation. Comparing between Figs. 5 and 6 for Δ[oxy-Hb] and Δ[tot-Hb], females clearly show focused and left-lateralized activation, while males exhibit wide-spread and bilateral activation. Post hoc analyses among channels revealed that females' focused activated region displayed large effect sizes ($P < .001$, Cohen's $d > .80$) of the gender difference effect (for Δ[oxy-Hb] in channels 5–9, 15; for Δ[tot-Hb] in channels 6, 8, 9, and 15). In other channels, the Cohen's d values for Δ[oxy-Hb] and Δ[tot-Hb] was within the range of (.30, .80). Thus, the activation of the region of the PFC activated in females during the task was more gender specific.

3.3. Brain–behavior correlations

Females showed positive correlations between hemodynamic parameters and behavioral performance, while males did not (Table 1). Specifically, in females, Δ[oxy-Hb] and Δ[tot-Hb] in the 3-back blocks showed significant positive correlations with *accuracy*, but inverse correlations with *response time*; Δ[oxy-Hb] in the 1-back blocks also showed an inverse correlation with *response time*; and Δ[deoxy-Hb] in the 1- and 2-back blocks also showed positive correlations with *accuracy*, but no significant correlation

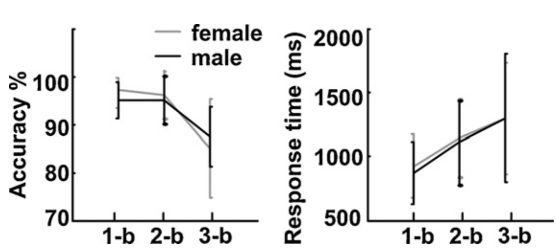

Fig. 4. Mean accuracy and mean response time for both sexes with relation to task load under verbal *N*-back tasks.

Table 1
Comparison of female and male correlations (*r-value*) between hemodynamic parameters and behavioral data.

Hemodynamic	Behavior	Task	Females	Males
Δ[oxy-Hb]	Accuracy	1-b	−.033	.138
		2-b	−.352	−.222
		3-b	.863***	−.263
	Response time	1-b	−.449*	−.184
		2-b	−.249	−.252
		3-b	−.473*	−.170
([tot-Hb]	Accuracy	1-b	−.033	.224
		2-b	.182	−.049
		3-b	.927***	−.263
	Response time	1-b	−.384	−.242
		2-b	−.374	−.239
		3-b	−.477*	−.276
Δ[deoxy-Hb]	Accuracy	1-b	.656**	.290
		2-b	.785***	.369
		3-b	−.359	−.029
	Response time	1-b	.382	.000
		2-b	.084	.040
		3-b	.233	−.112

* $P < .05$, ** $P < .01$, *** $P < .0001$; (two-tailed).

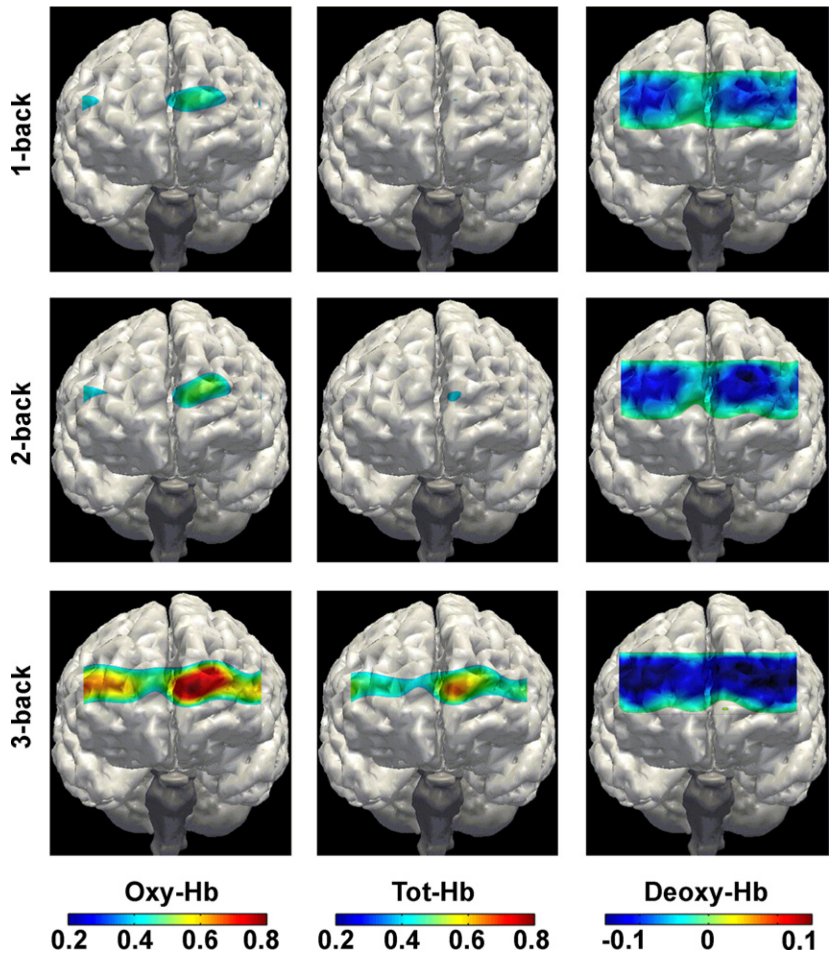

Fig. 5. Mean activation maps of females under verbal *N*-back tasks measured by fNIRS.

with *response time*. Accordingly, in females, the responders with higher accuracy tended to exhibit hemodynamic responses; in the quicker responders, enhanced supplies of oxygen (Δ[oxy-Hb]) and blood (Δ[tot-Hb]) were likely to be found. By contrast, males exhibited no significant brain–behavior correlations.

4. Discussion

The present study demonstrates specific effects of gender on both cognitive performance and functional activity in PFC as measured by hemodynamic responses during a verbal working memory (VWM) task. Males and females exhibited comparable accuracies and response times under various task loads. This result did not replicate the finding of a previous report of higher accuracy and slower response times in females versus males during a 1- and 2-back VWM task [43]. The unequal gender distribution and limited sample size in that study might have produced the biased result [37]. However, this finding is in line with many recent studies on comparable performance across gender in cognitive activities [18,14,4,37,48]. In contrast to the gender similarities in behavioral performance, gender differences were apparent in PFC hemodynamic responses, upholding our initial predictions and expanding our understanding of gender effects on the hemodynamic response (specified below).

The gender-specific activation patterns in PFC differed among hemodynamic parameters. Δ[oxy-Hb] and Δ[tot-Hb] exhibited significant gender differences under all task loads, while Δ[deoxy-Hb] did not. The amplitudes of Δ[oxy-Hb] and Δ[tot-Hb] were significantly higher in males than females. A prior fNIRS study has also observed higher Δ[oxy-Hb] in PFC of males during a word fluency task [25]. Another fNIRS study of a verbal fluency task did not observe a clear influence of gender on Δ[oxy-Hb] in temporal PFC [20], which might be due to the differences in the task and brain area of interest relative to ours. Of note, this gender-specific brain activation evidenced by Δ[oxy-Hb] and Δ[tot-Hb] is similar to results of two fMRI studies on gender differences in hemodynamics during WM tasks that suggested a left lateralization in females [4,43]. On the other hand, Δ[deoxy-Hb] mostly displayed gender similarity. Since Δ[deoxy-Hb] has been suggested to be the major factor determining the BOLD signal, it is understandable that no clear [18,37] or reliable [14] gender differences can be observed by fMRI during a WM task.

The measured gender-specific brain activation pattern during a VWM task provides evidence relevant to the debate on gender-specific activation during language processing. Some studies have claimed bilateral activation in females and left-hemispheric dominance in males in language processing [34,41,42,21], while others have argued for left-lateralized activation in both sexes, and especially in women [18,35,6,50]. Our result is compatible with the latter viewpoint. That is, males showed bilateral activation with slight left-side dominance, whereas females mainly showed left PFC activation. In addition, the strong activation of the left PFC in both sexes also supports similarity of lateralization across the sexes for language processing tasks, regardless of WM involvement [18].

The combination of behavioral performance and gender-specific PFC activation points to females' more efficient hemodynamic supplies in PFC during a VWM task. Females displayed much lower

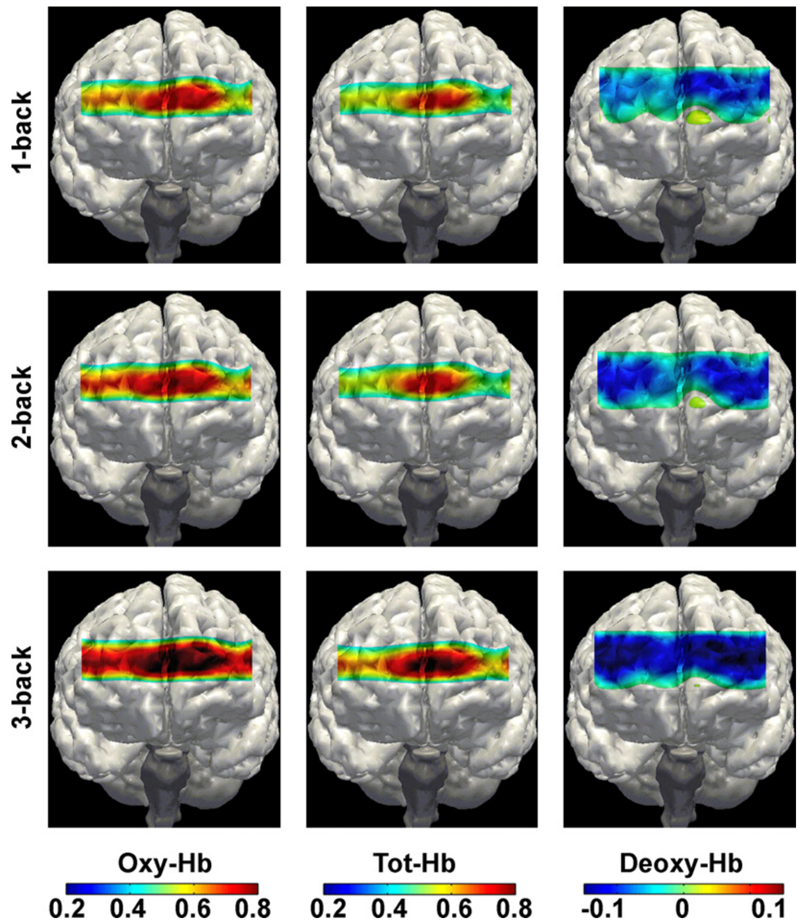

Fig. 6. Mean activation maps of males under verbal *N*-back tasks measured by fNIRS.

amplitudes of ([oxy-Hb] and ([tot-Hb] than males (Figs. 5 and 6) at the same level of performance (Figs. 3 and 4). The amplitudes of Δ[tot-Hb] and Δ[oxy-Hb] reflect an increased energy supply for neural activity in the form of blood and oxygen. The higher amplitudes of those in males indicate an enhancement of the energy supply for brain activity; their lower amplitudes in females indicate more efficient execution of PFC functions. Additionally, females completed the task as well as males by engaging a smaller brain region. Particularly, females exhibited positive correlations between hemodynamic parameters and behavioral performance, but males exhibited no correlations at all. The finding of the female-specific brain–behavior correlations, in line with the inverse intelligence-activation relationship, provides hemodynamic evidence for the neural efficiency hypothesis (e.g., less activation in more capable individuals) [32,11,15].

The left PFC in females has been reported to play a crucial role in relations among hormones, cognitive performance and brain activity [38]. Here, similarly, females mainly showed enhanced hemodynamic supply in the left PFC. Together with the beneficial effects of estrogen on women's WM in hormone replacement therapy [10,26], the hypothesized relationships of sex hormones, the hemodynamic supply in the left PFC and cognitive performance seem to be plausible, and hence might be required to fully understand the gender effect.

It should be pointed out that the employed fNIRS probe could not cover the whole PFC region. Measurement of the whole PFC could provide exhaustive results regarding the gender-specific activation. In addition, most subjects in the study majored in science and engineering. This has been taken into account by a counterbalanced design; however, future studies should recruit more subjects majoring in the arts, business, and other disciplines in both sex groups.

In summary, this fNIRS study provides further evidence for gender-specific PFC activation under VWM: (1) Δ[oxy-Hb] and ([tot-Hb], not Δ[deoxy-Hb], were shown to be sensitive indicators of gender differences. Males showed bilateral activation with slight left-dominance, whereas females showed left-lateralized activation; the females' activated region was shown to be more sensitive to gender than other regions. (2) Females, with positive correlations between hemodynamic parameters and behavioral performance, required a lower hemodynamic supply in a smaller region of PFC than males to perform equally well on the task. Overall, this study reinforces the effect of gender in hemodynamics-interpreted functional imaging studies; provides further insights into the complex interactions among gender, cerebral hemodynamics and behavioral performance; and emphasizes the importance of PFC in unraveling how females differ from males.

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