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The feasibility of 2-back task with alphabets and functional transcranial Doppler sonography in assessing hemispheric lateralization of working memory in Chinese

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Abstract

Background: Hemispheric asymmetry studies of working memory are mainly carried out in western countries. Data on Chinese is limited in this area of research. On the other hand, working memory assessment can be limited by the temporal resolution of the imaging modality as well as the design of the cognitive paradigm. These methodological limitations influence result interpretation hence hinder cross study comparison. Hemispheric study of memory using a pure working memory paradigm on native Chinese speakers, using a hemodynamic technique with high temporal resolution is thus mandatory. *Objective:* We aimed to investigate the feasibility of the functional transcranial Doppler sonography (fTCD) and 2-back task with alphabets in assessing the hemispheric lateralization of memory in healthy right-handed Chinese. *Methods:* Thirteen healthy right-handed Chinese subjects (7 males and 6 females, 19-22 years old) were included. Bilateral monitoring of the cerebral blood flow velocity (CFBV) changes in their left and right middle cerebral arteries (MCAs) was performed using fTCD during their performance of a 2-back working memory task with alphabets. Differences of CBFV change between left and right MCAs were analyzed, and the laterality index (LI) was determined. *Results:* Left lateralization was found in all subjects, with females performed better than males ($p < 0.05$). No difference in age, response time and LI between the male and female subjects could be observed ($p > 0.05$). A weak correlation was found between performance accuracy/response time and LI ($r^2 = 0.12$).
Conclusion: To the best of our knowledge, this is the first report on the use of fTCD in memory function assessment in Chinese. The consistency of our results with previous studies demonstrates the feasibility as well as the potential application of the 2-back task with alphabets and fTCD, as a bedside assessment system of memory function in native Chinese speaking population.

INTRODUCTION

Memory, especially working memory, plays an important role in human life. Working memory is responsible for short-term storage and online manipulation of information necessary for higher cognitive functions such as planning and problem-solving[1,2], with the prefrontal cortex as the primary executing region.[3-7] Brain lesion in different neural regions exerts different degree of deficits in brain function.[8] Information on the hemispheric memory dominance is of particular importance for risk evaluation on memory disturbance/impairment prior to a resective brain surgery[9], or electrode positioning of an electroconvulsive therapy.[10,11]

A wide range of imaging tests such as the intracarotid amobarbital procedure (or termed as the Wada test) and functional magnetic resonance imaging (fMRI) have been applied in the investigation of hemispheric lateralization of various cognitive activities. Invasiveness, ionizing radiation, prolonged procedure in intracarotid amobarbital procedure[12]; high cost, low temporal resolution[13,14] and the contraindication of having MRI exam for subjects with metallic implants are the most influencing drawbacks in providing a holistic picture in hemispheric lateralization research with optimum economy and safety.

Functional transcranial Doppler sonography (fTCD) is a more superior functional tool than

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intracarotid amobarbital procedure and fMRI in the context of hemispheric lateralization determination due to its low cost, high portability and non-invasiveness.[15] fTCD applies similar principle as fMRI in hemispheric lateralization determination – the level of increase in cerebral blood flow velocity (CBFV) is directly related to the level of cerebral activation during an engagement of a cognitive task.[16-19] It has been reported that the high temporal resolution of fTCD allows real-time bilateral monitoring of CBFV change during language and cognitive processing.[18,20-23] Recent studies also demonstrated that fTCD and fMRI are highly correlated with the Wada test (gold standard) in the determination of cerebral lateralization.[24,25]

fTCD has been mainly applied in the quantification of hemispheric perfusion differences in language.[23,24,26] Only one recent study utilized fTCD in working memory hemispheric lateralization determination using alphabetic language speaking population.[27] However, the successfulness of fTCD in working memory hemispheric lateralization assessment might be affected by the possible hemodynamic difference between the alphabetic and logographic language speaking populations.[28] Thus, a wider application of fTCD in working memory lateralization assessment awaits the feasibility investigation using subjects from a logographic language speaking population e.g. Chinese.

Cognitive style adopted during the mental task poses a greater effect in determining the hemispheric lateralization than the type of stimulus provided.[6,7] Nystron's investigation found a greater activation for region expected for verbal memory in an object working memory task. They suggested that subjects may apply verbal approach in naming object stimuli and practice subvocal rehearsal for memorization, thus activating verbal memory area.[29] In a recent study which applied fTCD in the assessment of memory function on Italians, subjects were requested to encode and immediate recall of a short written text describing a room. Left hemispheric dominance was found in the subjects, however, the authors pointed out that processing of this verbal material could involve visuospatial imagery resources.[27] Therefore, the appropriateness of the cognitive task is crucial for a pure memory function examination.

In this study, we aimed to investigate the feasibility of fTCD and 2-back working memory task with alphabets in assessing the laterality of memory processing in healthy right-handed Chinese.

METHODS

Subjects

Seventeen healthy right-handed Chinese subjects, aged from 18 to 40 years, were recruited in this study. Due to the lack of an acoustic temporal bone window, fTCD could not be performed in 4 subjects whom were excluded from this research. A total of 13 right-handed subjects (7 males and 6 females) were included in the present study, aged from 19 to 22 years old (mean ± SD, 20.7 ± 0.85 years old). All subjects were university students who have received at least 8 years of secondary and tertiary education. English was the medium of instruction for all our subjects. Handedness was assessed by the Edinburgh Handedness Inventory[30], which is a questionnaire-based assessment requesting the subject to indicate their preferences in the use of hands in the following activities: (1) writing, (2) drawing, (3) throwing, (4) using scissors, (5) using toothbrush, (6) using knife (without fork), (7) using a spoon, (8) using a broom (upper hand), (9) striking match, and (10) opening box (lid). Laterality quotient of all subjects were ranged from 75% to 100% (mean value, 94.6 ± 7.61%), indicating a strong right-handedness. None of the subjects had previous history of neurological, cardiovascular or psychiatric disease. No medication or caffeine-containing beverage intake was allowed within 6 hours before the experiment. Informed consent, approved by the Ethics Sub-committee of the Hong Kong Polytechnic University, was obtained from each participant.

Transcranial Doppler scanning

Subjects were allowed to rest at least 20 to 30 minutes for the stabilization of hemodynamics, before the study of blood flow velocity in the extracranial and intracranial arteries. The blood pressure of each subject was monitored during the experiment. Color Doppler sonography of extracranial arteries including subclavian, carotid and vertebral arteries was performed with a diagnostic medical ultrasound system (HDI 5000 Ultrasound System, Philips Medical Systems Company, USA) in conjunction with a 5–12 MHz linear array transducer on each subject to exclude the presence of any stenosis or intimal thickening that could alter the intracranial cerebral blood flow. With the subjects in a sitting position, a dual system of 2 MHz transducers in conjunction with the TCD system (Multi-Dop® X4, DWL Elektronische Systeme, GmbH, Germany) was

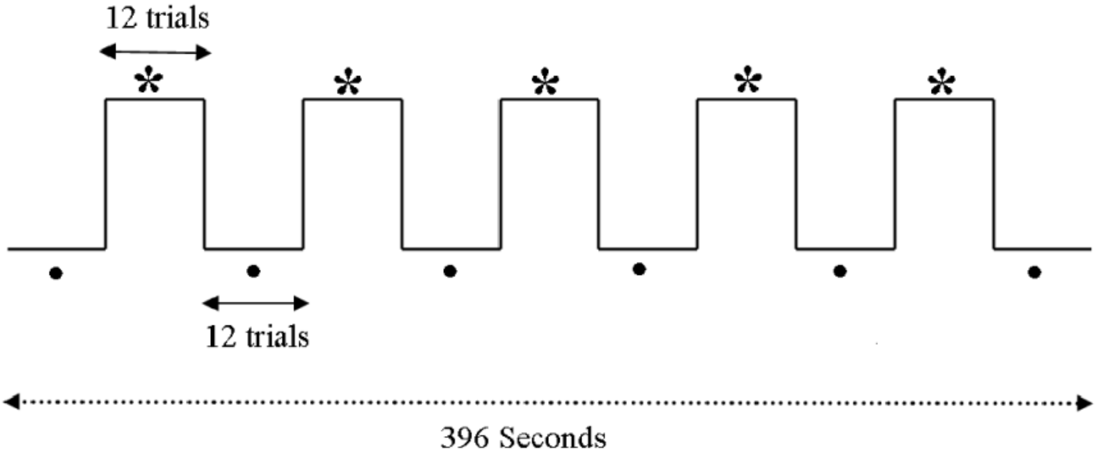

Figure 1. A schematic diagram showing the blocked paradigm of the 2-back memory task. Both activation (*) and resting (•) blocks contain 12 trials, and each trial lasts for 3 seconds.

adopted for simultaneous recording of CBFV in the middle cerebral artery (MCA) on both left and right sides while they were performing the 2-back memory task. Two transducers were attached onto the left and right temporal bone windows by an elastic headband. The Doppler sampling depth was confined to 50 to 55 mm from the skin surface, which is at the main stem of MCA, for all the subjects. All the recordings were taken in the same room with constant environmental conditions.

Two-back memory task

The 2-back memory task, a well recognized cognitive task that continuously stimulates brain activity for working memory assessment[31], was presented by the computer in front of the subject using the software Eprime (Psychology Software Tools, Inc., Pittsburgh, USA). A rehearsal session was given to each subject to practice the memory task. Each subject was asked to perform the task twice and a total of 2 runs of CBFV in left and right MCAs were acquired for analysis. Fifteen minutes break was provided for the subjects between 2 runs. In each run, the 2-back task started with a 36-second baseline period and followed by five 72-second blocks (Figure 1). Each block consisted of a memory activation period of 36 seconds and a resting period of 36 seconds. In each memory activation period, 9 alphabets were randomly chosen from 24 alphabets for presentation except ‘Q’ and ‘O’ due to their similarity. Four of the chosen alphabets were repeatedly presented at an interval of 2 alphabets. Each alphabet was presented on a black screen for 1 second followed by a 2-second crosshair for fixation. Subject was requested to determine whether the presented item was identical as the one presented 2 stimuli before during the activation periods (Figure 2A), and to respond by pressing key “0” on the keyboard using the right index finger. The presentations in the baseline and resting periods were identical to those in the activation periods except the alphabets were replaced by asterisks.[32-34] Subject was requested to press the key “0” every time an asterisk was presented to them (Figure 2B). The total duration of the task was 6 minutes and 32 seconds.

Data analysis

All the fTCD data sampling at the rate of 50 Hz was subjected to the Matlab R2007a (Mathworks, Inc., Natick, MA, USA) for data analysis. A median filter of the 5th order was applied to the data to reduce the artifactual spikes. In order to reduce the large inter-individual variations of absolute blood flow velocities[35,36] and to remove the dependence of insonation angle[37], the CBFV of the left and right MCA in each block was normalized separately to the baseline values. The mean CBFV for a period of 3 seconds before each activation phase was chosen as the baseline for normalization here because the CBFV acquired within this period was close to the start of memory activation in each block. Any block which showed persistent artifacts was excluded in the following analysis. The normalized CBFV in 2 runs of the fTCD data were concatenated. The linear trend of the normalized CBFV was removed by subtracting the straight lines of best fit with break points at the start of the activation phases. A bandpass filter of 0.01–0.04 Hz was then applied to remove the components of cardiac and

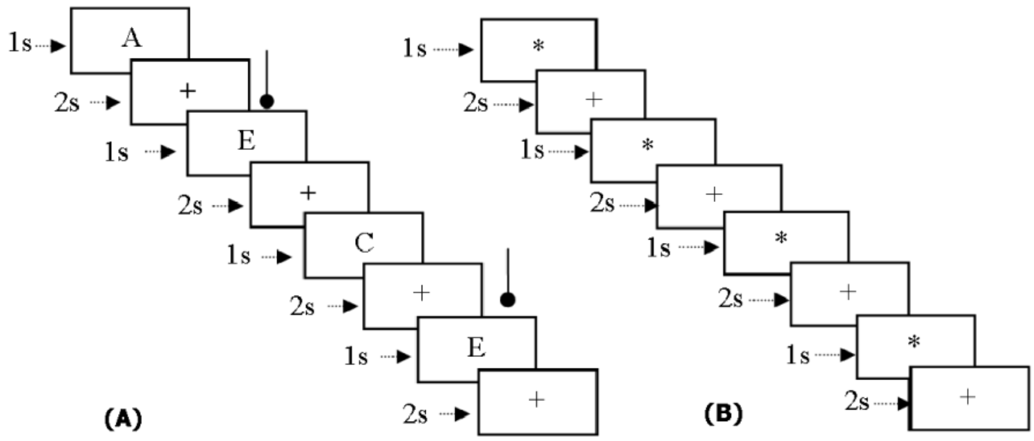

Figure 2. A schematic diagram showing the contents in (A) an activation block with black arrows indicating the 2-back sequence, and (B) a resting block. In the activation block, the 2 round-ended arrows indicate the alphabet that is repeatedly presented.

respiratory motions in the data so that the CBFV after bandpass filtering would be independent of the effects of cardiac and respiratory pulsation. The hemodynamic changes during memory activation and resting were then averaged with 0.02-second resolution in a 72-second window. The baseline was corrected to the mean CBFV for a period of 3 seconds before each activation phase to study the percentage change of CBFV in MCA relative to baseline. Since button clicking was required in both activation and resting phases, increase in blood flow due to motor response of clicking was removed from the data by subtracting the resting phase from the activation phase. Differences of CBFV change between left and right MCAs were analyzed by the Wilcoxon test and classified as significant at $p < 0.05$; the laterality index (LI) was determined using the same analysis strategy as in the study by Deppe *et al*.[37] Moreover, student's t-test was used to test for the differences in age, performance accuracy, response time and LI between the male and female subjects. Multiple regression analysis was performed to investigate the effect of performance accuracy and response time on LI.

RESULTS

Hemispheric lateralization of memory processing

The blood pressures of the subjects were within the normal range.[38] The 2-back memory task with alphabets was associated with an increase in the CBFV during the activation block when compared with the resting block ($p < 0.05$) (Figure 3). Almost all subjects (except s12) demonstrated a statistically significant difference of CBFV between the left and right MCAs ($p < 0.05$). The LI of the subjects ranged from 0.04 to 2.56 (Table 1), with a mean ± SD of 0.97 ± 0.78, indicating a left lateralization in verbal working memory processing.

Dependence of LI on performance accuracy and response time

A regression model was computed as:

$$LI = -2.42437 + 0.00247 * \text{Response Time} + 0.02192 * \text{Accuracy} + E$$

The p values of the intercept, response time and accuracy were 0.48, 0.31 and 0.47 respectively. The r^2 of this regression model was 0.12, indicating weak correlations between the response time and LI (Figure 4A), and between performance accuracy and LI (Figure 4B).

Gender difference in the performance accuracy

The accuracy achieved by the female subjects was significantly higher than that by the males, with a mean ± SD of 97.92 ± 2.28% in females compared to 86.9 ± 8.48% in males ($p = 0.01$). However, no difference could be seen between the male and female subjects in terms of their age (21.17 ± 0.4 years old in females vs 20.29 ± 0.95 years old in males) ($p = 0.06$), response time (515.37 ± 58.26 ms in females vs 594.77 ± 126.38 ms in males) ($p = 0.19$) and LI (1.17 ± 0.64 in females vs 0.8 ± 0.9 in males) ($p = 0.42$).

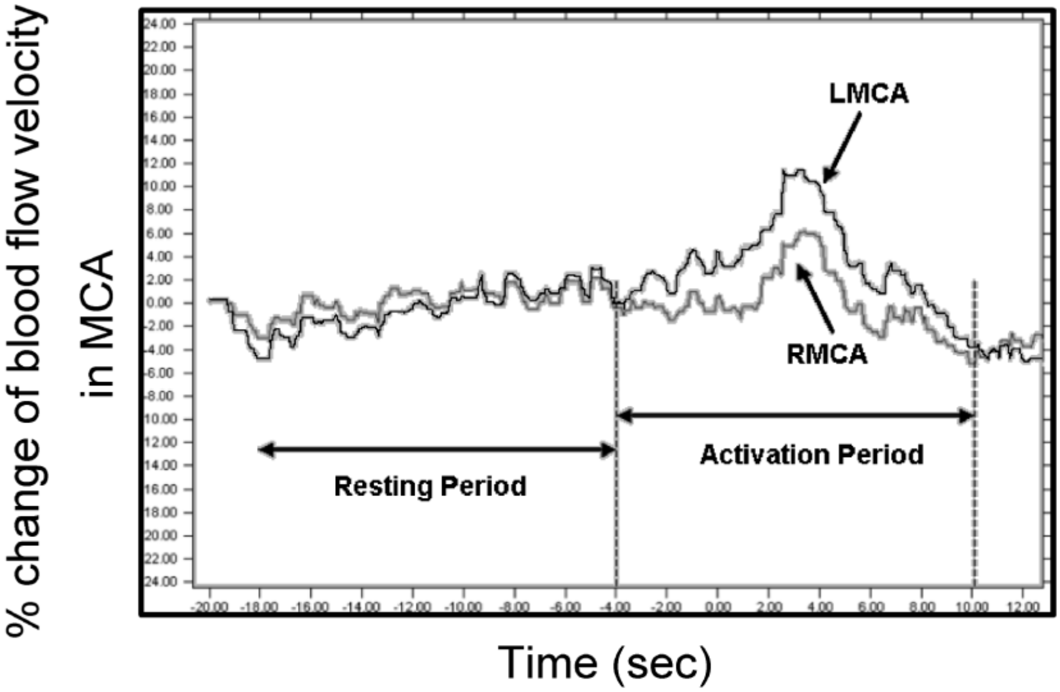

Figure 3. A screenshot of the percentage change of the blood flow velocity of the right and left middle cerebral arteries (RMCA and LMCA respectively) in the resting and activation periods of one of the subjects during his performance of the 2-back memory task. Results analyzed by the software AVERAGE.

Table 1: Subject characteristics, their performance in the 2-back test (accuracy and response time), and results of fTCD

Subject	Sex	Age	Accuracy (%)	Response Time (ms)	Wilcoxon p value (2-tail)	LI
s01	F	21	100.00	555.88	<0.001	1.06
s02	F	21	100.00	506.00	<0.001	1.70
s03	F	21	100.00	462.25	<0.001	0.35
s04	F	22	95.83	611.67	0.037	2.12
s05	F	21	95.83	492.08	<0.001	0.84
s06	F	21	95.83	464.33	<0.001	0.93
s07	M	19	91.67	430.63	0.023	0.41
s08	M	20	83.33	447.63	0.042	0.30
s09	M	20	87.50	535.00	<0.001	0.67
s10	M	20	75.00	740.00	<0.001	1.40
s11	M	20	91.67	644.00	<0.001	2.56
s12	M	22	79.17	635.42	0.478	0.04
s13	M	21	100.00	730.75	0.033	0.20

Wilcoxon test with $p < 0.05$ indicates a significant difference in the CBFV between the left and right MCAs during the 2-back memory task performance. The positive value of the LI (laterality index) indicates a left lateralization for working memory in all our subjects.

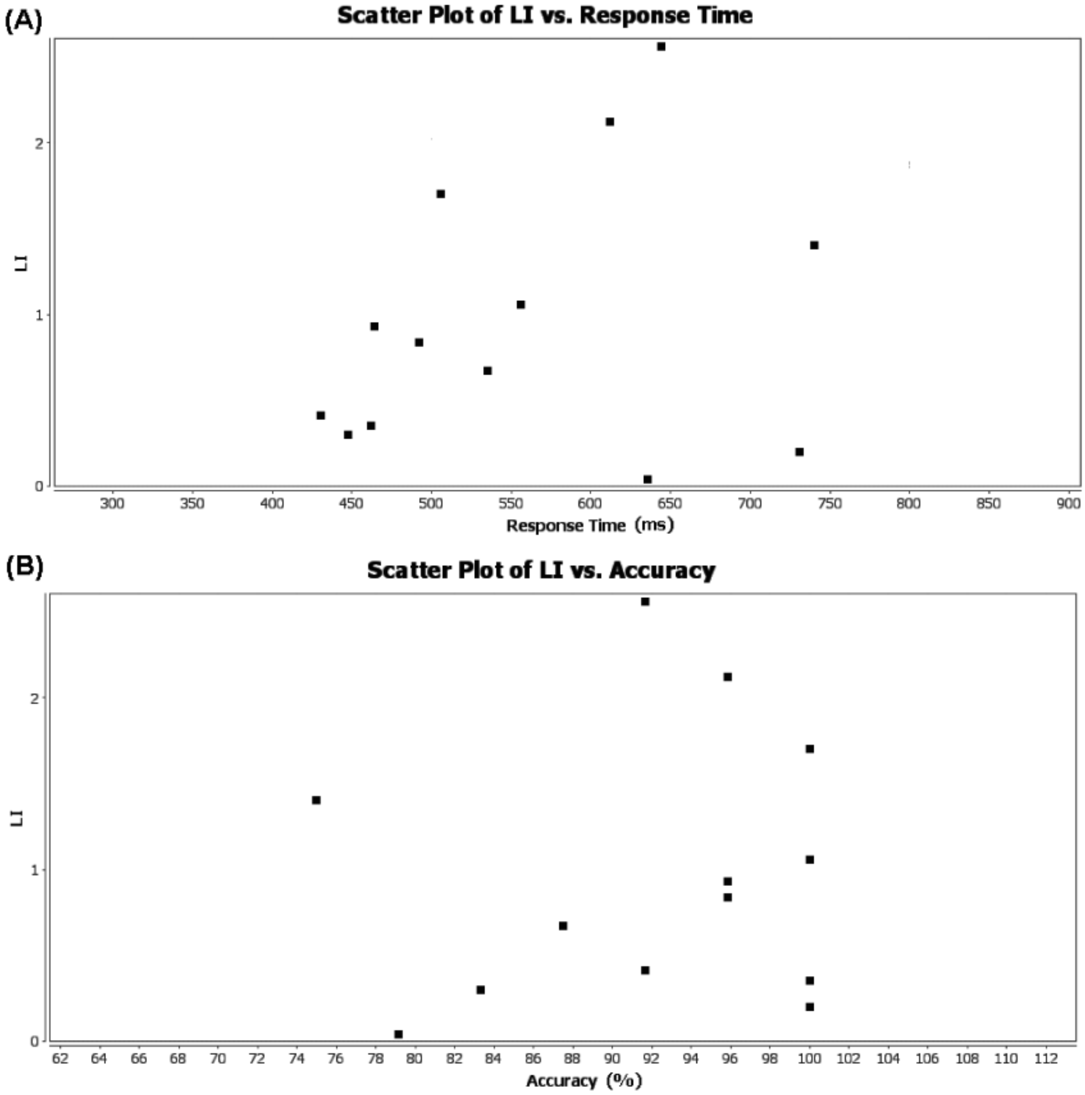

Figure 4. Scatter plots from multiple regression analysis on the correlations of (A) response time and (B) performance accuracy with LI (laterality index).

DISCUSSION

The aim of this study was to investigate the feasibility of fTCD and 2-back memory task with alphabets in assessing the hemispheric lateralization of working memory processing in healthy right-handed native Chinese. Increase in blood supply to both hemispheres of the brain is needed to cope with an increase in cognitive demand. By comparing the level of increase in blood supply (as reflected by the blood flow velocities), the dominant hemisphere for a particular cognitive function can then be determined. In this study, the CBFV change obtained from both left and right MCAs indicated the presence of an increased hemodynamic response from resting to activation phases (Figure 3). The reason for the absence of CBFV difference between both MCAs in s12 is yet to be investigated. Nevertheless, LI calculated from the CBFV data revealed a left lateralization of working memory processing in all our subjects.

Two-back memory task with alphabets

We used 2-back task with alphabets because this is a well established task for working memory assessment.[31] The choice of alphabets in the paradigm originates from the slight difference of brain activity in the phonological processing between Chinese characters and alphabetic words.[39] In addition to the common language processing areas shared between Chinese language and alphabetic language, Tan *et al*. reported that the processing of Chinese characters' phonology involves the left dorsal lateral frontal cortex as well, which is also one of the major brain areas that are activated in working memory literature.[39] To avoid any bias in the assessment of memory lateralization, we chose alphabets instead of characters to be incorporated in the 2-back memory task. As the paradigm itself does not contain words and characters as in other verbal working memory tasks, the contribution of activations in left hemisphere due to language processing, which cannot be differentiated in fTCD signals, will be reduced.[40,41]

All our subjects were determined as left lateralized indicating the success of the 2-back task with alphabets in accessing working memory processing in Chinese, provided that the subjects do not interpret the alphabets as false fonts. On the other hand, it has been reported that women are found to have a better performance in working memory task than that of men.[3,4,42] Despite the small sample size in this study, the behavioral results of our subjects support these findings. In addition, our results suggested that hemispheric lateralization during memory encoding is unaffected by gender, which is consistent to a similar fTCD report by Bracco *et al*. using a larger number of subjects.[27] The consistency of our results with previous working memory studies in other countries therefore strongly suggest that 2-back task with alphabets could be adopted in Chinese population for the assessment of hemispheric lateralization of memory, without the need of modification.

Language system and memory function

Previous studies on memory processing in the prefrontal cortex mainly focused on non-human primates such as adult rhesus monkeys (Macaca mulatta).[43,44] The difference in prefrontal cortex size and the amount of brain sulci between monkeys and human species[45] may impose an uncertainty in extrapolating non-human primates data for analyzing the prefrontal cortex region in human. Other memory hemispheric lateralization studies were carried out in populations speaking alphabetic languages such as English, German or Italian.[27,46,47] Tan *et al*. pointed out the differences between the Chinese and English/alphabetic writing system: (1) Chinese is based on the association of meaningful morphemes with graphic units, while alphabetic systems are based on the association of phonemes with graphemic symbols; (2) Chinese characters are of square and nonlinear configuration whereas alphabetic words are linear in structure.[28] It has been reported that different language related neural pathways were activated when the memory task was visually presented in different language systems.[39,48] A meta-analysis using activation likelihood estimation was performed on the data from 19 published brain mapping studies of phonological processing in reading (6 with Chinese and 13 with alphabetic language systems). It was reported that the left posterior sites of temporoparietal regions were important for alphabetic languages, while the posterior neural system involving the dorsal aspect of left inferior parietal regions assists in carrying out phonological processing of Chinese words.[39] A strong positive correlation between the verbal memory and language lateralization has been demonstrated.[47] Further studies also reported on the dependence of working memory representation on the language processing.[46,47]

Despite the possible hemodynamic difference between populations of different language system, numerous neuroimaging studies on working memory used populations speaking alphabetic languages reported a left hemispheric dominance for verbal stimulus.[3,6,7,42] Moreover, addition of language substrate for left lateralization in working memory assessment was also demonstrated.[46] Our findings are consistent with those in the previous studies using similar 2-back memory task irrespective of the issue on bilingual and different language system. A few other fMRI studies using bilinguals further support our findings: (1) Xue *et al*. used unequal bilinguals (i.e. subjects are proficient in Chinese but not English) showed that although subjects performed better at tasks in their native language (Chinese) than in English, working memory tasks in both first (Chinese) and second (English) languages evoked a similar pattern of left dominance activation.[49] (2) Chee *et al*. reported that equal bilinguals i.e. subjects had high proficiency in both English and Chinese, demonstrated an elevated activation at left insula for working memory.[40] The consistency of our results with previous fMRI studies on bilinguals suggest that fTCD might be applied for the assessment of hemispheric lateralization of memory processing in a wide range of subjects, including alphabetic and logographic language speaking populations.

This study has a few limitations: (1) Knecht *et al*. pointed out that fTCD is weak in detecting minute hemispheric activation. In addition, fTCD detects a territories supplied by MCAs but cannot spot out whether it is a critical region for a particular mental task.[16] Hemispheric lateralization is usually a subtle effect[4], fMRI is more superior than fTCD in studying small activation as low as about 1% signal change.[50] A cross validation of our findings with fMRI may be useful in verifying our results. (2) Our subjects belong to a logographic language speaking population; it is possible that they might have recognized the shape of the alphabetic (as in recognizing Chinese characters) instead of naming the stimuli for memory processing (see also (1) of *Suggestions for future memory processing experiment*). The certainty of our subjects in using verbal working memory processes during the 2-back task with alphabetic would need to be proven by the fMRI examination, which offers a high spatial resolution for the demonstration of the neural path. (3) The present findings were acquired in a small sample group, which limit the generalization of the findings. Future study of healthy individuals of a larger sample size would increase the confidence on its application to the bedside assessment of memory lateralization.

Suggestions for future memory processing experiment

Based on our experience, a few technical aspects on the experimental design should be noted when studying verbal working memory: (1) The 2-back working memory paradigm can be improved by mixing both upper and lowercase letters as the stimuli. This can ensure the encoding and subvocalization of the letter stimuli are as verbal phonemes rather than visual recognition of their shapes[29], which may trigger the use of object strategy in memorizing the letters. (2) We used alphabets in the current working memory paradigm because it has been well documented and induce less language effect than words. As the brain areas activated by false fonts have been documented in a recent fMRI study[41], exploration of the feasibility using working memory task containing Chinese radicals which do not have meaning but can be pronounced may provide a better probe for the fTCD memory lateralization assessment. (3) The level of neural activation between subjects can be better controlled by using an identical stimulation sequence during the memory task, in addition to setting the amount of stimulus within each activation phase constant (as in this experiment).

CONCLUSIONS

We successfully applied fTCD in demonstrating an elevated cerebral blood flow during neural activation, for the determination of the hemodynamic response of memory processing in healthy right-handed Chinese. Left lateralization of memory function was observed in all our subjects, which is consistent with the results obtained in populations speaking alphabetic languages.[3,6,7,27,42,46,47] Our study suggests the potential of 2-back task with alphabets and fTCD as a bedside assessment system for the hemispheric lateralization investigation of memory, in logographic (e.g. Chinese) as well as alphabetic[27] language speaking populations. Our results are expected to provide the basis for the future study of hemispheric dominance in memory processing using fTCD, especially in Chinese with neuropathological conditions. As a forerunner in this neurological aspect, we suggested improvements on working memory paradigm design to further evaluate the feasibility of fTCD in working memory hemispheric lateralization assessment in Chinese, before its actual application in clinical trials.

DISCLOSURE

The authors declare no conflict of interest.

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