Radiology

Sex Differences in Working Memory after Mild Traumatic Brain Injury: A Functional MR Imaging Study[1]

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Purpose: To evaluate sex differences in mild traumatic brain injury (MTBI) with working memory functional magnetic resonance (MR) imaging.

Materials and Methods: Research ethics committee approval and patient written informed consent were obtained. Working memory brain activation patterns were assessed with functional MR imaging in 30 patients (15 consecutive men and 15 consecutive women) with MTBI and 30 control subjects (15 consecutive men and 15 consecutive women). Two imaging studies were performed in patients: the initial study, which was performed within 1 month after the injury, and a follow-up study, which was performed 6 weeks after the first study. For each participant, digit span and continuous performance testing were performed before functional MR imaging. Clinical data were analyzed by using Kruskal-Wallis, Mann-Whitney *U*, Wilcoxon signed rank, and Fisher exact tests. Within- and between-group differences of functional MR imaging data were analyzed with one- and two-sample *t* tests, respectively.

Results: Among female participants, the total digit span score was lower in the MTBI group than in the control group (P = .044). In initial working memory functional MR imaging studies, hyperactivation was found in the male MTBI group and hypoactivation was found in the female MTBI group compared with control male and female groups, respectively. At the 6-week follow-up study, the female MTBI group showed persistent hypoactivation, whereas the male MTBI group showed a regression of hyperactivation at visual comparison of activation maps. The male MTBI group was also found to have a higher initial ß value than the male control group (P = .040), and there was no significant difference between the male MTBI group and the male control group (P = .221) at follow-up evaluation, which was comparable to findings on activation maps. In the female MTBI group, average ß values at both initial and follow-up studies were lower compared with those in the female control group but were not statistically significant (P = .663 and P = .191, respectively).

Conclusion: Female patients with MTBI had lower digit span scores than did female control subjects, and functional MR imaging depicted sex differences in working memory functional activation; hypoactivation with nonrecovery of activation change at follow-up studies may suggest a worse working memory outcome in female patients with MTBI.

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Sex differences in outcomes after traumatic brain injury (TBI) have been addressed in many studies (1–11). Controlled experiments have shown better outcomes after TBI in female animals, but human observation studies show mixed results (1–11). Observation studies may be confounded by many factors, including different symptom reporting among women and men (11). Therefore, a more objective measurement, such as imaging findings, is crucial in avoiding such bias.

Mild TBI (MTBI) represents the majority of TBI cases and is a common medical problem that affects cognitive and vocational function, as well as quality of life in some individuals. Difficulty with working memory is a commonly reported impairment after TBI (12). Working memory dysfunction may result from gray and white matter damage after TBI. However, conventional anatomic imaging techniques, including magnetic resonance (MR) imaging and computed tomography (CT), generally fail to show focal lesions in patients with MTBI. Functional MR imaging performed with blood oxygen level–dependent signals is increasingly being used in patients with MTBI. Previous studies have shown various changes in working memory activation pattern in patients with MTBI (13–27). Such patients may differ from control subjects in terms of working memory activation pattern despite similar performance of neuropsychologic tasks, a finding that suggests that functional MR imaging may have increased sensitivity for detecting MTBI. To our knowledge, no previous reported MTBI study has focused on sex differences in functional activation. To improve our understanding of sex differences in cognitive outcome after MTBI, we conducted this study to see whether there are sex differences in working memory functional activity at functional MR imaging.

Materials and Methods

Subjects and Tasks

This prospective study was approved by a local research ethics committee. All participants provided written informed consent. Between September 2010 and May 2012, consecutive patients with MTBI from our three affiliated hospitals were prospectively identified for enrollment in this study. The following inclusion criteria were used: *(a)* an age of 17 years or older; *(b)* MTBI, as defined by criteria of the American Congress of Rehabilitative Medicine; and *(c)* findings of a healthy brain at CT (28). Exclusion criteria included prior traumatic brain injury, any other neurologic disease, a current or past history of psychiatric illness, current use of psychoactive medications, important systemic medical illness (the general health questionnaire was used to screen for mental illness), left handedness, and any dental appliances that might distort functional MR images or any contraindications to MR imaging. For the control groups, healthy volunteers were recruited from a staff of hospital co-workers by way of an advertisement. The same exclusion criteria were applied.

All participants underwent neuropsychologic testing, including digit span, continuous performance test (CPT), and two *n*-back working memory task functional MR imaging studies (*n* = 1, 2). Digital span is a short-term memory test that measures how many

Advances in Knowledge

- Functional MR imaging showed sex differences in working memory functional activity indicated by persistent hypoactivation in female patients with mild traumatic brain injury (MTBI) at initial and follow-up studies compared with initial hyperactivation and subsequent regression of hyperactivation in male patients with MTBI at visual comparison of activation maps.

- At initial studies, β values in a selected region of interest were higher in the male MTBI group than in the male control group (*P* = .040), whereas there was no significant difference between the male MTBI group and the male control group (*P* = .221) at follow-up study.

- In the female MTBI group, average β values in both initial and follow-up studies were lower than those in the female control group but did not indicate a statistically significant difference (*P* = .663 and *P* = .191, respectively); nonrecovery in activation may suggest a worse working memory outcome in female patients with MTBI.

Implications for Patient Care

- The sex differences in MTBI outcomes might lead to future development of separate management strategies for men and women with MTBI.

- Functional MR imaging has the potential to not only provide useful objective diagnostic information associated with working memory functional sequelae, but also to provide a sensitive measurement with which to monitor disease progression and treatment.

numbers a participant can remember in sequence. CPT measures a person's sustained and selective attention and impulsivity. Two block-designed working memory tasks were presented with E-Prime, version 2.0 (Psychology Software Tools, Sharpsburg, Pa). Each condition was conducted in a single run that consisted of three epochs, each of which contained 30 seconds of presenting numbers and 30 seconds of a fixation cross. Conditions were counterbalanced among participants; that is, each condition was preceded equally often and followed by each of the other conditions. In each n-back working memory task, participants attentively looked at a monitor with a series of number stimuli and were instructed to respond whenever the presenting numeral matched the numeral presented n items before ($n = 1, 2$). Before imaging, all participants were trained to ensure that they could perform a one-back task at an accuracy criterion of 70%. All participants achieved this standard in their first attempt.

Functional MR imaging Procedure

Imaging was performed with a 3.0-T MR imaging system (Discovery MR750; GE Healthcare, Milwaukee, Wis) and an eight-channel receiver-only head coil. Functional images were collected with a T2*-weighted single-shot gradient-echo echo-planar sequence and the following parameters: repetition time msec/echo time msec, 3000/35; flip angle, 90°; field of view, 230 mm²; matrix, 64 × 64; 40 sections; section thickness, 3 mm with a 1-mm intersection gap.

Functional MR imaging Processing and Statistics

Data processing was conducted by a medical physicist with 4 years of experience in analyzing functional MR imaging data. Data from functional MR images were preprocessed by using Statistical Parametric Mapping (SPM5; University College London, London, England) and implemented in Matlab version 7.9 (MathWorks, Sherborn, Mass). Data preprocessing included section timing correction, realignment

for head motion, spatial normalization to the Montreal Neurologic Institute template, and spatial smoothing with a 6-mm Gaussian kernel. For all subjects, the maximum head motions were controlled to less than 3 mm in translation and less than 3° in rotation.

In the first-level individual analysis, smoothed images were analyzed with the experimental condition by using a general linear model approach used with SPM5. The experimental condition was modeled by convolving a boxcar function with a canonical hemodynamic response function. The resultant contrast maps, which compared pairs of the working memory load conditions (two-back > one-back), were created on a voxel-by-voxel basis for each subject. These contrast maps were then used for the second-level multisubject and between-group random effects analyses.

For each group, a one-sample t test was conducted to identify the within-group activation. All statistical maps were set at a level of uncorrected significance threshold of $P < .01$. A two-sample t test was used to explore the sex effect on the activation maps in control groups (uncorrected $P < .01$). Activation maps that showed differences between the control and MTBI groups (initial condition) were also analyzed by separately using two-sample t test in each sex group (uncorrected $P < .01$). Visual comparison of activation maps was performed by three neuroradiologists, one with 20 years of experience and two with 10 years of experience.

Additional quantitative analysis was performed by acquiring β values within a selected region of interest (ROI) in each sex group. The ROI was defined by the union of activated regions in control, initial, and follow-up MTBI group activation maps. ROI analysis was carried out for each subject by using MarsBar toolbox *(http://marsbar.source-forge.net/).*

Statistical Analysis

A Kruskal-Wallis test was conducted to assess the differences in age and neuropsychologic test results in four groups (ie, control male, control

female, MTBI male, and MTBI female). Additionally, a Mann-Whitney U test was used for intergroup comparison between male and female subjects in the MTBI and control groups, as well as between control and MTBI subjects in each separate sex group. A Fisher exact test was used to assess the mechanism of injury and education level in male and female patients with MTBI. A Wilcoxon signed rank test was used to assess differences in β values between the follow-up and initial studies. A significance level of .05 was chosen.

Results

Demographic and Neuropsychologic Measures

During the study period, 38 patients with MTBI presented to our emergency or neurosurgery outpatient departments and were willing to participate in this study. Among these patients, eight (21%) were excluded because of contraindications to MR imaging ($n = 2$), a history of neurologic or psychiatric disease ($n = 1$), the presence of a dental appliance ($n = 1$), left handedness ($n = 2$), and an important medical illness ($n = 2$). The remaining 30 patients (15 men and 15 women) completed the protocol. The mechanism of injury included motor vehicle collisions, falls, sports injuries, and assault. Thirty control subjects, including 15 men and 15 women, were consecutively recruited for this study. All patients with MTBI and control subjects were Taiwanese. None of the patients with MTBI had a history of amnesia or loss of consciousness after the injury, and all patients with MTBI had a Glasgow Coma Scale score of 15 and an injury severity score of less than nine. No significant differences regarding mechanism of injury or education level were found with Fisher exact test.

No significant difference was found in age, digit span score, CPT, or accuracy of n-back testing in any of the four groups (ie, male and female control and male and female patients with MTBI) with the Kruskal-Wallis test. There was also no significant difference between

Table 1

Demographic Characteristics and Neuropsychologic Performance in Patients with MTBI and Control Subjects

Characteristic	Patients with MTBI			Control Subjects		
	Female (*n* = 15)	Male (*n* = 15)	*P* Value	Female (*n* = 15)	Male (*n* = 15)	*P* Value
Age (y)	35.18 ± 14.57 (22–67)	35.00 ± 14.97 (18–68)	.787	34.24 ± 9.36 (23–57)	33.65 ± 9.73 (21–46)	.662
Glasgow Coma Scale score	15	15		15	15	
Mechanism of injury			.17			
Motor vehicle collision	4	4		…	…	
Fall	9	7		…	…	
Assault	1	2		…	…	
Sports	1	2		…	…	
Education level			>.99			
High school	4	3		…	…	
College	11	12		…	…	
Digit span						
Total score	10.73 ± 2.31	12.67 ± 3.18	.072	12.83 ± 2.55	12.00 ± 2.10	.385
Forward	11.53 ± 1.96	12.67 ± 1.91	.113	12.00 ± 1.76	11.27 ± 2.10	.444
Backward	10.20 ± 2.75	11.47 ± 3.62	.278	12.33 ± 2.61	11.82 ± 1.78	.708
CPT						
Omission error	51.98 ± 11.44	54.80 ± 15.35	.954	49.31 ± 8.27	49.12 ± 10.92	.366
Commission error	52.10 ± 13.23	61.83 ± 32.29	.383	51.21 ± 8.73	45.70 ± 11.17	.205
Hit reaction time	55.19 ± 13.48	54.50 ± 7.33	.727	53.07 ± 7.56	57.29 ± 9.62	.165
n-Back performance						
One-back (% correct)	0.95 ± 0.08	0.95 ± 0.06	.578	0.94 ± 0.12	0.98 ± 0.03	.680
Two-back (% correct)	0.85 ± 0.13	0.85 ± 0.09	.586	0.91 ± 0.09	0.89 ± 0.10	.476

Note.—Unless otherwise indicated, data are the mean ± standard deviation, and data in parentheses are the range.

male and female subjects in both the MTBI and control groups (Table 1). Among male participants, there was no significant difference between patients with MTBI and control subjects in age (*P* = .383), digit span score (*P* = .495), CPT for omission (*P* = .269) or commission (*P* = .053) error, hit reaction time (*P* = .144), or accuracy of *n*-back testing (*P* = .097 for one-back and *P* = .108 for two-back) (Table 2). Among female participants, a lower digit span score was found in patients with MTBI than in control subjects (*P* = .044 in total score), although there were no significant differences in age (*P* = .901), CPT (omission error, *P* = .422; commission error, *P* = .860; and hit reaction time, *P* =. 907), or accuracy of n-back testing (*P* = .503 for one-back and *P* = .087 for two-back) (Table 2).

Functional MR Imaging Results

Both patients with MTBI and control subjects showed functional activation in bilateral frontal and parietal regions, a finding consistent with activation of working memory circuitry (Fig 1). In control subjects, more functional activation in two-back > one-back conditions was observed in female control subjects than in male control subjects (Fig 1, *A*). Findings of a two-sample *t* test confirmed this observation, with, especially, more frontal activations seen in female control subjects (Fig 2).

Among those with MTBI, different activation patterns were observed in male and female patients. Decreased activation in two-back > one-back conditions was observed in female patients with MTBI compared with female control subjects at the initial imaging study. On the contrary, increased activation in two-back > one-back conditions was observed in male patients with MTBI compared with male control subjects (Fig 1, *A* and *B*). Results of a two-sample *t* test confirmed these observations (Fig 3).

At the 6-week follow-up study, female patients with MTBI showed persistent hypoactivation, whereas male patients with MTBI showed a regression of hyperactivation and returned to a level of activation similar to that of control subjects (Fig 1, *C*). All three neuroradiologists interpreted these activation changes the same way.

The male MTBI group was found to have a higher β value within the selected ROI than the male control group (*P* = .040), and there was no significant difference between findings from the follow-up imaging study of the male MTBI group and that of the male control group (*P* = .221), which was comparable to the result seen at activation map observation. In the female MTBI group, average β values were lower at both initial and follow-up imaging studies compared with those in the female control group but were not significantly different (*P* = .663 and P = .191, respectively). There were no significant longitudinal changes of β

Table 2

Demographic Characteristics and Neuropsychologic Performance in Female and Male Participants

Characteristic	Female Participants			Male Participants		
	MTBI Group (n = 15)	Control Group (n = 15)	P Value	MTBI Group (n = 15)	Control Group (n = 15)	P Value
Age (y)	35.18 ± 14.57 (22–67)	34.24 ± 9.36 (23–57)	.901	35 ± 14.97 (18–68)	33.65 ± 9.73 (21–46)	.383
Glasgow Coma Scale	15	15		15	15	
Digit span						
Total score	10.73 ± 2.31	12.83 ± 2.55	.044	12.67 ± 3.18	12.00 ± 2.10	.495
Forward	11.53 ± 1.96	12.00 ± 1.76	.615	12.67 ± 1.91	11.27 ± 2.10	.081
Backward	10.20 ± 2.75	12.33 ± 2.61	.085	11.47 ± 3.62	11.82 ± 1.78	.979
CPT						
Omission error	51.98 ± 11.44	49.31 ± 8.27	.422	54.8 ± 15.35	49.12 ± 10.92	.269
Commission error	52.10 ± 13.23	51.21 ± 8.73	.860	61.83 ± 32.29	45.70 ± 11.17	.053
Hit reaction time	55.19 ± 13.48	53.07 ± 7.56	.907	54.50 ± 7.33	57.29 ± 9.62	.144
n-Back performance						
One-back (% correct)	0.95 ± 0.08	0.94 ± 0.12	.503	0.95 ± 0.06	0.98 ± 0.03	.097
Two-back (% correct)	0.85 ± 0.13	0.91 ± 0.09	.087	0.85 ± 0.09	0.89 ± 0.10	.108
β values	0.28 ± 0.29	0.35 ± 0.31	.663	0.48 ± 0.52	0.21 ± 0.19	.040

Note.—Unless otherwise indicated, data are the mean ± standard deviation, and data in parentheses are the range.

values comparing initial and follow-up imaging studies in both sex groups (P = .211 and P = .191 in the female and male groups, respectively).

Discussion

There were two major findings in this functional MR imaging study that focused on sex differences in patients with MTBI. First, although there was no significant difference in working memory performance between male and female patients with MTBI, female patients with MTBI had lower total digit span scores than did female control subjects, whereas no significant differences were observed between male patients with MTBI and male control subjects. Second, functional MR imaging revealed different activation patterns in male and female patients with MTBI during working memory tasks. To our knowledge, this study provides the first published evidence of sex differences in working memory functional activity in patients with MTBI. The results suggest that women may have worse working memory outcomes, and functional MR imaging showed sex differences in postinjury changes. These results may

change the future diagnostic work-up in patients MTBI and lead to separate management strategies for patients of different sexes.

Previous studies about sex differences in cognitive outcome of MTBI revealed mixed results (3,4). Many studies showed that women outperformed men in tasks of verbal memory and learning measures, skills that have generally been found to be stronger in healthy women compared with men. Although it was not significant, our present study also revealed higher digit span scores in female control subjects compared with male control subjects. It is important to know that the outcome differences in patients with MTBI could be masked by the baseline differences. In this study, no significant differences were found in working memory performance between male and female patients with MTBI regarding digit span scores and accuracy of the n-back test. However, lower digit span scores were found in female patients with MTBI compared with female control subjects, and no similar differences were observed in the male groups, suggesting a possible worse working memory outcome in female patients.

Numerous prior studies have shown that functional MR imaging may depict MTBI by showing changes in activation pattern during working memory tasks. Functional MR imaging studies performed in healthy subjects have revealed that working memory load is associated with increased activation of the bilateral frontal and parietal regions, a circuitry overlap with regions vulnerable to damage in traumatic brain injury. However, previous studies have demonstrated mixed patterns of activation change during working memory tasks after MTBI. The underlying mechanism of activation change and the cause of divergent patterns in MTBI are poorly understood. According to previous studies, hyperactivation after MTBI was explained as neural compensatory recruitment, which operates to maintain task performance (15,16,23,25). Failure to engage compensatory mechanisms after MTBI, which may result from more severe brain damage in corresponding areas, may cause a hypoactivation pattern and result in poorer performance (19,25). According to this hypothesis and our study results, we speculated that female patients with MTBI may sustain more severe injury
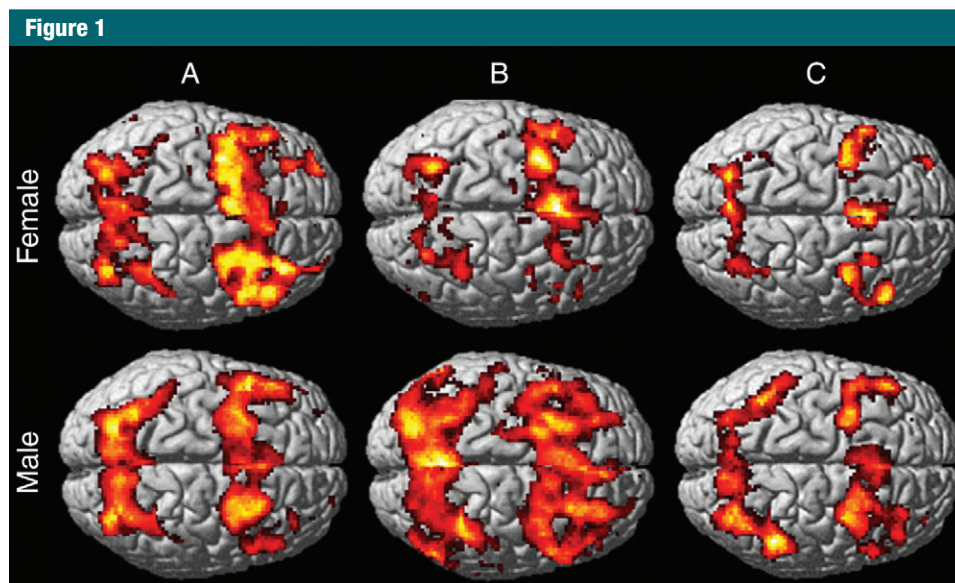
Figure 1: Working memory functional activation in healthy control subjects and patients with MTBI. Surface-rendered projection on a representative atlas brain (SPM5) shows areas of activation in response to increased working memory load (two-back > one-back condition). Note the presence of increased activation in bilateral frontal and parietal regions, a finding consistent with activation of working memory circuitry in each group. *A,* In control subjects, visual comparison of working memory activation patterns shows more activation in women than in men, especially in the frontal region. *B,* There is substantially less activation (ie, hypoactivation) seen in female patients with MTBI than in female control subjects, and there is substantially more activation (ie, hyperactivation) seen in male patients with MTBI than in male control subjects. *C,* At the 6-week follow-up study, female patients with MTBI showed a persistent hypoactivation pattern, whereas male patients with MTBI showed regression of hyperactivation and demonstrated a return to similar activation levels as those in male control subjects.

involving working memory circuitry, causing a hypoactivation pattern at functional MR imaging and worse performance of the digit span task. Several studies on baseline sex differences in functional organization of working memory and anatomic vulnerability of MTBI may help provide explanations. Previous studies have shown that, in patients with MTBI, anterior regions of the brain are more vulnerable to injury, and recent studies provided evidence for sex-specific working memory networks, whereby women consistently activate more limbic and prefrontal structures, which may contribute to a vulnerability of working memory injury in female patients with MTBI (15,26,29–31). Another finding suggestive of sex differences in working memory outcomes in this study is the longitudinal change of activation pattern at functional MR imaging. In this study, recovery of activation

Figure 2: Sex differences of working memory functional activation in healthy control subjects in response to increased working memory load (two-back > one-back condition). A voxel-by-voxel comparison of female (left image) and male (right image) control subjects shows more activation (arrows) in female control subjects than in male control subjects (display threshold, *P* < .01).

change was observed in male patients with MTBI, whereas female patients with MTBI showed persistent hypoactivation at 6-week follow-up imaging. According to the aforementioned hypothesis, the persistent hypoactivation seen in female patients with MTBI could suggest a more severe injury and poor recovery. However, without additional neurocognitive and
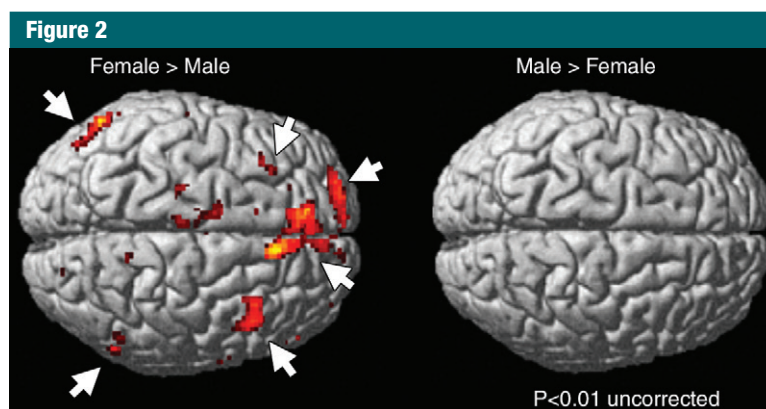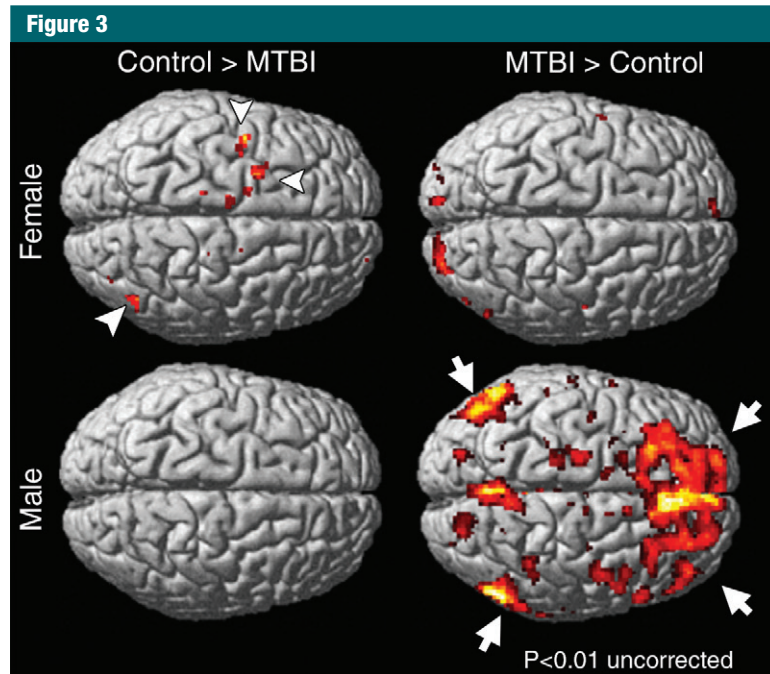
Figure 3: Sex differences of working memory functional activation at initial study of patients with MTBI compared with control subjects in response to increased working memory load (two-back > one-back condition). Voxel-by-voxel comparison of initial studies of patients with MTBI and control subjects shows a little more activation in the working memory circuitry (arrowheads) in female control subjects than in female patients with MTBI. However, substantially more activation (arrows) is seen in male patients with MTBI than in male control subjects.

neuropschologic testing, the significance of the hypoactivation pattern in working memory outcome remains unclear. Furthermore, in contrast to our study result, a previous longitudinal functional MR imaging study demonstrated increased activation at follow-up imaging compared with initial imaging findings after MTBI (23). More studies are needed to explore the source of such paradoxical results.

There are several limitations to our study. First, our results are limited to a small, heterogeneous group of patients with MTBI. Second, we do not control the information of hormone status, which has been shown to affect image and neuropsychologic data. Third, research has shown that different working memory tasks utilize different brain networks and that neural recruitment after MTBI is task dependent. Thus, in this study, the use of n-back task may not represent the overall condition.

Our study results are preliminary. Future studies with a larger sample size,

homogeneous inclusion criteria, and longer follow-up may help further clarify these findings. In addition, much more needs to be known about the relationships of sex hormones and cognitive outcomes by combining functional MR imaging and neuropsychologic variables with direct measurement of hormone levels, both at the time of injury and at follow-up studies. Furthermore, multimodality imaging studies, including diffusion tensor imaging for structure integrity, resting state functional connectivity study, cerebrovascular reactivity, susceptibility-weighted imaging, perfusion study, and MR spectroscopy for metabolite study, may be helpful in understanding the underlying pathophysiology and causes of sex differences in MTBI.

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