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Does gender influence cognitive outcome after traumatic brain injury?

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The aim of this study was to determine whether males and females differ in post-acute cognitive outcome following traumatic brain injury (TBI). Performances of 83 men and 75 women with mild to severe TBI were compared on measures of cognitive functions typically impacted by TBI (i.e., processing speed, executive functioning, and memory). Participants completed selected subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Among the participants with mild TBI, women scored significantly higher than men on a test of visual memory. There were no other significant gender differences in cognitive outcomes. These findings overall suggest that cognitive outcome after TBI does not differ according to gender, with the possible exception of memory functioning. Further research is needed to replicate this finding and determine which moderating variables may impact on the relationship between gender and cognitive outcome after TBI.

Keywords: Traumatic brain injury; Gender; Cognitive; Memory; Executive functioning.

Traumatic brain injury (TBI) is a topic gaining increasing recognition in recent years as a serious and under-recognised problem. About 1.5 million TBIs occur every year in the United States (Rutland-Brown, Langlois,

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Thomas, & Xi, 2006) with a higher incidence for men (651 per 100,000) than for women (429 per 100,000). As practitioners and researchers work to improve treatment for people with traumatic brain injury, one question that has yielded varied answers in the empirical literature is whether men and women have different cognitive outcomes after TBI.

One of the more established findings in the existing literature regarding normal gender differences in cognition is that females score higher on verbal cognitive tasks while males are superior performers on tests of spatial orientation and ability (Basso, Harrington, Matson, & Lowery, 2000; Halari et al., 2005; Janowsky, Chavez, & Zamboni, 1998). Differences in cognitive performance based on gender have also been studied in school environments, including scores from widely administered national aptitude tests. Scores from the Differential Aptitude Test (DAT) compiled from 1947 to 1980 among 98,382 girls and 95,462 boys in the 8th to 12th grades revealed that girls scored higher on subtests that measure abilities in spelling and language, while boys performed better on tests of mechanical reasoning and spatial relations (Feingold, 1988). Feingold notes, however, that these gender differences diminished over the years surveyed. These results are further supported by a finding that female performance on spatial ability tasks improved throughout childhood and adolescence, therefore minimising the gap between males and females in older age ranges (Barnfield, 1999).

There are mixed findings as to whether gender differences in verbal and visual abilities are also present in memory tasks. Lewin, Wolgers, and Herlitz (2001) found that males performed better on a visuospatial memory task that required them to look at a picture of stacked cubes with black and white sides and later recall which sides were black. Covassin et al. (2006) found, using the Immediate Measure of Performance and Cognitive Testing (Maroon et al., 2000), that males performed better on a task requiring visual memory of symbols, while females performed better on word memory tasks. In contrast, Janowsky et al. (1998) found no gender differences on the Toy Task (Smith & Milner, 1981) in ability to name objects that had been presented earlier or memory for spatial location of objects. Janowsky et al. (1998) however, had a smaller sample ($n = 48$) than Lewin et al. (2001) ($n = 185$) and Covassin et al. (2006) ($n = 1209$), so the Janowsky et al. study may not have had enough power to detect differences. It is also possible that the use of different methods to measure memory could have contributed to different findings. For example, the cube task used by Lewin et al. may have been more complex than other tasks and therefore able to show subtle differences.

The literature on normal gender differences in cognition largely addresses verbal and spatial abilities rather than abilities more relevant to a TBI population, such as executive functioning, processing speed, and attention. One study found that females performed better than males on a measure of clerical speed and accuracy, as measured by the DAT (Feingold, 1988). It is difficult to compare this, however, to literature regarding post-TBI findings due to different methods used (i.e., the DAT is a career aptitude test, while the TBI literature more often uses standard neuropsychological measures). Due to the lack of attention in the literature to possible normal gender differences in areas that tend to be affected by TBI, it is difficult to make predictions regarding gender differences in a TBI population.

The literature on gender differences in cognition after TBI has yielded mixed results. Dischinger, Ryb, Kufera, and Auman (2009) found that, among 115 men and 65 women with mild TBI, women were 2.5 times more likely than men to have post-concussive syndrome, defined as having four or more symptoms on the self-report concussion symptom checklist (Miller & Mittenberg, 1998) including physical, cognitive, or emotional symptoms. There is evidence that after a TBI, males may perform better than females on measures of attention and visual memory while females perform better than males in verbal list-learning and executive functioning (Liossi & Wood, 2009; Niemeier, Marwitz, Lesher, & Walker, 2007; Ratcliff et al., 2007; Schopp, Shigaki, Johnstone, & Kirkpatrick, 2001). The majority of evidence does not support gender differences in processing speed after TBI among adults (Broshek et al., 2005; Covassin, Schatz, & Swanik, 2007; Liossi & Wood, 2009). Among children, however, there is evidence that girls have faster processing speeds than boys after TBI (Donders & Nesbit-Greene, 2004; Donders & Woodward, 2003).

The findings regarding gender differences in attention and working memory after TBI are mixed. Schopp et al. (2001) found that 140 women showed greater decline from estimated premorbid functioning after TBI compared to 262 men on the Attention Index of the Wechsler Memory Scale – Revised (Wechsler, 1987) with no significant gender differences in injury severity. In contrast, Liossi and Wood (2009) found no gender differences in working memory as measured by the Wechsler Memory Scale – 3rd Edition (WMS-III; Wechsler, 1997b) and the Wechsler Adult Intelligence Scale – 3rd Edition (Wechsler, 1997a) post-TBI among 75 men and 75 women matched for severity of injury and estimated premorbid IQ. One possible reason for these different findings is that Liossi and Wood's participants were older, with the average age falling in the early 40s, while the average age in the Schopp et al. study was in the early 30s. In addition, Schopp et al. had a larger sample than Liossi and Wood and therefore had more power to detect differences.

There is some evidence that men have better memory than women post-TBI, while other research indicates that women show better verbal list-learning than men after TBI. Liossi and Wood (2009) found that, among participants matched for severity of injury and estimated premorbid IQ, men had better scores than women post-TBI on verbal and visual memory subtests of the

WMS-III. Among children, however, no gender differences have been found in memory after TBI (Donders & Woodward, 2003). Ratcliff et al. (2007) found that among 225 men and 100 women who showed no significant differences in injury severity or level of education, women performed better than men in verbal list-learning post-TBI. The findings regarding memory for contextualised verbal information, however, are less consistent. Ratcliff et al. found no gender differences on the Logical Memory subtest of the WMS while Liossi and Wood found that men performed better than women on Logical Memory. This might be related to the fact that Liossi and Wood's sample was older than Ratcliff et al.'s sample. Among children with TBI, no gender differences have been found in verbal list-learning (Donders & Nesbit-Greene, 2004).

There is some evidence that women have better executive functioning than men after TBI, although the size of the effect may be small. One study with a large sample (972 men and 359 women), with no gender differences in severity of injury, showed that women performed better than men on the Wisconsin Card Sorting Test (WCST; Axelrod et al., 1996) after TBI, with men being 1.55 times more likely than women to score in the impaired range on categories achieved (Niemeier et al., 2007). In smaller samples, however, Ratcliff et al. (2007) found no gender differences between 225 men and 100 women post-TBI on the WCST, and Liossi and Wood (2009) found no gender differences post-TBI between 75 men and 75 women on the Behavioural Assessment of the Dysexecutive Syndrome (BADS) battery (Alderman et al., 1996).

To summarise, the literature regarding gender differences in cognitive outcome post-TBI has yielded inconsistent results, but there is evidence that males may perform better than females on measures of attention while females perform better than males in verbal list-learning and executive functioning. The literature also shows gender differences in processing speed post-TBI among children but not adults.

One limitation of the existing literature is inclusion of people with relatively recent injuries and a lack of information on long-term outcomes and possible changes over time in relation to age or time since injury. Age and time since injury are important variables to take into account, as maturational changes across the lifespan are likely to vary between genders and to interact differentially with post-TBI changes. For example, menopause is a maturational factor that may affect outcome after TBI. Greendale et al. (2009) showed that women experienced a temporary decline in cognition during menopause. Davis et al. (2006) found better survival rates after TBI among post-menopausal but not pre-menopausal women compared to men.

Short-term hormonal cycles may also impact men and women differently and contribute to TBI outcome. Mordecai, Rubin, and Maki (2008) found that cognition varied across the menstrual cycle in women who use oral contraceptives, and others have found that implicit memory varies across the menstrual cycle (Maki, Rich, & Rosenbaum, 2002). Phillips and Sherwin (1992) showed that visual recall varied with the menstrual cycle and was correlated with progesterone levels.

There is a growing body of evidence that progesterone may have a beneficial effect on recovery from brain injury (Gibson & Murphy, 2004; Jones et al., 2005; Roof, Duvdevani, Braswell, & Stein, 1994; Roof, Duvdevani, & Stein, 1993, Wright et al., 2007). Roof et al. (1993) found that female rats showed less cerebral oedema following cerebral contusion compared to male rats, and pseudopregnant females, in which progesterone levels were high relative to oestrogen, showed virtually no post-injury oedema. Furthermore, the reduction of cerebral oedema in females was associated primarily with the presence of circulating progesterone. Several studies have shown that progesterone reduces neuronal damage and improves cognition after brain injury in rats and mice (Gibson & Murphy, 2004; He, Hoffman, & Stein, 2004; Jones et al., 2005; Roof et al., 1994). A phase II randomised clinical trial of progesterone treatment following TBI showed a significant benefit of progesterone for functional outcome among individuals with moderate TBI (Wright et al., 2007).

Testosterone has also been implicated as a moderator of outcome after TBI, but results regarding the nature of testosterone's role in brain injury are conflicting. Testosterone levels in men have been shown to be inversely associated with stroke severity and mortality after stroke (Jeppesen et al., 1996). Among male rats, testosterone has been shown to increase the neurotoxicity of glutamate with ischaemic injury (Yang et al., 2002). In contrast, Pan et al. (2005) showed that testosterone replacement accelerated functional recovery after brain injury in castrated rats.

It can be predicted that hormonal levels at the time of injury and hormonal changes in both the short-term (i.e., monthly cycles) and long-term (changes over the lifespan) are likely to play a role in cognitive outcome after TBI and to impact gender differences. These factors may help to explain inconsistencies in the literature regarding gender differences after TBI.

If there are consistent gender differences in cognition post-TBI, an understanding of these differences would help to shape treatment planning for cognitive rehabilitation. For example, if men tend to have more deficits in executive functioning after TBI while women have more deficits in attention, treatment approaches should be different for the two groups. Furthermore, knowledge of gender differences in cognition post-TBI will contribute to our understanding of the potential neuroprotective role of hormonal factors, and this is likely to lead to pharmacological treatments. The aim of the current study was to compare the cognitive outcome of adult men and women post-acutely following TBI in a sample with relatively equal numbers of men and women. Participants in this study were assessed at more years post-injury than in most of the existing literature. Processing speed, executive functioning, and memory were examined, as these broadly represent the areas impacted by TBI. In addition, this study controlled for estimated premorbid functioning, age, and age at injury. Outcome measures were plotted against age, age-at-injury, and time since injury to examine for possible non-linear relationships with these variables. It is important to control for these variables, as there may be differential developmental changes across the lifespan between men and women.

METHODS

Participants

Participants were part of a larger study on outcomes after TBI (Ashman et al., 2008; Cantor et al., 2008). Only participants with enough information about their injuries to classify severity (i.e., alteration in mental status through loss of consciousness or being dazed and confused, as well as approximate duration of alteration) were included in the analyses. Inclusion criteria were a history of TBI, time since injury of at least one year, and no history of a non-traumatic brain injury, such as stroke. Mean time post injury was 14 ± 13 years for men and 15 ± 15 years for women. Severity groupings were based on the American Congress of Rehabilitation Medicine's criteria, which defines mild TBI as involving a loss of consciousness (LOC) or alteration in mental status of less than 30 minutes. Participants with LOC of greater than 30 minutes were classified as having moderate–severe injuries. The study was approved by the Mount Sinai School of Medicine Institutional Review Board. The sample included 83 men and 75 women. See Table 1 for demographic information.

Measures

Cognitive outcome measures were chosen for the larger study on outcomes after TBI (Ashman et al., 2008; Cantor et al., 2008). Cognition was assessed through the Cambridge Neuropsychological Test Automated Battery (CANTAB), a brief computerised test battery (Morris, Evenden, Sahakian, & Robbins, 1986) that has been established as reliable, valid, and sensitive to cognitive changes in neurological and normal populations (De Luca et al., 2008; Elliott et al., 1997; Mehta et al., 2000). The tests are graded in difficulty to avoid ceiling effects and were designed to be independent of language and culture.

During administration, participants responded via a touch-screen or press pad, depending on the subtest. For this study, subtests were selected that assess the domains of interest: processing speed, attention, and memory. Age-normed *z*-scores were used as outcome measures for all tasks, with

TABLE 1
Injury and demographic information

	Males (n = 83)	*Females* (n = 75)
Mean age	48 ± 12	48 ± 14
Range	*25–81*	*19–79*
Mean age at injury	33 ± 14	33 ± 17
Range	*6–71*	*1–75*
Mild injury – n (%)	22 (41%)	32 (59%)
Moderate–severe injury – n (%)	61 (59%)	43 (41%)
Mean years post-TBI	14 ± 13	15 ± 15
Range	*0.5–63*	*1–57*
Median education level	Some college	Bachelor's Degree
Range	*Less than 8th grade–graduate degree*	*Some high school– graduate degree*
NART errors	9.68 ± 9.19	8.28 ± 8.62

higher z-scores always representing better performance. Outcome measures were categorised into the following domains:

- *Processing speed*: The Reaction Time Test was used to measure processing speed. This is a test of reaction time in which the participant must hold down a press pad until a dot appears in one of five locations, at which time the participant must touch the screen where the dot appeared. Five-choice reaction time (latency between stimulus and release of the press pad) and five-choice movement time (latency between release of the press pad and touching the screen) z-scores served as outcome measures.
- *Executive functioning*: The Intra-Extradimensional Set Shift (IED) Test assessed executive functioning. In this test, the participant sees pairs of shapes and must choose the correct shape based on a pattern, which might involve lines or colours. The participant must ascertain, through feedback, whether the correct answer is based on lines or colours. The relevant aspect changes throughout the test, necessitating the participant to establish and shift set. Six consecutive correct responses constitute a complete trial. Two z-scores, reflecting number of trials completed and number of errors, were used as outcome measures.
- *Memory*: The Pattern Recognition Test was used to assess visual memory. During this task, the participant is presented with a series of visual patterns. Next, the participant is presented with pairs of patterns comprised of a novel and a previously shown pattern, and the participant must identify the previously seen pattern. A z-score reflecting the percentage of correct answers served as the outcome measure.

Participants also completed the National Adult Reading Test (NART), a test that measures ability to pronounce words, as an estimate of premorbid intellectual ability (Nelson, 1982). The NART is established as a reliable and valid estimate of premorbid functioning (Crawford, Deary, Starr, & Whalley, 2000; Smith, Roberts, Brewer, & Pantelis, 1998). Demographic and injury information were collected through two self-report questionnaires: the Brain Injury Screening Questionnaire (Research & Training Center on Community Integration of Individuals with Traumatic Brain Injury, 1997) and the Living Life After TBI questionnaire (Gordon, Brown, & Hibbard, 1998).

Procedures

Participants with mild to severe TBI were recruited as part of a larger study (Ashman et al., 2008) conducted at Mount Sinai Medical Center between November 2002 and June 2007 through physician referrals, flyers that were posted in outpatient rehabilitation treatment areas and distributed at TBI support groups, contacting former research participants, and advertising online (e.g., Craig's List), in the newspaper, and in brain injury-related publications. All participants gave informed consent before being screened for study criteria. Recruitment resulted in 319 participants who consented, of whom 35 did not meet study criteria. An additional nine participants failed to complete the study due to fatigue or scheduling difficulties. All participants were screened for TBI, and medical documentation was obtained when available. For participants with a history of multiple TBIs, severity and time since injury information were determined based on the most severe TBI. Participants were compensated for their time. The CANTAB is an automated battery that requires only brief oral instructions, and it was administered by a trained research assistant. Completion of the chosen battery of subtests took about 30 minutes. After finishing the CANTAB, participants completed the self-report measures.

Data were first examined for potential confounding differences between men and women in the sample. Chi-square tests were used to determine differences in injury severity, and *t*-tests were used to determine differences in age, age at injury, education, and estimated premorbid intelligence between men and women. For variables where significant differences were found, correlation coefficients were used to determine whether these variables were related to outcome measures. Scatter plots were examined to identify possible nonlinear relationships between age or age at injury and outcome measures.

To examine the question of whether women have different cognitive outcomes from men after TBI, mean CANTAB *z*-scores of men and women were compared separately for the domains of processing speed, executive functioning, and visual memory using *t*-tests, MANCOVA, and MANOVA, depending on the number of variables being assessed and the need to covary potentially confounding variables identified in preliminary analyses.

RESULTS

All variables were normally distributed, with skewness and kurtosis within an acceptable range between -2 and $+2$. A chi-square test showed that males had significantly more severe injuries than females, so participants with mild and moderate–severe injuries were analysed separately.

There were no significant gender differences in the moderate–severe TBI group in age, age at injury, education, or NART scores. There were no significant gender differences in the mild TBI group in age, age-at-injury or NART scores. Females in the mild TBI group, however, were significantly more educated than males, and education correlated significantly with processing speed. Education was therefore covaried in the analysis of processing speed in the mild TBI group. Age and age-at-injury were plotted against all outcome measures using scatter plots among males and females separately to identify possible nonlinear relationships, and no relationships were evident from the graphs.

Table 2 displays mean *z*-scores and standard deviations for five-choice reaction time, five-choice movement time, IED stages completed, IED total errors, and pattern recognition percent correct. Mean performance levels ranged from average to impaired for processing speed, average to low average for executive functioning, and average to low average for memory. Impairment was most evident in processing speed.

Results in the moderate–severe TBI group

In the moderate–severe TBI group, MANOVAs were used to compare mean *z*-scores for processing speed (i.e., Reaction Time Test, five-choice movement time and five-choice reaction time) and the mean *z*-scores for executive functioning (i.e., IED number of trials completed and number of errors). A *t*-test was used to compare *z*-scores on tests of visual memory (i.e., Pattern Recognition percent correct). There were no significant gender differences in any of the outcome measures in this group.

Results in the mild TBI group

In the mild TBI group, a MANCOVA was used to compare mean *z*-scores on measures of processing speed covarying education; a MANOVA was used to compare mean *z*-scores on measures of executive functioning; and a *t*-test was used compare *z*-scores on tests of visual memory. Results showed that

TABLE 2
Mean scores and hypothesis testing by TBI severity and gender

Severity	*Mild*		*Moderate–Severe*	
Processing speed	**Male** (n = 22)	**Female** (n = 32)	**Male** (n = 61)	**Female** (n = 43)
Five-Choice Reaction Time z-scores	-2.07 ± 2.20	-1.58 ± 1.81	-1.79 ± 1.93	-1.86 ± 2.45
Five-Choice Movement Time z-scores	-1.31 ± 2.09	-0.64 ± 1.72	-1.19 ± 1.83	-1.09 ± 1.99
Hypothesis testing	$F = 0.112$, $p = .894$		$F = 0.081$, $p = .922$	
Executive functioning				
Intra-extradimensional Set Shift Stages Completed z-scores	-0.07 ± 0.98	0.20 ± 0.88	-0.23 ± 1.47	-0.13 ± 1.12
Intra-extradimensional Total Errors z-scores	-0.78 ± 1.23	-0.50 ± 0.96	-0.81 ± 1.15	-0.78 ± 1.13
Hypothesis testing	$F = 0.612$, $p = .546$		$F = 0.066$, $p = .936$	
Visual Memory				
Pattern Recognition % Correct z-scores	-0.88 ± 1.36	-0.18 ± 1.17	-0.97 ± 1.41	-0.95 ± 1.52
Hypothesis testing	$t = -2.027$, $p = .048$		$t = -0.076$, $p = .940$	

females performed significantly better than males in visual memory $t(52) = -2.027$, $p = .048$. No significant gender differences were found in any other outcome measures.

DISCUSSION

Overall, this study did not show substantial differences in post-acute cognitive outcome after TBI between men and women, with the exception of women performing better than men in visual memory following mild TBI. Findings in the existing literature regarding differences in problem-solving and processing speed (Donders & Nesbit-Greene, 2004; Donders & Woodward, 2003; Niemeier et al., 2007) were not supported.

Niemeier et al. (2007) found that women had better problem-solving ability on the WCST post-TBI compared to men in a large sample of 972 men and 359 women. The effect size in this study was small (Cohen's $d = 0.19$), so it is likely that the current study did not have enough power to replicate this finding. Similarly, Ratcliff et al.'s (2007) finding that males and females did not differ on the WCST used a sample of 225 males and 100 females, a smaller sample than in Niemeier et al.'s study. Further studies powered for small effect sizes are needed to replicate Niemeier et al.'s finding.

The finding of females having faster processing speed than males post-TBI was among children (Donders & Nesbit-Greene, 2004; Donders &

Woodward, 2003), so it is possible that processing speed is affected differently after TBI in children compared to adults. Among high school and college students, Broshek et al. (2005) found no differences in reaction time between males and females, which is consistent with the findings of the current study.

The finding of women having better visual memory than men post-TBI is unprecedented in the literature, and it would be interesting to see if future studies could replicate this finding. This finding is particularly notable in light of the literature indicating that men generally have better visual abilities than women after TBI (Basso et al., 2000; Halari at al., 2005; Janowsky et al., 1998).

One limitation of this study is that there was no prospective assessment of premorbid cognitive functioning. While difficult, it is possible to get premorbid measures of cognitive functioning by targeting a population prone to TBI, such as athletes or soldiers, and getting a baseline measure of functioning. Future studies might do so to get a better estimate of change from previous functioning. The trade-off of this method, however, is limiting generalisability by targeting a narrow population. The current study compensated for a lack of a premorbid testing by using a test of reading as an estimate of premorbid functioning, and analyses indicated no differences among men and women. In addition, there was a lack of information regarding neuroimaging and localisation of injury in this sample, so localisation of injury could not be taken into account. However, many cases involved diffuse injury to the brain and/or injuries that were not apparent in imaging, especially in the mild TBI group.

The current study's sample size limited the power and number of variables that could be included, and splitting the groups based on severity further contributed to this limitation. With larger sample sizes, future studies can examine a greater number of outcomes and potential mediating variables. For example, participants might be separated into age groups to look at gender differences during various stages of life. Future studies might also include both children and adults to determine whether outcomes differ between age groups. Time since injury is also an important variable to include in future studies.

The current study used a convenience sample comprised of patients from an urban setting who were willing to participate in a research study. Participants were recruited by referring physicians, from TBI support groups, or through flyers placed in outpatient rehabilitation areas, and they were therefore likely to be already identified as having a TBI and receiving treatment. While the sample was diverse in terms of ethnicity, education, and severity of injury, these findings may not generalise to individuals with undiagnosed TBI who are not receiving appropriate treatment.

Future studies might examine the relationship between hormones and cognitive outcome more closely by combining neuropsychological variables with direct measures of hormonal levels, both at the time of injury and follow-up. The current study used scatter-plots to examine changes in relation to age or age at injury, a method that would capture long-term but not monthly changes such as hormonal cycles, and no relationship was evident. Future research might also incorporate brain-imaging techniques such as volumetric magnetic resonance imaging (MRI) analysis or diffusion tensor imaging into the research design to examine possible contributions of structural differences in the brain to cognitive outcome after TBI. Future studies may also examine the interaction between gender, cognition, and functional and emotional outcomes post-TBI. Coping mechanisms, changes in mood, substance abuse, and socialisation likely differ between the genders and may interact with cognition, leading to different outcomes between men and women post-TBI. For example, level and type of daily activities might impact cognitive recovery, and vice versa.

Conclusions

The current study provided evidence that men and women receiving treatment for TBI do not differ significantly in cognitive outcome post-TBI, with the exception of visual memory, a finding that needs to be confirmed through replication. Questions that remain include how cognitive outcome post-TBI may be affected by the interaction between gender and other factors such as paediatric vs. adult injuries, hormonal changes, and existing structural differences in the brain between men and women. Future research on gender differences post-TBI is needed that includes measures of hormone levels, baseline functioning, and brain imaging, as well as samples that look at paediatric vs. adult injuries as moderating factors.

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