Sex Differences in Depressive Symptoms and Their Correlates After Mild-to-Moderate Traumatic Brain Injury

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ABSTRACT

The purpose of this secondary data analysis, guided by allostatic load theory, was to compare depressive symptoms and their correlates in men and women following mild or moderate traumatic brain injury (n = 159). Using general linear modeling procedures in the Statistical Analysis Software, women reported significantly higher Center for Epidemiological Studies-Depression scores compared with men. According to the Neurobehavioral Functioning Inventory subscales, women also reported higher somatic and motor symptoms and difficulties with memory and cognition. Further, women within the first 6 months of their injury reported higher levels of depressive and depressive–somatic symptoms, perceived chronic stress, pain, memory difficulties, and somatic symptoms. These findings were no longer present at the 6- to 12-month or >12-month cutoffs. Women's depressive symptoms during the early recovery period are explained by higher symptom loads and perceived stress, yet mechanisms responsible for these differences remain to be elucidated. Future research is needed to describe hormonal, perceptual, or brain structure differences that may account for these findings. Findings from such research will most likely to contribute to our understanding of postconcussion syndrome.

Fifty million persons in the world are estimated to be injured or disabled by traffic crashes, the leading cause of traumatic brain injury (TBI; World Health Organization [WHO], 2004). Male individuals are twice as likely to experience a TBI compared with female individuals (Centers for Disease Control and Prevention, 2007). However, the WHO's document urges that more study be focused on women with disability (WHO, 2004). To that end, this secondary analysis compares the depression experience of male and female individuals after mild-to-moderate TBI.

Following TBI, one may experience significant cognitive, behavioral, physical, and emotional challenges. One such challenge is depression, the most prevalent mood disorder following TBI, with a reported incidence between 10% and 77% (Alderfer, Arciniegas, & Silver, 2005). Yet, given higher prevalence rates for clinical depression (Kelly, Tyrka, Anderson, Price, & Carpenter, 2007; Piccinelli & Wilkinson, 2000; Weekes, MacLean, & Berger, 2005) and postconcussion syndrome (McCauley, Boake, Levin, Contant, & Song, 2001; Wood, 2004) in women, it seems important that we understand whether men and women experience depression differently. The purpose of this secondary analysis was to describe differences of men and women in post-TBI depressive symptoms and their correlates (stress, pain, symptoms, and health perception) after mild-to-moderate TBI. The determination of sex differences may shed light on the development of post-TBI depression and PCS and the timing and type of related therapies.

Children and young adults and those older than 75 years are the ones most commonly affected by TBI. Common mechanisms of injury include falls or motor vehicle crashes (Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2007). Over 90% of persons admitted to hospitals for TBI are considered to have mild TBI (MTBI), defined as a neurological condition characterized by a brief loss of consciousness (less than 30 minutes) or neurological symptoms at the time of the injury and posttraumatic amnesia less than 24 hours (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004; Kraus, Schaffer, Ayers, Stenehjem, & Shen, 2005).

Moderate TBI has been defined as those with an admission Glasgow Coma Scale (GCS) score between 9 and 12 and posttraumatic amnesia duration of approximately 1 week (Kashluba, Hanks, Casey, & Millis, 2008; Teasdale & Jennett, 1974; Vitaz, Jenks,

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Raque, & Shields, 2003). Whereas persons with MTBI are commonly assessed and released to home management after a brief emergency department visit (Bazarian, McClung, Cheng, Flesher, & Schneider, 2005), those classified with moderate TBI are typically discharged to their home once GCS scores improve to the mild category (GCS range = 13–15; Vitaz et al., 2003). Those with mild-to-moderate TBI are the focus of these analyses.

Background

Stress and Women

In general, women tend to report higher levels of psychological stress, and women with physical disabilities report higher levels of stress than do the general population (Hughes, Taylor, Robinson-Whelen, & Nosek, 2005). An interesting finding was that there is emerging evidence that biological stress responses, including those associated with the sympathoadrenal and hypothalamic–pituitary–adrenal (HPA) axes, tend to be lower in women between puberty and menopause compared with men of the same age (Kajantie & Phillips, 2006). It is unknown whether there are sex differences in reports of psychological stress after TBI, although given the association of stress with PCS and risk of women for PCS, one might speculate that after TBI, women would report higher levels of stress.

Depression, Stress, and Their Correlates in Women

According to the psychiatric literature, the prevalence of depression disorders is greater for women than for men (Kessler, 2003). We also know that strong positive relationships exist between stress and depression (Davidson et al., 2002; Nemeroff & Vale, 2005). Finally, women with depression report more somatic symptoms, including pain, than do men (Silverstein, 1999, 2002). This study sought to provide additional data to help sort out relationships among sex, depressive symptoms, stress, and pain after mild-to-moderate TBI.

Within the psychiatric literature, there are numerous studies focusing on sex differences in relationships between stress and depression. Despite the persistent findings that depression is twice as common in women as that in men (Piccinelli & Gomez Homer, 1997), explanations for this prevalence remain unclear. Proposed explanations include (a) gonadal hormones (Darnall & Suarez, 2009; Lasiuk & Hegadoren, 2007), (b) early life stressors yielding long-term dysregulation of the HPA axis (Heim & Nemeroff, 2001, 2002; Heim et al., 2000) or reductions in brain volumes (Bremner et al., 2000; Videlbech & Ravin Kilde, 2004), or (c) history of abuse in early life resulting in heightened neurobiological responses to stress or reductions in brain volumes (Weiss, Longhurst, & Mazure, 1999).

> The most commonly reported response to traumatic stress in women is depression, and women with depressive symptoms also tend to experience an array of other stressful life events.

In adult women, the most common response to traumatic stress is depression (Kendler, Gardner, & Prescott, 2000). In addition, women with depressive symptoms are more likely to experience other stressful events (Hammen, 2003). These findings suggest that there is a strong relationship between stress, especially interpersonal stress, and depression for women.

Finally, higher somatic distress and generalized pain are present in women with depressive symptoms, even with statistical adjustments in distress and healthcare utilization (American Psychiatric Association, 2000; Meares et al., 2007; Silverstein, 1999, 2002). Women with current diagnoses of major depression and a somatoform pain disorder who had been severely abused reported significantly higher somatic distress compared with women without abuse or less severe abuse (Walker et al., 1992). In laboratory experiments, women have been found to be more sensitive to noxious stimuli when compared with men. What is unknown is how gender roles, pain-coping strategies, and pain-related expectations interact in the relationship between pain, depression, and gender (Fillingim, 2000). Taken together, these studies suggest that both gender (social processes) and sex (biological processes) may interact to explain depression after TBI.

Stress, Depression, and TBI

Within the TBI literature, there is emerging evidence that increased levels of preinjury and postinjury chronic stress are associated with post-TBI outcomes, including psychological function and depressive symptoms. Bay, Kirsch, and Gillespie (2004) reported that a significant and positive relationship was present between preinjury chronic stress (childhood adversities and stressful life events) and postinjury depressive symptoms. Preinjury and postinjury chronic stress explained 67% of the variance in postinjury depressive symptoms when time since injury was

included in the models (Bay et al., 2004). Further analyses indicated that postinjury chronic stress completely mediated the relationship between depressive symptoms and postinjury psychological function. In addition, hypocortisolemia, a biological indicator of chronic stress, was noted (Bay, Sikorskii, & Gao, 2009). Thus, after TBI, stress and depressive symptoms are positively associated and explain poor outcomes. Yet, these analyses revealed no sex differences.

After TBI, depressive symptoms and major depression are prevalent and have heterogeneity in their expression (Bay, Hagerty, & Williams, 2007; Jorge & Starkstein, 2005; Moldover, Goldberg, & Prout, 2004). For those with MTBI, depressive symptoms can be detected as early as the first week after injury, and their presence at this time predicts the 12-week onset of major depression disorder (Levin et al., 2005). Variations in the expression of depression have been reported according to symptoms and time of onset. Within the first 6 months after TBI, when the limbic system is most likely implicated (Jorge, Acion, Starkstein, & Magnotta, 2007; Jorge et al., 2004), autonomic and anxiety symptoms are most prevalent (Jorge et al., 2004). Those developing a mood disorder during the first several months after moderate to severe injury were noted to have a size reduction in their hippocampus. Further, reduced activation in frontal–temporal regions of the brain was noted in male athletes with concussion and depressive symptoms (Chen, Johnston, Petrides, & Ptito, 2008; Jorge et al., 2007). Thus, autonomic and anxiety symptoms of depression are more likely when there is limbic system involvement. The limbic system is also involved in stress perception (Dickerson & Kemeny, 2004).

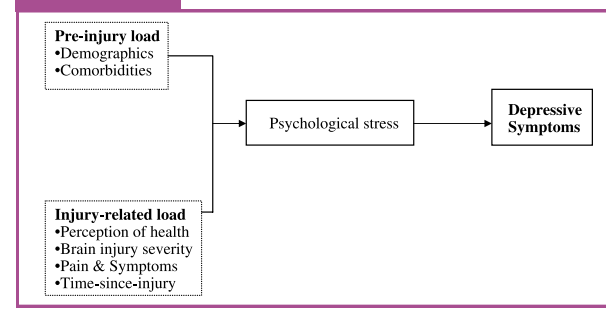
In contrast, depression occurring more than 6 months from the time of injury is more strongly associated with psychosocial concerns. Vegetative symptoms, including early morning awakening, anhedonia, and cognitive difficulties, characterize later-onset depression (Jorge, Robinson, & Arndt, 1993). Hibbard et al. (2004) further compared those with and without post-TBI depression and noted the following patterns: (a) early resolution for some, (b) a chronic state for others, or (c) a delayed-onset phenomenon. They further noted that pain was present in those with more chronic depression. Thus, depressed symptoms vary according to the time of onset.

What remains unanswered from these studies that have explored the relationship between brain trauma, stress, and depressive symptoms is whether depressed symptoms or their correlates vary according to sex. Although little is known about post-TBI depression for female individuals, they are more at risk for PCS (Meares et al., 2007; Ruff, 2005; Wood, 2004). In general, persons with PCS report persistent symptoms, such as depression, anxiety, pain, cognitive difficulties, fatigue, or sleep disorders for more than 12 weeks (McCauley, Boake, Levin, Contant, & Song, 2001; Wood, 2004). The pathophysiology and treatment of PCS remain elusive despite decades of debate (Ruff, 2005; Wood, 2004). However, there seems to be consensus for the involvement of stress in the development of this disorder (Ponsford et al., 2000; Rees, 2003; Ruff, 2005). Therefore, we believe that a better understanding of sex differences in the expression of depression and its correlates, including perceived stress, may also shed light on the development PCS.

Thus, on the basis of disability and psychiatric literature and guided by McEwen's allostatic load theory, we propose that women are more at risk for depressive symptoms after mild-to-moderate TBI and that postinjury chronic stress is a major explanatory factor in this relationship (see Figure 1).

According to the allostatic load theory, the brain communicates with the immune and endocrine systems to respond flexibly to day-to-day stress to maintain health and the absence of disease. Yet, when the stressors become more chronic, these regulatory systems become worn, its flexibility is impaired, and biological systems are dysregulated. Termed *allostatic load*, this biological dysregulation occurs when stress systems can no longer withstand the day-to-day stressors and biological system breakdowns occur. During deterioration of physiological mechanisms, such as the HPA axis, cardiovascular stress systems, and immune function, disease states are more likely, including clinical depression. Factors contributing to this lack of flexibility include genetics, poverty, or ''risky families'' characterized by systems of neglect or lack of nurturance and poor physical health. Thus, chronic stress is implicated in deterioration in the adaptive systems and leads to negative health outcomes, such as depression (McEwen, 2002).

FIGURE 1 Allostatic Load and Post-traumatic Brain Injury Depressive Symptoms



This study addressed the following research questions and hypothesis concerning a community sample of persons within 1–36 months of their TBI.

Question 1. Are there sex differences in the subjective reporting of brain injury symptoms, including depression, pain, stress, and brain injury symptoms (somatic, cognitive, motor, and communication)?

Question 2. After adjusting for preinjury characteristics, are there sex differences in self-reports of depression, pain, stress, and brain injury symptoms at different time-since-injury intervals?

Methods

We performed a secondary analysis of two cross-sectional data sets collected in the Midwest at outpatient rehabilitation clinics affiliated with large trauma hospitals specializing in brain injury assessment and treatment. The first study was conducted in 2000–2001, the second was in 2004–2006. These parent studies were developed to test the extent to which preinjury and postinjury chronic stress were associated with post-TBI depressive symptoms (Bay & Donders, 2008; Bay et al., 2004). Persons were eligible if they spoke English, were 18–60 years, experienced a mild or moderate TBI within the previous 36 months, were hospitalized at the time of the injury, and were not psychotic at testing. Those with other neurological disorders (except previous TBI) were excluded, including those with history of stroke, dementia, multiple sclerosis, or Parkinson disease.

Those represented in these analyses reflect a specialized sample. All were hospitalized and met admission criterion for TBI; this is in contrast to other studies that included those individuals who may have had a brain injury diagnosed through retrospective assessment. All were referred to specialized treatment centers for various reasons. Some received inpatient rehabilitation and required structured follow-up. Others were noted to have cognitive, physical, or psychosocial difficulties that persisted after the injury and were resistant to traditional primary care therapies.

Admitting personnel or neuropsychologists within nine outpatient rehabilitation clinics were involved in participant recruitment. Although there was a 3-year lapse between study 1 and study 2 recruitment, nearly similar sites and personnel participated. In all settings and after complete neuropsychological assessments, eligible persons were offered information about the study and the opportunity to speak further with research staff. Then, research staff explained the study goals and methods, answered questions, and obtained signed informed consent, according to human subjects' protection guidelines. Using scripted messages, no effort was made to oversample for persons with depression or women.

Exact data for those who met the eligibility criteria but refused to participate were not recorded. However, we estimated that nearly 350 persons were eligible for these two studies; we have complete data for 159 persons. Anecdotally, those who refused stated they were ''too busy,'' ''had already been asked enough questions,'' ''had too much going on,'' or were concerned about confidentiality given their litigation status.

Measures

Demographic data such as age, level of education, and employment status were obtained by interview at intake. Persons were also asked, using checklists, about their prior health history including physician-diagnosed neurological, psychiatric, or substance abuse history. All persons rated their perceived present health state.

Injury data such as brain injury severity and time since injury (measured in months) were obtained from medical records. For this analysis, the GCS score was used to classify brain injury severity: If admitting GCS equals 13–15, then it is a mild injury; if admitting GCS equals 9–12, then it is a moderate injury. Because results for the CT were incomplete or missing for nearly one third in study 2, we were unable to further categorize those with MTBI as complicated or uncomplicated.

For the analyses of depressive, perceived stress, and brain injury symptoms, three intervals were created: (a) 6 months or less, (b) 6–12 months, and (c) more than 12 months. Because pain has been reported to be undertreated after TBI (Bazarian et al., 2005), we assessed present pain symptoms and dichotomized the time since injury for these reported symptoms to best capture a period of chronic pain for the (a) 3 months or less and (b) more than 3 months (Smith, Penny, Elliot, Chambers, & Smith, 2001).

Depressive symptoms were measured with the Center for Epidemiological Studies-Depression (CES-D; Radloff, 1977). This depression-screening instrument, designed to rate depressive symptoms in a community sample over the previous week, has well-established reliability and predictive, convergent, and concurrent validity and demonstrated reliability and validity with samples of persons with TBI (Bay et al., 2007; McCauley et al., 2006). It contains four positively worded items and four subscales within a 20-item scale. These subscales include depressed mood, interpersonal problems, positive affect, and somatic symptoms (CES-D-SOMA). In addition, the CES-D has well-recognized categories of depression severity and is reported to measure eight domains of the *Diagnostic and Statistical*

Manual of Mental Disorders-Fourth Revision, Text Revision (2000; Bay et al., 2007) Convergent validity with the Hamilton Rating Scale, frequently used with the TBI population, was established (r = .50 to .80; Radloff, 1977; see Table 1). In our sample, internal consistency was acceptable and Cronbach's alpha was .82 for CES-D-SOMA, .74 for CES-D-interpersonal problems, .86 for CES-D-depressed mood, .80 for CES-D-positive affect, and .92 for the entire CES-D scale.

For this study, we used the Perceived Stress Scale-14 with well-established linkages to depression and depressive symptoms (Cohen, Kamarck, & Mermelstein, 1983; Cohen, Kessler, & Gordon, 1995; Cohen & Rodriguez, 1995) to quantify the persons' perception of their chronic stress and its predictability and controllability during the previous 30 days. It has been used in repeated measures and intervention studies, as well as studies involving persons with disabilities, pain, and spinal cord injury (Cohen et al., 1983, 1995; Gerhart, Weitzenkamp, Kennedy, Glass, & Charlifue, 1999). It has good internal consistency and test–retest reliability (Cohen et al., 1995; Cohen & Rodriguez, 1995). Higher scores denote increased chronic perceived stress (Table 1). In our sample, Cronbach's alpha for the Perceived Stress Scale was .87.

At the time of testing, we assessed each participant's present pain level and associated descriptors of intensity with the McGill Pain Questionnaire-Short Form (Melzack, 1987). The McGill Pain Questionnaire-Short Form, a self-report rating of present pain and subjective intensity, was used to provide a pain-rating index and sensory and affective pain descriptors. For this analysis, we report the visual analogue scale, rated as 0 (*no pain*) and 10 (*severe pain*; see Table 1). Although we did not specifically query for the duration of pain, we inferred that because the self-reported pain was a recurring phenomenon, it may be considered as chronic.

Data concerning post-TBI symptoms were obtained from the Neurobehavioral Functioning Inventory (NFI). This 76-item self-report inventory contains six subscales and was developed using responses by over 700 persons with TBI (Kreutzer, Seel, & Marwitz, 1999). The subscales used included frequency self-reports of cognitive, communication, motor, and somatic difficulties. We do not consider the aggression and depression subscales in this analysis. Construct and criterion validities for these subscales exist, reflecting high internal consistency (Kreutzer, Marwitz, Seel, & Serio, 1996; Kreutzer et al., 1999). All items are positively worded; higher scores denote more frequent symptoms or difficulties. Cronbach's alpha coefficients revealed high levels of consistency within each scale, with ranges between .86 and .95 reported (Kreutzer et al., 1996). In our sample, internal consistency reliability (Cronbach's alpha) was .83 for somatic difficulties subscale, .95 for memory and cognition, .89 for communication, and .85 for motor difficulties subscale.

Procedures

Institutional review board approvals were obtained at all study sites. All injured persons signed informed consent after being informed about what was required for study involvement, and their questions were answered. Only in study 1 were the relative or significant others asked to participate to provide concurrent validity for the symptoms reported by the injured person by completing the family version of the NFI and CES-D. Because these data were highly correlated and paired t tests were nonsignificant, we did not collect relative or significant others data in study 2 (Bay et al., 2007).

The trained research aides (RAs) used an interview format to elicit demographic information, and TBI-related data were abstracted from the chart. Survey questionnaires were completed in the presence of the RA, typically at the rehabilitation clinic on a date and time selected by the injured person. In most situations, persons were enrolled in the study while engaged in outpatient rehabilitation therapies. Rescheduling of the session was done when the injured person indicated that they were fatigued or in pain. Rarely, the person indicated difficulty in reading the instrument because of visual impairment, then the RA read the survey items to the injured person. In appreciation for study participation, a small gift card was given to each injured person.

Data Analysis

Statistical Analysis Software version 9.1.3 (Statistical Analysis Software, 2002) was used for this analysis.

Research Question 1. Descriptive statistics by sex were obtained for demographic variables, including marital status, education, race, income, preinjury and postinjury employment, mechanism or injury, time since injury (in months), and litigation status. Chi-square tests for categorical variables and t tests for continuous variables were used to examine sex differences in injury-related and major study variables (perceived stress and pain and depressive, somatic, cognitive, motor, and communication symptoms).

Research Question 2. Generalized linear models were fit and related the outcomes of depression, chronic stress, severity of pain, and brain injury symptoms to sex and sex-by-time-since-injury interaction. At this time, we adjusted for injury severity;

TABLE 1. Demographic and Injury Characteristics of the Sample and Descriptive Statistics for Outcomes by Sex

Variables	Men (*n* = 82), *n* (%)	Women (*n* = 77), n (%)	Sex Differences (*p* value)
Study			.92
Study 1	39 (47.56)	36 (46.75)	
Study 2	43 (52.44)	41 (53.25)	
Age (years)			.10
<40	47 (57.32)	34 (44.16)	
40 and up	35 (42.68)	43 (55.84)	
Months since injury			.15
≤6	25 (30.49)	26 (33.77)	
6–12	27 (32.93)	15 (19.48)	
>12	30 (36.59)	36 (46.75)	
Injury severity			**.02**
Moderate	24 (29.63)	11 (14.47)	
Mild	57 (70.37)	65 (85.53)	
Education			.48
High school or less	23 (28.40)	24 (32.00)	
Post high school	30 (37.04)	21 (28.00)	
Associate degree and above	28 (34.57)	30 (40.00)	
Preinjury employment			.15
Employed	77 (93.90)	66 (85.71)	
Not employed	5 (6.10)	9 (11.69)	
Other	0 (0)	2 (2.60)	
History of prior TBI			.06
Yes	19 (23.17)	9 (11.69)	
No	63 (76.83)	68 (88.31)	
Prior psychiatric disorder			.44
Yes	19 (23.17)	22 (28.57)	
No	63 (76.83)	55 (71.43)	
Prior substance abuse			.10
Yes	17 (20.73)	7 (9.09)	
No	63 (76.83)	69 (89.61)	
Missing	2 (2.44)	1 (1.30)	
Overall health rating			.95
Excellent/Good	55 (51.40)	27 (51.92)	
Fair/Poor	52 (48.60)	25 (48.08)	
CES-D-somatic symptoms, *M* (*SD*)	8.34 (5.31)	10.03 (4.97)	**.04**
CES-D-depressed mood, *M* (*SD*)	5.99 (5.20)	7.62 (5.57)	.06
CES-D-positive affect, *M* (*SD*)	3.57 (3.19)	4.43 (3.16)	.09
CES-D-interpersonal problems, *M* (*SD*)	1.01 (1.46)	1.10 (1.43)	.69
CES-D-total, *M* (*SD*)	18.73 (12.80)	23.18 (12.48)	**.03**
Perceived stress, *M* (*SD*)	24.48 (8.63)	27.91 (7.34)	**<.01**
NFI Motor, *M* (*SD*)	18.18 (7.28)	20.57 (5.99)	**.03**
NFI Cognition, *M* (*SD*)	46.61 (16.61)	51.92 (14.21)	**.03**
NFI Somatic, *M* (*SD*)	22.35 (7.90)	24.94 (7.65)	**.04**
NFI Communication, *M* (*SD*)	23.27 (8.83)	25.62 (7.65)	.08
Pain severity, *M* (*SD*)	0.97 (1.72)	1.52 (2.01)	.06

Note. TBI = traumatic brain injury; CES-D = Center for Epidemiological Studies-Depression; NFI = Neurobehavioral Functioning Inventory.

history of neurological, psychiatric, or substance abuse disorder; age; and study membership. The latter was included in the models to account for the changes in standard care that occurred in 3 years that separated the periods of data collection for study 1 and study 2. Other explanatory variables to be included in the model were selected based on literature evidence for relevance to the research questions. Least squares means or adjusted means (Searle, Speed, & Miliken, 1980) were calculated by time since injury and sex, and differences by sex were examined. To investigate if the differences between sexes remain after controlling for cognitive aspect of depression, CES-D-SOMA was added as a covariate, and differences in the means of NFI Memory and Cognition subscale adjusted for CES-D-SOMA were tested by sex.

With data for 82 men and 77 women available for analysis, power was sufficient (.80 or greater) to detect effect sizes of .45 or greater for the sex differences. Such effect sizes are just below the cutoff for medium in Cohen's classification (Cohen, 1988).

Results

Research Question 1. Table 1 presents descriptive statistics for demographic variables, injury characteristics such as injury severity and perceived health, and time since injury, as well as outcome measures of depression; chronic stress; severity of pain; and symptoms of impaired cognition, communication, motor ability, and somatic difficulties. There were no sex differences in overall health rating, age, level of education, psychiatric or substance abuse history, and time since injury. Women were on average 12.8 months away injury, and men were 12.1 months (p = .65 for sex differences). Because the differences in history of previous TBI approached statistical significance, and differences in injury severity were statistically significant, indicating a higher rate of MTBI among women, these were adjusted for in all models (see Table 1). Statistically significant differences between men and women were found in the total CES-D (p = .03) and CES-D-SOMA (p = .04), perceived stress, and three of the four NFI subscales analyzed (except communication). Statistically significant differences were also noted by study perhaps in association with increased research dissemination about post-TBI depression after study 1.

Research Question 2. Table 2 lists the values of test statistics (F) and the p values for the tests of the significance of the explanatory variables in the linear models with outcomes of depression, chronic stress, and symptoms (including pain). A sex-by-time-since-injury interaction was significant in the models for the CES-D-SOMA, CES-D-total, three NFI subscales (Motor, Memory and Cognition, and Communication), and pain severity.

Table 3 presents the comparisons between the adjusted means for men and women at less than or equal to 6 months, 6–12 months, and more than 12 months since injury for all outcomes except severity of pain, when time intervals analyzed were 3 months or less and >3 months. Across all outcomes (except motor symptoms) and during the early time period (first 6 months), women had significantly worse scores than did men. For the Motor subscale of NFI, sex differences did not reach statistical significance; however, they were in the same direction (more favorable for men). At later time periods, no sex differences were found except for chronic stress, also significantly higher among women at 6–12 months postinjury (Table 3).

To determine if CES-D-SOMA could explain differences between men and women in reports of symptoms of cognitive difficulties, we ran the model described earlier with CES-D-SOMA as a covariate. The differences between adjusted means of NFI Memory and Cognition subscale for men and women ≤6 months postinjury remained significant ($p < .05$, data not shown). However, the magnitude of the difference in adjusted means became smaller when controlling for cognitive aspect of depression.

Discussion

In this cross-sectional secondary analysis of men and women who were referred for evaluation and treatment in outpatient rehabilitation clinics and living in the community, we noted significantly higher levels of depressive symptoms, perceived stress, and brain injury symptoms for women compared with men after mild-to-moderate TBI. Specifically, women reported higher frequencies of motor, cognitive, and somatic symptoms than did men. Further, we have begun to identify that women reported increased frequency of symptoms within 1–6 months after injury compared with men. The women in this study reported higher levels of depressive symptoms and chronic perceived stress despite our finding that perception of physical health did not differ by sex, suggesting the absence of sex differences in the overall illness perception.

Our findings continue to suggest that allostatic load theory may be a useful guide for longitudinal study as we disentangle the development of relationships between symptoms, perceived stress, and depression over time after TBI and expand our understanding of relevant physiological phenomenon for women compared with men. Further, women reported increased symptom frequencies in the 1- to 6-month period, a time identified by Jorge, Robinson, and Arndt (1993)

TABLE 2. Explanatory Relationships of Sex and Sex-by-Time-Since-Injury Interaction With Outcomes of Depression, Stress, and Motor, Cognition, Somatic Symptoms, and Pain

	CES-D-somatic Symptoms[a]		CES-D-total[b]		Perceived Stress[c]	
Explanatory Variables	***F***	***p***	***F***	***p***	***F***	***p***
Injury severity	21.43	<.01	10.33	<.01	7.64	<.01
Study	0.24	.63	0.02	.89	11.56	<.01
Prior TBI history	5.55	.02	4.88	.03	1.30	.26
Sex	3.14	.08	3.49	.06	7.79	**<.01**
Time since injury	3.19	.04	5.81	<.01	0.84	.43
Sex-by-time-since-injury interaction	4.94	**<.01**	3.30	**.04**	2.38	.10

	NFI Motor[d]		NFI Memory and Cognition[e]		NFI Somatic[f]	
Explanatory Variables	***F***	***p***	***F***	***p***	***F***	***p***
Injury severity	6.84	.01	11.82	<.01	12.15	<.01
Study	1.53	.22	0.70	.40	0.46	.50
Neurological disorder	0.30	.58	2.16	.14	5.10	.03
Sex	2.76	.10	4.14	**.04**	2.99	.09
Months since injury	6.50	<.01	10.60	<.01	3.94	.02
Sex-by-months-since-injury interaction	1.06	.35	6.37	**<.01**	5.11	**<.01**

	NFI Communication[g]		Pain Severity[h]	
Explanatory Variables	***F***	***p***	***F***	***p***
Injury severity	12.16	<.01	1.95	.16
Study	0.31	.58	51.88	.01
Neurological disorder	2.43	.12	0.61	.44
Sex	1.79	.18	11.53	.01
Time since injury	9.96	.01	2.35	.13
Sex-by-time-since-injury interaction	4.43	**.01**	7.53	**<.01**

Note. TBI = traumatic brain injury; CES-D = Center for Epidemiological Studies-Depression; CES-D-SOMA = CES-D-somatic symptoms; NFI = Neurobehavioral Functioning Inventory.
[a]CES-D-SOMA overall model: $F = 5.89$, $p < .01$, $R^2 = 24$. [b]CES-D-total overall model: $F = 4.55$, $p < .01$, $R^2 = .20$. [c]Perceived stress overall model: $F = 4.60$, $p < .01$, $R^2 = 20$. [d]NFI Motor overall model: $F = 3.57$, $p < .01$, $R^2 = 16$. [e]NFI Memory and Cognition overall model: $F = 6.94$, $p < .01$, $R^2 = 27$. [f]NFI Somatic overall model: $F = 4.70$, $p < .01$, $R^2 = 20$. [g]NFI Communication overall model: $F = 6.02$, $p < .01$, $R^2 = 24$. [h]Pain severity overall model: $F = 12.61$, $p < .01$, $R^2 = 34$.

and Jorge, Robinson, Arndt, Forrester, et al. (1993) as most associated with biological explanatory models of depression and autonomic and anxiety features of depressive symptoms.

However, before we discuss the specific findings of this analysis, several limitations need to be identified. This is a secondary analysis reflecting common variables from two data sets. Further analyses of these sex differences should reflect careful examination of factors known to be associated with stress and depression in women with disabilities, including social support, social isolation, and the presence of victimization or abuse (Hughes et al., 2005). Further, we believe that the study of sex and gender differences after TBI and their relationships with preinjury and postinjury stress and depressive symptoms should reflect a broader perspective using mixed methods. It is important to prospectively examine differences of men and women over time to understand dynamic relationships in the development of symptoms, stress, and depression while also gathering psychiatric and biological data. Further, generalizations from our analyses are limited to those recruited from specialty clinics, most likely representing those with persistent difficulties (Wood, 2004). Still, because this sample represents those seen and treated by specialists, it remains unknown what difficulties would be reported for those who did not receive specialty therapies.

TABLE 3. Adjusted Means of Stress, Depression, and Symptoms by Sex and Time Since Injury

Outcome	Months	Men, Least Squares Mean (SE)	Women, Least Squares Mean (SE)	Sex Differences (*p* value)
CES-D-somatic symptoms	≤6	6.27 (1.00)	9.98 (1.02)	**<.01**
	6–12	6.90 (0.96)	9.06 (1.37)	.16
	>12	10.85 (0.92)	9.20 (0.95)	.17
CES-D-total	≤6	13.89 (2.51)	22.25 (2.58)	**.01**
	6–12	16.01 (2.44)	21.65 (3.47)	.15
	>12	25.96 (2.35)	23.28 (2.40)	.38
Perceived stress	≤6	22.60 (1.61)	27.14 (1.65)	**.04**
	6–12	23.74 (1.56)	29.98 (2.22)	**.01**
	>12	26.33 (1.49)	26.34 (1.54)	.10
NFI Motor	≤6	15.45 (1.35)	18.71 (1.39)	.07
	6–12	16.48 (1.31)	18.75 (1.87)	.28
	>12	21.18 (1.25)	21.04 (1.29)	.93
NFI Cognition	≤6	35.61 (2.94)	48.36 (3.02)	**<.01**
	6–12	43.49 (2.85)	50.54 (4.06)	.12
	>12	56.71 (2.72)	51.29 (2.81)	.13
NFI Somatic	≤6	19.22 (1.54)	25.70 (1.58)	**<.01**
	6–12	20.64 (1.49)	22.85 (2.12)	.35
	>12	26.65 (1.42)	24.36 (1.47)	.22
NFI Communication	≤6	17.98 (1.59)	24.14 (1.63)	**<.01**
	6–12	21.59 (1.55)	22.88 (2.20)	.60
	>12	28.23 (1.48)	25.90 (1.52)	.23
Pain severity	≤3	0.50 (0.49)	2.86 (0.54)	**<.01**
	3+	0.97 (0.22)	1.22 (0.26)	.35

Note. TBI = traumatic brain injury; CES-D = Center for Epidemiological Studies-Depression; NFI = Neurobehavioral Functioning Inventory.

Results from our analysis indicate that women reported higher frequencies of total depressive and depressive–somatic symptoms as well as higher frequencies of memory difficulties and somatic and motor symptoms. These findings are similar to those expressed by persons with PCS, a syndrome more likely to occur in women (McCauley et al., 2001; Meares et al., 2007). Further, we note that women report greater chronic perceived stress, pain, and cognitive symptoms when significant preinjury variables were controlled (study, severity of TBI, and previous TBI history). These findings support those by Hughes et al. (2005) who reported that women with physical disabilities ($n = 415$) reported higher levels of stress. However, unlike Hughes et al., we did not find sex differences in demographic variables, such as income, marital status, education, or preinjury employment status, factors that we have previously referred to as *preinjury allostatic load* (Bay & Donders, 2008). Our findings do suggest that heightened levels of symptoms and stress of women may increase risk for post-TBI depressive symptoms (Bay & Donders, 2008; Bay et al., 2004; Rees, 2003; Wood, 2004). However, because of the cross-sectional nature of these data, such temporal relationships can best be determined with prospective study beginning soon after injury.

Women in our study reported significantly more somatic and depressive symptoms than did men within the 6-month time period from injury compared with time points more associated with chronic depression due to psychosocial difficulties. This is consistent with the findings by Meares et al. (2007) who noted increased likelihood for PCS in women who reported symptoms early after MTBI.

What is unknown is the relationship between the degree of symptom distress and the subsequent help-seeking behaviors for men and women after TBI. Particularly troublesome are the recent findings by Setnik & Bazarian (2007) who reported that

nearly 42% of those responding to an Internet survey failed to seek medical interventions for their TBI at the time of injury. It is possible that women during the 1- to 6-month time period had heightened physical symptoms and stress because of barriers encountered in the help-seeking experience. Further study about the sex and gender differences in the help-seeking experience would add clarity to this finding.

The women in our study reported more pain and somatic symptoms than did men. This finding is consistent with other reports (American Psychiatric Association, 2000; Fillingim, 2000; Silverstein, 1999, 2002). In addition, we agree with Weiss et al. (1999) and Fillingim (2000) and others who have suggested that it is critical to explore how gendered life experiences, both preinjury and postinjury, interact with biological sex differences in persons with TBI. In addition, the extent to which childhood adversity, sexual abuse, and stressful life events occurred prior to injury and the degree to which social roles and support and coping strategies are involved in depression for women compared with men is needed. In study 1, these preinjury variables did not reflect sex differences.

Finally, whereas others have reported that women with depression also report more anxiety-related symptoms (Piccinelli & Wilkinson, 2000), we did not collect anxiety data in both studies. In fact, we reported that anxiety, measured with the Profile of Mood State anxiety subscale, was not associated with sex (Bay & Bergman, 2006). Because anxiety has been reported to influence depressive symptom reports during the first 6 months after TBI, it is imperative that future studies with women and TBI include assessment of their anxiety (Jorge, Robinson, & Arndt, 1993; Jorge et al., 2004).

An interesting finding was that sex differences were no longer present at the 6- to 12-month cutoff or the >12-month cutoff, with the exception of chronic stress. Further, within the first 3 months after injury, reflecting those with and without chronic pain, women reported higher levels of pain during the earlier time period. The finding that women report different symptoms during the time period associated with more biologically based depression (Jorge, Robinson, & Arndt, 1993) suggests that biology may explain these differences. Multiple determinants have been offered to explain this vulnerability, including genetics (Bierut et al., 1999), a cognitive bias toward negative events (Nolan-Hoeksema, 1987), and changing levels of female ovarian hormones and serotonergic systems, which were also implicated in cognitive disturbances (Shors & Leuner, 2003). Whether our findings can be explained according to biological differences remains to be tested.

Finally, there are sociocultural explanations for vulnerability to stress-related disorders and depression. Recent reviews on stress-related mental health disorders suggest that women are more vulnerable to stressful events than are their male counterparts because of their increased orientation toward care for others in their social networks (Blehar, 2006; Piccinelli & Wilkinson, 2000). Taylor et al. (2000) posited that the ''fight-or-flight'' stress response may not universally portray the response of men and women to threat. Instead, they suggest that the response of women to threat is more associated with their affiliative proclivity. That is, during times of threat or stress, women respond with a ''tend-and-befriend'' response, and biological factors support this hardwired response toward protecting their offspring and selectively affiliating. They suggest different biological processes in this response, including oxytocin and endogenous opioid mechanisms.

Conclusion

This study provides an intriguing suggestion that there is a complex interaction between sex-related biological and gender-related social and interpersonal differences that blend together to form a gendered post-TBI depressive symptom perspective. We anticipate that this complexity will encourage further research with women, particularly in light of Healthy People 2010 and WHO goals and beginning empirical findings associated with women and disability.

Nursing Implications

This study begins to describe the unique characteristics of men and women following mild-to-moderate TBI and suggests that variations in assessment may be indicated. The neuroscience nurse must be aware that, although chronic stress may explain depressive symptoms, there are some sex differences in associated factors according to the time since injury. Early after injury, women seem to experience increased somatic, pain, cognitive, and motor type of symptoms. What is unclear is whether there are biological or sociocultural or preinjury medical histories that are relevant. Neuroscience nurses are in key positions to further investigate the extent to which female hormones, premorbid history of abuse or chronic stress, or sociocultural factors are contributing to these heightened symptoms. Further, because the average neuroscience nurse is positioned in multiple treatment settings, persons with TBI may present for assessment and treatment in outpatient clinics, emergency departments, mental health settings, or pain clinics. Regular assessment is required about the recency of head trauma as specialists are becoming increasingly aware that broad-based

screening for TBI should occur in various healthcare settings (Gordon, 2008).

Most importantly, nurses are advocates and coordinators of care for persons following TBI. It is critical that nurses become knowledgeable about the myriad of explanations for depression following brain trauma and articulate those likely explanations in team care plans and family meetings. Without a holistic perspective in the planning and evaluation of treatment for persons with mood disorders after TBI, care can become fragmented. Using a holistic perspective, neuroscience nurses are likely to target specific interventions toward stress and symptom management at optimal times.

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