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Effect of depression on cognition after mild traumatic brain injury in adults

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ABSTRACT

Objective: The current study examined the effect of depression on cognitive test performance in a sample of adults seeking treatment for a mild traumatic brain injury (MTBI). We hypothesized that patients with greater depressive symptoms would perform worse on tasks of fluid cognition compared to those without depression, after controlling for potential confounds.

Method: Patients ($N = 76$) completed a brief cognitive test battery (NIH Toolbox Cognition Battery; NIHTB-CB) and a depression screening questionnaire (PHQ-9) at 11.7-weeks post injury ($SD = 6.3$ range 2–26). Cognitive scores were adjusted for age, education, gender, and race/ethnicity. Depressive symptoms were examined continuously and dichotomized as: (1) total PHQ-9 score of ≥ 10 , the optimal cut-off for Major Depressive Disorder caseness from prior research, and (2) five or more symptoms of depression, including either depressed mood or anhedonia (i.e. DSM-5-based definition).

Results: Twenty-seven patients (35.5%) met DSM-5-based criteria for depression and 42 (55.3%) met criteria based on PHQ-9 > 10 . Depression symptom severity correlated with lower fluid cognition composite scores [$r = -.22, p = .05$] and contributed to the prediction of fluid cognition performance in a model that controlled for time since injury and crystallized cognitive abilities [$F(3, 72) = 7.49, p < .001$; $R^2 = 20.6\%$]. Examining specific NIHTB-CB fluid subtests, the largest group differences were seen on processing speed ($d = .40-.49$), cognitive flexibility ($d = .32-.36$), and episodic memory ($d = .20-.34$). Depression severity was strongly associated with overall post-concussion symptom burden ($r = .77, p < .001$).

Conclusion: Depression is a common comorbidity and an important factor to consider when interpreting neurocognitive test performance in adults with concussion in a clinical setting.

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KEYWORDS

Mild traumatic brain injury; MTBI; depression; cognition; neuropsychological functioning

Introduction

Within the first three months after a mild traumatic brain injury (MTBI), neuropsychological difficulties in attention, processing speed, learning/memory, and executive functioning (e.g. set-shifting, inhibition, working memory, fluency) are common (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Karr, Areshenkoff, & Garcia-Barrera, 2014; Schretlen & Shapiro, 2003). Assessment of cognition after MTBI may be complicated by depression. Depression commonly co-occurs with MTBI. Approximately 15–52% of patients with MTBI experience clinically significant depressive symptoms following a MTBI in the first-year post-injury (Bombardier et al., 2010; Lucas et al., 2016; van der Naalt et al., 2017). The cortical-limbic pathophysiology of MTBI and depression may overlap (Broshek, De Marco, & Freeman, 2015). Similar to MTBI, several reviews (Hammar & Ardal, 2009; McClintock, Husain, Greer, & Cullum, 2010) and meta-analyses (Henry & Crawford, 2005; Zakzanis, Leach, & Kaplan, 1999) have shown that Major Depressive Disorder (without MTBI) is associated with deficits in attention, processing speed, executive functioning, and learning/memory during the active phase of the illness.

Across the spectrum of traumatic brain injury (TBI) severity, depression is thought to exacerbate cognitive deficits (Barker-Collo et al., 2015; Rapoport, McCullagh, Shammi, & Feinstein, 2005; Silver, McAllister, & Arciniegas, 2009). There is limited evidence for this theory in MTBI. Moreover, the few available studies have produced mixed findings with respect to which cognitive domains are most impacted. In a clinic-referred sample of adults with mild or moderate TBI (57% with MTBI), those with co-morbid depression performed globally worse on neuropsychological measures of processing speed, working memory, episodic memory, and executive functioning compared to those without depression, at an average of seven months post-injury (Rapoport et al., 2005). In a community-based sample of adults with MTBIs, depression symptom severity correlated with worse cognitive performance (measures of processing speed and executive functioning, but not episodic memory) one year after injury (Barker-Collo et al., 2015). Another prior study stratified a mixed group of adult trauma patients (50% with MTBI, 7% moderate TBI, 43% non-head injury controls) by Major Depressive Disorder, and found that patients with depression scored lower on measures of memory, processing speed, and executive functioning (Levin et al., 2001). Although there is variability in the cognitive domains implicated by these studies, which may partially be due to the sample composition (e.g. MTBI only vs. mixed severity TBI), there is consistent evidence that people with MTBI and co-morbid depression perform worse on cognitive testing. However, a limitation of these previous studies is that none controlled for test-taking effort, or performance invalidity. This is important, given the associations between psychiatric symptoms and neurocognitive scores might be explained by response bias (Bigler, 2014).

The present study aimed to further investigate depression as a potential moderator in the assessment of cognition after MTBI. We examined the effect of depression on cognitive performance in a sample of adults at the time they presented for outpatient care for a recent MTBI, i.e. at a clinically relevant transition. Importantly, we excluded cases of performance invalidity to mitigate the potential confounds of symptom over-reporting or below-capacity test performance. Based on the bulk of the prior literature, we hypothesized that patients with greater depressive symptoms would perform worse across measures of fluid cognitive abilities (e.g. attention, processing speed, executive functioning, learning/memory), that is, demonstrate globally reduced cognitive performance.

Methods

Participants

Study participants were recruited consecutively from four outpatient concussion clinics in the greater Vancouver, British Columbia area between March 2015 and February 2017. Two of these clinics treat patients with work-related injuries, while the other two serve patients with non-work related injuries in the publicly funded health care system. All participants were civilians. Eligibility criteria were: (i) age 18 to 65, (ii) sustained an MTBI in the past six months based on the World Health Organization Neurotrauma (Holm, David Cassidy, Carroll, Borg, & Neurotrauma Task Force on Mild Traumatic Brain Injury of the WHO Collaborating Centre, 2005) Task Force's definition, (iii) fluent in English, and (iv) employed prior to injury, because the current study was embedded in a larger research program investigating return to work following MTBI. The present study received approval from the University of British Columbia Behavioral Research Ethics Board, the Vancouver Coastal Health Research Institute, and the Fraser Health Research Institute. Participation in this research study was voluntary. The measures described below were administered to consenting patients as part of a research battery (i.e. not in usual clinical care). The participants completed a series of measures at or soon after their first visit to the clinic. All assessments were administered by a trained research assistant, under the supervision of a board-certified neuropsychologist.

Measures

Depression was assessed with the *Patient Health Questionnaire – 9 (PHQ-9)*; Kroenke, Spitzer, & Williams, 2001), a self-report inventory that queries symptoms of depression over the past two weeks. Each question corresponds to a symptom of a Major Depressive Episode as defined by the DSM-5 (American Psychiatric Association, 2013). Each symptom is rated with the following choices: 'not at all,' 'several days,' 'more than half the days,' and 'nearly every day.' These labels correspond to a score of 0, 1, 2, and 3, respectively, with a total possible score range of 0–27. This variable was examined in a continuous manner in our main analyses. However, in an effort to make the findings more clinically applicable, we chose to operationalize clinically significant depression in two well-validated ways: (1) *Cut-off definition*: a total PHQ-9 score of 10 or greater, as recommended in the derivation study (Kroenke et al., 2001) for identifying cases of major depressive disorder. Meta-analyses reported the pooled sensitivity and specificity to be .77–.81 and .85, respectively, for this method (Manea, Gilbody, & McMillan, 2015; Mitchell, Yadegarfar, Gill, & Stubbs, 2016). (2) *DSM-based definition*: five or more symptoms that were rated as 'more than half the days' or 'nearly every day.' One of these symptoms had to either be depressed mood or anhedonia. The suicidal thoughts item was rated as positive if the response was 'several days' or more frequent. This DSM-based definition has been used in previous studies and has high sensitivity (.93) and specificity (.89) in identifying major depressive disorder in brain injured patients (Fann et al., 2005). Meta-analyses report a pooled sensitivity of .54–.57 and pooled specificity .93 in identifying depression with this definition (Manea et al., 2015; Mitchell et al., 2016). Another meta-analysis reported the sensitivity and specificity between the DSM-based and cut-off definitions are comparable (Gilbody, Richards, Brealey, & Hewitt, 2007).

The *British Columbia Postconcussion Symptom Inventory (BC-PSI)*; Iverson & Lange, 2003) is a 13-item self-report questionnaire that measures the frequency and intensity of physical,

Table 1. Description of the NIH toolbox-cognition domain subtests.

NIH toolbox task	Cognitive domain	Description
<i>Crystallized composite – experience/learning-based abilities</i>		
Picture vocabulary	Receptive vocabulary	Select the correct picture after hearing a word orally
Reading recognition	Verbal knowledge	Pronounce words aloud as accurately as possible
<i>Fluid composite – context-dependent brain processes that change with age/pathology</i>		
DCCS	Cognitive flexibility	Sorting cards based on rules that switch
Flanker	Attention/inhibition	Respond to target with conflicting surrounding information
List sort	Working memory	Mentally Re-order two sets of objects based on size
Picture sequence memory	Episodic memory	Recall a sequence of pictures in order
Pattern comparison	Processing speed	Discern whether two items are the same/different

Note: DCCS = Dimensional change card sort.

cognitive, and emotional symptoms over the past week using a six-point Likert scale. For each item, the frequency and intensity rating are multiplied together. This product score is then converted to a 0–4 item score that reflects both frequency and intensity. BC-PSI total score is obtained by summing the scores on the 13 individual symptoms (range: 0–52).

National Institutes of Health Toolbox Cognition Battery (NIHTB-CB; Weintraub et al., 2013) is a brief battery of cognitive tests created by the National Institutes of Health (NIH), and intended to be a unified platform for neurological research (Weintraub et al., 2013). The NIHTB-CB includes a series of objective, performance-based tasks to assess neuropsychological functioning (Weintraub et al., 2013, 2014) and it generates normed scores that represent an individual's crystallized functioning (i.e., acquired knowledge) and fluid cognitive functioning (i.e., situation dependent skills; Casaletto et al., 2016). The NIHTB-CB is administered on the computer with the assistance of a trained examiner. It consists of seven subtests (see Table 1), two of which measure crystallized cognitive ability and five that assess fluid cognitive abilities. Initial validation studies suggest that these tests have strong convergent validity with legacy neuropsychological instruments, strong test-retest reliability, and minimal ceiling or floor effects (Weintraub et al., 2014). Scores were adjusted for age, education, gender, and race/ethnicity according to the automated algorithm from Casaletto et al. (2016). The NIHTB-CB is a supplementary Common Data Element for TBI (NINDS, 2017). It has recently been used in two studies involving heterogeneous samples of people with TBIs who were more than one-year post injury (Holdnack, Iverson, Silverberg, Tulskey, & Heinemann, 2017; Tulskey et al., 2017).

The *Medical Symptom Validity Test* (MSVT; Green, 2004) is a performance validity test that is sensitive to effort and task engagement, but not cognitive impairment (Carone, 2008; Howe & Loring, 2009; Whitney et al., 2009). It is a computerized test that instructs examinees to memorize simple word pairs. Performance is scored as percentage correct on the three main indices (i.e. Immediate Recognition, Delayed Recognition, and Consistency). Given the large and well-established impact of sub-optimal motivation and effort on cognitive test performance (Fox, 2011; Lange et al., 2010; West et al., 2011), we excluded those who performed below the cutoff recommended in the test manual (Green, 2004).

Statistical analyses

A hierarchical linear regression analysis was conducted to assess the association between the dependent variable (i.e. fluid cognition composite score) and depression severity in this sequence of steps: (1) weeks since injury, crystallized cognition composite T-score, (2) total PHQ-9 depression score. Weeks since injury was chosen as a covariate because there may be an inherent relationship between the time since injury and cognitive scores due to the natural history of cognitive recovery from concussion during the first months after injury (Belanger et al., 2005; Karr et al., 2014; Schretlen & Shapiro, 2003). Crystallized cognition was used as a covariate because people who have lower intelligence scores premorbidly might be at higher risk for depression and subsequent cognitive impairment (Gale et al., 2008, 2009; Koenen et al., 2009). Moreover, there is a moderate correlation between Crystallized cognition and Fluid cognition on the NIHTB-CB in healthy adults; those with lower crystallized cognition are more likely to have low scores on the fluid cognition measures (Holdnack et al., 2017). Cohen's effect size (in standard deviation units) is reported for all group mean comparisons between those who screened positively as clinically depressed and those who did not. We chose not to conduct null hypothesis testing for every pairwise contrast because we did not have an a priori hypothesis that certain subtest(s) would be more affected. Our goal was to highlight domains that may be more affected, to generate hypotheses for future research. Moreover, the present study did not have sufficient statistical power for conducting these additional tests while controlling for multiple comparisons (familywise Type I error).

Results

A total of 273 patients were screened but many did not meet inclusion criteria (did not meet MTBI criteria, $n = 36$; loss of consciousness > 30 min, $n = 8$; injury greater than 6 months ago, $n = 26$; not employed pre-injury, $n = 16$; not fluent in English, $n = 4$; older than 65, $n = 3$). Further, 40 declined to participate and 38 could not be scheduled or did not attend the initial assessment. A total of 102 participants completed the study; however, 23 were removed due to suspected below-capacity performance (22.5% MSVT failure rate) and an additional 3 were excluded due missing NIHTB-CB data.

The 76 participants included in the analyses were an average of 41.0 years old ($SD = 11.4$; range = 21–64). Exactly half (50.0%) the sample were women and the majority (75.0%) were Caucasian, with 17.1% Asian, 3.9% First Nations, 2.6% Black, and 1.3% Hispanic. Regarding education, 5.3% had less than a high school education, 18.4% had a high school diploma, and 76.3% had more than a high school education. Workplace injuries were strongly represented in our sample (47.4%). Pre-injury mental health treatment was common (44.7%). A semi-structured interview classified how the injury occurred into the following mutually exclusive categories: struck by an object (i.e. fast moving inanimate object unintentionally hitting a relatively stationary head; 31.6%), fall (30.4%), motor vehicle accident (22.4%), sport (6.6%), assault (i.e. struck intentionally by another person; 3.9%), other (5.9%). The majority of 'struck by an object' MTBIs were workplace injuries (17 of 24; 70.8%). About one-third (32.9%) of the sample reported a loss of consciousness (LOC; denied = 50%, suspected but unwitnessed = 9.2%, unknown = 7.9%), 35.5% reported post-traumatic amnesia, and 84.2% reported acute confusion/disorientation. At the time of the assessment, most of the sample (86.8%) reported being eligible for financial compensation related to their injury. Participants

Table 2. Bivariate correlation matrix between key variables.

	1	2	3	4	5	6
1. Age	–					
2. Education	–.10	–				
3. Weeks since injury	.03	.27*	–			
4. PHQ-9 total (depression)	–.11	–.30**	–.17	–		
5. BC-PSI (Postconcussion Symptoms)	.08	–.14	–.09	.77**	–	
6. NIHTB-CB crystallized composite	.11	.07	–.06	.01	.01	–
7. NIHTB-CB fluid composite	.11	.21	–.20	–.22*	–.21	.37**

Notes: BC-PSI = British Columbia Postconcussion Symptom Inventory; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; PHQ-9 = Patient Health Questionnaire-9.

*Denotes a $p < .05$; **Denotes a $p < .01$.

were evaluated at an average of 11.7 weeks post injury ($SD = 6.3$, range 2–26). A minority of the sample had returned to work full time (13.2%), while the remainder reported being on leave (67.1%) or returning to work with reduced hours/responsibilities (17.1%; ‘other’ = 2.6%)

The average PHQ-9 total score was 11.25 (median = 11, $SD = 6.22$, range 0–25). See Table 2 for correlations among key variables. Education was associated with depression severity such that those with less education had higher depression scores. Depression (i.e. PHQ-9) and NIHTB-CB fluid composite were not associated with age (Table 2) or sex [PHQ-9, $t(74) = -.20$, $p = .84$; NIHTB-CB, $t(74) = .10$, $p = .92$]. Having a pre-injury history of mental health treatment (i.e. yes vs. no) was not associated with current depression severity [$t(74) = -1.59$, $p = .12$] or fluid cognition [$t(74) = -.05$, $p = .96$], and so not considered a covariate. The NIHTB-CB crystallized composite correlated with the fluid composite. There was a small (non-significant) negative relationship between number of weeks since injury and fluid cognition composite ($r = -.20$, $p = .08$), i.e. participants with longer latencies between their injury and assessment tended to perform worse. Depression severity was not related to weeks since injury ($r = -.17$, $p = .14$). Depression severity and post-concussion symptom burden were strongly associated.

A visual inspection of the scatterplot suggested a linear relationship between higher depressive severity and lower fluid composite scores (see Figure 1; $r = -.22$, $p = .05$). Step 1 of the hierarchical linear regression was significant [$F(2, 73) = 7.22$, $p = .001$] and predicted 14.6% of the variance in fluid cognition performance (i.e. adjusted R^2). The crystallized composite score was significant (standardized $\beta = .36$, $p = .001$), but weeks since injury was not (standardized $\beta = -.18$, $p = .10$). Adding PHQ-9 score to the model in Step 2 further accounted for 7.0% of the variance [change $F(1, 72) = 6.50$, $p = .01$] with the total model accounting for 20.6% ($R^2 = .26$) of the variance in fluid cognition scores [$F(3, 72) = 7.49$, $p < .001$]. Each independent variable was significant in this model [weeks since injury $\beta = -.23$, $p = .04$; crystallized composite $\beta = .36$, $p = .001$; PHQ-9 score: $\beta = -.27$, $p = .01$]. An effect size of $R^2 = .08$ was calculated based on the *additional* variance explained by the final step and the adjusted residual variance of the model. This effect is conventionally classified as small-to-medium in strength (Cohen, 1988).

Dichotomizing the sample showed that 42 patients (55.3%) screened positive for depression (PHQ-9 ≥ 10) and 27 patients (35.5%) met DSM-5-based criteria for depression. These groups did not differ based on age or sex, but those who screened positively for depression tended to have less education (Table 3). Those who screened positively for depression also had higher depression and postconcussion symptom scores compared to the group that did not screen positively for depression. The effect size differences between the depressed and non-depressed groups are presented in Table 4.

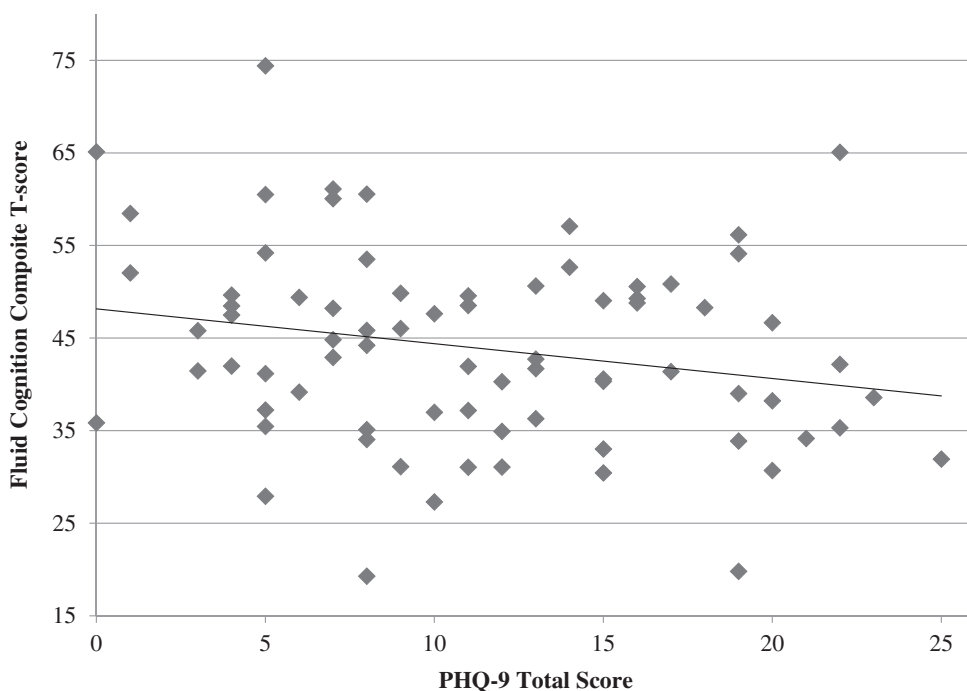


Figure 1. Scatter plot of total PHQ-9 score and fluid cognition composite T-score.

Table 3. Demographic and symptom severity comparisons between those who screened positively for depression and those who did not.

	Depressed (<i>n</i> = 42)	Non-depressed (<i>n</i> = 34)	<i>t</i> / χ^2	<i>p</i>
Cutoff definition (PHQ-9 total score > 10)				
Age (<i>M</i> , <i>SD</i>)	40.1 (12.1)	42.0 (10.4)	.73	.47
Sex (<i>n</i> , % female)	23 (54.8%)	15 (44.1%)	.85	.36
Education (<i>n</i> , %)	—	—	4.85	.09
Less than High School	3 (7.1%)	1 (2.9%)		
High School	11 (26.2%)	3 (8.8%)		
More than High School	28 (66.7%)	30 (88.2%)		
PHQ-9 Score (<i>M</i> , <i>SD</i>)	15.9 (4.1)	5.6 (2.6)	−12.75	<.001
BC-PSI (<i>M</i> , <i>SD</i>)	29.5 (8.9)	12.6 (8.1)	−8.60	<.001
	Depressed (<i>n</i> = 27)	Non-depressed (<i>n</i> = 49)	<i>t</i> / χ^2	<i>p</i>
DSM5 definition (Endorsed 5+ PHQ-9 items including 1+ cardinal symptom)				
Age (<i>M</i> , <i>SD</i>)	39.5 (12.5)	41.8 (10.7)	.85	.40
Sex (<i>n</i> , % female)	12 (44.4%)	26 (53.1%)	.52	.47
Education (<i>n</i> , %)	—	—	7.17	.03
Less than High School	3 (11.1%)	1 (2.0%)		
High School	8 (29.6%)	6 (12.2%)		
More than High School	16 (59.3%)	42 (85.7%)		
PHQ-9 Score (<i>M</i> , <i>SD</i>)	17.9 (3.5)	7.6 (3.9)	−11.38	<.001
BC-PSI (<i>M</i> , <i>SD</i>)	31.6 (8.7)	16.6 (10.1)	−6.53	<.001

Notes: BC-PSI = British Columbia Postconcussion Symptom Inventory; *M* = mean; PHQ-9 = Patient Health Questionnaire-9; *SD* = standard deviation.

Table 4. Cognitive task descriptive statistics and effect size (Cohen's *d*) differences between the depressed group and the non-depressed group.

	Depressed (<i>n</i> = 42)		Non-depressed (<i>n</i> = 34)		Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Cutoff definition (PHQ-9 total score > 10)					
Fluid cognition composite	41.81	9.27	46.54	11.43	-.45
DCCS	44.12	9.74	47.50	11.32	-.32
Flanker	44.18	12.23	45.81	10.98	-.14
List sort	45.84	9.81	47.96	8.43	-.23
Picture sequence memory	44.76	9.17	48.07	9.93	-.34
Pattern comparison	44.72	12.43	49.80	12.90	-.40
	Depressed (<i>n</i> = 27)		Non-depressed (<i>n</i> = 49)		Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
DSM5 definition (Endorsed 5+ PHQ-9 items including 1+ cardinal symptom)					
Fluid cognition composite	42.05	9.67	44.96	10.88	-.28
DCCS	43.18	10.81	46.98	10.25	-.36
Flanker	44.86	10.16	44.94	12.48	-.01
List sort	48.37	9.92	45.91	8.79	.26
Picture sequence memory	44.98	9.93	46.93	9.44	-.20
Pattern comparison	43.01	12.30	49.19	12.67	-.49

Notes: Negative *d*-values indicate the depressed group scored lower. PHQ-9 = Patient Health Questionnaire-9. DCCS = Dimensional Change Card Sort.

Discussion

In a sample of patients seeking outpatient care after sustaining an MTBI, those who endorsed more depressive symptoms on a validated self-report measure (PHQ-9) performed worse on tests of fluid cognition when covarying for time since injury and crystallized cognition. When patients were dichotomized on depression status using previously validated PHQ-9 cut-off scores, the depressed group scored one-third to one-half of a standard deviation below the group with no depression on a fluid cognition composite score, corresponding to a small to medium effect size (Cohen, 1988). These data support our hypothesis that comorbid depression can account for cognitive deficits after MTBI. Clinicians should be cautious about attributing poor neuropsychological test performance to MTBI (i.e. brain injury) in patients with high depressive symptoms. Using a biopsychosocial framework that considers comorbid depression symptoms would likely help practitioners to design a maximally effective treatment plan for patients who are slow to recover from MTBI (Panczykowski & Pardini, 2014; Wäljas et al., 2014).

Rates of clinically significant depression were high in this sample, which is consistent with previous literature on this topic (Bombardier et al., 2010; Lucas et al., 2016; van der Naalt et al., 2017). Over half the sample screened positive for depression using the standard cutoff score and about one-third of the sample met DSM criteria for Major Depressive Disorder based on their pattern of PHQ-9 item endorsement. Our sampling strategy likely contributed to the high co-occurrence of depression. Many of the patients in this cohort were slow-to-recover. Only 13.2% of the sample had fully returned to work by their assessment at ~12 weeks post injury. They were recruited from an outpatient clinic where they were seeking treatment for ongoing problems related to MTBI.

Examining the effect size differences between groups using the standard PHQ-9 cutoff score, the depressed group performed worse than the non-depressed group on all five fluid cognition subtests (i.e. small-to-medium effect sizes), consistent with global-diffuse

hypothesis of depression (Landrø et al., [in press](#); Veiel, 1997). To aid interpretation and clinical applicability, effect sizes are presented in standard deviation (SD) units. For example, a Cohen's *d* value of $-.5$ means that, on average, a patient with depression will score $-.5$ SD lower than a patient without depression (or 5 T-score points). There was some range in effect sizes across the fluid cognition subtests, however. Pattern Comparison appeared to show the greatest difference between the two groups. This subtest measures processing speed, which is commonly cited as impaired in the depression literature (Hammar & Ardal, 2009; McClintock et al., 2010). The subtests with the smallest effect sizes between the depressed and non-depressed groups were the Flanker and List Sort tasks, which measure inhibition and working memory, respectively.

Similar to Lange et al. (2011), we found that those who screened positively for depression had greater overall postconcussion symptom burden. There are several possible interpretations of this association. For instance, depression may mimic or magnify concussion-like symptoms, depression may arise as a reaction to relatively severe concussion symptoms, worse depression *and* postconcussion symptoms may be driven by a third variable (e.g. underlying changes in neurobiology associated with a more severe MTBI, and/or underlying psychological factors associated with lifestyle changes and injury-related stressors), or the association between measures of depression and postconcussion symptoms may be an artifact of symptom overlap between these scales. This possible symptom overlap confound, which affects all studies assessing depression after MTBI, is related to endorsing non-specific symptoms possibly related to MTBI (e.g. sleep disturbance, difficulty concentrating), artificially inflating measures of 'depression' severity. Most compellingly, Cook et al. (2011) explored whether somatic and cognitive symptoms on a depression symptom inventory (PHQ-9) show evidence of differential item functioning (DIF) in TBI, using a primary care comparison group. None of the PHQ-9 items demonstrated statistically significant or meaningful DIF attributable to TBI, and the cumulative effects of non-significant DIF did not spuriously inflate PHQ-9 total scores (Cook et al., 2011). They concluded that the PHQ-9 is a valid screener for depression following TBI, and that all symptoms can be counted without concern about over-diagnosis. Nevertheless, we also attempted to address the non-specificity confound with sensitivity analyses using DSM syndromal criteria, consistent with prior studies (Fann et al., 2005). Theoretically, this could reduce the number of cases falsely classified as having depression due to elevated reporting of non-specific symptoms. In order to meet criteria for the DSM-based definition of depression in this study, patients had to endorse one of the cardinal symptoms of depression (i.e. depressed mood or anhedonia) on the majority of days during a two-week period in addition to at least four other symptoms of depression. Even in the presence of some postconcussion symptoms, these individuals would likely meet criteria for a depressive disorder. Consistent with this hypothesis, the fluid cognition composite effect size difference for those that screened positive for depression based on this definition appears to be more modest compared to the standard total score cutoff definition. It is worth noting that the processing speed (i.e. Pattern Comparison) effect size is somewhat comparable across the two methods of classifying depression, suggesting that this cognitive domain may be consistently associated with depression and less sensitive to how it is defined.

Other limitations of this study are noteworthy. Most importantly, depressive symptoms were characterized using a self-report questionnaire designed for depression case-finding. These patients did not undergo a diagnostic interview or face-to-face clinical assessment

by a mental health professional. Additionally, it is possible that other psychiatric comorbidities (e.g. anxiety disorders) could have contributed to our finding. A large proportion of the sample was eligible for compensation at the time of testing. A previous meta-analysis showed that people in litigation had worse cognitive performance as a function of *greater* time since injury (Belanger et al., 2005). To try to control for this potential confound, we excluded participants who failed performance validity testing (i.e. MSVT), which many prior studies of depression in MTBI have not. However, it is possible that some individuals in the final sample performed below their capacity but evaded detection with performance validity testing. The cross-sectional nature of this study limits the ability to infer causality about the relationship between depression and cognition. Because of conflicting findings from prior studies, we did not have a priori hypotheses about which specific cognitive domains would be most affected. We also had insufficient statistical power to test for significant differences between depressed vs. non-depressed subgroups for all cognitive domains (i.e. we were unlikely to detect between-group differences that were less than Cohen's $d = .65$ for the cut-off method/ $d = .68$ for the DSM-based method at $\beta = .80$ power and $p = .05$; Faul et al., 2009). We instead present effect sizes, so future studies can conduct a priori power analyses to collect data from an adequate sample. An additional limitation of the present study is that our participants were seeking specialty MTBI-related health care services. These results may not be generalizable to other samples.

In summary, rates of clinically significant depressive symptoms were high in this sample of individuals who were experiencing post-acute difficulties following MTBI. Additionally, patients with clinically significant depressive symptoms following MTBI had worse overall fluid cognitive functioning compared to patients without clinically significant depressive symptoms following MTBI. It will be important for future studies to examine the *unique* effect of depression when controlling for other psychological variables. These results have direct implications for the clinical assessment and treatment of MTBI to show the importance of considering depressive symptomatology when interpreting neuropsychological test performance.

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William Panenka has a clinical practice in forensic neuropsychiatry involving individuals who have sustained TBIs. Grant Iverson has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to MTBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical practice in forensic neuropsychology involving individuals who have sustained mild TBIs. He is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organizations. Noah Silverberg has a private practice in neuropsychology that includes consultation roles with professional sport organizations and disability insurance providers, including WorkSafeBC.

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References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Barker-Collo, S., Jones, K., Theadom, A., Starkey, N., Dowell, A., McPherson, K., ... BIONIC Research Group. (2015). Neuropsychological outcome and its correlates in the first year after adult mild traumatic brain injury: A population-based New Zealand study. *Brain Injury*, 29(13–14), 1604–1616. doi:10.3109/02699052.2015.1075143
- Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society: JINS*, 11(3), 215–227. doi:10.1017/S1355617705050277
- Bigler, E. D. (2014). Effort, symptom validity testing, performance validity testing and traumatic brain injury. *Brain Injury*, 28(13–14), 1623–1638. doi:10.3109/02699052.2014.947627
- Bombardier, C. H., Fann, J. R., Temkin, N. R., Esselman, P. C., Barber, J., & Dikmen, S. S. (2010). Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA*, 303(19), 1938. doi:10.1001/jama.2010.599
- Broshek, D. K., De Marco, A. P., & Freeman, J. R. (2015). A review of post-concussion syndrome and psychological factors associated with concussion. *Brain Injury*, 29(2), 228–237. doi:10.3109/02699052.2014.974674
- Carone, D. A. (2008). Children with moderate/severe brain damage/dysfunction outperform adults with mild-to-no brain damage on the Medical Symptom Validity Test. *Brain Injury*, 22(12), 960–971. doi:10.1080/02699050802491297
- Casaletto, K. B., Umlauf, A., Marquine, M., Beaumont, J. L., Mungas, D., Gershon, R., ... Heaton, R. K. (2016). Demographically corrected normative standards for the Spanish language version of the NIH toolbox cognition battery. *Journal of the International Neuropsychological Society*, 22(3), 364–374. doi:10.1017/S135561771500137X
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: L. Erlbaum Associates.
- Cook, K. F., Bombardier, C. H., Bamer, A. M., Choi, S. W., Kroenke, K., & Fann, J. R. (2011). Do somatic and cognitive symptoms of traumatic brain injury confound depression screening? *Archives of Physical Medicine and Rehabilitation*, 92(5), 818–823. doi:10.1016/j.apmr.2010.12.008
- Fann, J. R., Bombardier, C. H., Dikmen, S., Esselman, P., Warme, C. A., Pelzer, E., ... Temkin, N. (2005). Validity of the patient health questionnaire-9 in assessing depression following traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 20(6), 501–511.
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149–1160. doi:10.3758/BRM.41.4.1149
- Fox, D. D. (2011). Symptom validity test failure indicates invalidity of neuropsychological tests. *The Clinical Neuropsychologist*, 25(3), 488–495. doi:10.1080/13854046.2011.554443
- Gale, C. R., Deary, I. J., Boyle, S. H., Barefoot, J., Mortensen, L. H., & Batty, G. D. (2008). Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age. *Archives of General Psychiatry*, 65(12), 1410–1418. doi:10.1001/archpsyc.65.12.1410
- Gale, C. R., Hatch, S. L., Batty, G. D., & Deary, I. J. (2009). Intelligence in childhood and risk of psychological distress in adulthood: The 1958 National Child Development Survey and the 1970 British Cohort study. *Intelligence*, 37(6), 592–599. doi:10.1016/j.intell.2008.09.002

- Gilbody, S., Richards, D., Brealey, S., & Hewitt, C. (2007). Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): A diagnostic meta-analysis. *Journal of General Internal Medicine*, 22(11), 1596–1602. doi:[10.1007/s11606-007-0333-y](https://doi.org/10.1007/s11606-007-0333-y)
- Green, P. (2004). *Green's medical symptom validity test (MSVT) for microsoft windows*. Edmonton: Green's Publishing.
- Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression – A summary. *Frontiers in Human Neuroscience*, 3, 26. doi:[10.3389/neuro.09.026.2009](https://doi.org/10.3389/neuro.09.026.2009)
- Henry, J. D., & Crawford, J. R. (2005). A meta-analytic review of verbal fluency deficits in depression. *Journal of Clinical and Experimental Neuropsychology*, 27(1), 78–101. doi: [10.1080/138033990513654](https://doi.org/10.1080/138033990513654)
- Holdnack, J. A., Tulskey, D. S., Brooks, B. L., Slotkin, J., Gershon, R., Heinemann, A. W., & Iverson, G. L. (2017). Interpreting patterns of low scores on the NIH toolbox cognition battery. *Archives of Clinical Neuropsychology*, 32(5), 574–584. doi:[10.1093/arclin/acx032](https://doi.org/10.1093/arclin/acx032)
- Holdnack, J. A., Iverson, G. L., Silverberg, N. D., Tulskey, D. S., & Heinemann, A. W. (2017). NIH toolbox cognition tests following traumatic brain injury: Base rates of low scores. *Rehabilitation Psychology*, 62(4), 474–484. doi:[10.1037/rep0000145](https://doi.org/10.1037/rep0000145)
- Holm, L., David Cassidy, J., Carroll, L., Borg, J. J., & Neurotrauma Task Force on Mild Traumatic Brain Injury of the WHO Collaborating Centre. (2005). Summary of the WHO collaborating centre for neurotrauma task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine*, 37(3), 137–141. doi:[10.1080/16501970510027321](https://doi.org/10.1080/16501970510027321)
- Howe, L. L. S., & Loring, D. W. (2009). Classification accuracy and predictive ability of the medical symptom validity test's dementia profile and general memory impairment profile. *The Clinical Neuropsychologist*, 23(2), 329–342. doi:[10.1080/13854040801945060](https://doi.org/10.1080/13854040801945060)
- Iverson, G. L., & Lange, R. T. (2003). Examination of 'postconcussion-like' symptoms in a healthy sample. *Applied Neuropsychology*, 10(3), 137–144. doi: [10.1207/S15324826AN1003_02](https://doi.org/10.1207/S15324826AN1003_02)
- Karr, J. E., Areshenkoff, C. N., & Garcia-Barrera, M. A. (2014). The neuropsychological outcomes of concussion: A systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*, 28(3), 321–336.
- Koenen, K. C., Moffitt, T. E., Roberts, A. L., Martin, L. T., Kubzansky, L., Harrington, H., ... Caspi, A. (2009). Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. *American Journal of Psychiatry*, 166(1), 50–57. doi:[10.1176/appi.ajp.2008.08030343](https://doi.org/10.1176/appi.ajp.2008.08030343)
- Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, 16(9), 606–613. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11556941>
- Landrø, N. I., Stiles, T. C., & Sletvold, H. (in press). Neuropsychological function in nonpsychotic unipolar major depression. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 14(4), 233–240. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11725217>
- Lange, R. T., Iverson, G. L., Brooks, B. L., & Ashton Rennison, V. L. (2010). Influence of poor effort on self-reported symptoms and neurocognitive test performance following mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, 32(9), 961–972. doi:[10.1080/13803391003645657](https://doi.org/10.1080/13803391003645657)
- Lange, R. T., Iverson, G. L., & Rose, A. (2011). Depression strongly influences postconcussion symptom reporting following mild traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 26(2), 127–137. doi:[10.1097/HTR.0b013e3181e4622a](https://doi.org/10.1097/HTR.0b013e3181e4622a)
- Levin, H. S., Brown, S. A., Song, J. X., McCauley, S. R., Boake, C., Contant, C. F., ... Kotrla, K. J. (2001). Depression and posttraumatic stress disorder at three months after mild to moderate traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, 23(6), 754–769. doi:[10.1076/jcen.23.6.754.1021](https://doi.org/10.1076/jcen.23.6.754.1021)
- Lucas, S., Smith, B. M., Temkin, N., Bell, K. R., Dikmen, S., & Hoffman, J. M. (2016). Comorbidity of headache and depression after mild traumatic brain injury. *Headache: The Journal of Head and Face Pain*, 56(2), 323–330. doi:[10.1111/head.12762](https://doi.org/10.1111/head.12762)
- Manea, L., Gilbody, S., & McMillan, D. (2015). A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *General Hospital Psychiatry*, 37(1), 67–75. doi:[10.1016/j.genhosppsych.2014.09.009](https://doi.org/10.1016/j.genhosppsych.2014.09.009)

- McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology*, 24(1), 9–34. doi:[10.1037/a0017336](https://doi.org/10.1037/a0017336)
- Mitchell, A. J., Yadegarfar, M., Gill, J., & Stubbs, B. (2016). Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: A diagnostic meta-analysis of 40 studies. *British Journal of Psychiatry Open*, 2(2), 127–138. doi:[10.1192/bjpo.bp.115.001685](https://doi.org/10.1192/bjpo.bp.115.001685)
- van der Naalt, J., Timmerman, M. E., de Koning, M. E., van der Horn, H. J., Scheenen, M. E., Jacobs, B., ... Spikman, J. M. (2017). Early predictors of outcome after mild traumatic brain injury (UPFRONT): An observational cohort study. *The Lancet Neurology*, 16(7), 532–540. doi:[10.1016/S1474-4422\(17\)30117-5](https://doi.org/10.1016/S1474-4422(17)30117-5)
- Panczykowski, D. M., & Pardini, J. E. (2014). The multidisciplinary concussion management program. *Progress in Neurological Surgery*, 28, 195–212. doi:[10.1159/000358780](https://doi.org/10.1159/000358780)
- Rapoport, M. J., McCullagh, S., Shammi, P., & Feinstein, A. (2005). Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 17(1), 61–65. doi:[10.1176/jnp.17.1.61](https://doi.org/10.1176/jnp.17.1.61)
- Schretlen, D. J., & Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry (Abingdon, England)*, 15(4), 341–349. doi:[10.1080/09540260310001606728](https://doi.org/10.1080/09540260310001606728)
- Silver, J. M., McAllister, T. W., & Arciniegas, D. B. (2009). Depression and cognitive complaints following mild traumatic brain injury. *American Journal of Psychiatry*, 166(6), 653–661. doi:[10.1176/appi.ajp.2009.08111676](https://doi.org/10.1176/appi.ajp.2009.08111676)
- Tulsky, D. S., Carlozzi, N. E., Holdnack, J. A., Heaton, R. K., Wong, A., Goldsmith, A., & Heinemann, A. W. (2017). Using the NIH Toolbox Cognition Battery (NIHTB-CB) in individuals with traumatic brain injury. *Rehabilitation Psychology*, 62, 413–424. doi:[10.1037/rep0000174](https://doi.org/10.1037/rep0000174)
- Veiel, H. O. F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, 19(4), 587–603. doi:[10.1080/01688639708403745](https://doi.org/10.1080/01688639708403745)
- Wäljas, M., Lange, R. T., Hakulinen, U., Huhtala, H., Dastidar, P., Hartikainen, K., ... Iverson, G. L. (2014). Biopsychosocial outcome after uncomplicated mild traumatic brain injury. *Journal of Neurotrauma*, 31, 108–124. doi:[10.1089/neu.2013.2941](https://doi.org/10.1089/neu.2013.2941)
- Weintraub, S., Dikmen, S. S., Heaton, R. K., Tulsky, D. S., Zelazo, P. D., Bauer, P. J., ... Gershon, R. C. (2013). Cognition assessment using the NIH toolbox. *Neurology*, 80(11, Supplement 3), S54–S64. doi:[10.1212/WNL.0b013e3182872ded](https://doi.org/10.1212/WNL.0b013e3182872ded)
- Weintraub, S., Dikmen, S. S., Heaton, R. K., Tulsky, D. S., Zelazo, P. D., Slotkin, J., ... Gershon, R. (2014). The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: Validation in an adult sample. *Journal of the International Neuropsychological Society*, 20(6), 567–578. doi:[10.1017/S1355617714000320](https://doi.org/10.1017/S1355617714000320)
- West, L. K., Curtis, K. L., Greve, K. W., & Bianchini, K. J. (2011). Memory in traumatic brain injury: The effects of injury severity and effort on the Wechsler Memory Scale-III. *Journal of Neuropsychology*, 5(Pt 1), 114–125. doi:[10.1348/174866410X521434](https://doi.org/10.1348/174866410X521434)
- Whitney, K. A., Shepard, P. H., Williams, A. L., Davis, J. J., & Adams, K. M. (2009). The medical symptom validity test in the evaluation of operation Iraqi freedom/operation enduring freedom soldiers: A preliminary study. *Archives of Clinical Neuropsychology*, 24(2), 145–152. doi:[10.1093/arclin/acp020](https://doi.org/10.1093/arclin/acp020)
- Zakzanis, K. K., Leach, L., & Kaplan, E. (1999). *Neuropsychological differential diagnosis*. Swets & Zeitlinger. Retrieved from https://books.google.com/books/about/Neuropsychological_Differential_Diagnosis.html?id=1m7LDmFON5oC