January 2013

The Impact Of Pre-Injury Levels Of Depression Among Complicated And Uncomplicated Cases Of Mild Traumatic Brain Injury On Functional Outcomes 3 Months Post-Injury

Raj Kumar
Yale University, raj.kumar@yale.edu

Raj Kumar, MPH Candidate '13

The Impact of Pre-Injury Levels of Depression among Complicated and Uncomplicated Cases of Mild Traumatic Brain Injury on Functional Outcomes 3 months post-Injury

Acknowledgements:

Michael Bracken, PhD, Susan Dwight Bliss Professor of Epidemiology, Yale School of Public Health

Angelle Sander, PhD, Associate Professor, Baylor College of Medicine

Allison Clark, PhD, Assistant Professor, Baylor College of Medicine

Table of Contents:

Abstract:

Background:

The reason why people recover slowly, or fail to recover completely by three months following mTBI is not fully understood. Minimal research has focused on pre-injury depression as a risk factor for recovery after injury. There has also been minimal investigation of the interaction of pre-injury depression with structural brain damage, such as those evidenced on neuroimaging. This pilot study will prospectively examine the effect of pre-injury depression levels among complicated and uncomplicated cases of mTBI.

Methods:

Patients were recruited consecutively from the Emergency Room (ER) of Ben Taub General Hospital, in Houston, TX, from April 2000 to January 2004. Pre-injury depression was assessed using the Center for Epidemiological Studies-Depression Scale (CES-D) in the context of the month prior to injury. The outcome measures were assessed at approximately three months post-injury, and included affective/behavioral, physical, cognitive, and mental health components.

Results:

There were 186 (84%) that completed the follow-up interview at 3-months time. Using the CES-D total scores, the sample was categorized into 3 different levels of pre-injury depression, normal (CES-D <16), mild (CES-D 16-20), and moderate-severe (CES-D $\geq$ 21).

Compared to normal individuals, moderate-severely depressed mTBI patients report significantly worse symptoms on four of five measures. There was no association between mild depression and outcomes. The interaction of pre-injury depression level and complicated mTBI did not prove to be a significant predictor for any of the outcome measures.

Conclusion:

The data does suggest that moderate-severe pre-injury depression does appear to be a risk factor for poor affective/behavioral, cognitive, physical, and mental health outcomes at three months compared to normal individuals. However, patients with mild pre-injury depression are not at the same increased risk for worse outcomes. The data did not support an interaction effect between pre-injury depression and complicated mTBI. The primary limitation of this study is assessing depression up to 30 days prior to injury, shortly after the injury. More research to address this question should be the focus of future studies.

List of Tables:

Table 1: Selected Covariates by Level of Depression^ (n=186): Ben Taub Hospital, Houston, TX (April 2000 to January 2004)

Co-variate:	**Normal Depression**	**Mild Depression**	**Moderate/Severe Depression**	**P-value**
Age, mean (SD, range)	34.20 (12.3, 54.0)	29.00 (11.2, 41.0)	33.15 (11.1, 39.0)	0.672
Education (years), mean (SD, range)	10.78 (4.0, 20.0)	9.67 (3.7, 12.0)	10.70 (3.5, 18.0)	0.259
Gender, n (%)				0.161
Male	105 (80.2)	14 (77.8)	22 (64.7)	
Female	26 (19.9)	4 (22.2)	12 (35.3)	
Race, n (%) ^				0.089
White	20 (15.3)	1 (5.6)	5 (14.7)	
Black	24 (18.3)	6 (33.3)	13 (38.2)	
Hispanic	87 (66.4)	11 (61.1)	16 (47.1)	
Language, n (%)				0.059
Spanish	60 (45.8)	7 (41.2)	23 (67.7)	
English	71 (54.2)	10 (58.8)	11 (32.4)	
Involved in Litigation Trial, n(%)				0.156
Yes	26 (20.5)	4 (22.2)	2 (6.3)	
No	101 (79.5)	14 (77.8)	30 (93.8)	
Baseline GCS score, mean (SD, range)	14.95 (0.2, 1.0)	14.92 (0.3, 1.0)	14.89 (0.5, 2.0)	0.078
CT scan result, n (%)				
Positive	72 (55.8)	8 (47.1)	8 (25.0)	0.008*
Negative	57 (44.2)	9 (52.9)	24 (75.0)	

^= Measured by Center for Epidemiological Studies-Depression Scales (CES-D)
*=Statistically significant at α=0.05

Table 2: Selected Covariates by HI-FI PCL Score^(n=186): Ben Taub Hospital, Houston, TX (April 2000-January 2004)

Co-variate:	**Affective/Behavior: Mean (SD)**	**Cognitive: Mean (SD)**	**Physical Dependency: Mean (SD)**
Age,			
18-30	1.48 (1.6)	1.34 (1.5)	0.99 (1.2)
31-43	1.52 (1.8)	1.34 (1.7)	1.23 (1.5)
44-56	1.04 (1.1)	0.96 (1.36)	1.07 (1.2)
≥ 57	1.29 (2.0)	1.21 (2.24)	0.94 (1.4)
Gender,			
Male	1.30 (1.6)	1.20 (1.6)	1.08 (1.4)
Female	1.82 (1.7)	1.54 (1.5)	1.02 (1.0)
Race,			
White	1.23 (1.7)	1.26 (1.6)	0.96 (1.2)
Black	1.74 (1.7)	1.55 (1.7)	1.23 (1.4)
Hispanic	1.34 (1.6)	1.17 (1.5)	1.03 (1.3)
Language,			
Spanish	1.50 (1.7)	1.36 (1.6)	1.08 (1.3)
English	1.31 (1.5)	1.14 (1.5)	1.02 (1.2)
Education,			
Less than High School	1.43 (1.7)	1.18 (1.5)	0.97 (1.3)
High School Degree	1.38 (1.4)	1.26 (1.3)	1.33 (1.5)
Some College	1.56 (1.8)	1.55 (1.8)	1.00 (1.0)
College Degree	1.37 (1.9)	1.52 (2.4)	1.32 (1.7)
Graduate/ Professional Degree	0.45 (0.7)	0.61 (0.8)	0.67 (0.7)
Involved in Litigation Trial,			
Yes	2.28 (1.9)	1.87 (1.7)	1.64 (1.6)
No	1.23 (1.5)	1.17 (1.5)	0.94 (1.2)
Baseline GCS score			
13	0.43 (0)	0.22 (0)	0 (0)
14	2.04 (2.0)	1.63 (2.2)	2.10 (1.9)
15	1.29 (1.5)	1.07 (1.3)	1.00 (1.3)
CT scan result,			
Positive	1.21 (1.5)	0.97 (1.3)	0.93 (1.2)
Negative	1.65 (1.7)	1.58 (1.8)	1.21 (1.4)

^: The HI-FI Symptom Severity Scale ranges from an average score of 1-7, with higher average scores indicating more severe symptoms.

Table 3: Selected Covariates by SF-36 Summary Score^(n=186): Ben Taub Hospital, Houston, TX (April 2000-January 2004)

Co-variate:	SF-36 PCS*: Mean (SD)	SF-36 MCS¥: Mean (SD)
Age,		
18-30	46.9 (9.3)	51.3 (10.6)
31-43	45.7 (10.8)	49.3 (12.6)
44-56	45.9 (11.4)	54.1 (7.1)
≥ 57	43.4 (11.3)	52.1 (13.6)
Gender,		
Male	46.3 (10.4)	51.8 (10.9)
Female	45.8 (9.7)	48.7 (11.4)
Race,		
White	41.4 (10.5)	51.5 (11.1)
Black	43.7 (11.1)	48.6 (11.4)
Hispanic	48.3 (9.1)	52.0 (10.9)
Language,		
Spanish	43.3 (10.5)	50.3 (11.2)
English	49.3 (8.8)	52.1 (10.8)
Education,		
Less than High School	48.4 (9.4)	52.2 (10.9)
High School Degree	42.7 (11.0)	50.9 (10.6)
Some College	46.3 (10.0)	48.5 (11.5)
College Degree	44.2 (12.1)	50.3 (13.0)
Graduate/ Professional Degree	41.4 (8.0)	59.0 (3.3)
Involved in Litigation Trial,		
Yes	41.5 (11.5)	48.6 (12.5)
No	47.2 (9.8)	51.8 (10.7)
Baseline GCS score		
13	54.1 (0)	63.3 (0)
14	41.6 (11.0)	52.4 (11.7)
15	45.4 (10.4)	51.9 (11.3)
CT scan result,		
Positive	46.5 (9.7)	52.8 (11.3)
Negative	46.0 (10.8)	49.6 (10.9)

^The SF-36 score are on a scale of 0-100, where higher scores are indicative of more positive health perceptions
*PCS: Physical Component Summary
¥MCS: Mental Component Summary

Table 4: Multiple Linear Regression Model with Interaction term (n=186): Ben Taub Hospital, Houston, TX (March 2000-January 2004)

Outcome measure:	**^HI-FI: Affect/Behavior**		**^HI-FI: Cognitive**		**^HI-FI: Phys. Depend.**		**¥SF-36: PCS**		**¥SF-36: MCS**	
Explanatory variable:	Beta (SE)	P	Beta (SE)	P	Beta (SE) p	P	Beta (SE) p	P	Beta (SE) p	P
Age (years)	-0.006 (0.01)	0.54	-0.005 (0.01)	0.60	0.004 (0.01)	0.61	-0.091 (0.06)	0.14	0.030 (0.07)	0.70
Education (years)	0.009 (0.04)	0.82	0.066 (0.04)	0.07	0.045 (0.03)	0.14	-0.199 (0.23)	0.39	-0.017 (0.26)	0.95
Language										
Spanish	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
English	0.123 (0.29)	0.68	-0.106 (0.28)	0.71	-0.101 (0.24)	0.68	-5.606 (1.82)	0.0024*	-1.240 (2.08)	0.55
Litigation status										
No	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Yes	1.395 (0.32)	<0.001*	1.003 (0.30)	0.0012*	0.925 (0.26)	0.0005*	-8.271 (1.96)	<0.0001*	-4.850 (2.23)	0.03*
CT scan results										
Negative	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Positive	-0.098 (0.28)	0.73	-0.161 (0.27)	0.56	-0.010 (0.23)	0.96	-2.285 (1.75)	0.19	2.424 (1.77)	0.09
Depression Level										
Normal	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Mild	0.308 (0.58)	0.60	1.095 (0.56)	0.051	0.403 (0.48)	0.40	3.475 (3.58)	0.33	-4.922 (4.09)	0.23
Mod/Severe	1.293 (0.38)	0.001*	1.207 (0.37)	0.0013*	0.636 (0.32)	0.046*	-4.667 (2.37)	0.050*	-2.813 (2.71)	0.30
Interaction										
CT*Mild	0.208 (0.82)	0.80	-0.582 (0.79)	0.46	-0.002 (0.68)	0.99	-4.02 (5.06)	0.43	0.543 (5.78)	0.93
CT*Mod/Sev	-0.696 (0.75)	0.36	-0.532 (0.72)	0.46	-0.262 (0.62)	0.67	3.17 (4.64)	0.50	-8.044 (5.30)	0.13

*: Indicates statistical significance at the 0.05 level
^: The HI-FI Symptom Severity Scale ranges from an average score of 1-7, with higher average scores indicating more severe symptoms
¥: The SF-36 score are on a scale of 0-100, where higher scores are indicative of more positive health perceptions

Table 5: Sensitivity Analysis: Among only Uncomplicated mTBI Patients (n=91): Ben Taub Hospital, Houston, TX (March 2000-January 2004)

Outcome measure:	**^HI-FI: Affect/Behavior**		**^HI-FI: Cognitive**		**^HI-FI: Phys. Depend.**		**¥SF-36: PCS**		**¥SF-36: MCS**	
Explanatory variable:	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Age (years)	0.001 (0.02)	0.94	-0.0004 (0.01)	0.98	0.017 (0.01)	0.14	-0.193 (0.08)	0.02*	-0.011 (0.10)	0.91
Education (years)	0.075 (0.06)	0.24	0.111 (0.06)	0.09	0.035 (0.05)	0.48	0.162 (0.35)	0.65	-0.621 (0.42)	0.14
Language										
Spanish	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
English	-0.012 (0.44)	0.98	-0.290 (0.44)	0.52	0.013 (0.34)	0.97	-10.00 (2.43)	<0.0001*	4.120 (2.89)	0.16
Litigation status										
No	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Yes	1.240 (0.47)	0.001*	0.714 (0.47)	0.13	0.782 (0.36)	0.035	-8.818 (2.59)	0.001*	-2.890 (3.08)	0.35
Depression Level										
Normal	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Mild	0.352 (0.64)	0.58	1.091 (0.64)	0.09	0.390 (0.49)	0.43	3.387 (3.52)	0.33	-4.929 (4.18)	0.24
Mod/Severe	1.320 (0.43)	0.003*	1.199 (0.43)	0.007*	0.596 (0.33)	0.08	-3.980 (2.38)	0.10	-3.644 (2.82)	0.20

*: Indicates statistical significance at the 0.05 level
^**:** The HI-FI Symptom Severity Scale ranges from an average score of 1-7, with higher average scores indicating more severe symptoms
¥**:** The SF-36 score are on a scale of 0-100, where higher scores are indicative of more positive health perceptions

Table 6: Sensitivity Analysis: Among only Complicated mTBI Patients (n=90): Ben Taub Hospital, Houston, TX (March 2000-January 2004

Outcome measure:	**^HI-FI: Affect/Behavior**		**^HI-FI: Cognitive**		**^HI-FI: Phys. Depend.**		**¥SF-36: PCS**		**¥SF-36: MCS**	
Explanatory variable:	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Age (years)	-0.016 (0.014)	0.24	-0.012 (0.01)	0.32	-0.011 (0.01)	0.38	-0.013 (0.09)	0.89	0.132 (0.10)	0.19
Education (years)	-0.042 (0.04)	0.35	0.027 (0.04)	0.50	0.048 (0.04)	0.23	-0.521 (0.30)	0.09	0.551 (0.33)	0.10
Language										
Spanish	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
English	0.317 (0.39)	0.42	0.142 (0.35)	0.69	-0.109 (0.35)	0.76	-1.202 (2.71)	0.66	-8.09 (2.91)	0.007*
Litigation status										
No	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Yes	1.675 (0.32)	<0.001*	1.408 (0.38)	<0.001*	1.094 (0.38)	0.0054	-7.452 (2.92)	0.013*	-7.576 (3.14)	0.02*
Depression Level										
Normal	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Mild	0.377 (0.41)	0.47	0.404 (0.47)	0.40	0.255 (0.47)	0.59	0.267 (3.61)	0.94	-3.425 (3.89)	0.38
Mod/Severe	0.532 (0.33)	0.37	0.645 (0.53)	0.23	0.340 (0.53)	0.53	-1.871 (4.09)	0.65	-9.476 (4.40)	0.03*

*: Indicates statistical significance at the 0.05 level

^: The HI-FI Symptom Severity Scale ranges from an average score of 1-7, with higher average scores indicating more severe symptoms

¥: The SF-36 score are on a scale of 0-100, where higher scores are indicative of more positive health perceptions

Background:

Traumatic Brain Injury (TBI) is a leading cause of mortality and morbidity in the United States, and individuals of all ages, races, and income are affected. [1] Each year in the United States, roughly 1.4 million Americans suffer a TBI. Of these individuals, 1.1 million visit Emergency Departments (ED), 235,000 require extended hospitalization, and roughly 50,000 die as a result of injury.[2] However, it is noted that a survey analysis done in the late 1990's showed a 51% decrease in TBI-related hospital admissions from 1980 to 1995.[3] This is likely the result of a shift in care for less severe TBI cases from extended hospitalization to outpatient clinics.

The leading cause of TBI is falls, which account for 35.2% of cases.[4] Falls cause half (50%) of TBI's among children age 0 to 14, and 61% of TBI's among adults over age 65.[4] The second leading cause is motor vehicle accidents, which account for 17.3% of cases.[4] These types of injuries account for the largest percentage of TBI-related deaths. Another major cause of TBI's are struck by/against events, which include colliding with a moving or stationary object. This represents about 16.5% of TBI events. Assaults account for roughly 10% of cases of TBI.[5]

Although TBI can occur among any age, sex, or race, there are high risk groups. Males are nearly 60% more likely than females to suffer a TBI.[6] There exists a bimodal age distribution of cases of TBI, with children 0 to 14, and adults over 65 at the greatest risk for injury. Active military personnel and athletes are two particularly high risk groups, with blast injuries in combat and sports-related concussions being the most common source of injuries in these groups, respectively.[6]

Mild Traumatic Brain Injury (mTBI) cases account for roughly 80% of all TBI's. Individuals who have sustained a mTBI experience cognitive, physical, and emotional symptoms in the first few months post-injury[7]; however, 80-90% of patients recover to pre-morbid form

within three months after the injury.[8,9] Unfortunately, roughly 10-20% of individuals do not fully recover in all aspects within three months. [8,9] This subgroup of patients has been termed by researchers as the "miserable minority."[10] The reason why people recover slowly or fail to recover completely from mTBI is not fully understood. The family and societal burden that results from individuals not returning to pre-injury function, makes mTBI a significant public health and economic concern. In fact, it is estimated that the direct and indirect costs (i.e. loss of productivity) of TBI per year total an estimated $76.5 billion in the United States.[11]

Further, the major risk factors for poor recovery following mTBI identified in the literature include: a history of pre-existing physical limitations, prior neurological problems (e.g. stroke or epilepsy), previous brain injuries, and female sex.[12] One risk factor for recovery that has received limited research is the development of depression following mTBI.[13-15]

Much less work has been done in considering pre-injury depression as a risk factor for recovery after injury. Depression is a common and debilitating psychiatric disorder in the general population, affecting roughly 8% of Americans over 12 years old.[16] Persons who are depressed have feelings of sadness, loneliness, irritability, hopelessness, agitation, and guilt that may be accompanied by a myriad of physical symptoms.[17] The World Health Organization has recognized depression as the leading cause of disability worldwide.[18] The effect of pre-injury depression on recovery course among mTBI patients is currently unclear.

Ponsford et al.[8] studied this question, and found a subgroup of 24% of mTBI patients who still suffered symptoms at three months. These authors reported that individuals who had persistent problems were more likely to have a history of previous psychiatric issues or significant life stressors. They suggest that these continuing psychological problems will negatively affect a person's ability to cope with the injury, which leads to a greater persistence of

symptoms. It is noted that Ponsford and colleagues did not specifically explore pre-injury depression, but rather looked at psychological adjustment and concurrent life stress.

Rapoport et al.[19] examined the impact of major depression on outcome by prospectively following 170 mTBI patients that were admitted to a tertiary referral center for trauma patients. The patients were given a Structural Clinical Interview for DSM-IV (SCID) from a psychiatrist shortly after injury. They reported that 15.3% of their sample had major depression at the time of injury, and these individuals were more likely to have worse subjective and objective outcomes. Suhr & Gunstad[20] compared groups of patients with depression and brain injury, without depression and brain injury, depression without brain injury, and controls without brain injuries or depression, for neuropsychological and cognitive outcomes. The authors found that depression, not brain injury status, largely accounted for the elevation in cognitive symptom reporting.

On the contrary, other studies have failed to establish a significant association between pre-injury depression and outcomes. One case-control study found no significant difference in outcomes between pre-injury depressed and non-depressed patients on the reporting of somatic, cognitive, sensory, and affective symptoms at three months after injury.[21] Another prospective study found virtually no relationship between having a pre-injury psychiatric problem and having persistent physical, psychological, and behavioral outcomes.[22] Mooney et al.[23] retrospectively analyzed medical records and conducted patient interviews regarding pre-injury mental health conditions and found no significant association between pre-injury depression and post-injury disability, including physical, psychological, and behavioral symptoms.

In addition to the psychological aspects, mTBI has a notable neurological impact on the brain. The nature of mTBI is characterized by immediate physiological changes that can be

thought of as a multi-layered neuro-metabolic cascade that involves ionic shifts, abnormal energy metabolism, lower cerebral blood flow, and diminished neuro-transmission.[24] The most common method used in ED's today to assess neurological deterioration is the Computed Tomography (CT) scan.[25] There is a subgroup of patients known as "complicated" mTBI cases that are classified by neuroradiologists to have intracranial injuries that appear as space-occupying regions in a CT scan. The space occupying regions are the result of differences in density between these regions and adjacent brain tissue. [26] Larger volumes of the space-occupying regions are indicative of greater intracranial damage in that area.[26] Williams and colleagues[27] noted that these patients had similar 6-month outcomes to patients with moderate TBI. Iverson[28] analyzed a group of complicated cases, and matched uncomplicated individuals, for recovery following mTBI. The results from this study showed that individuals with complicated mTBI have generally slower recovery in the first few weeks post-injury. This finding is consistent with another study that also showed poorer cognitive and affective outcomes for complicated mTBI patients 2-3 months post-injury.[29] Despite some evidence of a slower recovery from injury among complicated cases of mTBI, CT scan results alone do not predict good or poor outcome in the majority of patients.[30]

The reason why some mTBI patients still show residual health issues three months after mTBI is not well understood. Mild brain injury is, by nature, a very heterogeneous disorder with each individual case being unique in both its etiology and symptom presentation.[31] Physicians and researchers in the field have devoted much effort to identifying high risk patients for poor recoveries. However, there is still little consistent evidence in the literature for any individual risk factor strongly predicting outcome.[7] An interaction of many factors: psychological, neurological, social, and contextual likely impact the reporting of symptoms.[32] Other extraneous

factors (e.g. litigation status) may also substantially bias symptom reporting although firm evidence for this is lacking.

With the purpose to better understand the impact of pre-injury depression on recovery following brain injury, the present pilot study prospectively followed consecutive mTBI patients admitted to a Level 1 County Trauma Center in Houston, Texas. The study measured overall recovery, including physical, mental, and cognitive health three months after injury. Although there have been other follow-up studies of hospital-admitted mTBI patients[8,19-23], the strengths of this study are its larger sample size, high follow-up rate, and consecutive injury patient recruitment from the ED rather than patients admitted to tertiary centers only for clinical reasons. The study also looked at the impact of being a complicated versus uncomplicated case of mTBI based on CT scan. The results also considered the litigation status of a patient at the time of follow-up.

Materials and Method:

The patients in this study were recruited consecutively from admission records from the Emergency Department (ED) of Ben Taub General Hospital, a Level I Trauma Center in Houston, TX, from April 2000 to January 2004. The inclusion criteria for the study required the patient to have sustained a mTBI as defined by the Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine.[33] This definition includes four main criteria: 1) any period of loss of consciousness (LOC), 2) any loss of memory for events immediately before or after the accident, 3) any alteration in mental status at the time of the accident, and 4) focal neurological deficits that may or may not be transient. For the current study, medical documentation of altered consciousness was required, as well as an initial Glasgow Coma Scale (GCS) score between 13-15 in the ED. For cases where the initial GCS

score was depressed by alcohol, anesthetics/sedation, or intubation, the GCS score upon emergence from the intoxicated or sedated state was used, up to 6 hours after injury.

Exclusion criteria included a history or diagnosis of the following conditions: a previous head injury requiring hospitalization, a central nervous system disorder affecting cognitive functioning (e.g. stroke, dementia, epilepsy) or a major diagnosed psychiatric disorder (e.g. schizophrenia or bipolar disorder). Homeless individuals or transient visitors to the Houston area were not included due to the anticipated difficulty in follow-up.

Of the 271 persons meeting eligibility criteria, 222 provided informed consent and completed a baseline assessment an average of 10 days after injury. Informed consent and assessment were conducted during the patient's hospital stay only when participants were adequately oriented, as defined by a score greater than 76 on the Galveston Orientation and Amnesia Test (GOAT). Participants who were not oriented prior to discharge home from the ED were consented to be contacted within 2 weeks.

Outcome measures (described below) were administered at three months post-injury. All measures were written in English or Spanish and administered orally to the participants by an English- or Spanish-speaking, trained research assistant. Of those who completed baseline assessment, 186 individuals were followed and assessed at three months time.

Baseline Measures:

Center for Epidemiological Studies-Depression Scales (CES-D)

The CES-D is a 20-item self-report scale that evaluates depressive symptoms in the general population. The scale was administered by a trained bilingual research assistant while the patient is in the hospital. Each of the patients received an anonymous patient number. The interviewer's were instructed to ask the questions as they appear on the scale, and only answer

questions pertaining to the task. The questions were chosen from a pool of previously validated depression scales. Patients were asked to rate their symptom severity as: 1) rarely or none of the time, 2) some or a little of the time, 3) occasionally or a moderate amount of time, 4) most or all of time. In this study, the questions were asked in the context of *30 days prior to injury*. The four factors represented in this scale are: depressed affect, positive affect, somatic problems and retarded activity, and interpersonal relationship problems, with an emphasis on depressed affect.[34] The scores range from 0-60, with higher scores reflecting greater symptoms of depression. In the clinical setting, scores less than 16 are considered normal, scores of 16 to 20 mild depression, 21 to 26 moderate depression, and greater than 26 severe depression.[35] In this analysis, moderate and severe depression were combined into one subgroup. The internal consistency (Cronbach's alpha statistic) of the CES-D has been estimated at 0.85 in the general population, and 0.90 in a psychiatric patient population.[36]

Outcome Measures:

Thirty-Six-Item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Health Component Summary (MCS)

The SF-36 is a 36-item measure of overall perceived health, with higher scores reflective of more positive health perceptions. The test is a generic measure, as opposed to a test that targets a specific age or disease type. The scores range from 0-100 (lowest to highest), with the median score being approximately 53 in the general population for both the PCS and MCS.[37] In this study, Physical and Mental health component scores were constructed from eight subscales. The PCS included items pertaining to self-care, physical, social activities, bodily pain, and energy levels. The MCS involved questions pertaining to psychological distress, social and role disability due to emotional problems.[38] The SF-36 has a construct-based interpretation, meaning

it answers questions about the underlying meaning of overall health concepts.[39] In the general population, the Cronbach's alpha statistic ranges from 0.89 to 0.94 for the Physical Component and 0.84 to 0.91 for the Mental Health Component score.[40]

Head Injury-Family Interview (HI-FI) Problem Checklist (PCL):

The PCL of the HI-FI is a checklist of symptoms (e.g. Poor Balance, Difficulty Planning and Organizing, Depression) that is meant for specific administration to the TBI population. The form of the scale has two parts, symptom endorsement and symptom severity. The symptom endorsement scale requires the patient to provide a "yes/no" response to the presence of a problem. The symptom severity component requires the patient to rate on a 1-to-7 Likert scale to the "extent of a problem the symptom presents to daily functioning", with 1 being the most mild, and 7 being the most severe. If a patient said "no" to the existence of the symptom, they will be automatically assigned a 0 on the severity scale. For this study, the symptom severity scale is utilized.

Based on a factor analysis, the PCL was classified into three-factors. Factor 1 contains 14 items representing Affective/Behavioral problems, factor 2 contains nine items that correspond to Cognitive problems, and factor 3 contains eight items that represent Physical/Dependency problems.[41] For this study, each of the three factors is considered as a separate outcome measure.

Data Analyses:

Those individuals that reported a 7 for *every* item of the HI-FI PCL: Problem Severity score of a given factor were removed as an outlier due to the likelihood of an over-endorsement of symptoms. This was a total of 2 subjects in the entire sample. No other outliers were identified for the baseline or outcome variables. In the multivariate regression analyses, the variation

inflation factors (VIF) and tolerance were well below the threshold for variable elimination. Thus, there is likely no meaningful multicollinearity in the model.

In order to determine the demographic characteristics of the sample, frequency measures were utilized for the categorical variables, and means were used for the continuous variables. To examine the association of pre-injury depression and CT scan results with mental, physical, and cognitive health outcomes three months post-injury, a series of hierarchical linear regression models were performed, controlling for the covariates of age, education, language, and litigation status. In order to put the two and three-level categorical variables into the multivariate model, they were dummy coded using n-1 variables. For example, for depression, the model included the mild and moderate-severe depression variables, using normal individuals as a reference. The variables in the model include: age, education, language, litigation status, CT scan result, mild depression, and moderate-severe depression. There was a regression model run for each of the following outcomes: HI-FI PCL Affect and Behavior Problem Severity score; HI-FI PCL Cognitive Problem Severity score; HI-FI PCL Physical Dependency Problem Severity score; SF-36 PCS; and SF-36 MCS. The data was analyzed using SAS 9.2.[42]

Results:

There were 221 participants who completed the baseline assessment. Of this cohort, 186 (84%) completed the follow-up interview at three months time. The average age of the cohort was 33.6 years with 144 males (77%) and 42 females. The sample consisted of 28 Whites (15%), 44 Blacks (24%), and 114 Hispanics (61%). The mean number of years of education for the cohort was 10.6 years, with 62% of the sample having an annual income less than $30,000. There were 121 patients (95%) with a baseline GCS score of 15, 6 with a GCS of 14, and 1 with a GCS of 13. There were 32 patients (18%) in the sample that were involved in litigation at the

three month follow-up. The sample is comprised of 91(50%) complicated and 90 uncomplicated cases of mTBI. There were five participants whose CT scan results were missing.

The detailed demographic information of the study population is provided in **Table 1**, stratified by level of depression. Using the CES-D total scores, the sample was categorized into three different levels of pre-injury depression. The majority of the cohort (72%) was considered normal (CES-D total score ≤ 15). The mildly (CES-D total score 16-20) and moderate-severely (CES-D total score ≥ 21) depressed group consisted of approximately 10% and 18% of the sample, respectively.

The mean values for the HI-FI PCL symptom severity (0-7 range) for selected covariates are given in **Table 2.** The mean HI-FI PCL among individuals with complicated mTBI is 1.21 (0-5.7 range) for Affective/Behavioral-related symptoms, 0.97 (0-5.9 range) for Cognitive-related symptoms, and 0.93 (0-5.4 range) for Physical Dependency measures. The mean HI-FI PCL among individuals with uncomplicated mTBI is 1.65 (0-7 range) for Affective/Behavioral-related symptoms, 1.58 (0-7 range) for Cognitive-related symptoms, and 1.21 (0-5.9 range) for Physical Dependency measures.

The mean values for the SF-36 (0-100 range) summary scale for selected covariates are given in **Table 3.** The mean SF-36 PCS among individuals with complicated mTBI is 46.5 (20.5-65.6 range), and SF-36 MCS is 52.8 (16.7-66.8 range). The mean SF-36 PCS among individuals with uncomplicated mTBI is 46.0 (14.8-65.7 range), and SF-36 MCS is 49.6 (20.0-65.7 range).

There were five separate hierarchical multiple regression models (**see Table 4)** run for the three subscales of the HI-FI PCL (Affect/Behavior, Cognitive, and Physical Dependency) and two subscales of the SF-36 (Physical and Mental Component Score). The models controlled for the covariates of age, education, language, and litigation status.

HI-FI Affective and Behavioral Symptom Severity:

There was a significant association between moderate-severe pre-injury depression and affective and behavioral outcomes (β=1.293, p=<0.001). There was no evidence of any significant difference among mild pre-injury depression compared to normal (β=0.308, p=0.60). The data did not support an interaction of pre-injury depression and CT scan results to affective-behavioral outcomes (β=-0.696, p=0.36). The litigation status of the patient at the three month follow-up was highly associated with symptom reporting (β=1.395, p=<0.001).

HI-FI Cognitive Symptom Severity:

The data showed an association between moderate-severe pre-injury depression and cognitive outcomes (β=1.207, p=0.0013). There was a modest, but non-significant, association between mild pre-injury depression and cognitive outcomes (β=1.095, p=0.051). There was no interaction between pre-injury depression and CT scan results for cognitive outcomes (β=-0.532, p=0.46). The litigation status of the patient at three-months was strongly associated with cognitive symptom reporting (β=1.003, p=0.0012).

HI-FI Physical Dependency Symptom Severity:

There was marginal significance between moderate-severe pre-injury depression and physical dependency outcome measures (β=0.636, p=0.046). There was no relationship between mild pre-injury depression and physical dependency outcomes (β=0.403, p=0.40). The data did not support an interaction between pre-injury depression and CT scan results and physical dependency outcomes (β=-0.262, p=0.67). The litigation status of a patient at three-months was strongly associated with physical dependency outcomes (β=-0.925, p=<0.001).

SF-36 Physical Component Summary (PCS):

There was a modest association between moderate-severe pre-injury depression and greater symptom reporting on the SF-36 PCS (β=-4.667, p=0.050). There was no association between mild pre-injury depression and SF-36 PCS outcomes (β=3.475, p=0.33). There also was no interaction between pre-injury depression and CT scan result and PCS outcomes (β=3.170, p=0.50). The litigation status of patients showed a strong relationship with PCS outcomes (β=-8.271, p=<0.001).

SF-36 Mental Component Summary (MCS):

The data did not support a significant association between moderate-severe pre-injury depression and SF-36 MCS outcomes (β=-2.813, p=0.30). There was also no relationship between mild pre-injury depression and SF-36 MCS outcomes (β=-4.922, p=0.23). There was no evidence of an interaction between pre-injury depression and CT scan result and MCS outcomes (β=-8.044, p=0.13). There was a significant association between the litigation status of a patient and SF-36 MCS outcomes (β=-4.850, p=0.03).

Sensitivity Analysis:

Due to the small cell sizes in the interaction terms, two post-hoc sensitivity analyses models were performed by stratifying the CT scan results as complicated or uncomplicated to test the robustness of the data. The same covariates as the full analysis were included, and the estimates (β) for the depression categorical variable were compared. Among only uncomplicated mTBI cases (**see Table 5**), the estimates for moderate-severe depression were nearly identical to the full analysis for the HI-FI PCL outcomes: Affective/Behavior (β=1.320) Cognitive (β=1.199), Physical Dependency (β=0.596). Similarly, the SF-36 outcomes among only uncomplicated cases were also nearly identical to the full analysis (PCS: β=-3.980; MCS: β=-3.644).

In the model among only complicated mTBI patients (**see Table 6**), the estimates for the HI-FI PCL and SF-36 scales deviated slightly from the estimates calculated in the full analysis, especially among those with moderate-severe pre-injury depression. The HI-FI PCL outcome estimates for moderate-severe pre-injury depression were: Affective/Behavior: β=0.532; Cognitive: β=0.645; Physical Dependency: β=0.340. The SF-36 outcome estimates for moderate-severe depression were: PCS: β=-1.871, MCS: β=-9.476.

Discussion:

Due to the heterogeneous nature of mTBI, it is important to consider recovery following brain injury in a larger context by examining a variety of factors. Depression, a leading cause of disability in itself, has been understudied as a pre-morbid risk factor for recovery following mTBI. This pilot study prospectively examined the impact of pre-injury depression levels among complicated and uncomplicated cases of mTBI, while controlling for socio-demographic and selected contextual covariates. The data suggests that moderate-severe pre-injury depression appears to be an independent risk factor for poor affective/behavioral, cognitive, physical, and mental health outcomes at three months compared to normal individuals. Patients with mild pre-injury depression are not at the same increased risk for worse outcomes.

The data did not support an interaction effect between pre-injury depression and complicated mTBI, as assessed by presence of structural damage on the CT scan. Although the interaction term in this study did not prove to be statistically significant, this could be an artifact of small cell sizes in the interaction term, as evidenced by the sensitivity analysis that showed somewhat different model estimates among complicated and uncomplicated patients. In order to study the interaction between pre-injury depression and post-injury neurological deterioration,

there is a need for future studies with larger sample sizes to have sufficient power to detect an association if one exists.

The litigation status of patients shows a strong association with worse self-reporting of outcomes. Litigation status has not been widely considered in this area of research but this possible source of reporting bias suggests it is highly advised that future studies account for this variable when using any self-report measures of symptoms.

The primary limitation of this study is actually assessing pre-injury depression (up to 30 days prior to injury), shortly after the injury. The results of this pilot study should thus be interpreted with caution as there is a substantial likelihood of reverse causality. The strong association between the litigation status of a patient and outcomes is further evidence that bias in self-report data is likely among the mTBI population.

It is also important to note that this study was conducted among a low socio-economic, low education, and largely Hispanic patient population. As a result, there may be issues with the generalizability of the results. However, the age and gender distribution in this patient population is very comparable to the general TBI population.[43]

With the aforementioned considerations in mind, there is still a need for necessary protocols in place in hospitals to identify patients *soon after brain injury* that are particularly at risk for poor long-term recoveries. This can potentially have a large impact on treatment planning for clinicians. For example, patients can be entered into Cognitive Behavioral Therapy (CBT) for the treatment of depression, which has shown some promising results in the TBI population.[44] There is also evidence that antidepressant therapy, such as the drug sertraline, a common selective serotonin reuptake inhibitor (SSRI), can result in significant improvements in cognitive symptoms for mTBI patients with depression.[45]

As previously emphasized, there is no consensus in the literature to why a subset of mTBI patients fail to recover completely in three months. The role of pre-injury depression as a risk factor to recovery has shown mixed results in the literature. Due to the high prevalence of depression in the general population, there is a need to understand its role in the rehabilitation process for mTBI patients. It is advised that future studies specifically examine the role of pre-injury depression and post-injury neurological deterioration to explain functional outcomes. It is necessary to find more objective ways to assess pre-injury depression, such as clinically diagnosed depression from medical records or family and spouse interviews. It is the hope that stronger evidence in this area will assist in a shift towards a more patient-focused treatment plan for mTBI patients instead of a one size fits all treatment that is common in hospitals today.[46]

References:

1. Coronado, V. G., Xu, L., Basavaraju, S. V., McGuire, L. C., Wald, M. M., Faul, M. D., ... & Hemphill, J. D. (2011). *Surveillance for traumatic brain injury-related deaths: United States, 1997-2007*. US Department of Health and Human Services, Centers for Disease Control and Prevention.

2. Corrigan, J. D., Selassie, A. W., & Orman, J. A. L. (2010). The epidemiology of traumatic brain injury. *The Journal of head trauma rehabilitation*, *25*(2), 72-80.

3. Thurman, D., & Guerrero, J. (1999). Trends in Hospitalization Associated with Traumatic Brain Injury. *JAMA*,*282*(10), 954-957.

4. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.

5. Coronado, McGuire, Faul, Sugerman, Pearson. The Epidemiology and Prevention of TBI (in press) 2012.

6. Langlois JA, Rutland-Brown W, Thomas KE. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths.* Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

7. Carroll L, Cassidy D, Peloso P, Borg J, van Holst H, Holm L, Paniak C, and Pepin M. (2004). "Prognosis for Mild Traumatic Brain Injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury." *Journal of Rehabilitation Medicine*. 43: 84-105.

8. Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, et al. (2000). Factors influencing outcome following mild traumatic brain injury in adults. *J of the International Neuropsychological Society*; 6: 568-79.

9. Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Psychiatry*, *18*(3), 301.

10. Ruff, R. M., Camenzuli, L., & Mueller, J. (1996). Miserable minority: emotional risk factors that influence the outcome of a mild traumatic brain injury. *Brain Injury*, *10*(8), 551-566.

11. Finkelstein E, Corso P, Miller T and associates. The Incidence and Economic Burden of Injuries in the United States. New York (NY): Oxford University Press; 2006.

12. Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. *BMJ* 2000; 320: 1631–1635.

13. Jorge, R., Robinson, R., Moser, D., Tateno, A., Crespo-Facorro, B., & Arndt, S. (2004). Major Depression Following Traumatic Brain Injury. *Arch Gen Psychiatry*, 61, 42-50.

14. Busch, C., & Alpern, H. (1998). Depression After Mild Traumatic Brain Injury: A Review of Current Research. Neuropsychology Review,8(2), 95-108.

15. Mathias, J & Coats, J. (1999). Emotional and Cognitive Sequelae to Mild Traumatic Brain Injury. *Journal of Clinical and Experimental Neuropsychology, 21(2),* 200-215.

16. "QuickStats: Prevalence of Current Depression* Among Persons Aged â‰¥12 Years, by Age Group and Sex — United States, National Health and Nutrition Examination Survey, 2007–2010." *Centers for Disease Control and Prevention.* N.p., n.d. Web. 19

Apr. 2013.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6051a7.htm?s_cid=mm6051a7_w>.

17. Scale, R. C. D., Scale, R. A. D., BDI, B. D. I., Inventory-II, B. D., Inventory-PC, B. D., Scale, E. P. D., ... & Scale-short, G. D. (2002). Screening for depression across the lifespan: a review of measures for use in primary care settings. *Am Fam Physician*, *66*(6), 1001-1009.

18. Lopez AD, Murray C. The global burden of disease, 1990–2020. Nature Med 4(11):1241–3. 1998.

19. Rapoport, M., McCullagh, S., Streiner, D., & Feinstein, A. (2003). The Clinical Significance of Major Depression Following Mild Traumatic Brain Injury. *Psychosomatics*, 44(1), 31-27.

20. Suhr, J. A., & Gunstad, J. (2002). Postconcussive symptom report: the relative influence of head injury and depression. *Journal of Clinical and Experimental Neuropsychology*, *24*(8), 981-993.

21. Cicerone, K., & Kalmar, K. (1997). Does premorbid depression influence post-concussive symptoms and neuropsychological functioning? *Brain Injury*, 11(9), 643-648.

22. Mooney, G., & Speed, J. (2001). The association between mild traumatic brain injury and psychiatric conditions. *Brain Injury*, 15(10), 865-877.

23. Mooney, G., Speed, J., & Sheppard, S. (2005). Factors related to recovery after mild traumatic brain injury. *Brain Injury*, *19*(12), 975-987.

24. Nortje, J., & Menon, D. K. (2004). Traumatic brain injury: physiology, mechanisms, and outcome. *Current opinion in neurology*, 17(6), 711.

25. Brown, C. V., Weng, J., Oh, D., Salim, A., Kasotakis, G., et al. (2004). Does routine serial computed tomography of the head influence management of traumatic brain injury? A prospective evaluation. *The Journal of Trauma and Acute Care Surgery, 57*(5), 939-943.

26. Lee, B., & Newberg, A. (2005). Neuroimaging in traumatic brain imaging. *NeuroRx, 2*(2), 372-383.

27. Williams DH, Levin HS, Eisenberg HM. (1990). Mild head injury classification. *Neurosurgery*; 27: 422-28.

28. Iverson G. (2006). Complicated vs. uncomplicated mild traumatic brain injury: Acute neuropsychological outcome. *Brain Injury*; 20: 1335-1344.

29. Borgaro SR, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. *Brain Injury* 2003;17:189–198.

30. Iverson GL, Franzen MD, Lovell M, Smith S. Complicated vs. uncomplicated mild head injury. *Journal of the International Neuropsychology Society*. 1998;4:75.

31. Ruff, R, and P Jurica. (1999). "In Search of a Unified Definition for Mild Traumatic Brain Injury." *Brain Injury* 13.12: 943-952.

32. Mooney, G., Speed, J., & Sheppard, S. (2005). Factors related to recovery after mild traumatic brain injury. *Brain Injury*,19(12), 975-987.

33. Kay T, Harrington DE, Adams R, et al. (1993). Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 8: 86-87.

34. Smarr, K., & Keefer, A. (2011). Measures of Depression and Depressive Symptoms. *Arthritis Care & Research*, 63(S11), S454-S466.

35. Zich, J., Attkisson, C., & Greenfield, T. (1990). Screening for Depression in Primary Care Clinics: The CES-D and the BDI . *The International Journal of Psychiatry in*

Medicine, 20, 259-277.

36. Radloff LS. The CES-D Scale: a self-report scale for research in the general population. *Appl Psychol Meas* 1977; 1: 385-401.

37. "SF-36 ." *Population Norms*. N.p., n.d. Web. 31 Mar. 2013. <www.sf-36.org/research/sf98norms.pdf>.

38. Ware Jr, J. E. (2000). SF-36 health survey update. *Spine*, *25*(24), 3130-3139.

39. Ware, J. E., Kosinski, M., Dewey, J. E., & Gandek, B. (2000). *SF-36 health survey: manual and interpretation guide*. Quality Metric Inc..

40. Ware JE, Kosski M, Keller SD. (2004) *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: The Health Institute.

41. Kay, T., Cavallo, M., Ezrachi, O., & Vavagiakis, P. (1995). The Head Injury Family Interview: A clinical and research tool. *Journal of Head Trauma Rehabilitation*, 10(2), 12-31.

42. SAS Institute Inc. 2010. SAS ® 9.2 Language Reference: Concepts, Second Edition. Cary, NC: SAS Institute Inc.

43. Thurman, D. J., Alverson, C., Dunn, K. A., Guerrero, J., & Sniezek, J. E. (1999). Traumatic brain injury in the United States: a public health perspective. *The Journal of head trauma rehabilitation*, *14*(6), 602-615.

44. Khan-Bourne, N., & Brown, R. G. (2003). Cognitive behaviour therapy for the treatment of depression in individuals with brain injury. *Neuropsychological Rehabilitation*, *13*(1-2), 89-107.

45. Fann, J. R., Uomoto, J. M., & Katon, W. J. (2001). Cognitive improvement with treatment of depression following mild traumatic brain injury. *Psychosomatics*, *42*(1), 48-54.

46. Thompson, H. J., McCormick, W. C., & Kagan, S. H. (2006). Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. *Journal of the American Geriatrics Society*, *54*(10), 1590-1595.