

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study
<b>AUTHORS</b>	Ma, Hon-Ping; Ou, Ju-Chi; Yeh, Chun-Ting; Wu, Dean; Tsai, Shin-Han; Chiu, Wen-Ta; Hu, Chaur-Jong

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Barry J. Hoffer and Jonathan Miller Case Western Reserve University School of Medicine
<b>REVIEW RETURNED</b>	31-Oct-2013

<b>GENERAL COMMENTS</b>	<p>This is an interesting study of the sequelae of mild (m) TBI in a Taiwan population. The study shows data from a relatively large number of subjects, no doubt because of the extensive clinical data registry system in that country. While the data appear quite solid and the analysis is sound, there are some additional consideration that should be explored in the Discussion.</p> <p>In this article, the authors measured depression, anxiety, and sleep in patients who suffered mild traumatic brain injury (mTBI) at baseline (250 patients) and after 6 weeks (100 patients) using four subjective but validated scales for anxiety (Beck Anxiety Inventory), depression (Beck Depression Inventory), daytime sleepiness (Epsworth Sleepiness Scale), and sleep quality (Pittsburgh Sleep Quality Index). These results were compared with data from 100 healthy individuals. mTBI patients were found initially to suffer significantly worse sleep quality, depression, and anxiety, but sleep quality was not significantly different from the control group after six weeks, while depression and anxiety scores were still worse. Daytime sleepiness was not altered either at baseline or six weeks. The authors conclude that recovery of sleep disturbance after mTBI occurs more rapidly than depression or anxiety.</p> <p>This is an interesting study of the sequelae of mild (m) TBI in a Taiwan population. The study shows data from a relatively large number of subjects, no doubt because of the extensive clinical data registry system in that country. It is of interest that more women than men participated in the study, since in western countries, particularly the USA, there are significantly more men than women who suffer mTBI. The findings of the study are novel and have</p>
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	<p>important implications for the study of recovery after mTBI.</p> <p>While the data appear quite solid and the analysis is sound, there are some additional consideration that should be explored in the Discussion.</p> <ol style="list-style-type: none"> <li>1. In view of the changes in sleep quality, was there any specific data about REM vs non REM (i.e. dreaming, periods of working during the sleep period, etc). Certainly REM depravation could generate some of the symptoms of depression and anxiety reported here.</li> <li>2. The types of mTBI (transportation, falls) are of the concussive type. Were any participants subject to an industrial accident when blast over/under pressure would be the cause.</li> <li>3. The earlier recovery in sleep quality after mTBI is interesting, but it is worth noting that the measured sleep dysfunction in the control group (average score 5.7) is much higher than previously published values for healthy individuals (average score 2.7). [Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. <i>Psychiatry Res.</i> 1989 May;28(2):193-213] This should be discussed.</li> </ol> <p>Minor points:</p> <p>Abstract: line 10disturbances <u>has</u> (not have)</p> <p style="padding-left: 40px;">line 47      <u>diminished</u> (not diminishes)</p> <p>Results: p6 line 26      The value of 1.81 is the difference from TBI baseline, not the absolute value</p> <p style="padding-left: 40px;">p5 line 47      <u>participates</u> not participant</p>
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<b>REVIEWER</b>	Chung-Yao Hsu, MD, PhD Department of Neurology and Sleep Disorders Center, Kaohsiung Medical University, Kaohsiung, Taiwan
<b>REVIEW RETURNED</b>	31-Oct-2013

<b>GENERAL COMMENTS</b>	This is a large-scaled prospective case-control observational study investigating short-term recovery of sleep quality, daytime sleepiness, depression and anxiety in patients with minor traumatic brain injury. The results show faster recovery of sleep quality than
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	<p>recovery of depression and anxiety. This is an interesting finding and has been well discussed in the manuscript. The only concern is inadequate presentation and bias in statistical analysis described below.</p> <p>In statistical part, the authors mentioned that both parametric and non-parametric analysis were used. Unfortunately there is no description about which statistical method was used for which outcome variables. Based on the figure and knowledge in sleep medicine, data of PSQI for sleep quality and data of ESS for daytime sleepiness are not normally distributed. Linear regression was used in this manuscript for adjusting sex and age taking difference of PSQI and ESS as dependent variables are biased. Difference of PSQI and ESS are probably not normally distributed. Thus the major results showing statistical significance should be doubted.</p>
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### VERSION 1 – AUTHOR RESPONSE

Comments of Professor Barry J. Hoffer and Jonathan Miller

1. In view of the changes in sleep quality, was there any specific data about REM vs non REM (i.e. dreaming, periods of working during the sleep period, etc). Certainly REM deprivation could generate some of the symptoms of depression and anxiety reported here.

We thank reviewers' valuable comments. REM sleep does play an important role in mood disorders. The changes of REM sleep after mTBI are still controversial. This is certainly a major issue for study. However, in our study, sleep architecture was not measured. We have incorporated this point of view and describe this limitation into the discussion session. (page 8) Thanks again.

2. The types of mTBI (transportation, falls) are of the concussive type. Were any participants subject to an industrial accident when blast over/under pressure would be the cause.

No participant of this study had his mTBI due to industrial accident when blast over/under pressure. We have provided more information about the causes of mTBI in the discussion, page 7.

3. The earlier recovery in sleep quality after mTBI is interesting, but it is worth noting that the measured sleep dysfunction in the control group (average score 5.7) is much higher than previously published values for healthy individuals (average score 2.7). [Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989 May;28(2):193-213] This should be discussed.

We thank reviewers' valuable comments. In 2005, Tsai et al [reference 13] conducted a study by use of Chinese version of PSQI (CPSQI) and the average score in control group was 5.73, which is very close to our result. The discussion about the score difference is in page 7 and 8.

Minor points:

Abstract: line 10, disturbances has (not have), line 47 diminished (not diminishes)

Results: p6 line 26, The value of 1.81 is the difference from TBI baseline, not the absolute value, p5 line 47, participates not participant

We thank reviewers' help. We have corrected the errors.

Comments of Professor Chung-Yao Hsu

1. In statistical part, the authors mentioned that both parametric and non-parametric analysis were used. Unfortunately there is no description about which statistical method was used for which outcome variables.

We thank the reviewer for valuable comments. We have clarified and corrected the statistic methods in page 5.

2. Based on the figure and knowledge in sleep medicine, data of PSQI for sleep quality and data of ESS for daytime sleepiness are not normally distributed. Linear regression was used in this manuscript for adjusting sex and age taking difference of PSQI and ESS as dependent variables are biased. Difference of PSQI and ESS are probably not normally distributed. Thus the major results showing statistical significance should be doubted.

We thank the reviewer for valuable comments. We have redone the statistic analysis by use of generalized linear regression and mentioned this change in statistic method. Please see page 5 and Table 4. The results are the same.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Chung-Yao Hsu, MD, PhD Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
<b>REVIEW RETURNED</b>	28-Nov-2013

<b>GENERAL COMMENTS</b>	<p>I am not quite understanding the "table 4". What does the title "coefficients of generalized linear model between control participants and mTBI patients at baseline and 6 weeks post-injury" mean? Is it presented properly?</p> <p>This study focused on sleep disturbance in minor traumatic brain injury. It shows that sleep quality recovers more quickly than than anxiety and depression at six weeks. The findings are interesting and contributory in case the statistical method can be justified.</p>
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#### VERSION 2 – AUTHOR RESPONSE

We thank the reviewer for valuable comment. The title of Table 4 is revised to "Generalized linear regression coefficient estimates of four measurements in controls and mTBI patients at baseline and 6 weeks post-injury". The details of generalized linear model could be found in McCullagh, Peter and Nelder, John (1989). Generalized Linear Models, Second Edition. Boca Raton: Chapman and Hall/CRC'.