AWARD NUMBER: W81XWH-15-1-0603

TITLE: Why does acute post whiplash injury pain transform into chronic pain? Multi-modal assessment of risk factors and predictors of pain chronification

PRINCIPAL INVESTIGATOR: David Yarnitsky, Ph.D.

CONTRACTING ORGANIZATION: Technion Research and Development Foundation
Haifa, AE 31096 IL

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Fort Detrick, Maryland 21702-5012

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Why does acute post whiplash injury pain transform into chronic pain? Multi-modal assessment of risk factors and predictors of pain chronification

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5b. GRANT NUMBER:
W81XWH-15-1-0603

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Principal Investigator - Prof. David Yarnitsky, email: d_yarnitsky@rambam.health.gov.il

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Technion – Research and Development Foundation (TRDF),

Faculty of Medicine,
POB 9649, Haifa, Israel, Zip code: 31096

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT :

This project aim to find why some acute mTBI patients turn into chronic pain patients, and other do not. We recruit patients immediately after the accident, and get them through clinical, pshcyophysical and psychological assessment, brain MRI, EEG, and genetic tests. We then follow up on the pain levels along one year. All clinical work is done in Israel, analysis is done in cooperation with leading teams in the US, Canada and Australia. So far we recruited 346 patients, 196 of them participated in the first visit within 72 hours after the accident, 155 participants answered the 3 months follow up questions, 141 answered the 6 months, and 101 answered the 12 months follow up questions. 52 participated in the 6 months visit and 42 participated in the 12 months visit, of which 18 participants were tested in both sessions.

Based on our results so far, we can conclude:

a. In the hyper-acute post-mTBI stage the somatosensory changes are independent of the psychological state of the patients; despite normal psychological profile, the mTBI patients demonstrate pro-nociceptive pattern of psychophysical responses already at hyper-acute post-traumatic stage. In the context of the ongoing debate on the pathophysiological nature of the post-mTBI syndrome, our findings support its 'physical basis', free of mental influence, at least in the short time window after the injury.

b. On the clinical, demographic and psychophysical domains, chronic post-traumatic pain occurrence is predicted by acute head pain, low socioeconomic status and higher activity of central pain facilitatory pathways as reflected by enhanced summation of experimental pain perception Our results also indicate that throughout the year patients continue to express more pain in the neck, and females remain with higher levels of pain.

c. Patients age does seem to affect symptom development. Older patients (aged 36 and above) enter their chronic level of pain already at 1-month post-accident, and those younger than that only at 3-months post-injury. Seeing as baseline pain values remain predictive of subsequent pain it reinforces the need to be attuned to patients' self-reported pain at the time of injury and the importance for pain intervention within the first month post-accident in older patients with the hope of averting pain chronicity.

d. On the neurophysiological domains, baseline EEG activity predicts incidence and intensity of chronic post-traumatic pain. More specifically, higher EEG resting-state alpha power significantly associated with chronic headache and neck pain. Moreover, based on the parameters of intra-cortical connectivity, the patients that developed chronic pain had higher synchronization between the activity of pain-processing brain areas.

15. SUBJECT TERMS-

Mild traumatic brain injury, Pain perception, Pain modulation, fMRI, EEG, Chronic pain, Acute pain, Whiplash injury

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
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1. INTRODUCTION:

The study aims to explore why acute pain turns, in some patients, into chronic pain, and to develop tools for prediction of this transition. We use mild traumatic brain injury as our work model, to study which of the factors measured in the acute whiplash pain phase, influence the chronification of head and neck pain in these patients**.** Our objective is to construct a specific and sensitive tool, based on a broad assessment of pain modulation parameters obtained during acute pain, which allows understanding of the underlying mechanisms relevant for prediction of the transition to the chronic phase. This is a prospective, non-intervening, longitudinal study. Participants with mild traumatic brain injury are recruited when visiting the Rambam Health Care Campus ER immediately after the injury. Psychophysical, neurophysiological, psychological, imaging and genetic data are being collected within 72 hours. Patients are being followed up for one year.

2. KEYWORDS:

Mild Traumatic brain injury, Pain perception, Pain modulation, fMRI, EEG, Chronic pain, Acute pain, Whiplash injury

3. OVERALL PROJECT SUMMARY:

Tasks outlined in the approved SOW during year 3:

The study was first approved by Local IRB and director of the institution ("form 7") on 11/Oct/2015, and approved by the HRPO on 7/Mar/2016. Continuing review report was submitted and approved by the local IRB and HRPO every year.

Patients recruitment and experimental performance:

We started recruiting immediately after HRPO first approval on March 2016.
First subject was recruited on 31/Mar/2016.

Up to date, we recruited 346 patients, 196 of them participated in the first visit performed within 72 hours after the accident, and additional 63 patients participated in genetics data collection (blood samples and pain ratings during the follow up period). 155 participants answered the 3 months follow up questions, 141 answered the 6 months, and 101 answered the 12 months follow up questions. 52 participated in the 6 months visit and 42 participated in the 12 months visit, of which 18 participants were tested in both sessions.
The rest failed to continue with the protocol after giving their consent and are dropouts.

In order to further potentiate the consenting, recruitment and follow-up testing, we hired several research assistants and two physicians, which are responsible for recruitments and follow up.

By the end of Year 3, we submitted the request for extension without additional funding that was approved on Sep 2018.

Quad chart was updated again and changed according to the extension and is attached as an appendix A.

During November and December 2017, we had an internal audit by Rambam's research authority who checked our study files. All findings were minor, and recommendations were accepted, corrected and documented by the study team.

Regarding the experimental performance:
250 Blood samples were transferred to the genomic lab, and DNA was extracted. They have processed 250 DNA samples using SNP chips according to the manufacture protocol. BeadChips were then scanned. SNP QC for all samples was excellent with call rate above 99% of SNPs genotype. Data was shared with sub investigator Dr. Luda Diatchenko and her team. According to the bioinformaticists that looked through all the data, it is a good quality data, and will be analyzed when the group of samples will be higher.
We asked to add collection of RNA tubes on Feb 2018, and was approved together with the request for extension without additional funding's.

MRI scans were saved and backed up, as well as shared with sub investigator Prof. Vania Apkarian at Northwestern University, for analyzing and processing. The MRI team has been putting the data through the pre-processing pipeline, with the aim of cleaning up the data quality and identifying any missing scans. One of our PhD students associated with this project visited Apkarian's lab and learned and helped with the analysis of the imaging data.

Task 3. Patients follow-up:
3a. We collect data on clinical pain and analgesics consumption once a month, using a smart-phone application or personal phone-based follow-up along 1 post-recruitment year. All the participants requested to follow our pain scale application and report their pain rates during the first year following the accident. Those who cannot use the smart phone application, answer our pain questions on personal phone calls. 155 participants answered the 3 months follow up questions, 141 answered the 6 Months, and 101 answered the 12 months questions.

3b. Visits 6 and 12 months: 52 participated in the 6 months visit and 42 participated in the 12 months visit, of which 18 participants were tested in both sessions.
We realized that patients are not interested to participate in the follow up visits since the visit interferes with their work or other schedule, as opposed to the first visit where during the sick leave. Therefore, we added compensation for their time loss, and the number of completed follow up visits was increased.
3c. No additional visits were done at patient's demand in our special dedicated hospital clinic.

Task 4. Interim data analyses:
4a. Initial interim data was done during the last months. It is noted that by looking at cumulating follow up data, it seems that number of chronic pain patients exceeds the expected 20%. Since our initial recruiting numbers plan was based on a minimum of 20% chronic pain sufferers out of all our patients, we might be able to reach solid conclusion based on lower numbers of overall recruiters.

Analysis of QST and Selected Questionnaires, as well as analysis of Resting State EEG and pain-evoked potentials has been performed for most of the data collected.
Analysis of pain progression for the first year post injury has been performed for patients who have reached one year post injury. In addition prelimanary analysis has been done on clinical dtat collected during the 6 months follow up visits.

The preliminary results, abstracts to conferences and accepted papers are detailed below in sections 4, 5 and 7.

4b. Ongoing review of quality of the imaging data is performed by the team at Northwestern University, USA.

4c. Ongoing review of psychophysical and neurophysiological data is performed by our team at the Technion as well as the sub investigator at University of Haifa, Israel.

4d. Consultation regarding the psychological data is done by the team at Griffith University, Australia.

During a meeting with all PIs and their study team, on Sep 13 2018, during the IASP meeting, we decided that each group would analyze its data together with pain profile, demographics, psychophysical and neurophysiological data. After the initial analysis performed by each group (MRI, EEG, Genetics) we will perform a comprehensive analysis of our data using the big data methodology models.

4. KEY RESEARCH ACCOMPLISHMENTS:

Several abstracts to scientific meetings were submitted:

Abstract 1. Kuperman et al "Acute head pain, low socioeconomic status and less-efficient CPM predict post-whiplash chronic pain occurrence". The poster presentation was accepted to the 10th Congress of the European Pain Federation, EFIC in September 2017.

Abstract 2. Granovsky et al "Whiplash- associated pain chronification; the predictive role of resting stage EEG Alpha power and acute pain". The poster presentation was accepted to the 10th Congress of the European Pain Federation, EFIC in September 2017.

Abstract 3. Kuperman et al "Age as a predictive factor for post-mTBI pain chronification timeline". The poster presentation was accepted to the 2018 IASP in Boston.

Several months ago we published a first paper from this study: “Psychophysical-psychological dichotomy in very early acute mTBI pain: A prospective study”. The paper was published in Neurology. This work presented the results of QST, demographic and pain-related psychological variables from the first 100 patients comparing them to the data from a group of 80 healthy controls. This paper shows that the observed somatosensory changes in the hyper-acute post-mTBI stage are independent of the psychological state,

thus supporting the organic basis of the WAD clinical picture, at least in this time window.

Another paper now is in the final stages of preparation: "Post mTBI pain chronification: the effect of age". This paper aims to investigate whether behavior of pain along the first year after mild traumatic brain injury depends on age. Our results show that the pain level in the older patients' pain stabilizes within a month from injury, whereas in younger patients, the pain levels decrease, and stabilize only after the third month. This suggests that therapeutic interventions should be most successful if administered within the age-relevant time window.

The papers and abstracts are copied below in appendix 12

5. CONCLUSION:

Based on our results so far, we can conclude:

e. In the hyper-acute post-mTBI stage the somatosensory changes are independent of the psychological state of the patients; despite normal psychological profile, the mTBI patients demonstrate pro-nociceptive pattern of psychophysical responses already at hyper-acute post-traumatic stage. In the context of the ongoing debate on the pathophysiological nature of the post-mTBI syndrome, our findings support its 'physical basis', free of mental influence, at least in the short time window after the injury.

f. On the clinical, demographic and psychophysical domains, chronic post-traumatic pain occurrence is predicted by acute head pain, low socioeconomic status and higher activity of central pain facilitatory pathways as reflected by enhanced summation of experimental pain perception Our results also indicate that throughout the year patients continue to express more pain in the neck, and females remain with higher levels of pain.

g. Patients age does seem to affect symptom development. Older patients (aged 36 and above) enter their chronic level of pain already at 1-month post-accident, and those younger than that only at 3-months post-injury. Seeing as baseline pain values remain predictive of subsequent pain it reinforces the need to be attuned to patients' self-reported pain at the time of injury and the importance for pain intervention within the first month post-accident in older patients with the hope of averting pain chronicity.

h. On the neurophysiological domains, baseline EEG activity predicts incidence and intensity of chronic post-traumatic pain. More specifically, higher EEG resting-state alpha power significantly associated with chronic headache and neck pain. Moreover, based on the parameters of intra-cortical connectivity, the patients that developed chronic pain had higher synchronization between the activity of pain-processing brain areas.

6. CHANGES/ PROBLEMS

By the end of Year 3 we asked for extension without additional funding, that was approved on Sep 2018.

We asked to add collection of RNA tube that was approved together with the request for extension.

7. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

"Psychophysical-psychological dichotomy in very early acute mTBI pain: A prospective study ".Kuperman P, Granovsky Y, Granot M, Bahouth H, Fadel S, Hyams G, Ben Lulu H, Aspis O, Salame R, Begal J, Hochstein D, Grunner S, Honigman L, Reshef M, Sprecher E, Bosak N, Sterling M, Yarnitsky D. Neurology. 2018 Sep 4;91(10):e931-e938. doi: 10.1212/WNL.0000000000006120. Epub 2018 Aug 1.

Abstract 1. Kuperman et al "Acute head pain, low socioeconomic status and less-efficient CPM predict post-whiplash chronic pain occurrence". The poster presentation was accepted to the 10th Congress of the European Pain Federation, EFIC in September 2017.

Abstract 2. Granovsky et al "Whiplash- associated pain chronification; the predictive role of resting stage EEG Alpha power and acute pain". The poster presentation was accepted to the 10th Congress of the European Pain Federation, EFIC in September 2017.

Abstract 3. Kuperman et al "Age as a predictive factor for post-mTBI pain chronification timeline". The poster presentation was accepted to the 2018 IASP in Boston.

The papers and abstracts are copied below in appendix B.

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Prof. David Yarnitsky (Technion)
Project Role:	PI
Researcher Identifier:	ORCID ID: 0000-0002-2293-2090
Nearest person month worked:	3
Contribution to Project:	Prof. Yarnitsky has performed work in the area of supervising and advising all study activities mentioned above in section 1 "Accomplishments", in addition to recruitment of subjects.

Name:	Dr. Yelena Granovsky (Technion)
Project Role:	CI
Researcher Identifier:	Research gate name: Yelena Granovsky
Nearest person month worked:	1
Contribution to Project:	Dr. Granovsky completed the IRB submissions, HRPO submissions, stuff training to PhD students. Dr. Granovsky is responsible for analyzing the psychophysical and neurophysiological data collected in this study.

Name:	Prof. Michal Granot (Haifa University)
Project Role:	CI
Researcher Identifier:	ORCID ID: 0000-0002-5105-1209
Nearest person month worked:	1
Contribution to Project:	Prof. Granot is responsible for the work in the area of psychophysics and neurophysiology data analysis related to our study.

Name:	Prof. A Vania Apkarian (Northwestern University)
Project Role:	CI
Researcher Identifier:	ORCID ID: 0000-0002-9788-7458
Nearest person month worked:	1
Contribution to	Prof. Apkarian approved the MRI protocol and scans. He is

Project:	responsible for the work in the area of Imaging.
Name:	Dr. Luda Diatchenko (McGill University)
Project Role:	CI
Researcher Identifier:	ORCID ID: 0000-0002-1350-6727
Nearest person month worked:	1
Contribution to Project:	Dr. Diatchenko is responsible for all the work in the area of Genetic data related to our study.
Name:	Michele Sterling (Prof. Sterling changed her institution, and now works in the University of Queensland. She will prepares papers to be submitted to the DoD grant officer regarding the institution change)
Project Role:	CI
Researcher Identifier:	ORCID ID: 0000-0001-8242-2685
Nearest person month worked:	1
Contribution to Project:	Prof. Sterling is responsible for all the work in the area of psychological data related to our study.
Name:	Shiri Fadel (Technion)
Project Role:	Project administrator
Researcher Identifier:	
Nearest person month worked:	4
Contribution to Project:	Shiri is responsible for all the administrative work related to our study, HRPO submissions and communications, pain application development, purchases, FITBIR accounts, preparing all study documentations relates to the study, preparing study checklists for MRI team, ER team, pain team, working together with ER coordinators to identify new subjects.
Name:	Tzipora Miriam Kuperman (Technion)
Project Role:	PhD student
Researcher Identifier:	

Nearest person month worked:	12
Contribution to Project:	Tzipora is responsible for preparing all study documentations relates to the study, work together with the ER team, pain team, recruitment of subjects and performing study procedures.

Name:	Maya Reshef (Technion)
Project Role:	Research assistant
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Maya assists Tzipora and Shiri with all study procedures and administrative tasks.

Name:	Shoshana Cristal (Technion)
Project Role:	PhD student
Researcher Identifier:	
Nearest person month worked:	6
Contribution to Project:	Shoshana assists Tzipora and Shiri with all study procedures and administrative tasks.

Name:	Aviho Marco (Technion)
Project Role:	MSc student
Researcher Identifier:	
Nearest person month worked:	12
Contribution to Project:	Aviho is responsible, together with Tzipora for preparing all study documentations relates to the study, work together with the ER team, pain team, recruitment of subjects and performing study procedures.

Name:	Hen Berkovitz (Rambam Health Care Campus affiliated to the Technion)
Project Role:	Study coordinator / Study nurse
Researcher Identifier:	
Nearest person month worked:	1
Contribution to	Hen identifies potential patients in the ER, and assists the sub

Project:	investigators during the recruitment in the ER, she also takes blood for the genetic tests.

Name:	Dr. Noam Bosak (Rambam Health Care Campus affiliated to the Technion)
Project Role:	Study Physician
Researcher Identifier:	
Nearest person month worked:	6
Contribution to Project:	Dr. Bosak identifies potential patients in the ER, complete the recruitment procedure in the ER, as well as conduct the neurological assessments during 6 and 12 months visits.

Name:	Dr. Chen Buxbaum (Rambam Health Care Campus affiliated to the Technion)
Project Role:	Study Physician
Researcher Identifier:	
Nearest person month worked:	8
Contribution to Project:	Dr. Buxbaum identifies potential patients in the ER, complete the recruitment procedure in the ER, as well as conduct the neurological assessments during 6 and 12 months visits.

Name:	Dr. Tariq Abu Raya(Rambam Health Care Campus affiliated to the Technion)
Project Role:	Study Physician
Researcher Identifier:	
Nearest person month worked:	2
Contribution to Project:	Dr. Abu Raya identifies potential patients in the ER, complete the recruitment procedure in the ER, as well as conduct the neurological assessments during 6 and 12 months visits.

Name:	Bar Rosh (Technion)
Project Role:	Research assistant
Researcher Identifier:	
Nearest person	1

month worked:
Contribution to Project: Bar assists Tzipora, Avihu and Shiri with all study procedures

Name: Roni Castin (Technion)

Project Role: Research assistant
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Roni assists Tzipora, Avihu and Shiri with all study procedures

Name: Elliot Sprecher (Rambam Health Care Campus affiliated to the Technion)
Project Role: Statistician
Researcher Identifier: ORCID ID: 0000-0001-8564-1090
Nearest person month worked: 1
Contribution to Project: Elliot performs the statistics and advises the study team regarding the statistical analysis of the data collected in the study.

Name: Dr. Alex Frid (Technion)
Project Role: Post Doc
Researcher Identifier: ORCID ID: 0000-0003-3487-9060
Nearest person month worked: 1
Contribution to Project: Alex assists Dr. Granovsky with analysis of EEG data

Name: Alina Razinski (Technion)

Project Role: Research assistant
Researcher Identifier:
Nearest person month worked: 2
Contribution to Project: Alina assists Shiri with all the administrative work of the study

Name:	Taha Abdullah (Northwestern University)
Project Role:	Technician
Researcher Identifier:	ORCID ID: 0000-0003-3373-7597
Nearest person month worked:	12
Contribution to Project:	Taha assists Prof. Apkarian with analysis of brain images. He download data provided from the Technion, perform data quality checks on a subset of the images using independent component analysis to identify general sources of noise, and performed teleconference with Rambam research group to provide suggestions for data collection.

Name:	Diane Rackziegel (Northwestern University)
Project Role:	Technician
Researcher Identifier:	
Nearest person month worked:	12
Contribution to Project:	Diana assists Prof. Apkarian with analysis of brain images

Name:	Rami Jabakhanji (Northwestern University)
Project Role:	Technician
Researcher Identifier:	ORCID ID: 0000-0002-9100-5071
Nearest person month worked:	12
Contribution to Project:	Rami assists Prof. Apkarian with analysis of brain images

Name:	Research Assistant Professor Lejian Huang (Northwestern University)
Project Role:	Technician
Researcher Identifier:	ORCID ID: 0000-0003-1753-2372
Nearest person month worked:	3
Contribution to Project:	Haung assists Dr. Apkarian with analysis of brain images. He downloads data provided from the Technion, performs data quality

	checks on a subset of the images using independent component analysis to identify general sources of noise, and performed teleconference with Rambam research group to provide suggestions for data collection.

Name:	Ryan Lichtenwalter, (McGill University)
Project Role:	Research Analyst
Researcher Identifier:	
Nearest person month worked:	4
Contribution to Project:	Under Dr. Diatchenko's supervision, Ryan was responsible for assisting with all aspects of the data cleaning and management, as well as data management related to the study.

Name:	Nancy Levesque, (McGill University)
Project Role:	Research Coordinator
Researcher Identifier:	
Nearest person month worked:	2
Contribution to Project:	Under Dr. Diatchenko's supervision, Nancy was responsible for assisting with all aspects related to the assays conducted on the samples of the study.

9. REPORTABLE OUTCOMES: see abstracts and papers below in appendix B.

10. OTHER ACHIEVEMENTS: see posters and papers below in appendix B.

11. REFERENCES: Mentioned in paper #1 appendix B.

12. APPENDICES:

Appendix A: Quad Chart
Appendix B: Papers and abstracts

Appendix A: Quad Chart

Why does acute post whiplash injury pain transform into chronic pain?
Multi-modal assessment of risk factors and predictors of pain chronification

MR130308; To construct a specific and sensitive tool for prediction and for understanding of the mechanisms relevant for transition from acute to chronic pain in mild traumatic brain injury / whiplash head and neck pain patients

Award Number: W81XWH-15-1-0603

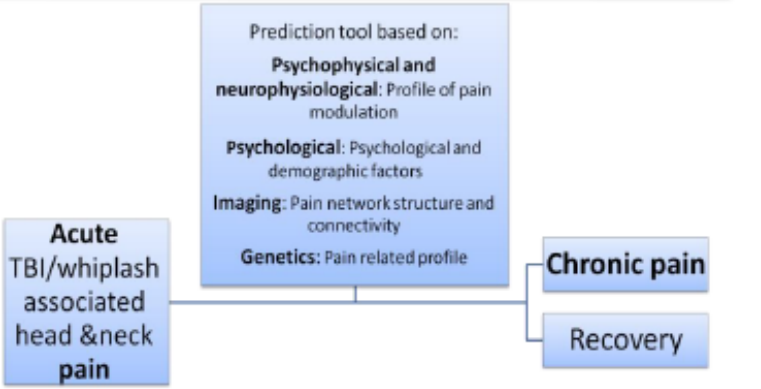
PI: David Yarnitsky **Org:** Technion – Israel Institute of Technology **Award Amount:** $1,499,904

Study Aim(s)

- Construction of a tool that predicts, based on parameters collected at time of entry into the study, the prognosis of mild traumatic brain injury (TBI)/whiplash related acute pain into either chronic pain or recovery
- Understanding of the processes that lead to chronification, based on data collected at entry, 6 months and 12 months after injury.

Approach

A prospective, non-intervening longitudinal study, assessing (i) relevant brain structure and connectivity (ii) neurophysiology and psychophysics, (iii) pain-related genetics, (iv) psychological and demographic parameters, for predicting the transition of acute head and neck pain due to mild TBI/whiplash into chronic pain.



Each of the parameters of pain modulation, brain structure and connectivity, pain genetics and psychological factors contributes to transition to chronic pain. We will combine them in one cohort of mild TBI to construct a specific and sensitive prediction tool for pain chronification

Timeline and Cost

Activities CY	Y1- 16	Y2-17	Y3-18	Y4-19
Building experimental setup				
Patients recruitment				
Patients follow-up				
Interim and final data analysis				
Reports and papers preparation				
Estimated Budget ($K)	253	245	269	733

Updated: (Oct 21, 2018)

Goals/Milestones (Example)

CY16 Goal – Building experimental setup and start of recruitment
☑ Functionality tests of the equipment; study's personal training, starting of the patients recruitment, initiation of the data collection.

CY17 Goal – Data collection phase
☑ Experimental and clinical data collection including the follow-up, initial data analysis.

CY18 Goal – Completion of data collection and final data analysis
☑ Continuation and finalization of the data collection; data analysis
☑ Final statistical analysis, study report and papers preparation

Comments/Challenges/Issues/Concerns
Cohort will include civil populations.

Budget Expenditure to Date
Projected Expenditure: $1,499,904
Actual Expenditure: Around $767,000

Appendix B:

Paper #1:

Accepted for publication in Neurology attached to our email.
(NEUROLOGY/2017/871228)

Psychophysical-psychological dichotomy in very early acute mTBI pain: A prospective study

Authors: Pora Kuperman, MPH; Yelena Granovsky, PhD; Michal Granot, PhD; Hany Bahouth, MD; Shiri Fadel, BSc; Gila Hyams, RN, MA; Hen Ben Lulu, RN; Osnat Aspis, RN, MA; Rabia Salame, RN, MHA; Julia Begal, MD; David Hochstein, MD; Shahar Grunner, MD; Liat Honigman, PhD; Maya Reshef; Elliot Sprecher, PhD; Noam Bosak, MD; Michele Sterling, PhD; David Yarnitsky, MD, PhD

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Julia Begal, General Surgery Department, Rambam Health Care Campus

David Hochstein, General Surgery Department, Rambam Health Care Campus

Shahar Grunner, General Surgery Department, Rambam Health Care Campus

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Noam Bosak, Department of Neurology, Rambam Health Care Campus

Michele Sterling, Recover Injury Research Centre, NHMRC Centre of Research Excellence in Road Traffic Injury Recovery, The University of Queensland

David Yarnitsky, Director, Department of Neurology, Rambam Healthcare Campus

Characters in Title: 89

Word Count for Abstract: 237

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Number of Tables: 4

Number of Figures: 0

Number of References: 19

Supplemental Data: Patient Consent Form and STROBE Statement

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Abstract

Objective: To characterize the pain related somatosensory and psychological presentation of very early acute patients with an mTBI.

Methods: Patients with an mTBI participated in a prospective observational study undergoing clinical, psychophysical and psychological assessment within 72 hours post-accident. Healthy controls underwent similar protocol.

Results: 100 acute patients with an mTBI (age 36 ±12.5 (SD), range 19-67, 42 females) and 80 healthy controls (43 ± 14.3, 24-74, 40 female) participated. Patients with an mTBI demonstrated a pro-nociceptive psychophysical response in most tests, such as less-efficient pressure-pain-threshold conditioned pain modulation (PPT-CPM) (0.19±.09 vs. 0.91±.10 kg, $p < .001$) and lower temperature needed to elicit a Pain50 response (44.72±.26 vs. 46.41±.30 ℃, $p < .001$). Their psychophysical findings correlated with clinical pain measures, for example Pain50 temperature and mean head ($r = -.21$, $p = .045$) and neck ($r = -.26$, $p = .011$) pain. The pain catastrophizing magnification subscale was the only psychological variable to show difference from the controls, while no significant correlations were found between any psychological measures and the clinical or psychophysical pain measures.

Conclusions: There appears to be a dichotomy between somatosensory and psychological findings in the very early acute post-mTBI stage; while the first is altered, and is associated with the clinical picture, the second is unchanged. In the context of the ongoing debate on the pathophysiological nature of the post-mTBI syndrome, our findings support its 'physical' basis, free of mental influence, at least in the short time window after the injury.

Introduction:

Traumatic brain injury (TBI) is responsible for over 1.7 million deaths, hospitalizations and ER visits annually in the US, with 75% characterized as mild TBI (mTBI). Whiplash and mTBI present similar post-trauma symptoms, such as concussion-like impairments[1]. At the chronic stage, both patients with whiplash associated disorder (cWAD) [2,3] and mTBI post-motor vehicle collision (MVC) [4] demonstrate, among other symptoms, persistent neck pain, headache, and sleep difficulties, which interrupt daily living. cWAD is associated with central somatosensory pro-nociceptivity as demonstrated by local and widespread hyperalgesia to experimental pain stimuli, inefficient conditioned pain modulation (CPM) and enhanced temporal summation (TS) of pain.[5] Whether these changes are a physiological direct consequence of the trauma, or due to psychological factors, such as the higher presence of anxiety, depression, and psychological distress, observed among cWAD [6,7], is still debated, some even posit feigning as their source [8]. Like cWAD, patients in the acute post-injury stage also show somatosensory changes [9], sometimes as early as 7 days post-injury [10]. While researchers [11] have noted immediate psychological symptoms, like elevated levels of distress within one-month post-whiplash, others[12] suggested a delayed appearance, such as elevated levels of anxiety and depression only among patients at least 2 years post-injury. The present study prospectively explored somatosensory and psychological presentation in very early acute mTBI (<72h post-accident), a time-frame not yet explored. Finding a dichotomy between the somatosensory and psychological changes in this time window would provide support to the organic basis of the somatosensory hypersensitivity and pain syndrome in this context.

Materials and Methods

Participants

Patients were recruited when visiting the Rambam Health Care Campus Emergency Room (RHCC-ER). Inclusion criteria: diagnosis of mTBI injury in road accident up to 24 hours before ER arrival; direct or indirect head and neck injury, Glasgow coma scale (GCS) 13-15 with no subsequent decline; no traumatic brain findings in computed tomography (CT) if performed; no, or shorter than 30 minutes loss of consciousness and presence of alteration in brain function (eg. confusion, disorientation)[13]. Age 18-70, both males and females. Exclusion criteria includes: other major bodily injuries at present accident; prior chronic head/neck pain that requires regular treatment; neurological disease that might affect test performance or interpretation such as neurodegenerative diseases; any head and neck injury in past year.

Healthy controls were recruited via advertisement as part of a healthy control study. Inclusion criteria: Absence of neurological, psychiatric, or chronic pain disorders; ability to give informed consent, communicate, and understand study instructions. Exclusion criteria: diagnosed psychiatric, cognitive, and /or neurological disorders, use of analgesic, anti-depressant or anti-anxiolytic medications on a regular basis (except for oral contraceptives), known pregnancy. Participants asked to avoid analgesic medication at least 24 hours prior to experiment.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review board of Rambam Health Care Campus approved the study protocol in accordance with The International Helsinki Declaration (No. 0601-14 for patients with an mTBI, No. 0614-15 for healthy controls). Written informed consent was obtained from each participant in the presence of a certified physician prior to any data collection or assessment.

Study Design

Patients with an mTBI are part of an ongoing study wherein clinical and demographic data are collected, including assigning a (whiplash associated disorder) WAD grade when recruited. A

session was scheduled within 72 hours post-injury (average days since accident =1.7 ±0.9) for MRI, clinical, psychophysical, pain-related psychological and neurophysiological assessment. Blood was drawn for genetics. MRI session included: anatomical, 2 fMRI, and DTI scans. Clinical baseline assessment consisted of patients self-reported pain levels and use of analgesics. Patients with an mTBI underwent both static and dynamic sensory testing and filled out baseline questionnaires.

In this manuscript we report the results of protocol shared between patients with an mTBI and healthy controls namely: electrical temporal summation (eTS), pressure and heat conditioned pain modulation (CPM) assessments, and selected psychological questionnaires.

Data Availability Policy

Anonymized data not published within this article can and will be made available to any qualified investigator upon request from the corresponding author.

Outcome Measures

Clinical Pain

Participants were asked to rate, via phone application or text message, the following measures referring to the preceding 24h: 1. On a Numerical Pain Scale (NPS) of 0-100: mean pain in the head, mean pain in the neck, maximum pain in the head, and maximum pain in the neck. 2. Overall health on a scale of 0-100 where 0 represents no health and 100 represents ultimate health. 3. Pain medications consumed for post-accident pain.

Pain-Related Psychological Assessment

Participants were asked to complete the following questionnaires, using the validated Hebrew version of each[14,15], before the psychophysical assessment:

Pain Catastrophizing Scale (PCS). 13 item questionnaire rated from 0 to 4, representing three components of pain catastrophizing: rumination, magnification, and helplessness.

Pain Sensitivity Questionnaire (PSQ). 17 item questionnaire, rated from 0 to 10 in terms of pain intensity, regarding painful situations occurring in daily life. The PSQ provides a total and two subscale scores (*PSQ-moderate, PSQ-minor).*

Hospital Anxiety and Depression Scale (HADS). 14 item questionnaire, rated from 0 to 3, used to determine anxiety and depression in individuals with physical health problems. HADS provides a separate score for each.

Psychophysical Assessment

In short, the experiment was composed of thermal pain thresholds; mechanical temporal summation; electrical temporal summation; followed by a familiarization stage. After a 5-minute break Pain50 temperatures were individually determined. The session was then composed of a single trial of sequenced 'test-stimuli' (pressure pain threshold followed by tonic heat application) stand-alone and then re-assessed under ‘conditioning’ stimulus (parallel conditioned pain modulation paradigm). A five-minute rest interval was provided between the two.

The measures detailed below refer to assessments performed on both healthy controls and patients with an mTBI.

Electrical temporal summation was measured by delivering electrical stimuli with a constant current stimulator (Digitimer DS5, Digitimer Ltd, WelWyn Garden City, England) to the skin overlying the belly of the left Brachioradialis muscle, starting at 5mA and increasing initially at a rate of 5mA per stimulus until the participant indicates pain sensation. The pain threshold value was then increased by 30%. Ten repetitive stimuli were delivered with inter-stimulus interval (ISI) of 1s. NPS was obtained after first application, and after the last of the ten stimuli.

Temporal summation magnitude was calculated as absolute difference between last and first pain scores.

Participants underwent a short training with pressure, heat and cold modalities in order to familiarize them with the sensations evoked by noxious stimulation. Training included: exposure to 3 short contact-heat stimuli (43, 45, and 47 °C), each lasting for 7 seconds, with the thermode being slightly moved between stimuli; exposure to 3 short pressure stimuli; and exposure to cold water (8-10 ºC) by non-dominant hand immersion in the bath for 5 seconds. Participants were asked to rate pain intensity (NPS) at the end of the immersion; if the temperature failed to evoke pain of 20 or greater, (0-100 NPS), it was lowered to 4-6ºC.

Determination of test-stimuli intensity (Pain50) was performed, wherein the test-stimulus temperature which induced a pain response of 50 (0-100 NPS) was individually determined. Initial stimuli of 46°, 45° and 47°C were applied. Participants were asked to report their level of pain during each stimulus. If none evoked a Pain50 response, additional stimuli were applied accordingly. The specific temperature, to the half-degree, found to evoke Pain50 response served as the test-stimulus for the rest of the paradigm.

Conditioned pain modulation assessments: The test-stimulus was comprised of two types of consecutive stimuli. A combination of 3 pressure-pain threshold stimuli on the trapezius muscle with an ISI of 3-5s, followed by a tonic 20s contact heat stimulus on the dominant volar forearm at the Pain50 temperature. The pressure stimuli were delivered with a 1x1 cm contact FDN 100 Pressure Algometer (Wagner Instruments, Greenwich, Conneticut, USA) with the experimenter increasing the pressure by 0.5 kg/s (corresponding to 50 kPa/s). Heat stimuli were delivered with a 3x3cm contact Peltier probe of the Thermal Sensory Analyzer, rate of increase 2°C/s, rate of decrease 8°C/s (TSA, Medoc, Israel).

After a 5-minute break, the 'conditioning stimulus' is given by 10 second immersion of the non-dominant hand in the cold-water bath. Then the 3 pressure-pain threshold measurements and 'thermal test stimulus' were repeated during the immersion. Pain ratings to the heat stimulus obtained at 2, 10, and 20 seconds post-initiation, pain ratings to the conditioning stimulus obtained 10 and 60s post-initiation. The difference between the 'test stimuli' (mean score of last two heat pain ratings and mean pressure-pain threshold value) obtained during the 'conditioning stimulus' vs. the baseline application was taken as the conditioned pain modulation response, where negative values indicate more efficient heat pain-conditioned pain modulation and positive values more efficient pressure-pain threshold-conditioned pain modulation.

Statistical Analysis

We employed median tests, Wilcoxon rank sums tests, or independent groups t-tests (unequal variances), as appropriate based upon characteristics of the data distributions, and full factorial 2-way ANOVAs with the measures of group, sex and their interactions. JMP (SAS Institute, Cary, NC) was used for the analyses.

Sex differences were examined in the group of patients with an mTBI using unequal variances t-test or Chi square tests as appropriate.

Spearman correlations were employed to examine the relationship between psychological characteristics and psychophysical assessments, as well as between clinical characteristics and psychophysical assessments in the patients with an mTBI .

Data Availability

Statement here.

Results:

Clinical Characteristics

One-hundred patients with acute mTBI post-accident (age range 19-67 years, mean±SD, 36 ±12.5, 42 female) and eighty healthy controls (range 24-74 years, 43 ± 14.3, 40 female) were recruited.

32 of 100 patients with acute mTBI indicated analgesic consumption in the preceding 24 hours; 31 took paracetamol or an NSAID, one was provided morphine.

We found that in the very early acute post-mTBI stage females exhibit higher levels of head pain, as well as express pain in significantly more areas of the body as compared to males. There was a non-significant trend of higher neck pain in females. There was no significant difference in WAD Grade distribution (reported WAD Grades of 0-2) age, or years of education (Table 1).

Psychophysical responses in mTBI patients and controls

Comparing psychophysical responses between patients with an mTBI and controls, we found that for most measures the patients with an mTBI demonstrated a pro-nociceptive response. In addition, independent of participant status (patients with an mTBI or control), for most measures females showed a more pro-nociceptive pattern of response. For electrical temporal summation and pressure-pain threshold stand-alone stimulus, although the model is significant, this is due to sex, in that females have a significantly overall higher electrical temporal summation, and lower pressure-pain threshold score than males. For heat pain stand-alone males had a significantly higher NPS score (Table 2).

Pain-related Psychological Variables

For most pain-related psychological variables no significant differences were found between patients with an mTBI and healthy controls. However, a significant difference was found in the magnification subscale of pain catastrophizing, where patients with an mTBI exhibited greater pain magnification, with all other subscales and total score exhibiting no significant differences.

In sex related sub-analysis, female patients with an mTBI exhibit significantly more anxiety than both male groups (Table 3).

Correlations between Clinical, Psychophysical and Psychological Findings

Numerous significant correlations were found between clinical measures of pain and psychophysical findings (Table 4). Yet, no significant correlations were found between measures of anxiety or pain magnification and any of the psychophysical variables, and no significant correlations were found between anxiety or pain magnification and any of the clinical measures of pain.

Discussion:

This study found a pro-nociceptive pattern of pain processing in very early acute post-mTBI patients with several significant correlations between the patients with mTBIs' measures of clinical pain and psychophysical measures. Yet, these patients showed no significant differences from healthy controls in most pain-related psychological variables and said psychological findings showed neither correlation to clinical pain measures nor to the observed psychophysical measures. As such, the changes in pain perception in this context seem to be free of mental influence and support their acceptance as physiological, or 'organic', in nature.

Our results of enhanced pain sensitivity in the very early acute stage are in-line with the meta-analysis of work on patients with cWAD [5] which found that measures of mechanical stimuli, such as pressure algometry, commonly applied to patients with whiplash, evidenced hyperalgesia. For local sites this was seen as early as 7 days post-injury. Comparatively, our work is innovative as it explores the very-acute post-injury stage, showing how early the hyperalgesia can already be discerned. Less work has focused on thermal stimuli in remote sites; studies in the cervical area show reduced cold and heat pain thresholds in patients with cWAD at

least 3 months post-injury, the time-point used for chronicity in that work[5]. The observed hypersensitivity to both heat and cold in remote locations found in our work complement and expand upon these findings, as we see hyperalgesia to static thermal measures, even in the very early acute post-injury stage and in areas remote to the injury.

Our findings of non-enhanced electrical temporal summation in patients with an mTBI compared to healthy controls seems contrary to previous work which has demonstrated enhanced temporal summation among patients with cWAD [5] and to the intuitive expectation that pro-nociceptivity will be expressed by enhanced electrical temporal summation . A possible explanation is that development of ascending facilitation is delayed, and does not express itself in the early time window examined in our study. It is also important to keep in mind that the patients with an mTBI demonstrated significantly higher pain scores than healthy controls, as such it is possible that their summation scores were limited by a ceiling effect, as they had already reached their upper limit of pain just with a single stimulus, before the application of the series used to elicit the summation effect. Our findings of significantly less-efficient pressure-pain threshold-conditioned pain modulation do comply with the pro-nociceptivity, and concurs with previous work [16] which found significantly lowered pressure-pain threshold-conditioned pain modulation in remote sites in patients with acute WAD recruited within 1-month post-whiplash. Thus, it is possible that dynamic conditioned pain modulation tests, which involve mechanical stimulation can also be a useful clinical tool for understanding continued post-mTBI pain.

The findings of various significant correlations between patients with an mTBIs' clinical pain and observed psychophysical hypersensitivity serve to deepen existing knowledge, as correlation analyses in previous work oftentimes focused only on the correlation between high and low

levels of pain and sensory hypersensitivity, and not on the full spectrum of clinical pain; for instance, a meta-analysis on musculoskeletal pain [17] found correlation between symptom severity and local pressure pain sensitivity in patients with chronic knee osteoarthritis. Wherein, when separated into groups of high and low symptom severity, those individuals in the high severity group indicated greater pressure pain sensitivity both locally and in remote sites. Our results show a more direct correlation. For example, a greater number of painful body areas, as well as higher levels of pain in the head and neck, all showed independent correlations with higher local pressure pain sensitivity. We acknowledge that the clinical pain measures are obviously interrelated, for example mean and maximum head pain, but maintain that they have their own meaning and are therefore both noteworthy to be mentioned.

It has been suggested that there is a concept of 'whiplash culture' which determines the prognosis of individuals who have undergone whiplash trauma. This is to say that cWAD symptoms may be attributed to factors other than the physical bodily trauma, in that it is a 'social illness' or a condition based on 'symptom expectation' which differs across cultures. A meta-analysis [8] on available evidence supporting this notion was performed and found to be inconclusive, suggesting that there is some research supporting the notion that chronic whiplash pain is influenced by factors other than physical ones, but what these are one cannot to say for certain. The absence in our results of overall differences in the psychological pain sensitivity self-assessment questionnaires, depression, or most forms of catastrophizing between patients with an mTBI in the very early acute stage and healthy controls, as well as the lack of correlations between the observed anxiety and pain magnification and psychophysical assessments or clinical measures of pain, lends itself to the thought that the somatosensory

changes which happen post-mTBI, at least in examined time window, are organic rather than psychological-based in nature.

Although our study found almost no psychological changes in the very early acute mTBI stage, the minimal differences observed do suggest an avenue for continued research. It could be informative to monitor the enhanced anxiety observed specifically among female patients with an mTBI as previous research [18] has shown that symptoms of anxiety at baseline increased the risk of prolonged whiplash suffering. The same can be said for the significant findings of the magnification subscale, as a study of patients with chronic whiplash [19] found that the magnification subscale of the pain catastrophizing scale contributed a significant unique variance to the prediction of pain. The finding suggests that the magnification component of catastrophizing may be a risk factor for heightened pain experience following mTBI injury and should also be examined longitudinally. In Israel no litigation procedures are settled during the first-year post-accident, thus compensation should have little to no effect on pain perception in the very early acute stage.

The study has several limitations. The first, although following the same protocol, the two study cohorts were examined by different examiners. Second, it is possible that there was a selection bias in the clinical population, as not all patients who came in to the ER were recruited. For example, it is possible that patients who did not speak Hebrew and as such were not recruited, would have presented different results. Addition of other psychological questionnaires, like those addressing psychological distress, may have also altered the findings. Lastly, psychophysical tests might influence one another if performed in series due to either participant fatigue, or sensitization of the pain perception system. It is possible that different tests, or tests done separately would bring about other results.

It would appear from the results that there is a dichotomy between somatosensory and psychological changes in the very early acute post-mTBI stage, with changes to pain perception happening almost immediately after injury. The lack of significant psychological differences in the same time-frame suggests that mental changes may take longer to develop, lending support to the assertion that the pathophysiology of the clinical pain reported post-mTBI is mostly organic, free of mental influences.

Table 1: mTBI Group Characteristics:

Clinical Characteristic	**Male (mean±SD), median (range) or %**	**Female (mean±SD), median (range) or %**	**P-value**
n=	58	42	
Age	33.5 (19-67)	36.5 (19-65)	0.222
Education	12 (6-22)	14 (12-20)	0.104
Head Pain-Mean NPS	47.18±3.87	61.00±4.72	**0.026**
Neck Pain Mean NPS	50.59±3.93	59.07±4.56	0.162
Head Pain Maximum NPS	56.29±3.96	69.05±4.50	**0.036**
Neck Pain Maximum NPS	56.09±4.04	67.73±4.30	0.052
Number of Painful Areas	2.94±.15	3.56±.23	**0.030**
WAD Grade 0	11 (18.97%)	6 (14.29%)	
WAD Grade I	40 (68.97%)	24 (57.14%)	
WAD Grade II	7 (12.07%)	12 (28.57%)	0.117
Previous Medical History	12 (20.69%)	15 (35.71%)	0.096

P values are t-test or chi-square based as appropriate.

Table 2: Psychophysical findings

QST Test (Units)	**Males HC (LSM±SEM)**	**Males Whiplash (LSM±SEM)**	**Females HC (LSM±SEM)**	**Females Whiplash (LSM±SEM)**	**Model P**	**Group*Sex P**	**Group P**	**Sex P**
n=	40	58	40	42				
EPT (mA)	188.00±20.32	170.37±15.70	155.24±19.22	131.56±18.98	0.207	0.871	0.269	0.057
1st Electrical Pulse (NPS)	12.82 ±3.47	35.39± 2.70	16.89 ± 3.28	35.26±3.26	**<0.001**	0.513	**<0.001**	0.539
10th Electrical Pulse (NPS)	31.59 ± 4.38	54.79±3.37	52.92±4.15	68.82±4.08	**<0.001**	0.363	**<0.001**	**<0.001**
Electrical TS (NPS)	19.83± 3.39	19.40± 2.83	36.73± 3.39	33.56±3.43	**<0.001**	0.675	0.584	**<0.001**
Pain50 Temp (°C)	47.23±.42	45.35±.33	45.60±.42	44.10±.39	**<0.001**	0.627	**<0.001**	**<0.001**

1st Cold Water (NPS)	31.13±3.62	37.07±3.03	32.83±3.62	52.44±3.54	**<0.001**	**0.014**	**<0.001**	**0.049**
PPT Test Stimulus (kg)	3.42±.20	3.31±.17	2.55±.20	1.96±.20	**<0.001**	0.220	0.074	**<0.001**
PPT Conditioned (kg)	4.57±.27	3.57±.23	3.52±.23	2.11±.26	**<0.001**	0.863	**<0.001**	**<0.001**
PPT CPM (kg)	1.17±.14	.26±.12	.24±.12	.11±.14	**<0.001**	0.172	**<0.001**	**0.014**
Heat Pain Test Stimulus (NPS)	42.60±4.03	44.30±3.11	31.09± 3.81	36.02±3.66	**0.037**	0.659	0.367	**0.008**
Heat Pain Conditioned (NPS)	31.95±3.61	36.58±3.11	27.27±3.91	29.62±3.62	0.273	0.694	0.360	0.117
Heat Pain CPM (NPS)	-12.36± 2.80	-9.49± 2.32	-9.45±2.75	-7.20± 2.72	0.616	0.907	0.333	0.325

Table 3: Pain-Related Psychological findings

Questionnaire Scale	Males HC (LSM±SEM)	Males Whiplash (LSM±SEM)	Females HC (LSM±SEM)	Females Whiplash (LSM±SEM)	Model P	Group*Sex P	Group P	Sex P
n=	40	58	40	42				
PSQ Moderate	6.15±.25	5.70±.23	6.38±.25	5.66±.25	0.105	0.591	0.017	0.698
PSQ Minor	4.17±.24	4.00±.21	4.29±.24	4.17±.24	0.925	0.917	0.538	0.536
PSQ Total	5.16±.23	5.04±.21	5.33±.23	5.10±.23	0.806	0.809	0.431	0.598
PCS Rumination	7.70±.64	8.78±.57	7.83±.64	8.75±.64	0.452	0.899	0.109	0.942
PCS Magnification	4.20±.43	5.71±.38	3.63±.45	4.70±.43	**0.003**	0.607	**0.002**	0.061
PCS Helplessness	9.53±.94	10.65±.85	8.93±.94	11.13±.94	0.331	0.562	0.075	0.948
PCS Total	21.43±1.78	24.14±1.58	20.38±1.78	24.58±1.79	0.141	0.889	0.024	0.644
HADS-	.57±.05	.52±.04	.57±.05	.67±.05	0.105	0.118	0.486	0.080

Depression								
HADS-Anxiety	.65±.05	.62±.04	.67±.05	.84±.05	**0.004**	**0.028**	0.104	**0.011**

Table 4: Correlations between Clinical Characteristics and Psychophysical Variables

	WAD Grade			**Number of Painful Areas**			**Mean Head Pain**			**Mean Neck Pain**			**Maximum Head Pain**			**Maximum Neck Pain**		
	ρ	**P**	**n**	**ρ**	**P**	**n**	**ρ**	**P**	**n**	**ρ**	**P**	**n**	**ρ**	**P**	**n**	**ρ**	**P**	**n**
1st Electrical Pulse	.10	0.329	96	.01	0.890	95	.25	**0.016**	94	.32	**0.002**	94	.17	0.094	94	.28	**0.006**	94
10th Electrical Pulse	.14	0.187	96	.29	**0.004**	95	.32	**0.002**	94	.36	**<0.001**	94	.28	**0.006**	94	.38	**<0.001**	94
Electrical TS	-.03	0.804	96	.27	**0.007**	95	.17	0.100	94	.17	0.110	94	.18	0.090	94	.20	0.051	94
Pain50 Temp	-.04	0.682	98	-.08	0.425	97	-.21	**0.045**	95	-.26	**0.011**	95	-.17	0.099	95	-.27	**0.009**	95
1st Cold Water NPS	.09	0.406	97	.24	**0.017**	96	.24	**0.021**	94	.07	0.490	94	.22	**0.037**	94	.10	0.316	94
PPT Test	.01	0.89	98	-	**0.01**	97	-.27	**0.008**	95	-.23	**0.025**	95	-.22	**0.03**	95	-.24	**0.019**	95

Stimulus		8		.25	**4**									**2**				
PPT Conditioned	.01	0.943	97	-.20	0.051	96	-.31	**0.002**	94	-.30	**0.004**	94	-.28	**0.007**	94	-.31	**0.003**	94
PPT CPM	-.04	0.644	97	.03	0.789	96	-.14	0.167	94	-.12	**0.033**	94	-.19	0.058	94	-.23	**0.026**	94

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Paper #2 in late stages of preparation (the abstract of the paper):

Abstract

This prospective observational study aims to investigate pain behavior along the first year after mild traumatic brain injury, including its relation to age. The study cohort consisted of 103 patients (age range 19-67, median age 36, 43F) with acute mTBI post-MVC who underwent assessment within 72 hours post-accident and provided head and neck pain scores at baseline, 3, and 6 months post-accident, 84 patients provided scores at 1-year. The reciprocal time regression model found that the age group by reciprocal month interaction ($p=0.031$), as well as reciprocal time from injury ($p<0.001$), sex ($p<0.001$), and pain site ($p=0.008$) significantly influenced pain progression. For the overall group, pain initially decreases and then stabilizes around month 3. The age group by month interaction shows that after rapid decline for both groups, older patients' pain stabilizes earlier, around a month post-injury, whereas this occurs only around month three for the younger group. This suggests that therapeutic interventions should be most successful if administered within the age-relevant time window. Pain distribution in the area of injury at one-year post-accident exhibits a bimodal distribution (Shapiro-Wilk $p<0.001$), wherein patients seem to either be pain-free ($n=48$) or reporting moderate-severe pain levels ($n=26$), with very few reporting mild pain ($n=10$). This distribution is different from expected chronified pain, for example after surgery. Brain injury might generate unique changes in pain processing that generate this bimodal distribution.

Abstract #1:

ACUTE HEAD PAIN, LOW SOCIOECONOMIC STATUS AND LESS-EFFICIENT CPM PREDICT POST-WHIPLASH CHRONIC PAIN OCCURRENCE

Pora Kuperman, Yelena Granovsky, Michal Granot, Hany Bahouth, Shiri Fadel, Gila Hyams, Hen Ben Lulu, Osnat Aspis, Rabia Salama, Yulia Begal, David Hochstein, Shahar Grunner, David Yarnitsky

Background
Research has shown that 50% of individuals involved in mild car accidents (GCS 13-15) will suffer chronic pain.
Aim
To assess the relationship between acute head/neck pain, Quantitative Sensory Testing (QST) measures, and demographic data on chronic pain development 3 months post-accident.
Methods
Head/neck pain, static and dynamic QST measures, and demographic data were compiled within 72h post-accident, and taken into a logistical regression model to predict chronic post-traumatic pain occurrence. At 3-months 38 patients had follow-up data, 27 of which expressed clinically significant pain (VAS>30), and 11 not (VAS≤30).
Results
An overall logistical regression model was significant ($p=0.020$). Of the parameters included, acute head pain was significant ($p=0.0345$), with pressure pain threshold- conditioned pain modulation (PPT-CPM) and monthly salary evidencing trends ($p=0.0524$ and 0.0714, respectively).
A model based on these three measures was found to be significant ($p<0.001$). Acute head pain ($p=0.002$) and monthly salary ($p=0.033$) were significant, with higher pain values and low salary associated with greater likelihood of developing chronic pain. In this model, PPT-CPM did not maintain significance. However, when PPT-CPM is divided based on chronicity and compared to controls significance is found ($p=0.004$) with less-efficient CPM-PPT in chronic pain vs. controls (post-hoc $p=0.003$).
Conclusions
The occurrence of post-traumatic head/neck pain can be predicted by a combination of acute head pain and low monthly salary.
Independently, a pro-nociceptive pain modulation profile (PMP) as expressed by less-efficient PPT-CPM also influences chronic pain development.
Acknowledgment: Supported by US Department of Defense, Health Affairs Office, No. W81XWH-15-1-0603

Abstract #2:

WHIPLASH-ASSOCIATED PAIN CHRONIFICATION; THE PREDICTIVE ROLE OF RESTING-STATE EEG ALPHA POWER AND ACUTE PAIN

Yelena Granovsky, Pora Kuperman, Michal Granot, Hany Bahouth, Shiri Fadel, Gila Hyams, Hen Berkovich, Osnat Aspis, Rabia Salama, Yulia Begal, David Hochstein, Shahar Grunner, David Yarnitsky

Background and Aims. Acute pain intensity is an important factor for pain chronicity. Resting-state EEG alpha activity characterizes various pain states. Chronic post-traumatic pain is common after whiplash. We assessed the predictive value of acute headache/neck pain, and EEG alpha power on chronic whiplash pain intensity.

Methods. Head/neck pain and midline resting-state EEG were assessed within 72h after mild road accident. Thirty-eight patients (ages 19-67 yrs; 21 F) had follow-up data, and were determined as having clinically meaningful pain (>30 VAS; N=27) or no (N=11).

Results. Chronic head/neck pain group was characterized by higher acute head ($p<0.001$) or neck pain ($p=0.034$) scores, and by higher peak alpha power ($p=0.009$, Pz). In line, acute headache correlated with chronic headache ($r=0.479$; $p=0.003$); acute neck pain correlated with chronic neck pain intensity ($r=0.492$, $p=0.002$). Similarly, high peak alpha power was associated with higher chronic pain scores (Pz, $r=0.598$, $p=0.002$, head; $r=0.525$, $p=0.007$, neck). Regression model ($p=0.012$) including age and gender, confirmed the predictive effect of alpha power ($p=0.006$) but not acute headache ($p=0.102$) on chronic headache intensity. For the neck pain ($p=0.001$), both alpha power ($p=0.012$) and acute neck pain ($p=0.008$) predicted chronic pain intensity.

Conclusions. High EEG resting-state alpha power, possibly due to acute pain or stressful situation, predicts chronification of post-whiplash pain. Stronger contribution of acute neck pain and not headache to chronic pain intensity may suggest the primarily role of neck trauma in chronicity of whiplash.

Acknowledgment. Supported by US Department of Defense, Health Affairs Office, No. W81XWH-15-1-0603

Abstract #3:

Age as a predictive factor for post-mild Traumatic Brain Injury pain chronification timeline

Pora Kuperman, Noam Bosak, Yelena Granovsky, Michal Granot, Hany Bahouth, Shiri Fadel, Hen Ben Lulu, Avihu Marco, Chen Buxbaum, Elliot Sprecher, David Yarnitsky

Aim of Investigation: To assess post-whiplash mTBI head and neck pain evolution from the very early acute stage (<72h) to 1-year post-injury. This is of interest as status quo literature holds that those who will recover post-whiplash do so within 3-6 months post-injury, with up to 50% of individuals experiencing long term persistent pain, but offers no further delineation of pain change and/or progression within this time period. This time window may in fact be crucial for appropriate intervention to avert the time-course to chronicity, and as such should be investigated.

Methods: 116 mTBI patients (46F, age range 19-67, median age 35) underwent baseline QST testing, filled out pain-related psychological and demographic questionnaires and provided mean pain ratings for head and neck (0-100 NPS). Pain ratings were provided again at 3, 6, and 12 months post-injury. For analysis the patient group was split, by median age, in to young (19-35yr) and old (36-67yr) as it has been suggested that age might affect post-mTBI symptom development. A mixed model ANOVA for repeated measures tested the effect of month after the injury, gender, pain site (head/neck), age group (young/old), and the significant psychological parameters (Pain Catastrophizing Total and TIPI Agreeableness) on pain levels at months 1,3,6 and 12. Separate models were built to investigate the head-neck pain correlation at each of the time points, as well as the ability of head and neck pain at baseline to predict subsequent head and neck pain along the 1-year time axis.

Results: The ANOVA model was significant ($p < 0.001$), where month from injury ($p < 0.001$), gender ($p < 0.001$), pain site ($p = 0.038$) and month*age group interaction ($p = 0.006$) were significant components. Overall pain reduction is observed, where baseline pain is significantly higher than that of all subsequent timepoints; months 3,6, and 12, are statistically similar. Month by age group interaction shows that older patients' pain stabilizes in the acute stage (month 1), whereas pain remains unchanged only at month 3 (chronic stage) for the younger group. Females express significantly more pain than males, and the neck is a significantly more painful site than head.

Head/Neck pain is always significantly correlated, with neck pain the significantly more dominant pain at months 1 ($r=.68$, $p=0.004$) and 3 ($r=.63$, $p=0.037$).

Separately, both head and neck pain at baseline are predictive of subsequent pain in those areas (head: month 1,3 $p < 0.001$, month 6 $p = 0.012$, month 12 $p=0.016$; neck month 1,3 $p<0.001$, month 6 $p = 0.006$, month 12 $p = 0.048$).

Conclusions: Overall post-whiplash mTBI patients express a reduction in self-reported head and neck pain from the time of their accident to 1-year following, where pain levels remain statistically unchanged from the 3-month mark, reinforcing this time window as crucial for pain intervention. Throughout the year patients continue to express more pain in the neck, and females remain with higher levels of pain. Interestingly, age does seem to affect symptom development, where those aged 36 and above enter their chronic level of pain already at 1-month post-accident, and those younger than that only at 3-months post-injury. Seeing as baseline pain values remain predictive of subsequent pain it reinforces the need to be attuned to patients' self-reported pain at the time of injury. That is to say, taken together, pain intervention for those above 35 years of age should take place within the first month post-accident with the hope of averting pain chronicity, while those younger than that seem to have a slightly longer preventative window.

Acknowledgment: Supported by US Department of Defense, Health Affairs Office, No. W81XWH-15-1-0603

Why does acute post whiplash injury pain transform into chronic pain?
Multi-modal assessment of risk factors and predictors of pain chronification

MR130308; To construct a specific and sensitive tool for prediction and for understanding of the mechanisms relevant for transition from acute to chronic pain in mild traumatic brain injury / whiplash head and neck pain patients

Award Number: W81XWH-15-1-0603

PI: David Yarnitsky **Org:** Technion – Israel Institute of Technology **Award Amount:** $1,499,904

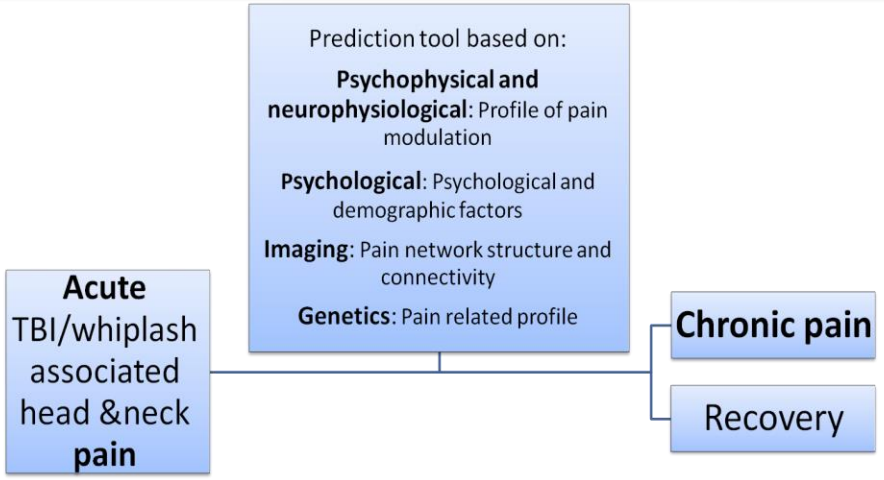
Study Aim(s)

• Construction of a tool that predicts, based on parameters collected at time of entry into the study, the prognosis of mild traumatic brain injury (TBI)/whiplash related acute pain into either chronic pain or recovery

• Understanding of the processes that lead to chronification, based on data collected at entry, 6 months and 12 months after injury.

Approach

A prospective, non-intervening longitudinal study, assessing (i) relevant brain structure and connectivity (ii) neurophysiology and psychophysics, (iii) pain-related genetics, (iv) psychological and demographic parameters, for predicting the transition of acute head and neck pain due to mild TBI/whiplash into chronic pain.



Each of the parameters of pain modulation, brain structure and connectivity, pain genetics and psychological factors contributes to transition to chronic pain. We will combine them in one cohort of mild TBI to construct a specific and sensitive prediction tool for pain chronification

Timeline and Cost

Activities / CY	Y1- 16	Y2-17	Y3-18	Y4-19
Building experimental setup				
Patients recruitment				
Patients follow-up				
Interim and final data analysis				
Reports and papers preparation				
Estimated Budget ($K)	253	245	269	733

Goals/Milestones (Example)

CY16 Goal – Building experimental setup and start of recruitment

☑ Functionality tests of the equipment; study's personal training, starting of the patients recruitment, initiation of the data collection.

CY17 Goal – Data collection phase

☑ Experimental and clinical data collection including the follow-up, initial data analysis.

CY18 Goal – Completion of data collection and final data analysis

☑ Continuation and finalization of the data collection; data analysis

☑ Final statistical analysis, study report and papers preparation

Comments/Challenges/Issues/Concerns

Cohort will include civil populations.

Budget Expenditure to Date

Projected Expenditure: $1,499,904

Actual Expenditure: Around $767,000

Updated: (Oct 21, 2018)