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AWARD NUMBER: W81XWH-15-1-0603

TITLE: Why does Acute Postwhiplash Injury Pain Transform into Chronic Pain? Multimodal Assessment of Risk Factors and Predictors of Pain Chronification

PRINCIPAL INVESTIGATOR: Prof. David Yarnitsky

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                         Fort Detrick, Maryland 21702-5012

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Why does Acute Postwhiplash Injury Pain Transform into Chronic Pain? Multimodal Assessment of Risk Factors and Predictors of Pain Chronification

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Principal Investigator - Prof. David Yarnitsky

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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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. In the first year the study underwent complex administrative steps including build up of dedicated team, and approval of all required actions. Practically, receuitment has started towards the end of year one, and so far 54 patients were recruited, out of which 34 are in the study. Communication with the international research team is ongoing, and cumulative data has been, or being passed for their assessment on ongoing basis. There is still not enough data to justify interim analyses. We expect to substantially accelerate the recruitment rate in the second year of the project.

15. SUBJECT TERMS-
Mild traumatic brain injury, Pain perception, Pain modulation, fMRI, EEG, Chronic pain, Acute pain, Whiplash injury

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a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU		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. Acute whiplash patients 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:

Pre-study task: Apply for local IRB and for HRPO:

The study was 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 on 26 July 2016 and by HRPO on 22 Sep 2016.

Task 1. Building the experimental setup:

The setup of the study was completed, including the following:

   i. We organized and trained team, and determined work procedures for the clinical stage of the experiment. The ER team is responsible for identifying and recruitment of subjects.
   ii. We purchased 64channels EEG system for the data acquisition.
   iii. We determined working procedures with the Technion genetic lab.
   iv. We exercised data transfer between our site and the MRI center in Chicago.
   v. We trained physicians in the various test protocols and questionnaires of the study.
   vi. One graduate student along with a research assistants were trained for the study protocol; they are responsible for the data collection and preliminary analysis
   vii. We determined MRI protocols and training of the technical staff.
   viii. A meeting of the study investigators was held during the world pain conference in Japan in Sept 29th, 2016. Participants: Yarnitsky, Granovsky, Granot, Sterling, Maixner, Belfer, Diatchenko. Progress was reviewed, issues regarding performance and analysis discussed,

Task 2. Patients recruitment and experimental performance:

We started recruiting immediately after HRPO approval on March 2016.

First subject was recruited on 31/Mar/2016.

54 subjects were recruited by the end of September 2016. 34 subjects eventually participated in the study. 20 subjects had withdrawn their consent mainly due to MRI scanner availability and scheduling issues, or excluded from the study since they could not complete the MRI scan (claustrophobic subjects for example).

We ran into a few problems in the process -
The first obstacle in our recruitment was one of the inclusion criteria in protocol Ver. 3 that required performance of brain CT and no finding in the test. We realized that most of the mild TBI subjects undergo only skull X-Ray scans and not head CT. Recruitment during April and May included only 4 patients due to this point. Accordingly, we decided to change criteria, since participants were eventually going to have brain imaging by MRI, and not require CT as inclusion criterion. This was in protocol Ver. 3.1 that was approved by local IRB on 19/May/2016.

The second time consuming activity was adding the participating physicians to our study, obtaining the local IRB and HRPO approval for them, as well as training them. All 10 physicians were trained during June 2016 and the number of recruited patients has then increased. We recruited 39 subjects from June to August 2016.

Another problem was the availability of the MRI scanner: Most of the subjects out of the 20 that withdrew their consent, did it since the scheduled MRI scans were not at a convenient time. In some cases the MRI scanner was not available at all. We had several meetings with the MRI team and starting 1/Sep/2016 we have a log with pre scheduled time slots for the 3T MRI scanner each week. On Sep the withdrawal rate decrease and only 2 subjects withdrew their consent. 1 subject was excluded due to overweight precluding completion of the MRI scan.

During September we also added the evening ER team as recruiters in order to increase the number of recruitments. The Quad chart was updated and changed according to all above mentioned changes, and is attached as an appendix A (the first version is a clean version, and in the second version the changes marked in purple).
We hope that the solutions we found and mentioned above will lead us to higher recruitment rate than the initial months of the recruitment period.

Regarding the experimental performance:
24 Blood samples were transferred to the genomic lab, and DNA was extracted. The rest will be delivered soon.
MRI scans were saved and backed up, as well as delivered to Northwestern University. We had a conference video call in order to review the details of scanning with the Chicago Team, and to improve the cooperation of the subjects during the scans and the accuracy of the subject's pain ratings during the scans.

Part of the collected data was uploaded to the FITBIR. Several conference calls with FITBIR team were held and we built new forms together in order to upload all the rest of the 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. 27 participants follow our pain scale application and report their pain rates every month. The others answer our pain questions on personal phone calls.
3b. Visits 6 and 12 months were not done yet. Visit 6 months, will be done during Oct 2016 for the first patient.
3c. No additional visits were done at patient's demand in our special dedicated hospital clinic.

Task 4. Interim data analyses:
4a. Interim data was postponed since we recruited 34 subjects only. We will conduct the interim analysis when 200 subjects will be recruited. 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 recruitees.
4b. Ongoing review of quality of the imaging data is performed by the team at Northwestern University, USA. The analysis of cumulating results will be done together with the interim analysis.
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.

4. **KEY RESEARCH ACCOMPLISHMENTS:**
   Nothing to report (Based on our recruitment rate we do not have a key research accomplishment at this stage. We are in the process of improving the recruitment rate all the time, and we hope that in the next annual report we will have key research accomplishments).

5. **CONCLUSION:**
   This project has undergone long and difficult initiation steps, due to its complexity and the need to undergo both local and US based approvals for all steps. Further, many local coordination problems encountered in the preliminary stages were taken care of. We now face a well organized operation with clear procedure, trained teams, and cooperative ER leadership, and expect to recruit patients at a rate that will bring us to large enough numbers to be able to conclusively analyze the data.

6. **CHANGES/ PROBLEMS**
   See section 3 OVERALL PROJECT SUMMARY task 2 above, pages 4-5.

7. **PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**
   Nothing to report.

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	<u>Prof. David Yarnitsky (Technion)</u>
Project Role:	PI
Researcher Identifier:	Research gate name: David Yarnitsky (no specific number)
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:	<u>Dr. Yelena Granovsky (Technion)</u>
Project Role:	CI
Researcher Identifier:	Research gate name: Yelena Granovsky
Nearest person month worked:	2
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:	<u>Prof. Michal Granot (Haifa University)</u>
Project Role:	CI
Researcher Identifier:	Research gate name: Michal Granot
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 Project:	Prof. Apkarian approved the MRI protocol and scans. He is 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:	Prof. Michele Sterling (Griffith University)
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 check lists for MRI team, ER team, pain team, working together with ER coordinators to identify new subjects.

Name:	<u>Tzipora Miriam Kuperman (Technion)</u>
Project Role:	PhD student
Researcher Identifier:	
Nearest person month worked:	9
Contribution to Project:	Tzipora is responsible for preparing all study documentations relates to the study, preparing study check lists for MRI team, ER team, pain team, recruitment of subjects and performing study procedures.

Name:	<u>Maya Reshef (Technion)</u>
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:	<u>Hen Berkovitz (Rambam Health Care Campus affiliated to the Technion)</u>
Project Role:	Study coordinator / Study nurse
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Hen identifies potential patients in the ER, and assists the sub investigators during the recruitment in the ER, she also takes blood for the genetic tests.

Name:	<u>Osnat Aspis (Rambam Health Care Campus affiliated to the Technion)</u>
Project Role:	Study coordinator / Study nurse
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Osnat identifies potential patients in the ER, and assists the sub investigators during the recruitment in the ER, she also takes blood for the genetic tests.

Name:	<u>Dr. Alexis Baria (Northwestern University)</u>
Project Role:	Technician
Researcher Identifier:	ORCID ID: 0000-0001-6999-4021
Nearest person month worked:	5
Contribution to Project:	Alexis assists Dr. 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.

9. **REPORTABLE OUTCOMES:** Nothing to report.

10. **OTHER ACHIEVEMENTS:** Nothing to report.

11. **REFERENCES:** Nothing to report.

12. APPENDICES:

Appendix A: Quad Chart (clean version) and in the second version the changes marked in purple

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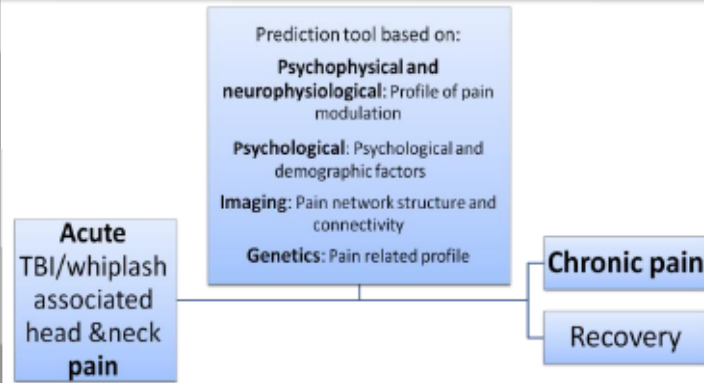PI: David Yarnitsky   Org: Technion – Israel Institute of Technology   Award Amount: $1,499,904

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.

Prediction tool based on:
Psychophysical and neurophysiological: Profile of pain modulation
Psychological: Psychological and demographic factors
Imaging: Pain network structure and connectivity
Genetics: Pain related profile

Acute TBI/whiplash associated head & neck pain → **Chronic pain** / Recovery

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	16	17	18
Building experimental setup				
Patients recruitment				
Patients follow-up				
Interim and final data analysis				
Reports and papers preparation				
Estimated Budget ($K)		220	650	630

Updated: (Oct 10th 2016)

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 Goals – 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 both military and civil populations.
Budget Expenditure to Date
Projected Expenditure: $1,499,904
Actual Expenditure: Around $220,000

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Quad Chart (changes marked in purple)

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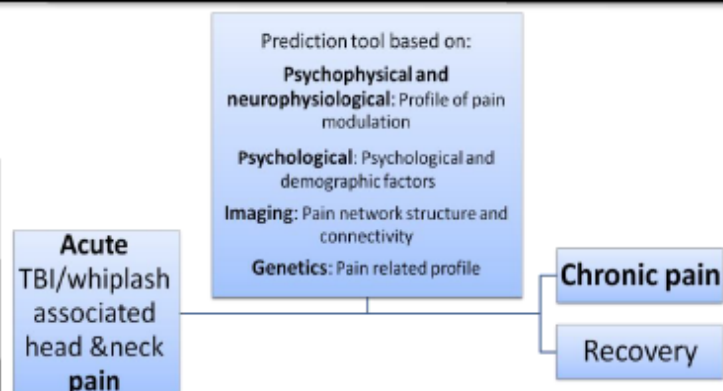PI: David Yarnitsky   Org: Technion – Israel Institute of Technology   Award Amount: $1,499,904

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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.

Prediction tool based on:

Psychophysical and neurophysiological: Profile of pain modulation

Psychological: Psychological and demographic factors

Imaging: Pain network structure and connectivity

Genetics: Pain related profile

Acute TBI/whiplash associated head &neck pain → Chronic pain / Recovery

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	16	17	18
Building experimental setup		▮		
Patients recruitment		▬	▬	
Patients follow-up		▬	▬	
Interim and final data analysis			▬	▬
Reports and papers preparation				▮
Estimated Budget ($K)		540 220	520 650	440 630

Updated: (Jan 6th 2016 Oct 10th 2016)

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 Goals – 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 both military and civil populations.
Budget Expenditure to Date
Projected Expenditure: $1,499,904
Actual Expenditure: Study not yet started Around $220,000