

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

RECIPIENT:
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REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release. Distribution is unlimited.

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REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
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1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 25 Sep 2016 – 24 Sep 2017
4. TITLE AND SUBTITLE Why does Acute Postwhiplash Injury Pain Transform into Chronic Pain? Multimodal Assessment of Risk Factors and Predictors of Pain Chronification			5a. CONTRACT NUMBER	
			5b. GRANT NUMBER W81XWH-15-1-0603	
			5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) 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 , PO Box 9649 Ha'Aliya no 8, Bat Galim, Haifa, AE 31096 IL			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			10. SPONSOR/MONITOR'S ACRONYM(S)	
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT See next page				
15. SUBJECT TERMS Mild traumatic brain injury, pain perception, pain modulation, fMRI, chronic pain, acute pain, whiplash injury				
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 17
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U		
				19b. TELEPHONE NUMBER (include area code)

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 228 patients, 127 of them participated in the first visit within 72 hours after the accident, 85 participants answred the 3 months follow up questions, 70 answered the 6 months, and 34 answered the 12 months follow up questions. 19 participated in the 6 months visit and 12 participated in the 12 months visit.

Based on initial analysis it can be concluded:

- a.** In the hyper-acute post-mTBI stage the somatosensory changes are independent of the psychological state of the patients.
- b.** Acute head pain, higher electrical temporal summation, and low socioeconomic status predict chronic post-traumatic pain occurrence. Pressure-pain threshold- conditioned pain modulation was also explored as a predictive avenue.
- c.** High EEG resting-state alpha power significantly predicts chronic post-traumatic pain intensity.

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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 during year 2:

Apply for local IRB and for HRPO:

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 on 25/July/2017 and submitted to the HRPO on 15/Aug/2017.

Patients recruitment and experimental performance:

We started recruiting immediately after HRPO first approval on March 2016.

First subject was recruited on 31/Mar/2016.

228 subjects were recruited by the end of September 2017. 127 subjects went on to perform the tests on the study protocol and continue with the follow up. 68 did not perform the testing protocol mostly due to scheduling issues, but had given blood for the genetic assessment, and are in our follow up program. The rest, 33 patient, failed to continue with the protocol after giving their consent and are drop outs.

We ran into a few problems in the process of patients recruitment:

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. 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.

Up until today we added 15 physicians to our study, obtained local IRB approval for them, as well as trained them with the protocol, and inclusion, exclusion criteria. This was a mitigation to the problem of covering the largest hour span during the week we could for screening and recruiting patients in real time during their ER visit after the injury.

Another problem was the availability of the MRI scanner: Most of the subjects 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. This step enabled an increase in the rate of participation. During September 2016 we added the evening ER team as recruiters in order to increase the number of recruitments. On May 2017 we recruited a Neurologist to handle the recruitment and the follow up visits, and during Oct 2017 she will be replaced by another physician, in order to increase recruitment rate.

On July 2017 our study was submitted to the Israeli Defense Force for approval, in order to enable us recruiting soldiers. The study was not approved by the IDF ethics committee, since there is no direct benefit for the participating soldiers.

We hope that the solutions we found and mentioned above will lead us to higher recruitment rate. Despite all mentioned above we believe that by the end of Year 3 on Sep 2018 we would ask for extension without funds to the expiration date of the award. In that case our recruitment and follow up period will continue until Dec 2018, and final data analysis, reports and paper preparation will be done until Sep 2019.

Quad chart was updated again 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).

Regarding the experimental performance:

100 Blood samples were transferred to the genomic lab, and DNA was extracted. They have processed 96 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.

Dr. Diatchenko and Prof. Belfer visited our site for a thorough discussion of the research project, and visited the Genetic lab during June 2017 and were pleased with the process and the quality of the samples.

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 the PhD students associated with this project will visit Apkarian's lab next month for a few weeks stay in order to speed up the analysis of the imaging data. She will look into the clinical-psychophysical interaction with the imaging data for the patients recruited so far.

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. 85 participants answered the 3 months follow up questions, 70 answered the 6 Months, and 34 answered the 12 months questions.

3b. Visits 6 and 12 months: 6 patients completed both 6 and 12 months, 6 completed 12 months visit only, and 13 patients completed 6 months visit and will complete 12 months soon. 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 recruits.

Analysis of QST and Selected Questionnaires has been performed for patients 1-100.

Analysis of Resting State EEG has been performed for patients 1-83, with evoked potentials evaluated for patients 1-60.

MRI data has been pre-processed for patients 1-108, with scheduled training session for further analysis planned for the end of November 2017, wherein the Israeli PhD student will train with the Northwestern staff.

Pain pattern analysis for the 1st 6 months post-injury is currently being performed for all available data.

First results 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. The analysis of cumulating results will be done during November 2017 and at the end of the data collection.

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:

Preliminary data for the scientific report based on the results of 3 month follow-up from 62 whiplash patients who were tested at their acute post-traumatic phase by mid-August 2017. These data are reported in 2 scientific abstracts, and were presented as poster presentations at the 10th Congress of the European Pain Federation, EFIC in September 2017.

The abstract of Kuperman et al assessed the predictive role of clinical, demographic and quantitative sensory testing parameters assessed within 72h post-accident, and found that acute head pain, higher electrical temporal summation, and low socioeconomic status

predict chronic post-traumatic pain occurrence. Pressure-pain threshold- conditioned pain modulation was also explored as a predictive avenue.

Granovsky et al expanded the question for the role of resting-state EEG activity and found that high EEG resting-state alpha power significantly predicts chronic post-traumatic pain intensity. Please find both abstracts at section 7 below.

A first paper out of this study is in the final stages of writing. It analyses the baseline QST, demographic and pain-related psychological questionnaire data from the first 100 patients and a group of 80 healthy controls. This paper shows that in the hyper-acute post-mTBI stage the observed somatosensory changes are independent of the psychological changes, thus supporting the organic basis of the WAD clinical picture, at least in this time window.

5. CONCLUSION:

Based on our first results mentioned above, in a paper in preparation and in two abstracts, we can conclude, for now:

- a.** In the hyper-acute post-mTBI stage the somatosensory changes are independent of the psychological state of the patients
- b.** Acute head pain, higher electrical temporal summation, and low socioeconomic status predict chronic post-traumatic pain occurrence. Pressure-pain threshold- conditioned pain modulation was also explored as a predictive avenue.
- c.** High EEG resting-state alpha power significantly predicts chronic post-traumatic pain intensity

6. CHANGES/ PROBLEMS

See section 3 OVERALL PROJECT SUMMARY task 2 above, pages 5-6.

7. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

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 ($VAS \leq 30$).

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

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Prof. David Yarnitsky (Technion)
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: 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: 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: 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: 2
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: 3
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: 2
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 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: Dr. Noam Bosak (Rambam Health Care Campus affiliated to the Technion)
Project Role: Study Physician
Researcher Identifier:
Nearest person month worked: 5
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: Research Assistant Professor Lejian Huang (Northwestern University)
Project Role: Technician
Researcher Identifier: ORCID ID: 0000-0003-1753-2372
Nearest person month worked: 4
Contribution to Project: Haung 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.

Name: Dr. Alexis Baria (Northwestern University)
Project Role: Technician
Researcher Identifier: ORCID ID: 0000-0001-6999-4021
Nearest person month worked: 6
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 next page 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

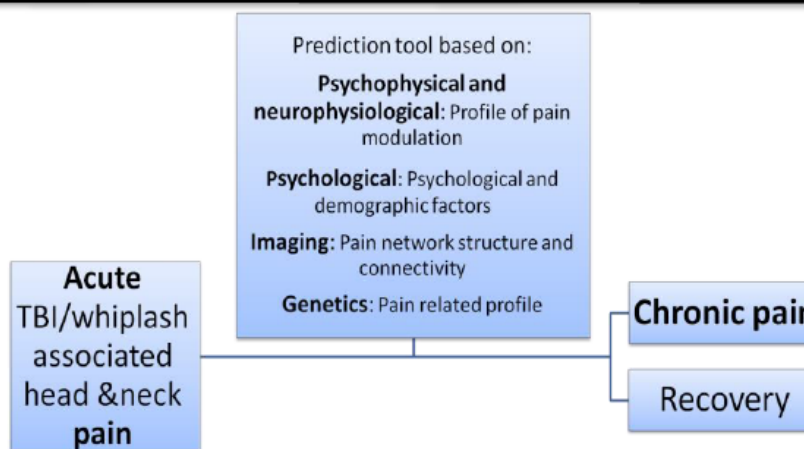


Study Aim(s)

- 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.



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)		257	177	1065

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 \$434,000

Updated: (Oct 19th 2017)

Quad Chart (changes marked in purple):

Why does acute post whiplash injury pain transform into chronic pain?

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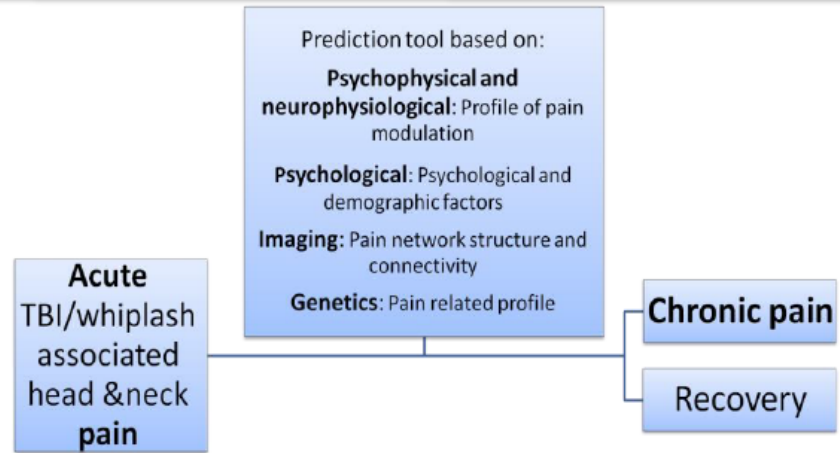


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Activities	CY	16	17	18
Building experimental setup		█		
Patients recruitment		██████████	██████████	██████████
Patients follow-up		██████████	██████████	██████████
Interim and final data analysis			██████████	██████████
Reports and papers preparation				█
Estimated Budget (\$K)		220-257	650-177	630-1065

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 **both military and** civil populations.

Budget Expenditure to Date

Projected Expenditure: \$1,499,904

Actual Expenditure: Around \$220,000-**\$434,000**

Updated: (Jan ~~6th~~ 2016-Oct 19th 2017)



Why does acute post whiplash injury pain transform into chronic pain?

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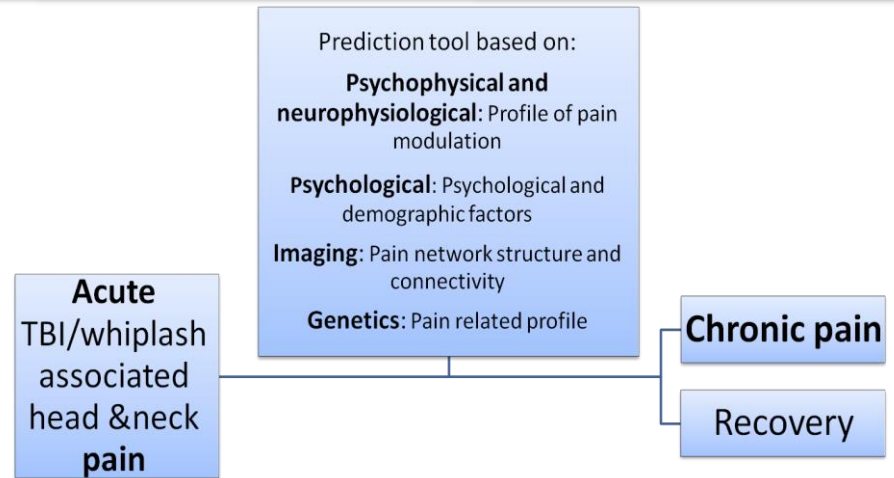
Award Amount: \$1,499,904

Study Aim(s)

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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)		257	177	1065

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 **\$434,000**