Photosensitivity and Pain in Traumatic Brain Injury

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mTBI Symposium

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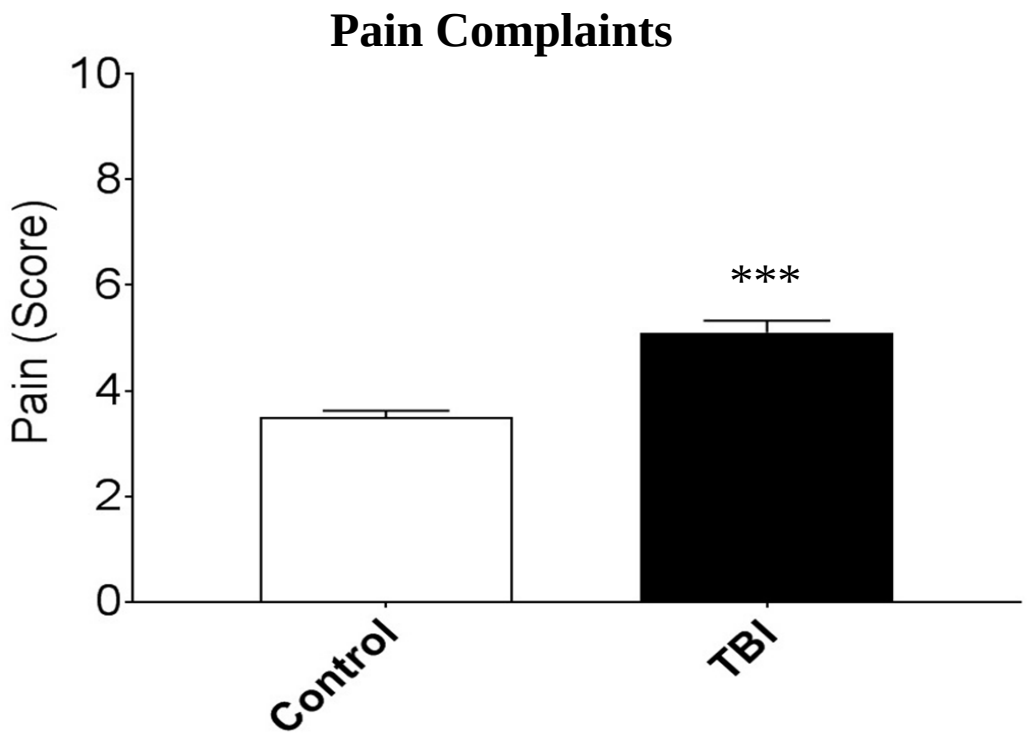
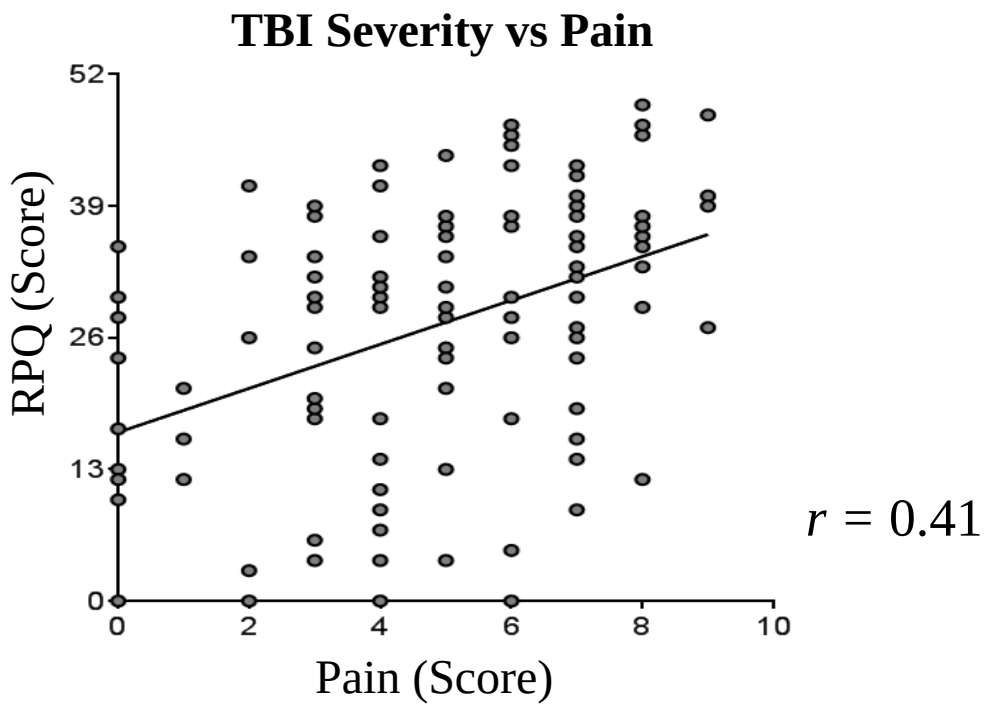
TBI and Chronic Pain

- Chronic pain is a common complaint from individuals with TBI (Nampiaparampil, 2008)
- Can occur in individuals 10+ years our from initially head injury



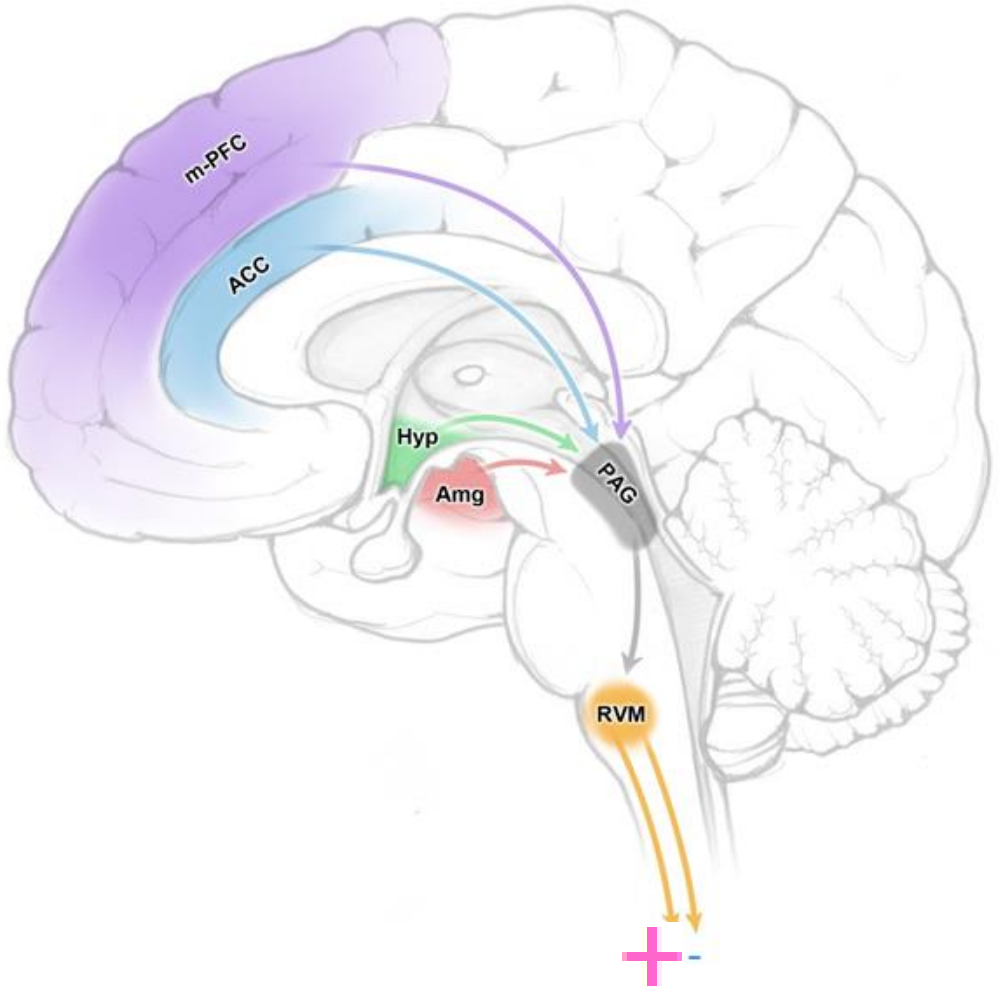


$r = 0.41$

Adapted from Balba & Elliott et al., 2018

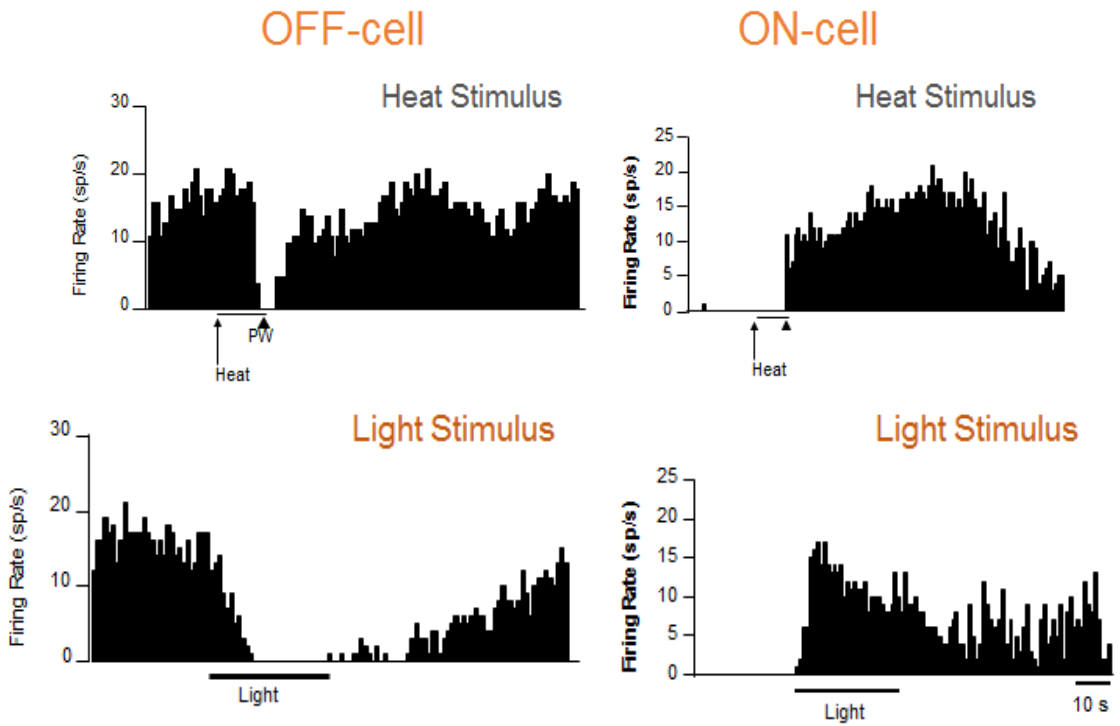
Central Sensitization

- Chronic pain often explained by “central sensitization”: heightened activity in pain-processing circuits at the spinal cord and in brain
- Responsible for allodynia and hyperalgesia
- Direct demonstration of central sensitization difficult in patients

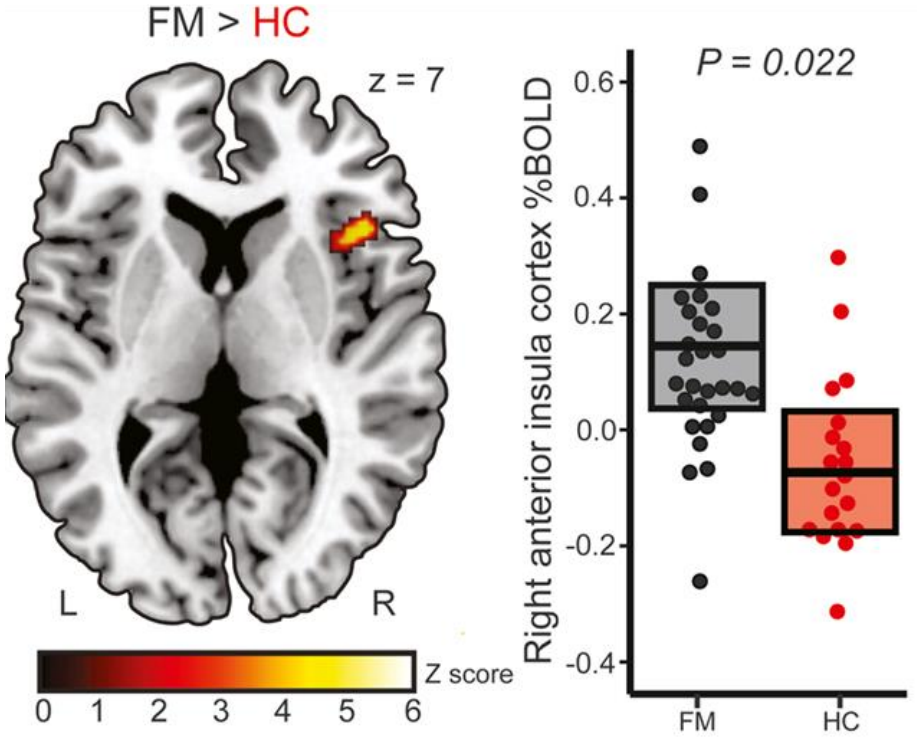


A Link between Light and Pain

- In rodent models, light can activate nociceptive neurons while simultaneously inhibiting anti-nociceptive neurons
- Patients with fibromyalgia report higher levels of photosensitivity, light can activate pain-related circuitry in these subjects



Martenson et al., 2016

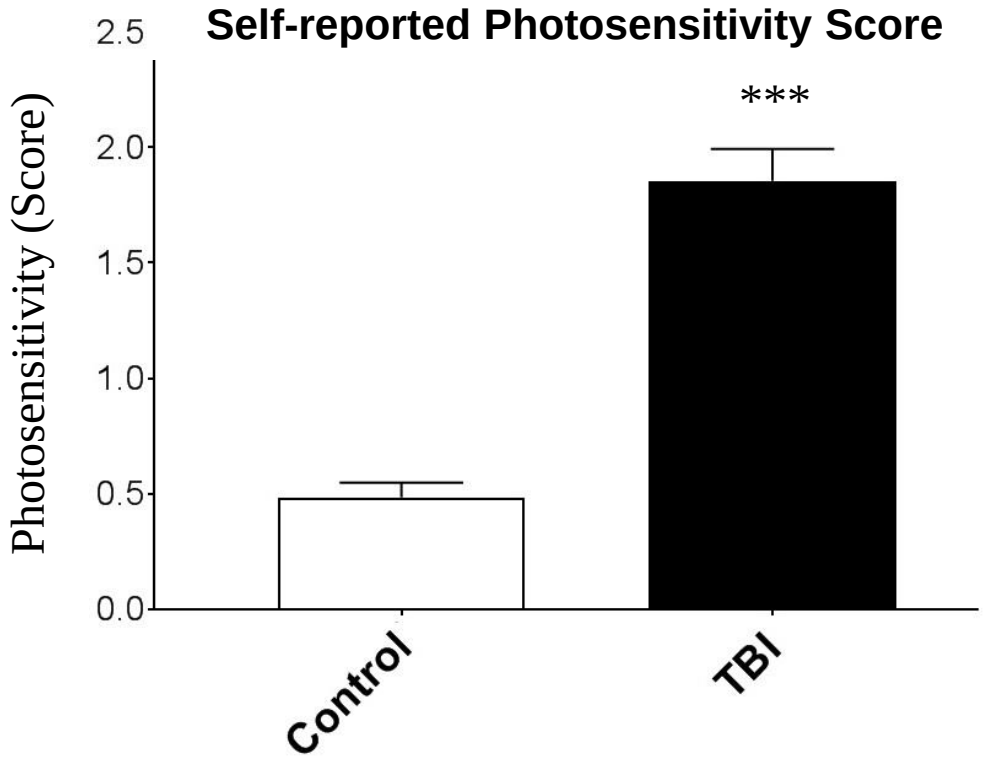


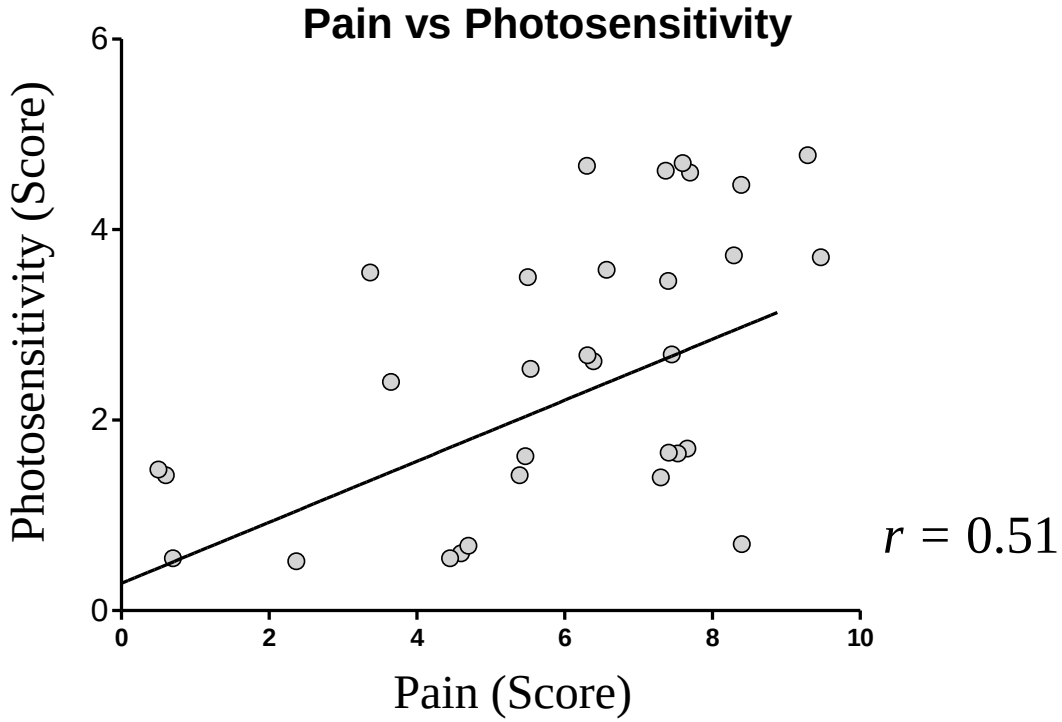
Harte et al., 2016

Photosensitivity and Pain in TBI

- Photosensitivity is a common symptom after TBI and can last for years after injury (Callahan et al., 2016; Balba et al., 2018)

- Photosensitivity complaints are correlated with pain complaints





Adapted from Balba & Elliott et al., 2018

Rationale for Current Study

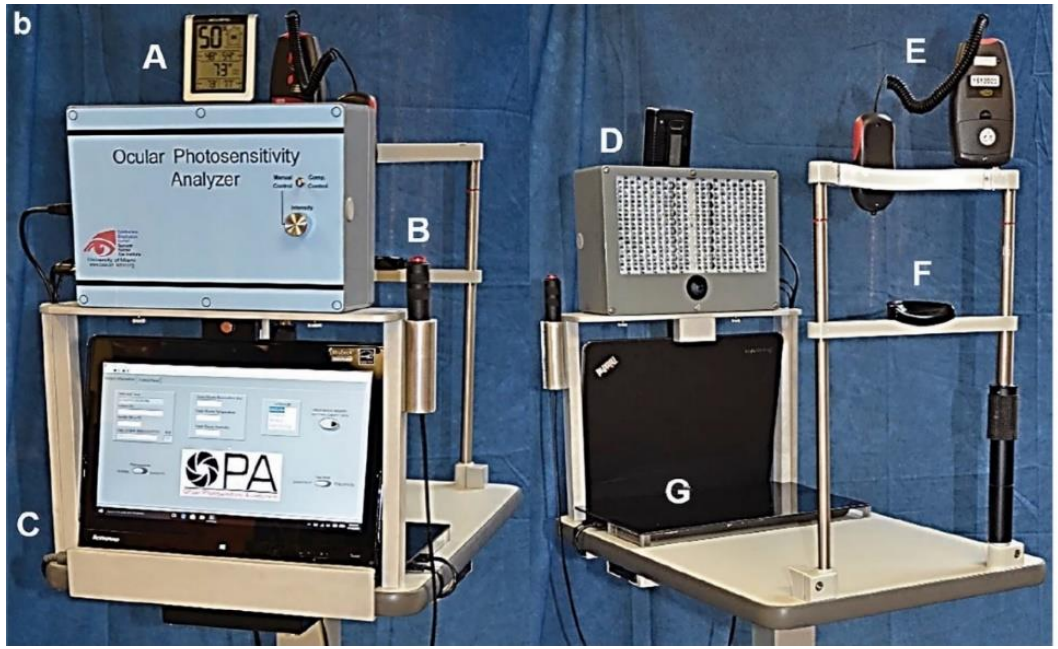
1. Test photosensitivity and pain thresholds using more objective measures in TBI subjects, with and without symptoms, and non-TBI subjects

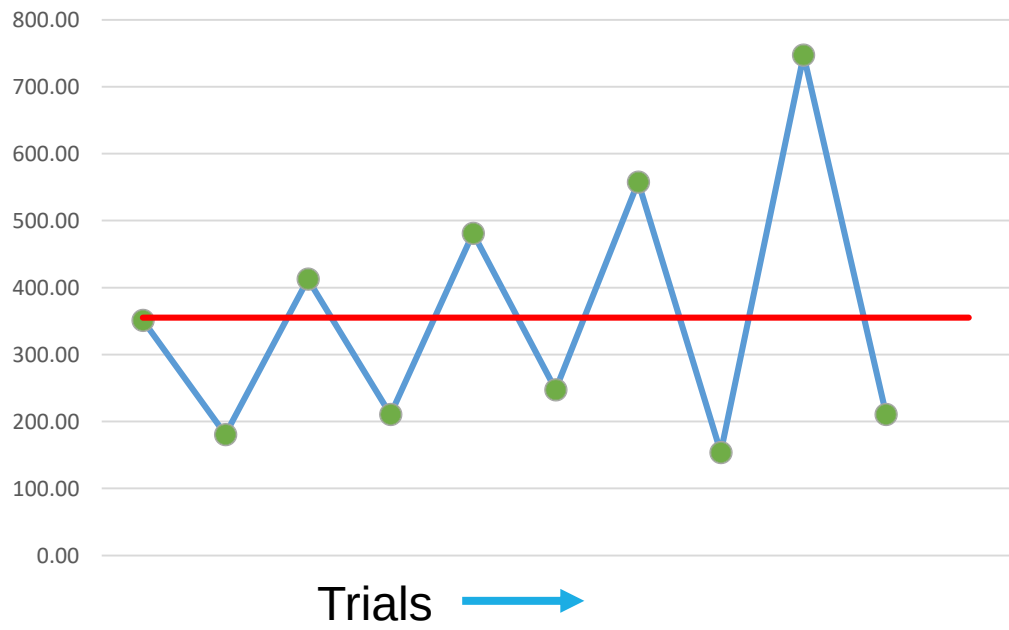
2. Determine whether photosensitivity is related to clinical pain complaints and whether light can activate pain-related circuitry in TBI subjects suffering from chronic pain

Methods

- Quantify visual photosensitivity thresholds (VPT) using Ocular Photosensitivity Analyzer

- Provides a continuous variable of photosensitivity using objective stimuli

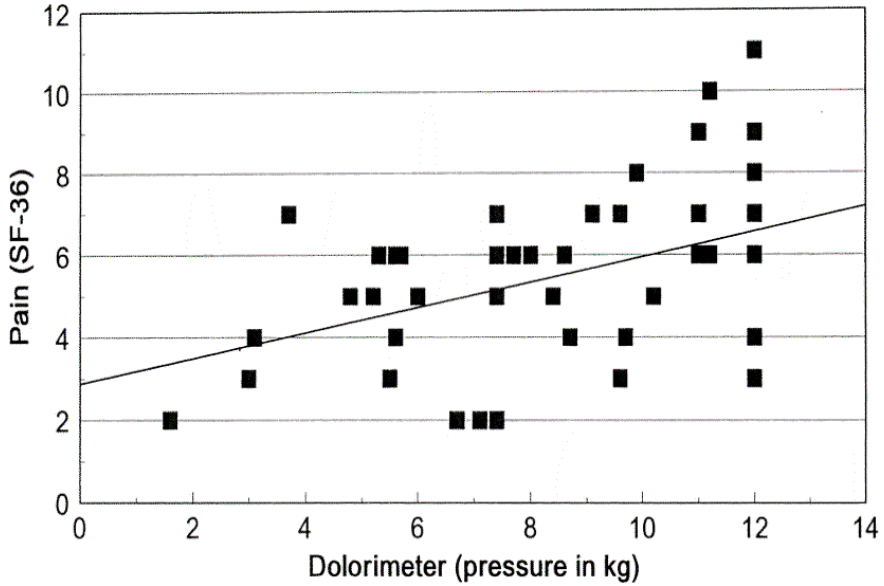




Verriotto et al., 2017

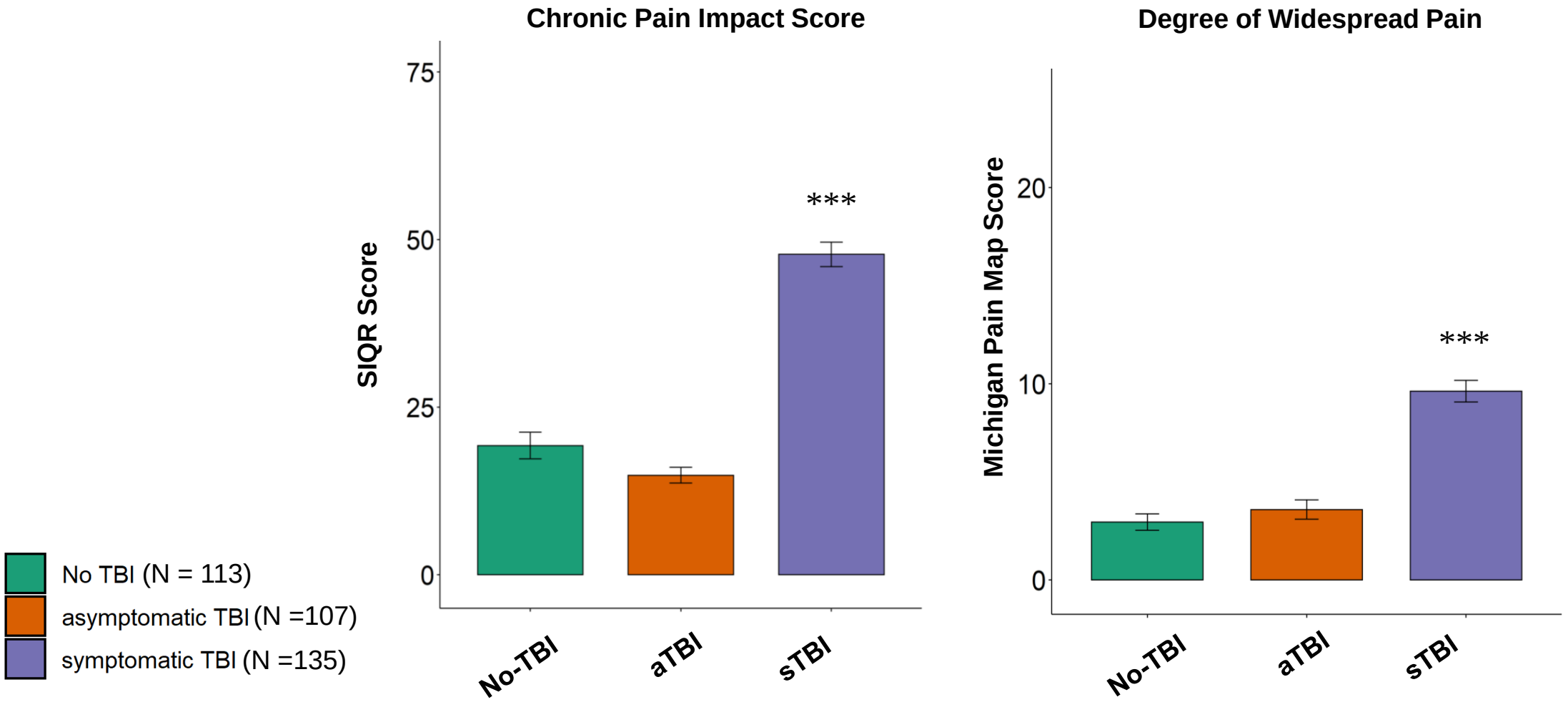
Methods

- Quantify pressure pain thresholds and tolerance levels using pressure algometry
- Correlates with pain complaints in other chronic pain populations
- Has been gold standard in pain research

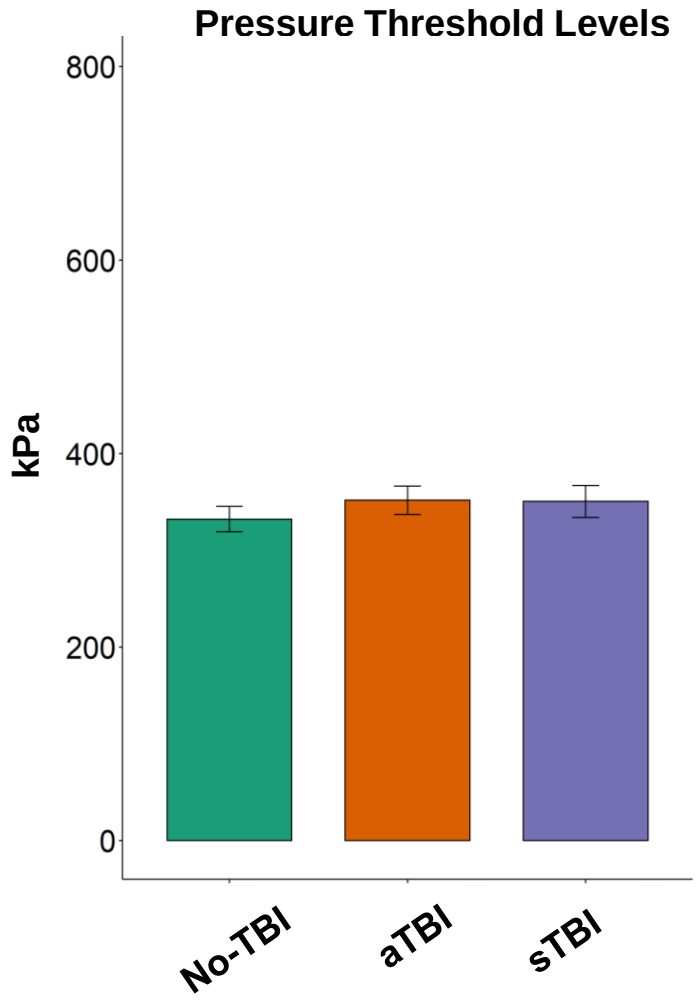


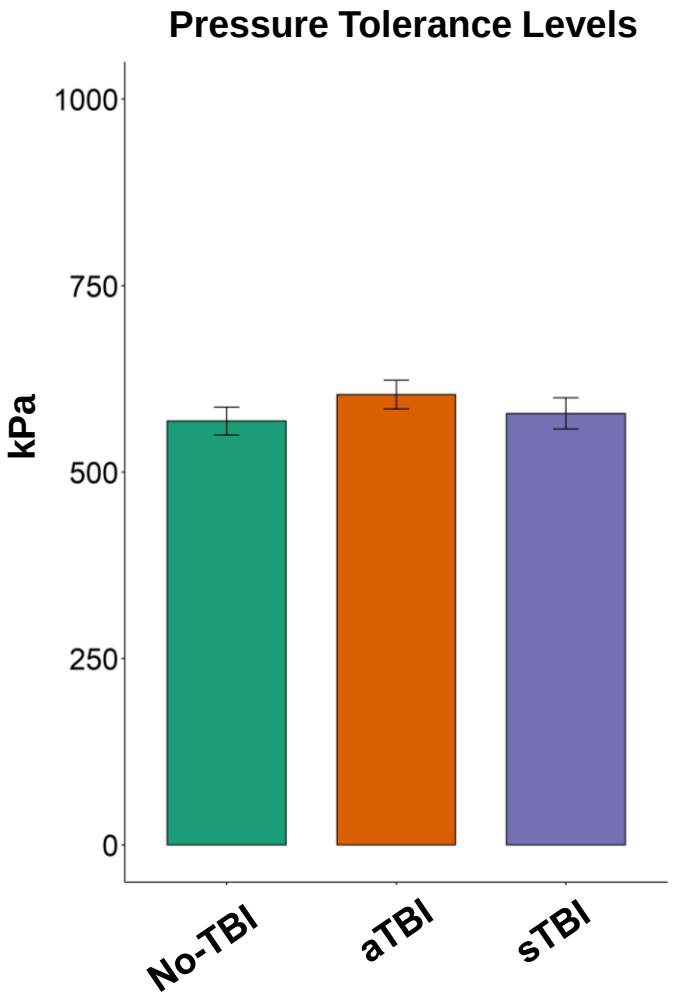
Clauw et al., 1999

Differences in Self-Reported Chronic Pain



No Differences in Pressure Algometry



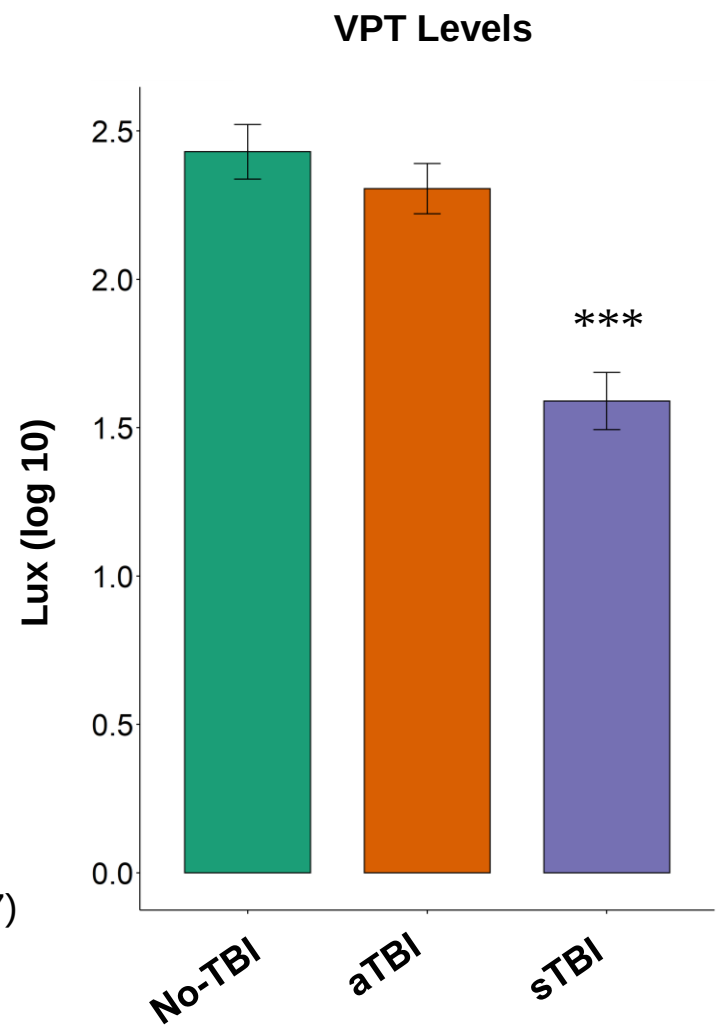


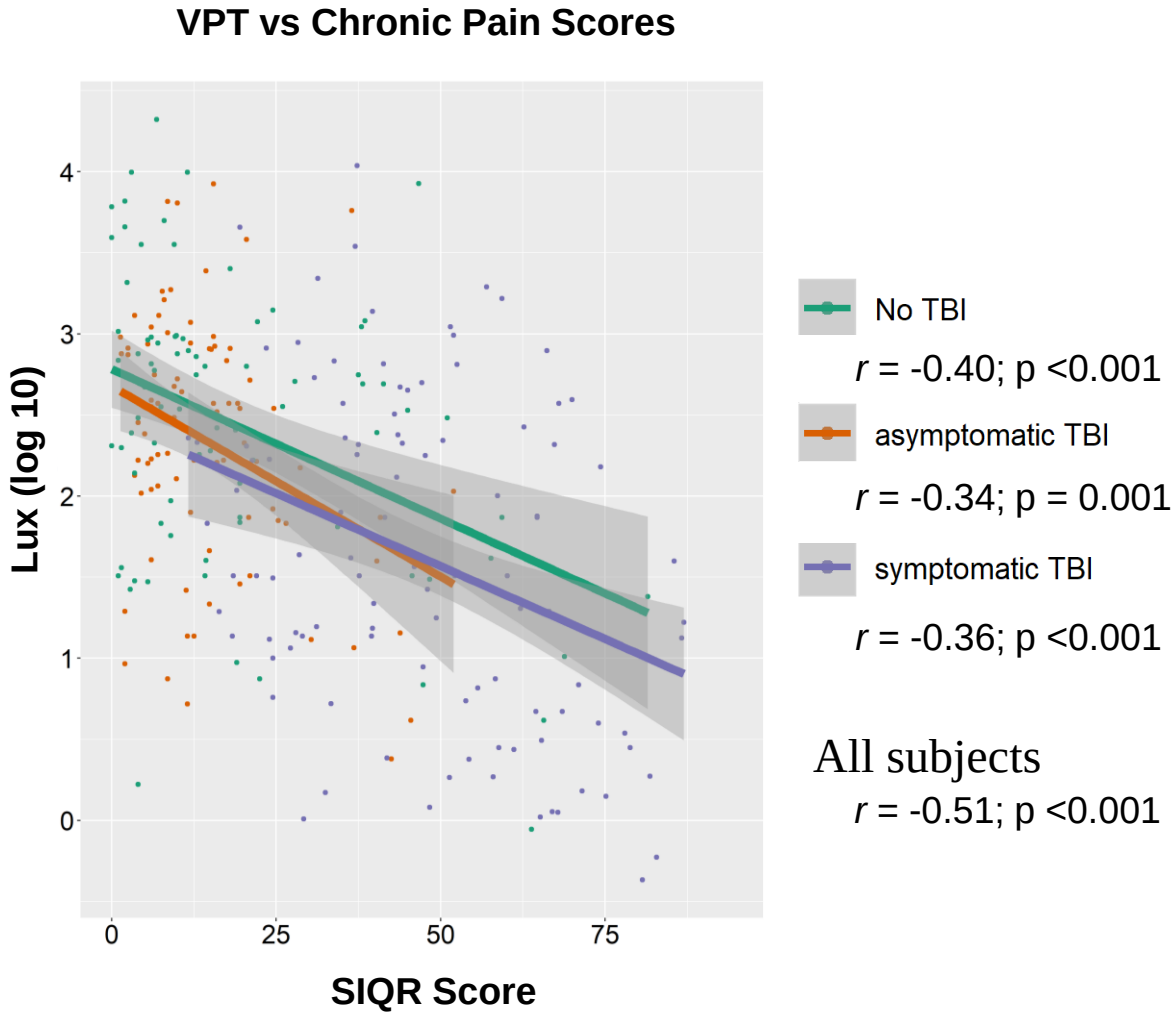
No TBI (N = 113)

asymptomatic TBI (N =107)

symptomatic TBI (N =135)

Strong Correlation between VPT and Chronic Pain

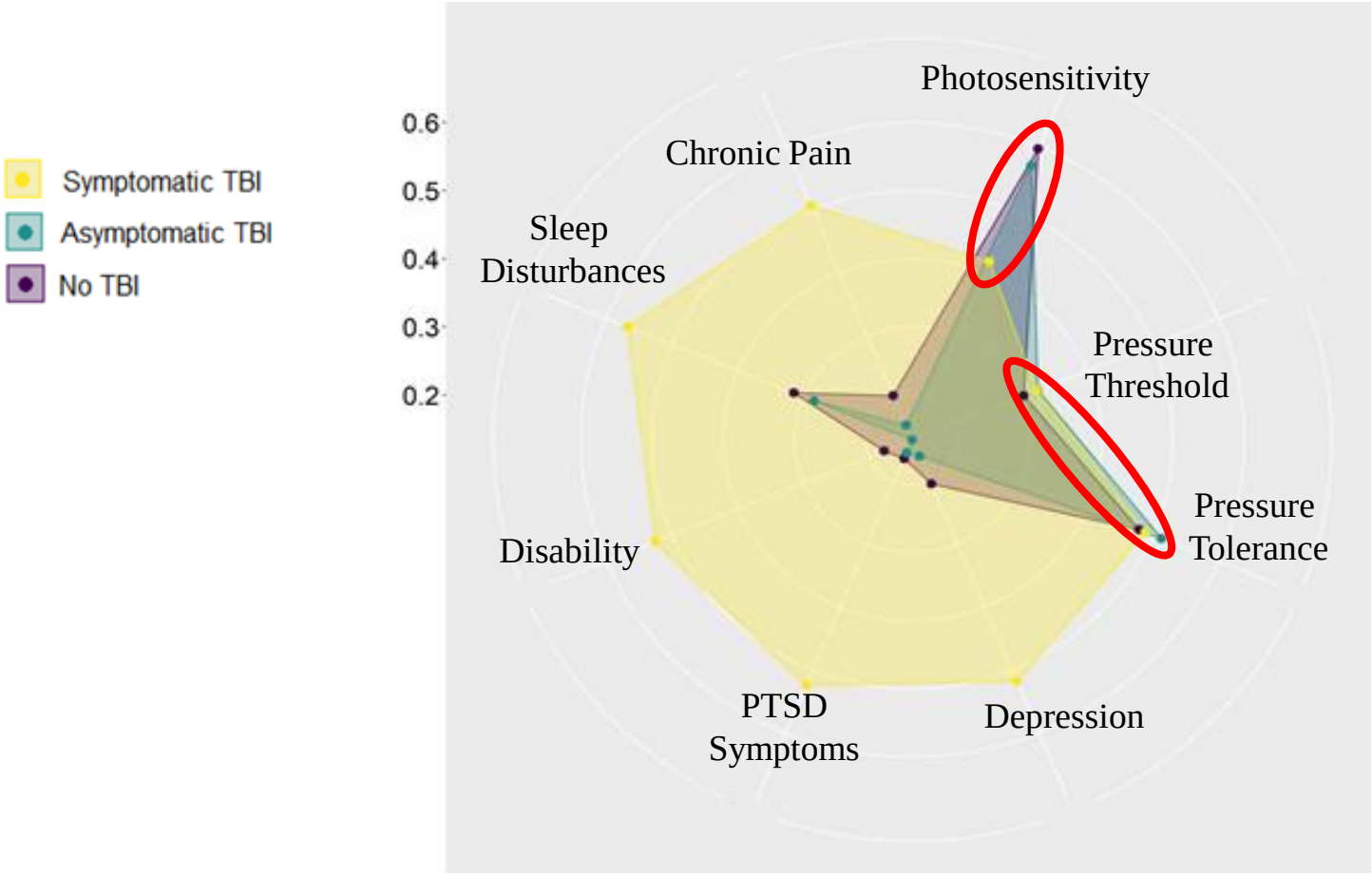




No TBI (N = 113)
asymptomatic TBI (N =107)
symptomatic TBI (N =135)

A Marker in Chronically Symptomatic TBI

- Symptomatic TBI group exhibit higher levels of chronic pain, sleep disturbances depression, PTSD symptoms, and disability than asymptomatic and non-TBI groups



Conclusions

- Photosensitivity could be used as a marker of central sensitization in “high-impact” chronic pain populations
  - These populations are often treated with ineffective opioid medications, this novel marker could inform new treatment options

- Future Directions:
  - Currently collecting fMRI data to test whether light is activating pain-related circuitry in out symptomatic TBI population
  - Longitudinal studies that track the progression of photosensitivity following TBI
  - Continuing rodent studies to better understand neural circuitry

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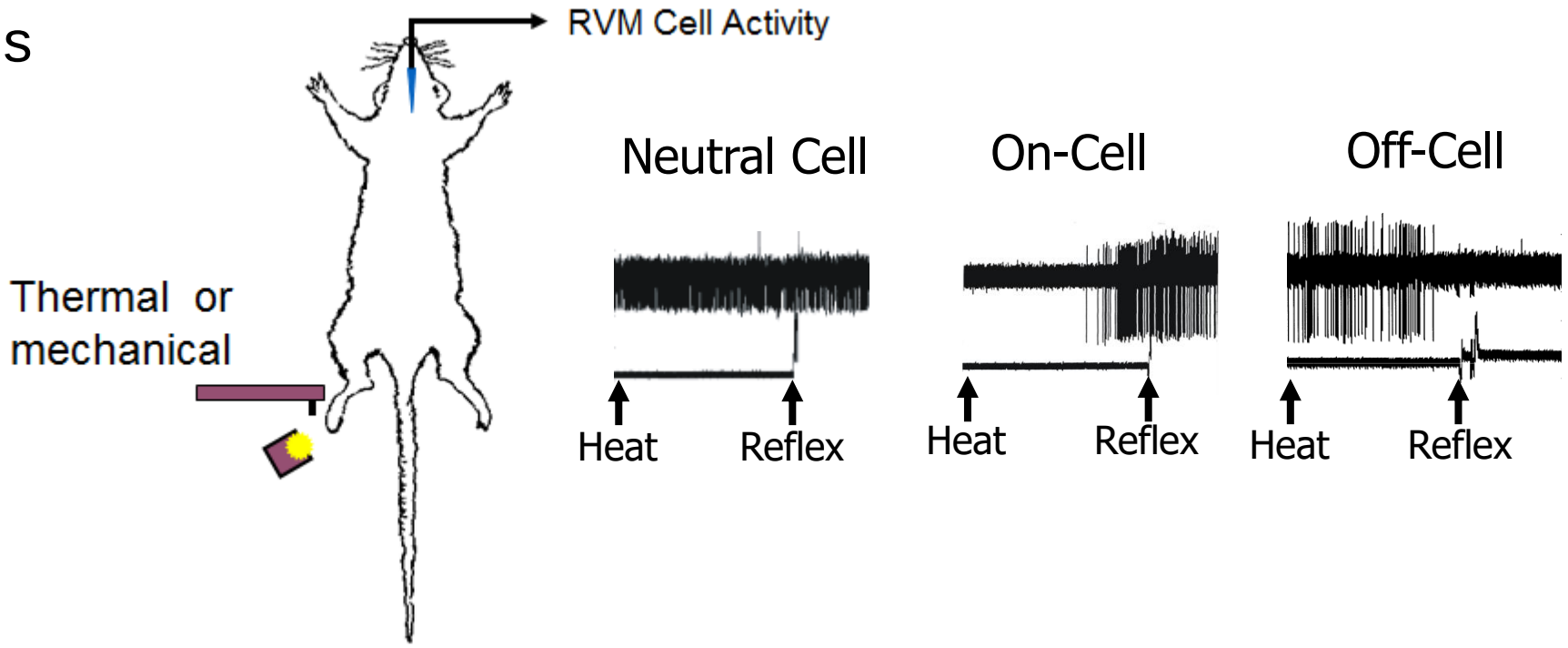
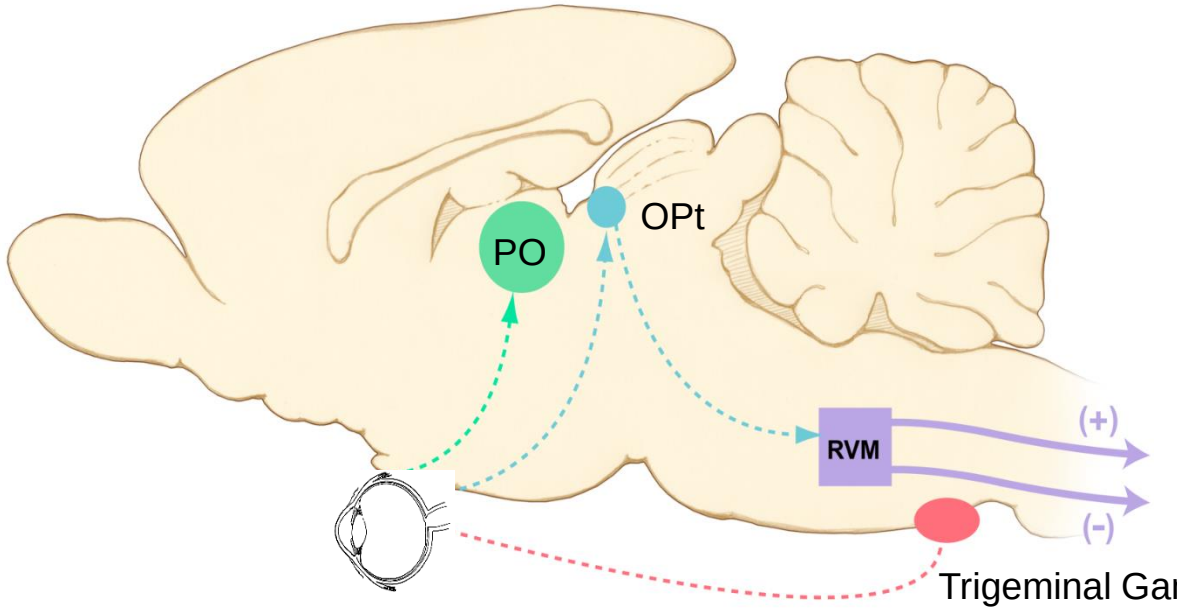
Links Between Light and Pain

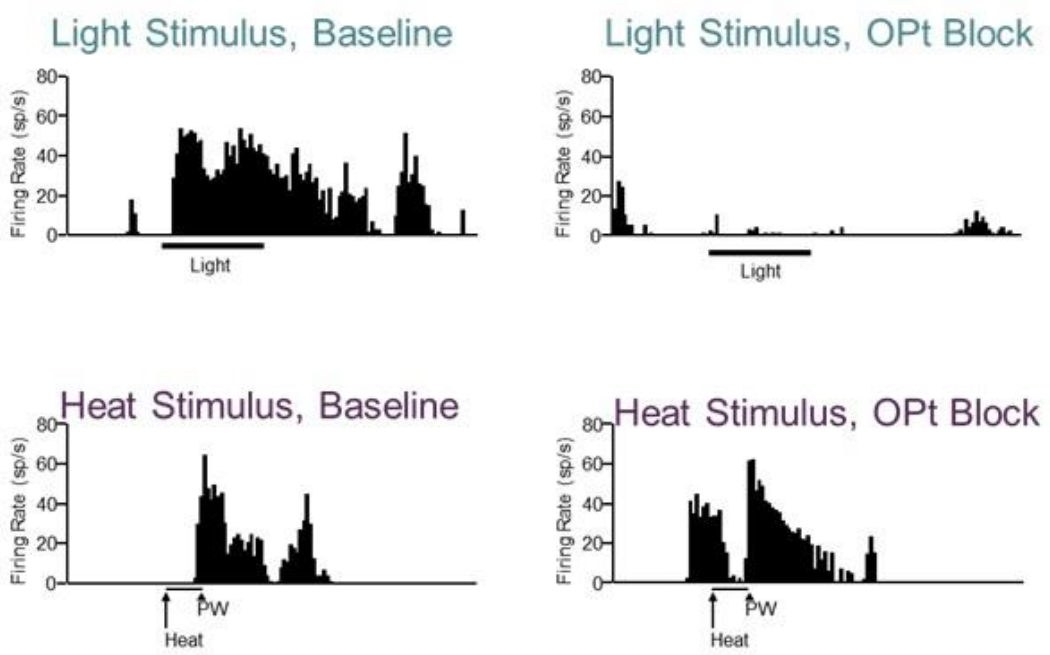
- The rostral ventromedial medulla (RVM) is key brain region encoding painful stimuli
- Electrophysiological recordings have characterized 3 types of neurons, 2 of which are responsive to painful stimuli
  - ON-cells
  - OFF-cells



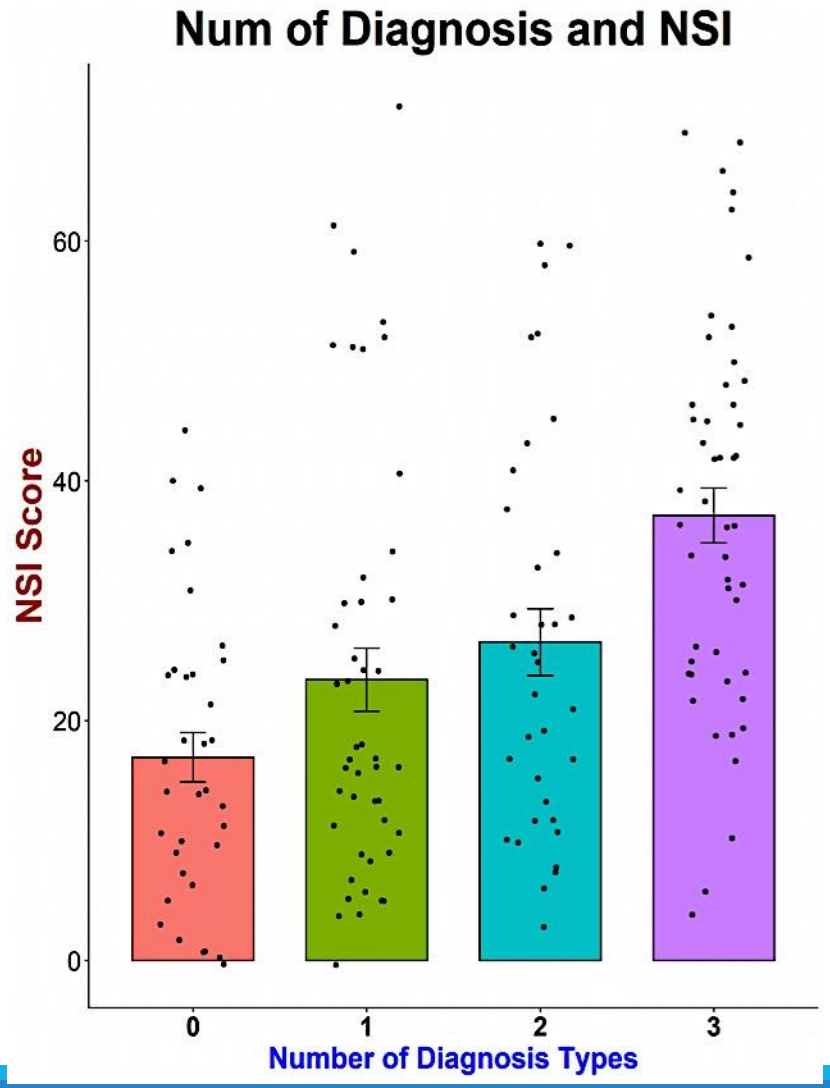
Links Between Light and Pain

- Response linked to intrinsic photosensitive retinal ganglion cells (ipRGCs)
- Encode environmental light levels through their activity
- Part of non-image forming vision
- Project to the olivary pretectal nucleus (OPt)
  - When OPt is blocked, ON/OFF cells no longer respond to light





“Triple (+) diagnosis” group reports more symptomatic TBI than all other groups (*P* <0.001)



TBI_Diagnosis_Type

0

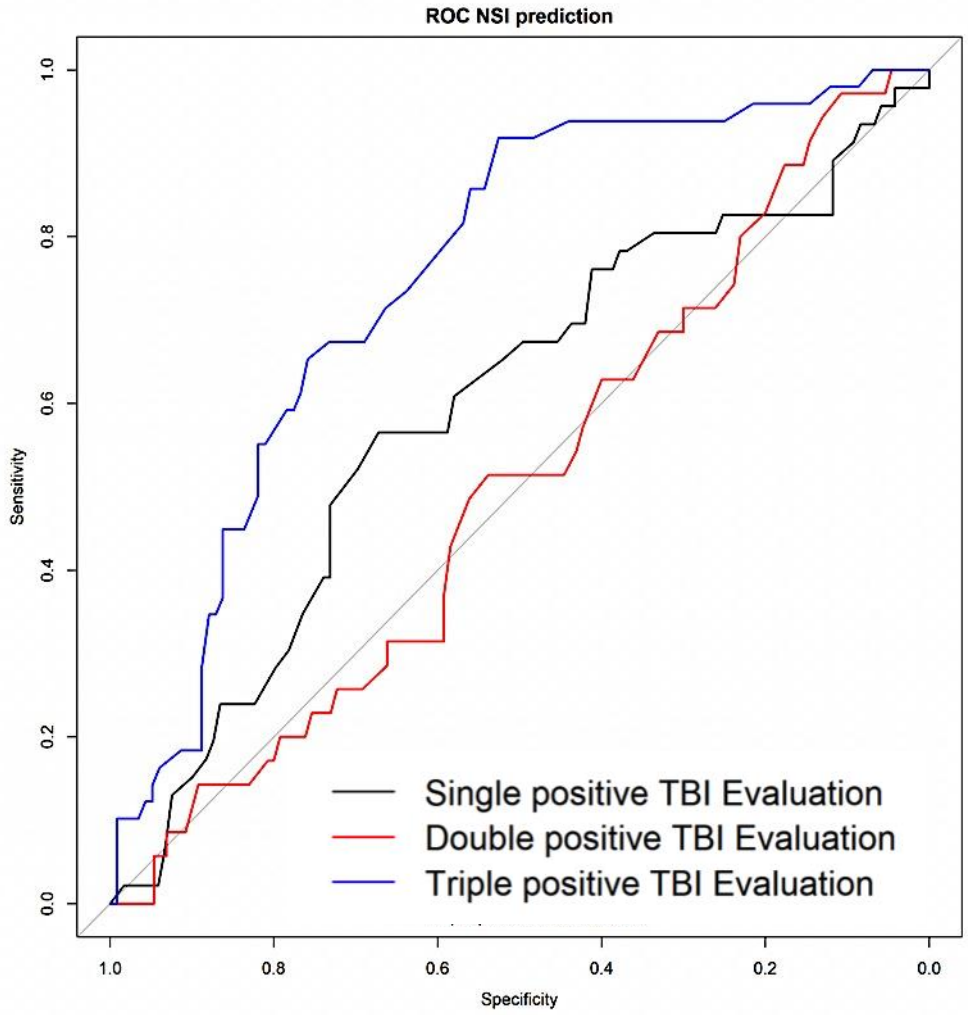
1

2 *

3 **

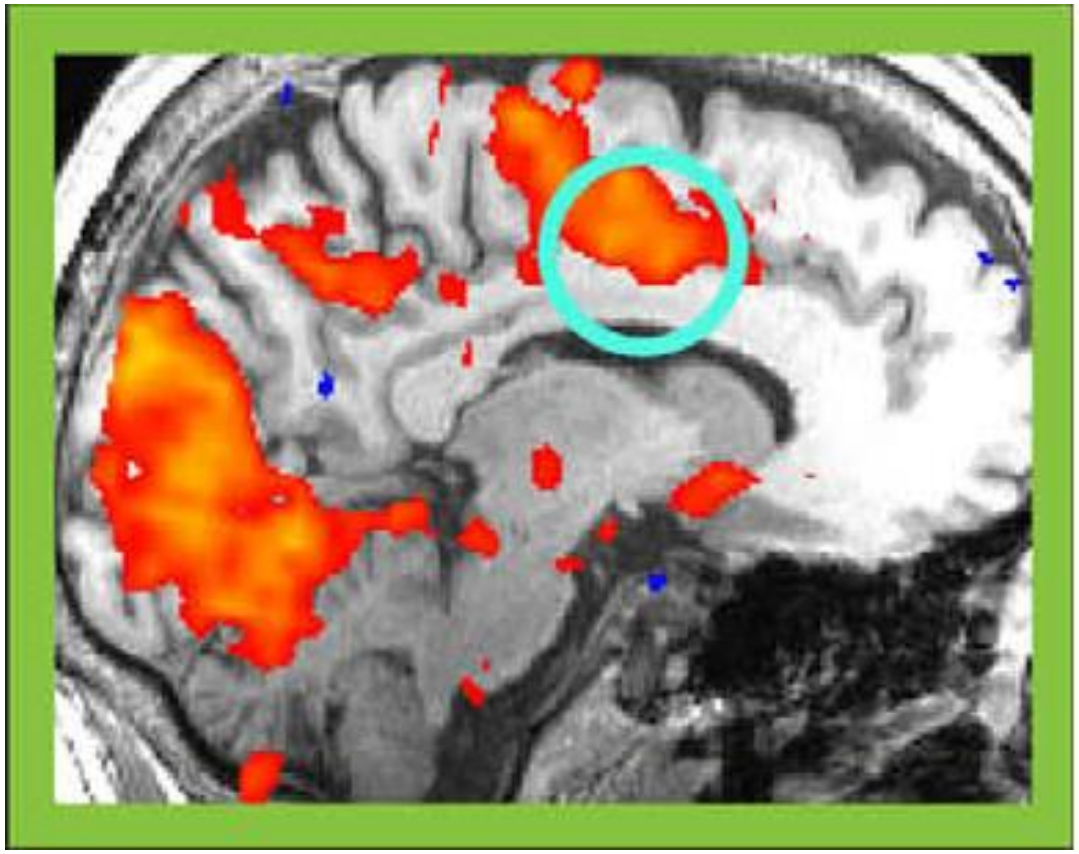
Self-report, Chart, or HTEC interview

ROC by Evaluation Congruency



- Number of positive diagnoses has a significant effect on accuracy of model:
  - Triple (+) had significantly higher AUC than Single (+) or Double (+).
  - Single (+) and Double (+) were no better than chance!
- TBI status is predicted by NSI scores only in Triple (+) subjects.

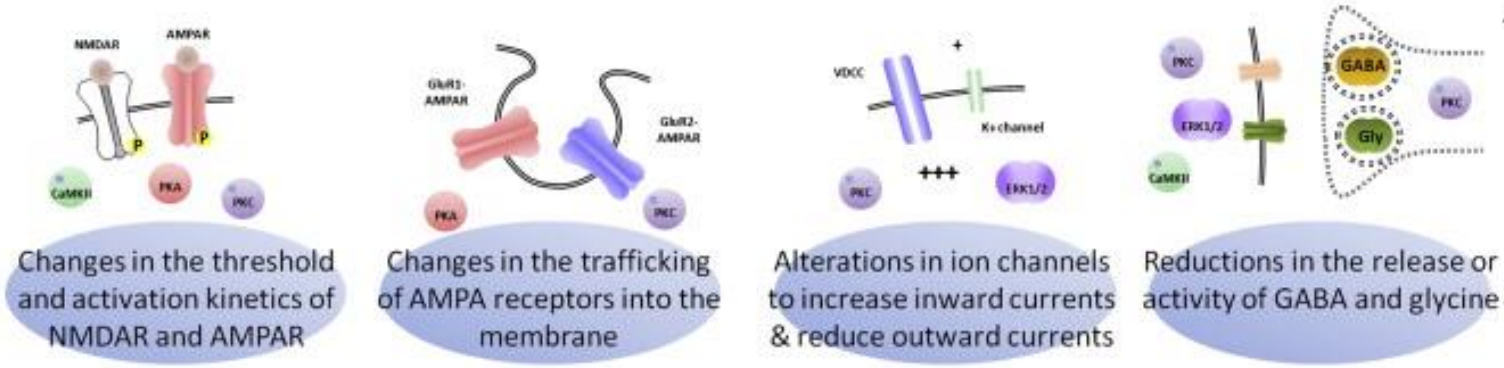
AUC=0.59; 95% CI [0.40, 0.61]; P = 0.01
AUC=0.51; 95% CI [0.49, 0.61]; P <0.001
AUC=0.76; 95% CI [0.68, 0.84]



(Moulton, 2009)

Nociceptive inputs

Effectors:



Changes in the threshold and activation kinetics of NMDAR and AMPAR

Changes in the trafficking of AMPA receptors into the membrane

Alterations in ion channels to increase inward currents & reduce outward currents

Reductions in the release or activity of GABA and glycine

Cellular processes:

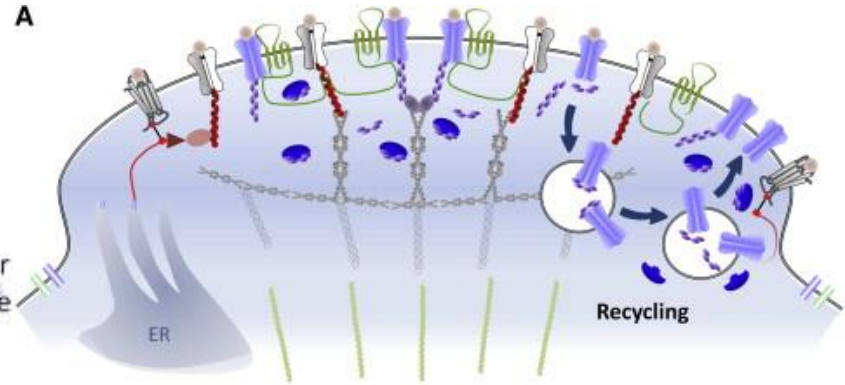
Increase of membrane excitability

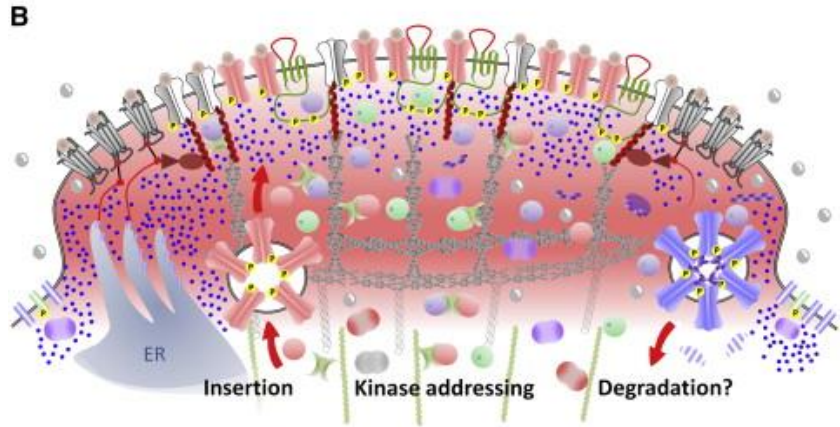
Synaptic facilitation

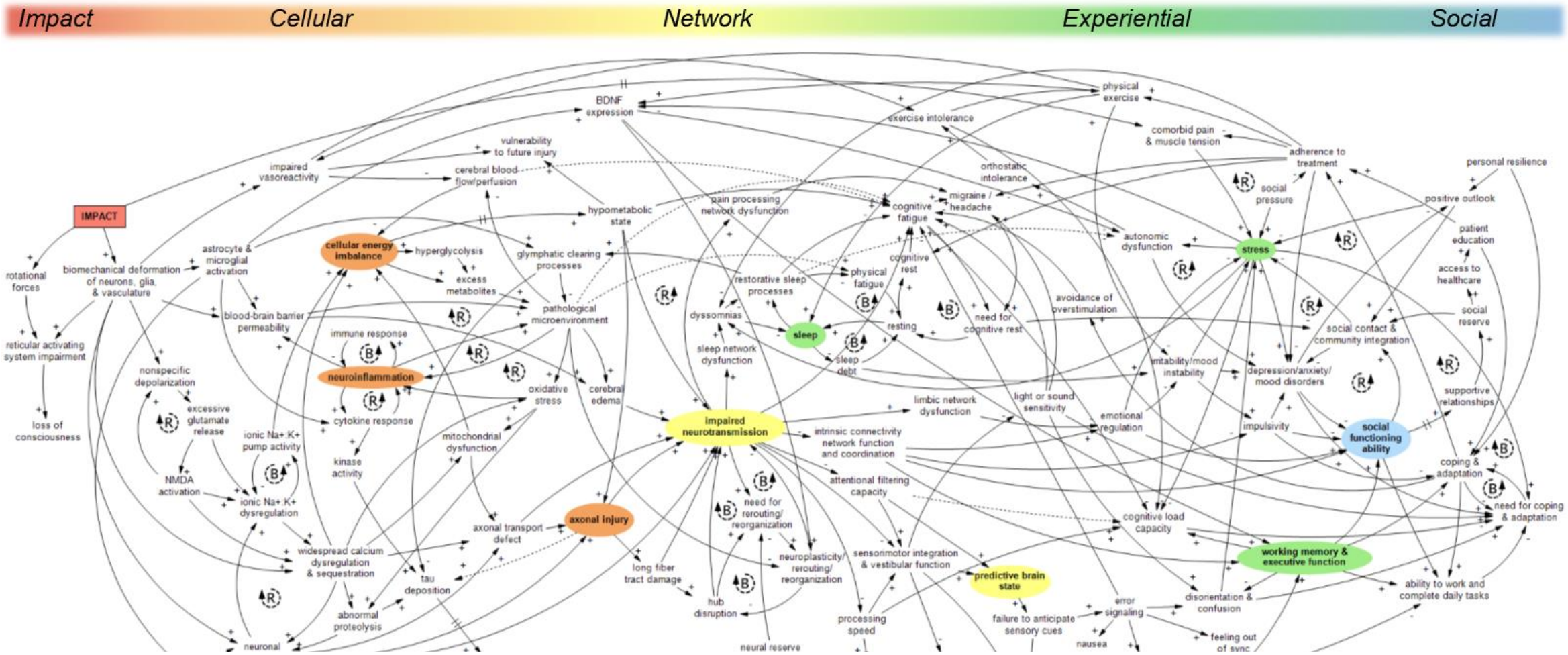
Disinhibition

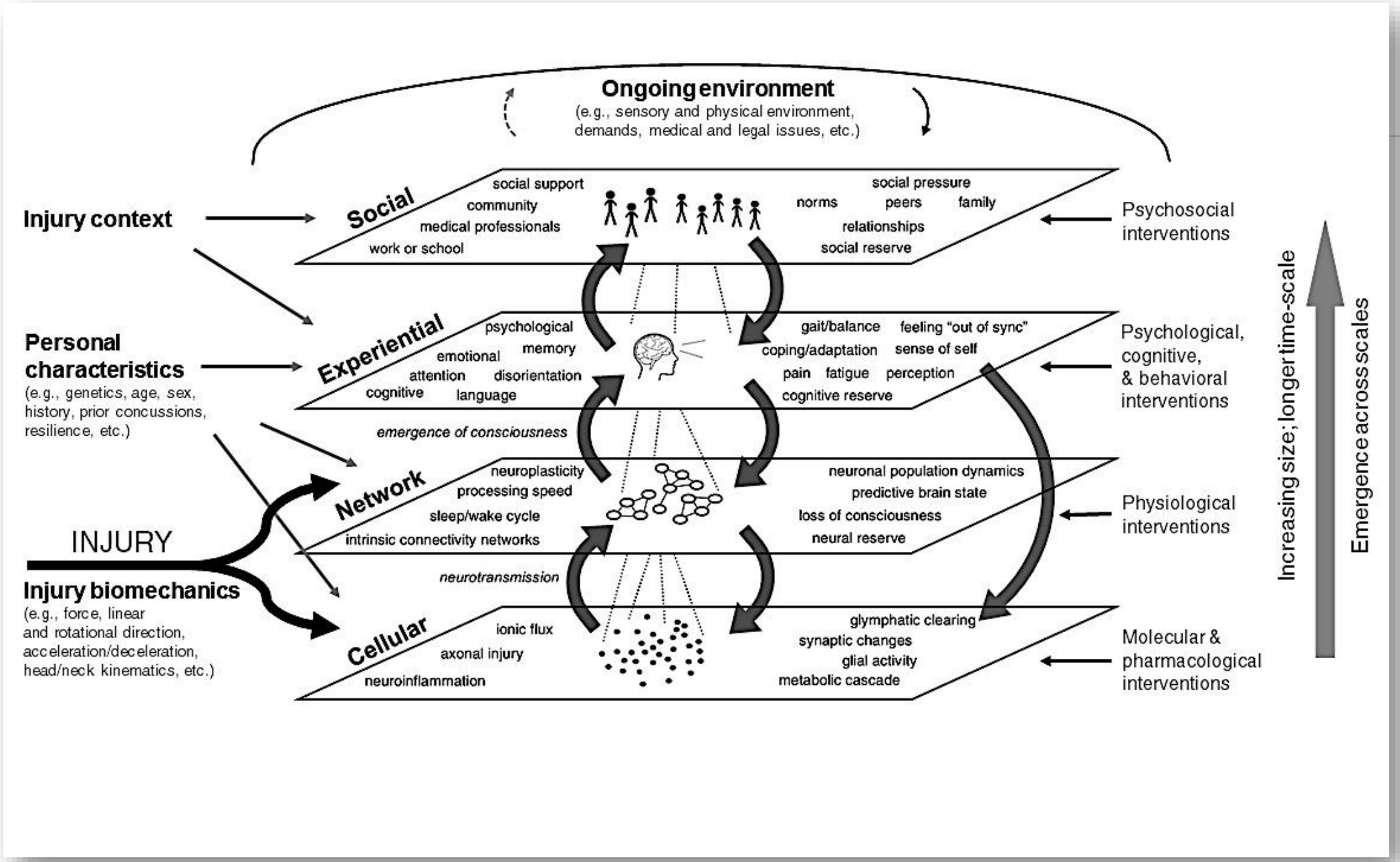
Central sensitization:

- Development of or increases in spontaneous activity
- Reduction in threshold for activation by peripheral stimuli
- Enlargement of their receptive fields (conversion of nociceptive-specific neurons to wide dynamic neurons that now respond to both innocuous and noxious stimuli)

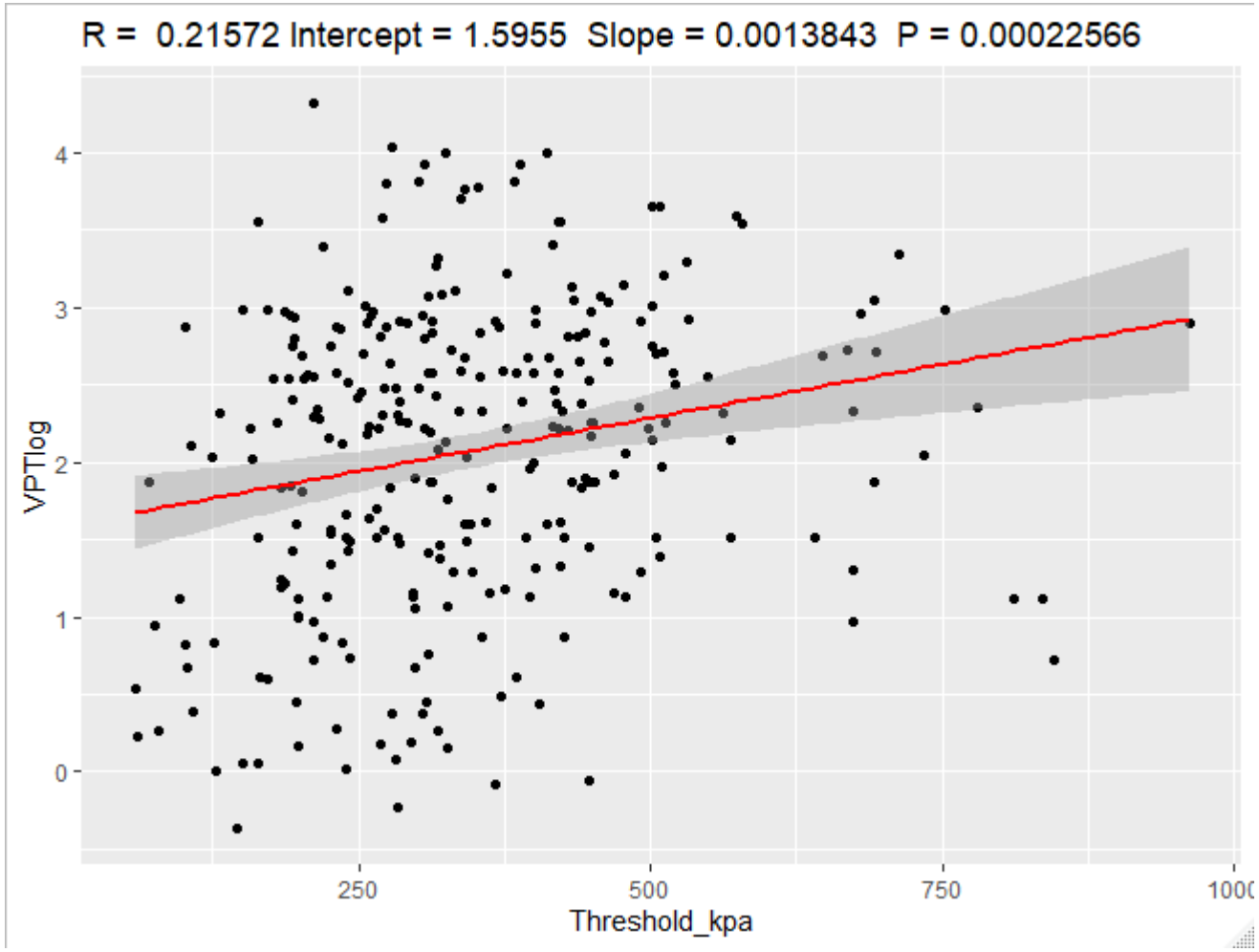




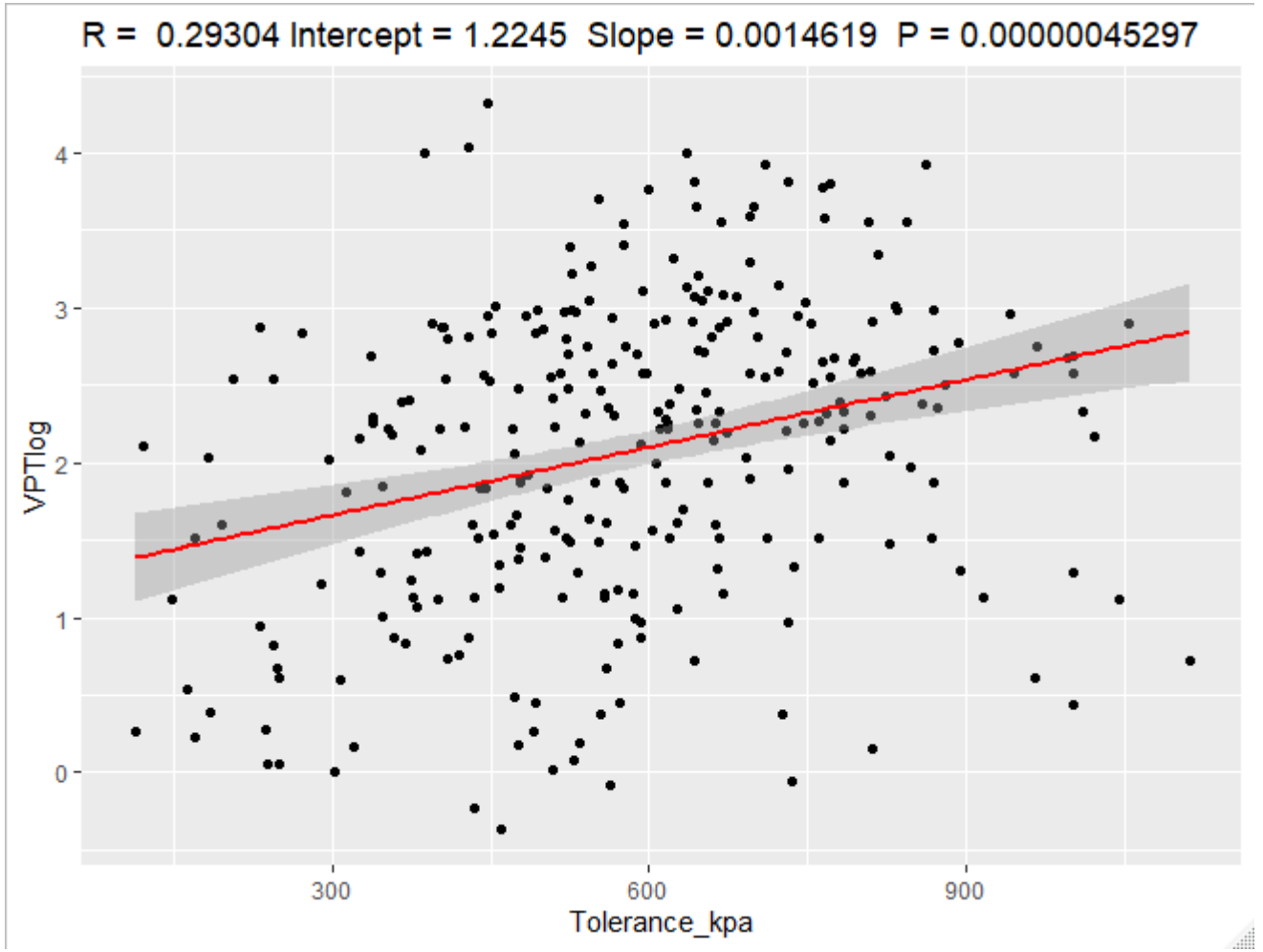

Impact
Cellular
Network
Experiential
Social
IMPACT
rotational forces
biomechanical deformation of neurons, glia, & vasculature
reticular activating system impairment
loss of consciousness
impaired vasoreactivity
vulnerability to future injury
cerebral blood flow/perfusion
BDNF expression
hypometabolic state
pain processing network dysfunction
physical exercise
exercise intolerance
comorbid pain & muscle tension
adherence to treatment
personal resilience
positive outlook
patient education
access to healthcare
social reserve
social contact & community integration
supportive relationships
coping & adaptation
need for coping & adaptation
ability to work and complete daily tasks
orthostatic intolerance
migraine / headache
cognitive fatigue
autonomic dysfunction
social pressure
stress
astrocyte & microglial activation
cellular energy imbalance
hyperglycolysis
excess metabolites
glymphatic clearing processes
blood-brain barrier permeability
pathological microenvironment
immune response
neuroinflammation
oxidative stress
cerebral edema
cytokine response
kinase activity
mitochondrial dysfunction
nonspecific depolarization
excessive glutamate release
NMDA activation
ionic Na+ K+ pump activity
ionic Na+ K+ dysregulation
widespread calcium dysregulation & sequestration
tau deposition
abnormal proteolysis
neuronal
axonal transport defect
axonal injury
long fiber tract damage
hub disruption
neural reserve
restorative sleep processes
dyssomnias
sleep network dysfunction
sleep
sleep debt
cognitive rest
physical fatigue
resting
need for cognitive rest
impaired neurotransmission
need for rerouting/ reorganization
neuroplasticity/ rerouting/ reorganization
limbic network dysfunction
intrinsic connectivity network function and coordination
attentional filtering capacity
sensorimotor integration & vestibular function
processing speed
predictive brain state
failure to anticipate sensory cues
error signaling
nausea
avoidance of overstimulation
light or sound sensitivity
emotional regulation
irritability/mood instability
depression/anxiety/ mood disorders
impulsivity
social functioning ability
cognitive load capacity
working memory & executive function
disorientation & confusion
feeling out of sync


Ongoing environment
(e.g., sensory and physical environment, demands, medical and legal issues, etc.)
Injury context
Personal characteristics
(e.g., genetics, age, sex, history, prior concussions, resilience, etc.)
INJURY
Injury biomechanics
(e.g., force, linear and rotational direction, acceleration/deceleration, head/neck kinematics, etc.)
Social
social support
community
medical professionals
work or school
social pressure
norms
peers
family
relationships
social reserve
Experiential
psychological
emotional
memory
attention
disorientation
cognitive
language
gait/balance
feeling "out of sync"
coping/adaptation
sense of self
pain
fatigue
perception
cognitive reserve
emergence of consciousness
Network
neuroplasticity
processing speed
sleep/wake cycle
intrinsic connectivity networks
neuronal population dynamics
predictive brain state
loss of consciousness
neural reserve
neurotransmission
Cellular
ionic flux
axonal injury
neuroinflammation
glymphatic clearing
synaptic changes
glial activity
metabolic cascade
Psychosocial interventions
Psychological, cognitive, & behavioral interventions
Physiological interventions
Molecular & pharmacological interventions
Increasing size; longer time-scale
Emergence across scales

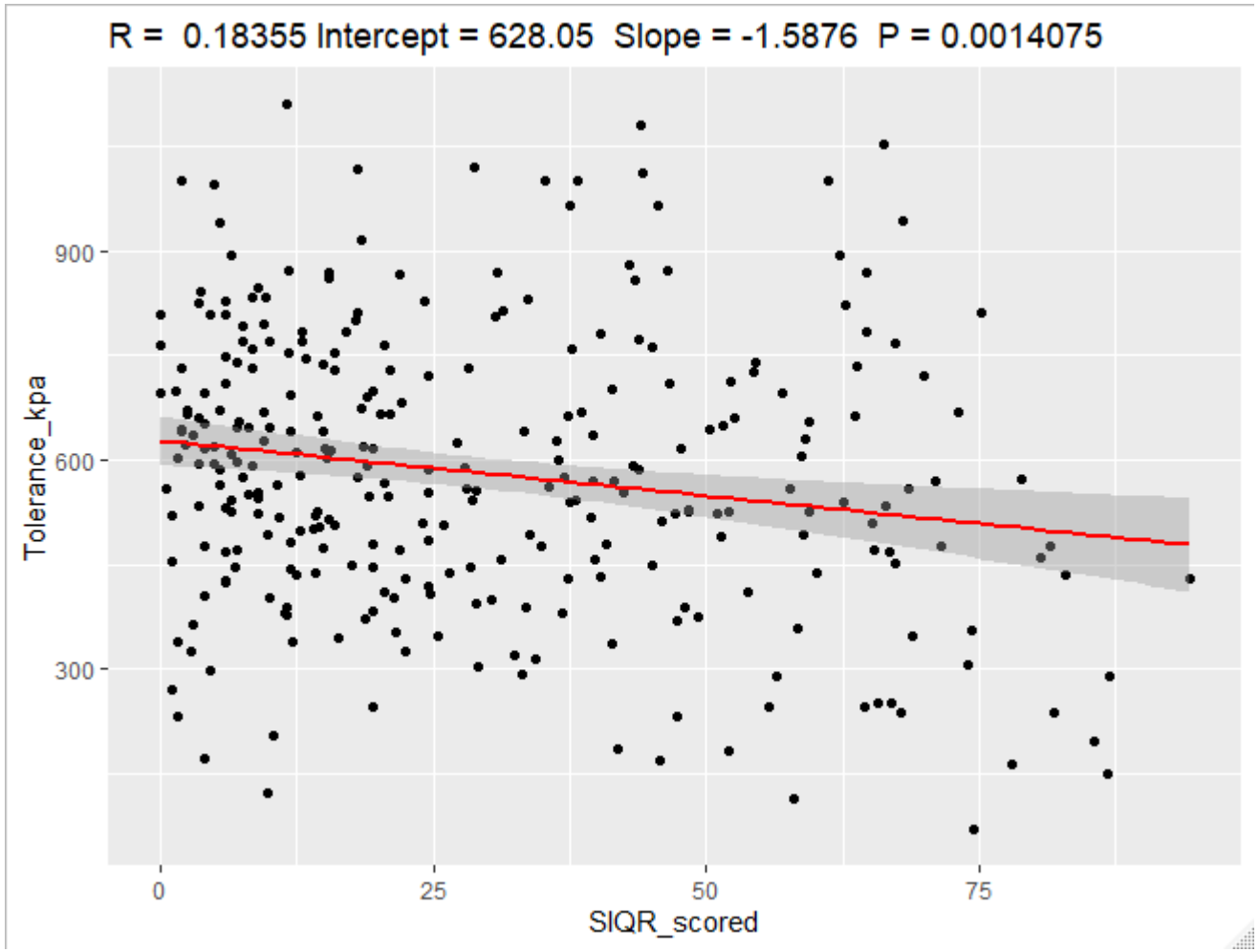
VPT vs Threshold



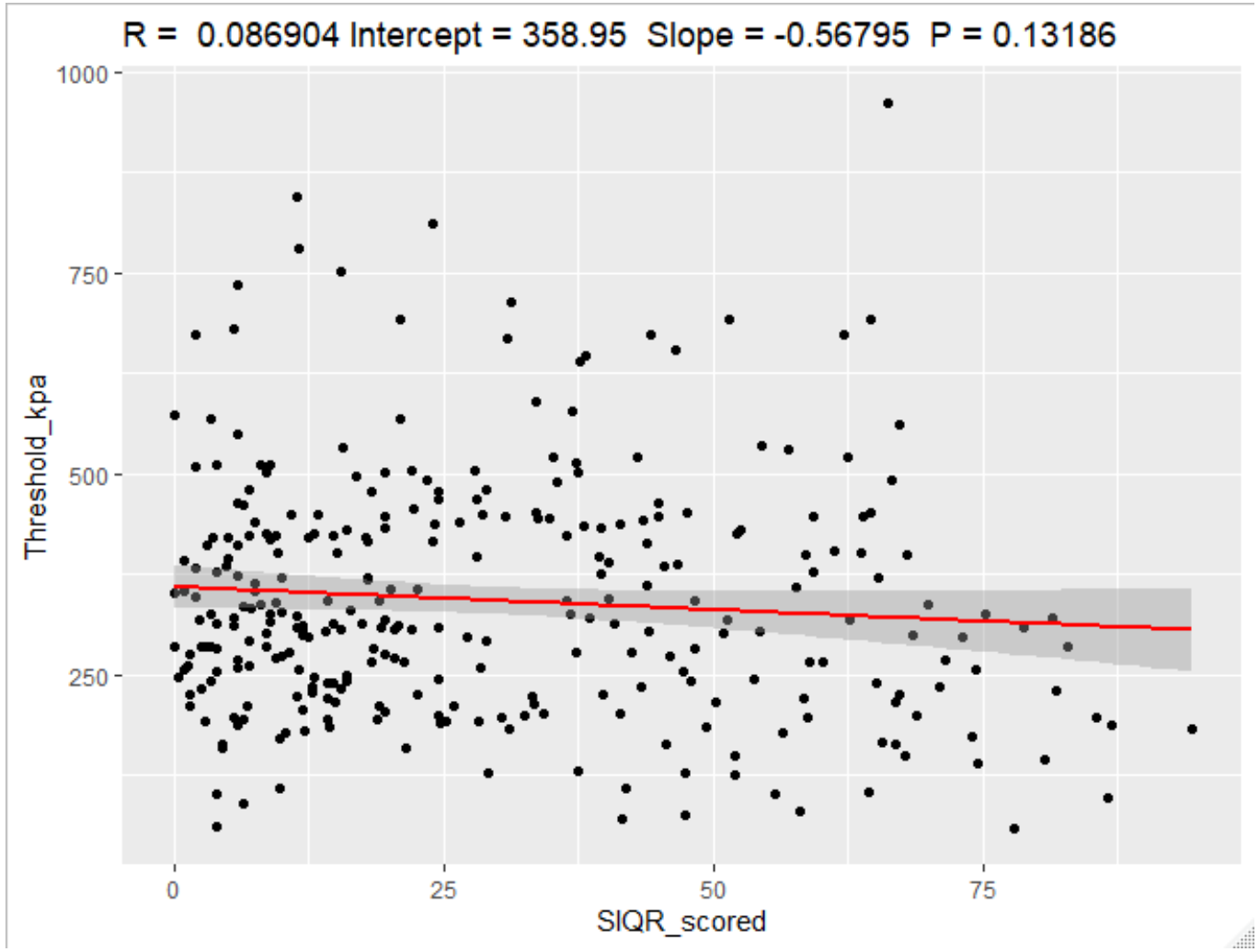
VPT vs Tolerance



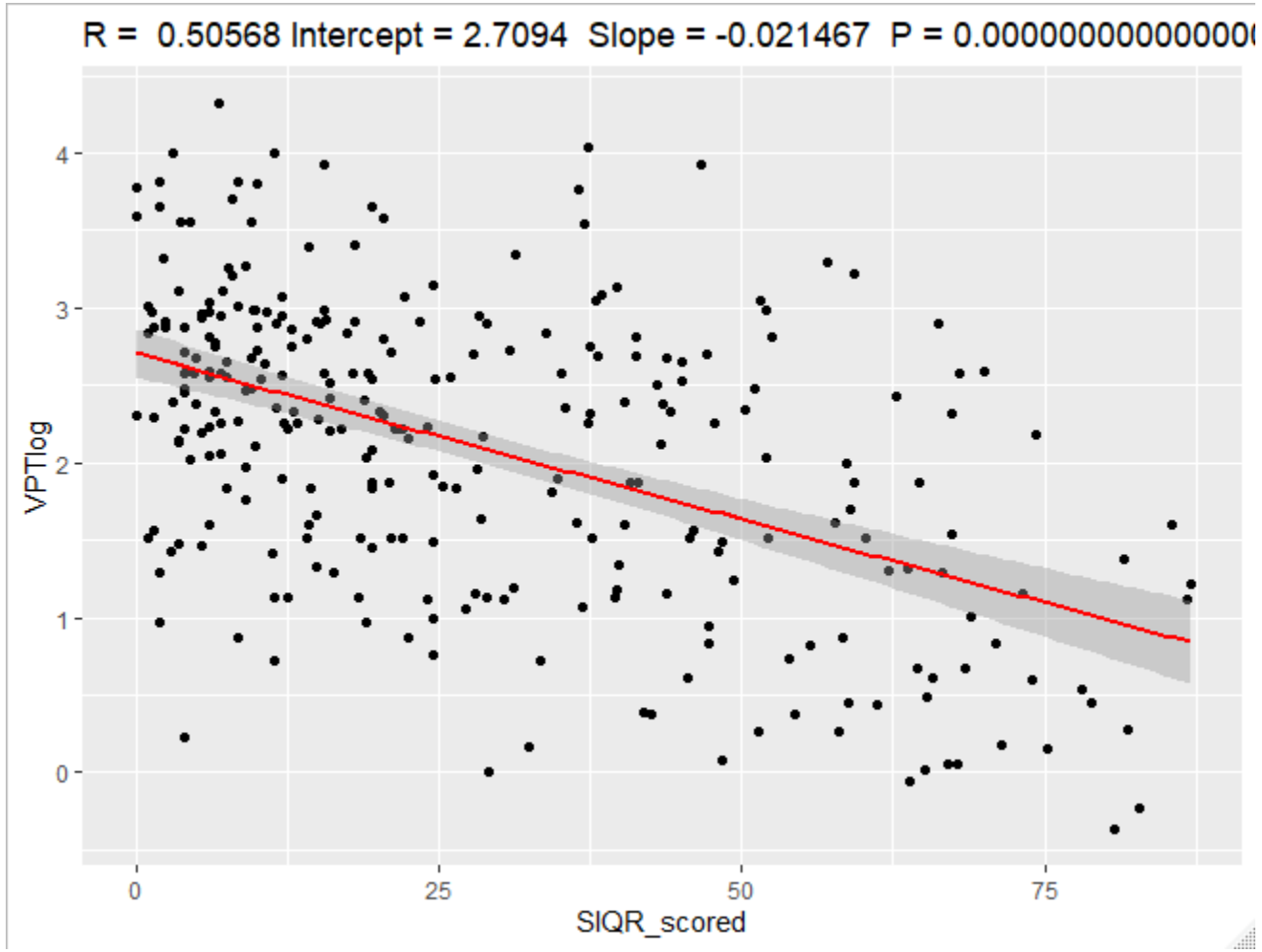
Tolerance vs SIQR



Threshold vs SIQR



VPT vs SIQR


R = 0.50568 Intercept = 2.7094 Slope = -0.021467 P = 0.000000000000000
VPTlog
SIQR_scored
0
1
2
3
4
0
25
50
75