Pain: chronic (FS-19)

Lorimer G Moseley (Australia)
Michael Thacker (United Kingdom)
David Walton (Canada)
Critical updates in chronic pain.

Lorimer Moseley  |  Mick Thacker  |  David Walton
Critical updates in chronic pain.

Critical updates regarding the brain

Lorimer Moseley  |  Mick Thacker  |  David Walton
Critical updates in chronic pain.

Critical updates regarding neuroimmune interactions

Lorimer Moseley | Mick Thacker | David Walton
Critical updates in chronic pain.

Critical updates regarding cognitive and behavioural aspects

Lorimer Moseley | Mick Thacker | David Walton
Critical updates regarding the brain in chronic pain.

Lorimer Moseley PhD FACP HMAPA.

University of South Australia

PAIN Adelaide
Bringing heads together for chronic pain
Consultancies:
Pfizer
Grunenthal
Worker’s Compensation boards Australia, NZ, Europe, North America
Providence Health Care, USA
Kaiser Permanente, USA
Our Futures ThinkNet Fellowship Scheme

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*Explain Pain* & translations | *Painful yarns. Metaphors & stories to help understand the biology of pain* | *Graded motor imagery handbook* | Explain pain handbook: Protectometer

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Arthritis Research Council UK

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A large population of brain cells – a neural network, representation or ‘neurotag’.
Representation or neurotag:
A large population of brain cells – a neural network or ‘neurotag’.

The brain is like a mass of neurotags influencing and competing against each other.
Representation or neurotag:
A large population of brain cells – a neural network or ‘neurotag’.

The brain is like a mass of neurotags influencing and competing against each other.

In physiotherapy, we are most interested in the neurotags that produce action, cognition and perception.
A network of representation or neurotag:

A large population of brain cells—a neural network or 'neurotag'.

The brain is like a mass of neurotags influencing and competing against each other.

In physiotherapy, we are most interested in the neurotags that produce action, cognition and perception.

What you think → What you feel → What you do

In physiotherapy, we are most interested in the neurotags that produce action, cognition and perception.
Chronic pain is chronic activation of the pain neurotag.

What you feel

In physiotherapy, we are *most* interested in the neurotags that produce action, cognition and perception.
What you think

What you feel

What you do
The brain is like a mass of neurotags influencing and competing against each other.
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The brain is like a mass of neurotags influencing and competing against each other.
Principles that govern neurotags:

• neuronal mass
• neuronal precision
• neuroplasticity

Nicolelis et al 2009
The ‘strength’ of the neurotag – number of neurones & their synaptic efficacy.

Principles of neurotags:

- neuronal mass
- neuronal precision
- neuroplasticity
Neuronal mass principle
Neuronal mass principle

This neurotag has greater neuronal mass than this one
The ‘strength’ of the network – number of neurones & their synaptic efficacy.

Inhibition of non-constituent brain cells.

Principles of neurotags:
- neuronal mass
- neuronal precision
- neuroplasticity
Neuronal precision principle

Multiple inhibitory interneurones make this neurotag precise
The ‘strength’ of the network – number of neurones & their synaptic efficacy.

Inhibition of non-constituent brain cells.

Use-dependence.

Principles of neurotags:
- neuronal mass
- neuronal precision
- neuroplasticity
In chronic pain.....
In chronic pain.....

The ‘strength’ of the neurotag – number of neurones & their synaptic efficacy.

The **neuronal mass** of protective neurotags is greater.

Principles of neurotags:
- neuronal mass
- neuronal precision
- neuroplasticity
The ‘strength’ of the network – number of neurones & their synaptic efficacy.

Inhibition of non-constituent brain cells.

The neuronal precision of protective neurotags is lower.

Principles of neurotags:
- neuronal mass
- neuronal precision
- neuroplasticity
Cortical body matrix:
Interconnected neurotags that subserve the regulation & protection of the body.

Moseley et al 2012 Neurosci Biobeh Reviews
The cortical body matrix.

In chronic pain, there seems to be an increase in strength and decrease in precision of protective neurotags.

Moseley et al 2012 Neurosci Biobeh Reviews
‘It is difficult to move.’

‘My handwriting has gone awry.’

‘It changes colour & goes cold.’

Sometimes it swells up for no reason – I haven’t even done anything!’

‘It feels swollen when it’s not.’

‘I sometimes feel odd sensations.’

‘Sometimes I don’t know where it is.’
Disrupted motor maps

Is their head turned to their left or right?

Is their trunk turned to their left or right?

Is this a left or right foot?

Is this a left or right hand?
People with chronic neck pain are less accurate for neck pictures but not other pictures.

Leake et al., In preparation
Chronic pain is associated with disruption for that body part, but not non-painful parts.

- **Accuracy (%)**
  - 90% (CRPS: Moseley 2004)
  - 88% (Neck: Leake et al 2012)

Test 2: Left/right neck rotation judgment task.
Tactile acuity is worse in chronic pain.

Catley et al. 2013 *Rheumatology*

---

**CONTROL** *(n = 122)*

**CHRONIC BACK PAIN** *(n = 67)*

---

**mm**
How do you know if it is abnormal?

Catley et al. 2013 *Rheumatology*

TPD >60mm = 90% confident that it is abnormal
How do you know one side is abnormal?

Wand et al. 2013 *Rheumatology* (n = 96)

A side-to-side difference in TPD on the back.

6mm = 90% confident that sides are different
How do you know it is worse in CRPS?

Catley et al. 2013 *Rheumatology*

Hand TPD = 3mm = 90% confident that it is abnormal
Knee TPD = 40mm = 90% confident that it is abnormal
Disrupted tactile maps in S1 - CRPS

Maihofner et al. 2003 Neurology

Juottonen et al. 2002 PAIN
OOPS! Have we all been looking at the wrong hand?

CRPS patient #14

Healthy hand

Affected hand

Healthy control

Dominant hand

Non-dominant hand

Di Pietro et al. (2014) Human Brain Mapping
Disruption of percept maps

Lewis et al. 2012
The **cortical body matrix** looks after us & our peripersonal space.

The **bioplasticity principle** explains increased strength of protective neurotags.

The **neuronal precision principle** explains the multisystem disruptions.
The implications are:

All evidence of danger has potential to trigger the strong protective neurotags – cognitive (think), perceptual (feel) and action (do).

Neuroplasticity principle means that threat reduction, graded exposure and precision retraining should help.
Evidence shows:

Explaining pain properly reduces pain & disability (level 1): threat reduction (optimised reassurance is the new black).

Retraining precision (graded motor imagery, sensory discrimination training) reduces pain and disability (Level 2).

Graded exposure to threat reduce pain and disability.
Update on Neuro-immune Interactions and Pain
WCPT – Singapore 2015

Dr Mick Thacker PhD Grad Dip Phys MSc FCSP
Senior Consultant (Pain)  Guy’s & St Thomas NHS Foundation Trust
Senior Lecturer - Sensory Functions Group Centre for Human and Aerospace Physiological Sciences. King’s College London.
Deputy Lead - Pain Research Section, Neuroimaging. Institute of Psychiatry. King’s College London.
Adjunct Senior Research Fellow University of South Australia.
Sorry I can’t be with you in person!
Outline of the Talk

• Neuro-immune interactions - Spinal cord

• Neuro-immune interactions - Brain

• Ideas re management
Pain Contextual Reconceptualisation – what were thought of as outputs can be considered inputs this includes the immune system.

Modified from Moseley 2007
The Immune system not only influence ‘lower level’ neuronal response to nociception but acts as a key communicator within ‘higher level’ neuronal nociception/pain processing.
Cytokines and chemokines act as signaling molecules between these systems.
Monocytes – macrophages and microglia are pleiotropic cells – serve several functions.
Glial Cells – Sticky-Stars

Astrocyte

- mGlu₅
- mGlu₃
- mGlu₄
- GLT1
- TGFβ growth factors
- Neuroprotection

Glutamate

- RANTES

Microglia

- mGlu₂
- mGlu₃
- mGlu₄/6/8
- TNFα, ROS Fas ligand
- Neurotoxicity
Nerve injury/nociception results in neurons and other cell types developing an “immune like” phenotype -
Traditional View of DH Sensitisation is too ‘Neurocentric’ – where are immune cells?

**Normal**

- **input**
- **AMP A**
- **NK1**
- **output**

**Facilitated**

- **input**
- **NMDA**
- **VGCC**
- **P2X3**
- **NO**
- **PGE2**
- **mGluR**
- **NK1**
- **AMP A**
- **NMDA**
- **trkB**
- **output**
Dorsal Horn neuro-immune interactions associated with pain.
CCL2 is a key mediator of microglia activation in neuropathic pain states

Michael A. Thacker \textsuperscript{a,b}, Anna K. Clark \textsuperscript{b}, Thomas Bishop \textsuperscript{a}, John Grist \textsuperscript{a}, Ping K. Yip \textsuperscript{a}, Lawrence D.F. Moon \textsuperscript{a}, Stephen W.N. Thompson \textsuperscript{a,1}, Fabien Marchand \textsuperscript{a}, Stephen B. McMahon \textsuperscript{a,c,*}

\textsuperscript{a} Neurorestoration group, Wolfson Centre for Age Related Diseases, Kings College London, Wolfson Wing, Hodgkin Building, Guy’s Campus, London, SE1 1UL, London, UK
\textsuperscript{b} Academic Department of Physiotherapy, Kings College London, London, UK
\textsuperscript{1} The London Pain Consortium, UK

Gao & Ji 2010
Glial Cells are activated by and release cytokines and chemokines which activate pre and post synaptic neurons.
Microglia reaction spreads as well as local response

Figure 3

Thacker et al 2009
GFAP staining of astrocytes – note their abundance and distribution.
The Tripartite Synapse

**NEURAL THRESOME**

Several decades of study have focused on working out what is happening at the tripartite synapse.

1. Astrocytes, a type of glial cell, have extensions that wrap around the gaps, or synapses, between neurons.

2. One neuron signals to another by releasing neurotransmitters into the synapse.

3. These transmitters are also taken up by the astrocyte.

4. Once activated, astrocytes experience an increase in intracellular calcium and release transmitters of their own into the synapse. These can enhance or inhibit synaptic activity.

Astrocytes have thousands of connections with neuronal synapses, other astrocytes and blood vessels. Signals initiated at a single synapse may propagate elsewhere.
Quadripartite Synapse

We now think it really is a neural ‘Foursome’.

Glial cells control the available amount of neurotransmitters and ions in a process known as volume transmission.
The human Blood-Brain Barrier (BBB) and Blood Spinal Cord Barrier are controlled in part by Glial Cells.
Nociception and nerve injury are associated with an increased leakiness of the Blood-Spinal Cord & Blood-Brain barriers in a non-segmental fashion.
Cytokines are transported to the brain and released across the BBB
Cytokines are implicated in disc disease.
Cytokine levels increase in the brain and DRG following disc injury
“A SICK BRAIN”

Cytokine produce
Illness behaviours

NOT MOVE
NOT THINK
NOT LEARN

↑ PAIN

Watkins et al. 2010

“...produce illness behaviours: not move, not think, not learn. ↑ Pain.”
Hypervigilance
(protection from attack)

Anxiety ← Arousal, Alarm

Withdrawal
(wound healing, infection fighting)

Fatigue, Anhedonia
Motor Slowing

Depression

Cortical

Subcortical

Inflammatory Cytokines

dACC
basal ganglia
Long-term trans-synaptic glial responses in the human thalamus after peripheral nerve injury

Richard B. Banati, Annachiara Cagnin, David J. Brooks, Roger N. Gunn, Ralph Myers, Terry Jones, Rolfe Birch and Praveen Anand

Fig. 2. \[^{11}C\] (R)-PK11195 PET and MRI after limb amputation. Schematic drawing: Peripheral nerve injury induces a trans-synaptic glial response, i.e., in the projection area of the second-order neuron. 36 months after amputation of the right forearm (Patient No. 1), no structural changes can be detected in the volumetric T1-weighted MRI (a,c). In contrast, \[^{11}C\] (R)-PK11195 PET superimposed onto the patients MRI (b,d) reveals a significant regional increase in \[^{11}C\] (R)-PK11195 binding, signifying the presence of activated glial cells in the area of contralateral left ventral posterolateral nucleus of the thalamus (white arrows).
Evidence for brain glial activation in chronic pain patients

Marco L. Loggia,1,2,* Daniel B. Chonde,1 Oluwaseun Akeju,3 Grae Arabasz,1 Ciprian Catana,1 Robert R. Edwards,2,4 Elena Hill,5 Shirley Hsu,1 David Izquierdo-Garcia,1 Ru-Rong Ji,1,6 Misha Riley,1 Ajay D. Wasan,2,4,7 Nicole R. Zürcher,1 Daniel S. Albrecht,1 Mark G. Vangel,1 Bruce R. Rosen,1,8 Vitaly Napadow1,2,9 and Jacob M. Hooker1
Increased Isotope Binding is –ve correlated with McGill Pain Questionnaire Scores, Pain at Scan and IL-6 plasma levels

Suggests an adaptive gliosis that is beneficial and may play a role in modulation of pain.

Jury is still out!

Loggia et al 2015
Important for Rx.

- **Inhibited Monitoring**
  - Underactive
  - Homeostasis

- **Activated**
  - Sub-Optimal Activation
  - Optimal Activation
  - Overactive
  - Nociceptive Input
  - Acute Stress
  - Acute Inflammation
  - Infection
Idea for Management

Change our construct - Understand pathophysiology
Reduce fear and anxiety
Understand that people in pain may not want to move/listen/learn

General Schema: when you choose “it” to do -

Understand what it is and how it works
Make it easier
Make it different
Do it in a nice environment
Do it with others
Do it at the right time of day
Enjoy doing it
Make it challenging but achievable
Know you are doing it and focus on doing it

Relax - Eat better - Sleep Better

N.B. Requires a Research and an Evidence Base which at present is absent/minimal.
Neural Mobilisation Attenuates Nociceptive Behaviours and Astrocytic Activity Post Nerve Injury
Movement has “entry” into the brain.

Exercise is an ‘Immune Stimulant’

Cotman and Berchtold 2002

Peterson & Pederson 2005
- CNS glia activation
- Release of cytokines
- Novel Neuro-immune interactions

• Breakdown of the blood/brain barrier
• Local cytokine release
• Altered neural structure/function
Dedicated to the memory of my great friend Louis Gifford
Acknowledgements

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  • Prof Pat Wall
  • Prof Steve McMahon
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  • Dr Fernando Zelaya
  • Dr Nick Spahr
  • Dr Duncan Hodkinson
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  • Kate Jolly

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• Dr David Butler (NOI group)
• Prof Tim Watson (University of Herts)

• All the great student’s whom I have learnt from
  – who ask difficult questions that need answering!

• My colleagues/friends at Guy’s & St Thomas’ NHS Foundation Trust
Thank you - Any Questions?

@dibbygibby

Email: michael.thacker@kcl.ac.uk
I think therefore I am?

Connecting mind and body for physical rehabilitation

David M. Walton PT, PhD
Assistant Professor, School of Physical Therapy
Western University, Canada
Objectives

- Describe the role of psychology in the genesis of chronic pain
- Discuss the physiological mechanisms that may explain the mind-body connection
- Discuss the properties of a new psychologically-focused tool for predicting chronic post-traumatic pain
The Real Challenge

Rate of chronic problems:
~30-50% of acute WAD
~40-60% of acute LBP
~20% of adult Canadian population
Conceptualizing Injury and Recovery
Swinging pendulum

It's all biomechanical

It's all psychological

Social / Environment?
Being human

Psychology

Biology

Sociology

Interact
A conundrum
Conclusions: These data suggest that derby drivers sustain less chronic neck pain after multiple car collision events than might otherwise be expected. Further study of this unique population of car drivers may contribute to understanding whiplash disorder.

Conclusion. Rodeo athletes appear to be in at least as many motor vehicle collisions as rodeo spectators, and 33% suffered the acute whiplash syndrome. Rodeo athletes appear, however, to be more resistant than spectators to developing prolonged pain and disability. (J Rheumatol 2006;33:975–7)

CONCLUSION

The head-banger’s whiplash is a self-limiting painful disorder. Pain that is the consequence of a “fun” event and was anticipated as likely to occur was time-limited and self-resolving. The easy resolution of the pain problem in the adolescent group is a tribute to the resilience of youth.
Course of Neck pain (WAD)

Sterling et al. *Pain* 2010

![Graph showing predicted NDI trajectories with 95% confidence limits and predicted probability of membership (%). Suggested cut-offs for the NDI are 0–8% (no pain and disability); 10–28% (mild pain and disability), 30–48% (moderate pain and disability), 50–68% (severe pain and disability) and >70% (complete disability) [13].](image-url)
Course of neck pain (mixed)

Walton et al. *Arch Phys Med Rehabil* 2014
Fig. 2. Mean LBP intensity and mean number of LBP days in eight trajectories identified in Model (iv): 1: Recovery (25% chiropractic practice [CP]; 10% general practice [GP]), 2: mild episodic (22% CP; 14% GP), 3: moderate ongoing not daily (13% CP; 17% GP), 4: late recovery (13% CP; 6% GP), 5: improvement with relapse (11% CP; 13% GP), 6: slow improvement (8% CP; 15% GP), 7: severe ongoing (3% CP; 18% GP), and 8: moderate ongoing daily (5% CP; 6% GP). Numbers in brackets are proportions in CP and GP. Bars indicate +/-standard deviation. LBP, low back pain.
**Course of neck and back pain – general consensus**

- **Majority of recovery occurs within first 3 months**
- **Most work indicates at least 3 trajectories:**
  - Quick and complete ‘recovery’ (~20-25%)
  - Little to no recovery with lingering severe interference (~15-25%)
  - Slow and possibly incomplete ‘recovery’ (~55-60%)
- **Pain, Self-Rated Disability and Duration of symptoms consistent predictors**
- **Generally stronger support for ‘psychosocial’ factors than ‘biological’ factors as predictors of chronic pain**
**Current state of evidence (WAD only)**

<table>
<thead>
<tr>
<th>High confidence of risk factors for chronicity</th>
<th>High confidence of no effect on outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔️ High pain intensity</td>
<td>Angular deformity of the neck</td>
</tr>
<tr>
<td>✔️ High neck-related disability</td>
<td>Impact direction</td>
</tr>
<tr>
<td>✔️ Post-traumatic stress symptoms</td>
<td>Seating position</td>
</tr>
<tr>
<td>✔️ Catastrophizing</td>
<td>Awareness of collision</td>
</tr>
<tr>
<td>+/- Cold hypersensitivity</td>
<td>Head rest in place</td>
</tr>
<tr>
<td>+/- *Mechanical hypersensitivity (distal &gt; local)</td>
<td>Older age</td>
</tr>
<tr>
<td></td>
<td>Vehicle speed</td>
</tr>
</tbody>
</table>

Walton et al. *Open Ortho*, 2013
# Current evidence for LBP (Chou and Shekelle, 2010)

<table>
<thead>
<tr>
<th>Strong evidence of risk</th>
<th>Moderate of inconsistent evidence of risk</th>
<th>No clear evidence of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonorganic signs (Waddell’s)</td>
<td>Non-supportive work environment</td>
<td>History of prior low back pain</td>
</tr>
<tr>
<td>Maladaptive Coping Behaviours</td>
<td>High baseline pain</td>
<td>Demographics (age, sex)</td>
</tr>
<tr>
<td>High self-report functional impairment (e.g. RMQ)</td>
<td>Presence of radiculopathy</td>
<td></td>
</tr>
<tr>
<td>Presence of psychiatric comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low general health status (e.g. SF-12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SR and MA of mediating variables
(Lee et al. *in press*)

We know:

- Pain
  - At inception
- Disability
  - At follow up
SR and MA of mediating variables
(Lee et al. in press)

We don’t know:

\[ a' \]

Pain
At inception

Mediating variable

Direct effect

Disability
At follow up

\[ b' \]
Results of MA in Longitudinal studies:
- Sig. mediators by strength: self-efficacy, distress, fear
- Not sig. mediator: catastrophizing
- “… no study tested the mediating role of physical or social constructs.”
Example: Sterling CPR (2013)

NDI

≤ 32

Age

≤ 35

Predicted: Full Recovery

> 35

33-39

≥ 40

Age

< 35

Hyperarousal subscale (PDS)

< 6

Neither predicted full recovery nor predicted chronic moderate/severe disability

≥ 6

Predicted: Chronic Moderate/Severe Disability
The Keele STarT Back Screening Tool

Patient name: __________________________ Date: ____________

Thinking about the last 2 weeks tick your response to the following questions:

1. My back pain has spread down my leg(s) at some time in the last 2 weeks
   Disagree 0  Agree 1

2. I have had pain in the shoulder or neck at some time in the last 2 weeks
   Disagree 0  Agree 1

3. I have only walked short distances because of my back pain
   Disagree 0  Agree 1

4. In the last 2 weeks, I have dressed more slowly than usual because of back pain
   Disagree 0  Agree 1

5. It’s not really safe for a person with a condition like mine to be physically active
   Disagree 0  Agree 1

6. Worrying thoughts have been going through my mind a lot of the time
   Disagree 0  Agree 1

7. I feel that my back pain is terrible and it’s never going to get any better
   Disagree 0  Agree 1

8. In general I have not enjoyed all the things I used to enjoy
   Disagree 0  Agree 1

9. Overall, how bothersome has your back pain been in the last 2 weeks?
   Not at all  Slightly  Moderately  Very much  Extremely
   □ 0 □ 0 □ 1 □ 1

Total score (all 9): _______________  Sub Score (Q5-9): _______________

<table>
<thead>
<tr>
<th>Total score</th>
<th>Sub score Q5-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or less</td>
<td>Low risk</td>
</tr>
<tr>
<td>4 or more</td>
<td>Medium risk</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
</tr>
</tbody>
</table>

Overall assessment:
- Low risk: 3 or less
- Medium risk: 4 or more
- High risk: 4 or more
Do Thoughts Predict Outcomes?

- **Catastrophizing** [Walton et al. 2013, Bostick et al. 2013, Sullivan et al. 2011]
- **Kinesiophobia** [Swinkels-Meewise 2006]
- **Fear-Avoidance** [Holden et al. 2010]
- **Sense of Victimization** [Sullivan et al. 2011]
- **Post-Traumatic Distress** [Sterling et al. 2005, 2006]
- **Expectations** [Ozegovic et al. 2009]
- **Generalized Anxiety** [Myrtveit et al. 2013]
- **Illness Representations** [Walton et al. 2015]
Fear-Avoidance model (Vlaeyen and Linton)

- Fear
- Catastrophizing
- Avoidance
- Hypervigilance
- Disuse
- Depression
- Disability
- Pain
- Injury
- Confrontation
- Recovery
- No Fear
The Walton 3-step method for preventing chronicity

1. See patients within hours of their event/injury
2. Give them high dose opioids
3. Teach them how to fill out disability questionnaires better
Who are the people that develop chronic problems?

Supposition:

If we could identify those people at risk of chronic problems early, then we could intervene and prevent its development.
Proving Cause-and-effect

Bradford-Hill criteria (1965)

1. Dose-response
   - More cause -> More effect

2. Strength of association
   - Needs to be strong enough to be convincing

3. Temporality
   - Cause always occurs before effect

4. Reversibility
   - Remove cause, remove (reduce) effect

5. Consistency
   - Findings 1-4 are consistent across studies

6. Biologic Plausibility
   - Does it make sense that A causes B?
Reversibility: Do cognitively-focused interventions *prevent* chronic problems?

- The evidence in neck pain would suggest no [e.g. Lamb et al. 2013, Jull et al. 2013]
- The evidence in low back pain is emerging but still unclear
  - Work based on the STarT Back tool suggests risk-stratified treatment (based on self-report) may be effective at preventing disability [e.g. Hill et al. 2011]
Consistent challenges

- We don’t generally know patients prior to their injury / inception
- Most tools used to date have been developed for use in chronic populations – unclear properties for use in acute
- The outcomes (what we’re trying to predict) are difficult to operationalize
A new measurement tool for acute distress

- The Traumatic Injuries Distress Scale (TIDS)
- 10 items, each rated 0 (never) to 2 (often)
- Designed from the ground up for acute (3 days to 3 weeks) traumatic injuries

- 3 subscales:
  - Functional Abasement / Disengagement ($\alpha = 0.86$)
  - Uncontrolled Pain ($\alpha = 0.83$)
  - Hyperarousal ($\alpha = 0.79$)
### TIDS

<table>
<thead>
<tr>
<th>Rate the extent to which you have been bothered by the following symptoms since your accident:</th>
<th>Never</th>
<th>Sometimes (less than half of the time)</th>
<th>Often (half of the time or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty thinking about anything other than the pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. A feeling of being overwhelmed by pain or other symptoms</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Flashbacks of the accident while you’re awake that feel very real</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. Feeling ‘wound up’, agitated or scared when in a place that reminds you of the accident (e.g. in a car, at work or on a slippery surface)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. Frustration at your inability to control your pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6. Loss of motivation to get up and start a new day</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. Loss of interest in your appearance</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8. A sense of worry</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9. Feeling 'numb' or disengaged, as if you were watching the world through a window</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10. Feelings of sadness</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
## Predictive validity

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Satisfaction</th>
<th>Disability</th>
<th>Pain NRS</th>
<th>PDS</th>
<th>HADS anx</th>
<th>HADS dep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Abasement / Disengagement</td>
<td>0.40</td>
<td>0.60</td>
<td></td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Pain</td>
<td>-0.61</td>
<td>0.52</td>
<td>0.42</td>
<td>0.60</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Hyperarousal</td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
</tbody>
</table>

Spearman’s Rho, all p<0.05
Surely it must go beyond the numbers someone circles on a form

and don't...

call me Shirley!
MVC EVENT

Biomechanical injury/pain experience

Stress response system activation
- CRF
- LC-NE system
- Cortisol

Resilient stress system
- Regulated stress system activation
- Appropriate cortisol feedback

Genetic influences
- Previous life history

Vulnerable stress system
- Exaggerated stress system activation
- Dysregulated cortisol feedback

Stress response contained

- Pain and emotional response resolves
- Confrontation
- Recovery

Stress system dysregulation

- Disuse
- Depression
- Disability
- Pain experience
- Hyperalgesia
- Allodynia
- Negative affectivity
- Threatening illness information
- Catastrophizing
- Avoidance and inactivity
- Pain-related fear

Dysregulation of
- limbic, paralimbic, and prefrontal regions
- descending pain modulation

McLean et al. 2005
Thin-skinned? Weak-willed? Misinformed?

- Trauma and pain are stressors
- Stress can be caused by, and manifest as, both physical and psychological phenomena
- Could the numbers that are being circled on those forms be surrogates for stress system dysregulation?
Effects of hypercortisolism

- Muscle catabolism
- Widespread pain
- Cognitive interference
- Sleep disturbance
- Interrupted digestion
- Memory (over)consolidation
- Disrupted inflammation through effects on inflammatory cytokines
  - Disordered tissue repair and healing
Genetic component

Polymorphisms in the glucocorticoid receptor co-chaperone FKBP5 predict persistent musculoskeletal pain after traumatic stress exposure

- Six polymorphisms of FKBP5 gene showed significant correlations with overall and neck pain 6 weeks after a motor vehicle collision (n = 949). This was then replicated in a sample of n = 53 sexual assault survivors.

“These results suggest that glucocorticoid pathways influence the development of persistent post-traumatic pain”

Bortsov et al. PAIN 2013
Converging evidence - imaging

The Temporal Development of Fatty Infiltrates in the Neck Muscles Following Whiplash Injury: An Association with Pain and Posttraumatic Stress

James Elliott Sterling

Jull 1, Michele

PLoS One 2011
Mediational analysis

POST-TRAUMATIC STRESS

PAIN

CERVICAL MUSCLE DEGENERATION

Elliott et al., 2011
Evidence

Elevated content of cortisol in hair of patients with severe chronic pain: A novel biomarker for stress

S. H. M. Van Uum\(^1,2,3\), B. Sauvé\(^4\), L. A. Fraser\(^1\), P. Morley-Forster\(^5\), T. L. Paul\(^1\), & G. Koren\(^4,6\)

\[ P < 0.01 \]

\[ P < 0.001 \]
Emerging evidence

Hair-Normalized Cortisol Waking Response as a Novel Biomarker of Hypothalamic-Pituitary-Adrenal Axis Activity following Acute Trauma: A Proof-of-Concept Study with Pilot Results

Pain Research & Treatment (2013)

David M. Walton,1 Joy C. MacDermid,2 Evan Russell,3 Gideon Koren,3,4,5 and Stan Van Uum6

N = 10 subjects within 3 weeks of traumatic injury (WAD or DRF)
Baseline tools:
• Emotional distress (Pain Catastrophizing)
• Pain
• 3 x salivary cortisol incl. CWR
• Hair cortisol
Results - Baseline

$r = 0.77$

$p$-value: 0.03

$r = 0.93$

$p$-value: 0.001
Results – Follow up (3 months)

- Correlation coefficient for Baseline unadjusted CWR vs. 3-month percent disability: $r = 0.23$
- Correlation coefficient for Baseline HnCWR vs. 3-month percent disability: $r = 0.7$
Does Acute Psych Distress cause Chronic Pain?

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>Prospective longitudinal modeling increasing evidence, but outstanding questions remain (which comes first?)</td>
<td>?</td>
</tr>
<tr>
<td>Consistency</td>
<td>Consistent evidence of a link between acute psych distress and longer-term follow-up</td>
<td>✓</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Evidence indicates linear relationships (more acute distress, more future pain)</td>
<td>✓</td>
</tr>
<tr>
<td>Strength</td>
<td>In regression / SEM models, acute psych distress explains ~5-20% of variance in outcome</td>
<td>?</td>
</tr>
<tr>
<td>Reversibility</td>
<td>So far inconsistent, equivocal, or no evidence that treating acute distress improves outcomes.</td>
<td>✗</td>
</tr>
<tr>
<td>Plausibility</td>
<td>The experience and reporting of pain necessarily includes a psych component. Stress-system dysregulation a promising bio link.</td>
<td>✓</td>
</tr>
</tbody>
</table>
Key Messages

- We’re now fairly good at identifying very high and very low risk of chronicity (~40% of pop’n).
- We’ve yet to really hit on a sound approach for preventing chronic pain.
- There is a clear association between psychological distress in the acute stage and outcomes 3-12 months later, but causation is a tougher nut.
- Choose your construct: We’d be hard-pressed to say any one psych distress tool is better than any other for prognostic purposes. Specificity?
Where to from here?

- Look at other stress systems
  - Endocrine
  - Immune/Inflammatory
  - Digestive
  - Neural
- Need more exploration of the social domain
- Don’t forget tissue pathology
- Longitudinal biobanking currently underway
- Identify new treatment targets to prevent chronic pain
- Stop clinical trials until mechanisms understood
With thanks..

Students
- Theo Versteegh, Swati Mehta, Josh Lee, Joe Putos, Stacey Guy, Tyler Beattie, Xiaotong (Nancy) Zhang

Collaborators
- Joy MacDermid, Jim Elliott, Michele Sterling, Stan Van Uum, Ruth Lanius, Lenerdene Levesque, and many others

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