Tricon 2018, Durban, South Africa

Neurocognitive sequelae of deep saturation diving exposure: a multi-factorial excitotoxic brain injury

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and: Rubina Alpitsis, Evan Symons, Toby Winton-Brown, Ian Gawthrope, Elisabete da Silva, Michelle Coleman, David Wright

AlfredHealth

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Caulfield HOSPITAL

Sandringham HOSPITAL

MSHC MELBOURNE SEXUAL HEALTH CENTRE

Dr Ian Millar

Diving & Hyperbaric Medicine Specialist and Occupational Physician
- **DMAC member**
- **Chair, Australian Standards – Occupational Diving**
- **Board Member, Australian Diver Accreditation Scheme 2003 – 2018**

Employee of a Government / University Hospital
- **Independent of any interested party**
- **Self funded travel to Bergen – reimburseable from education fund**
- **Principal Investigator for a research proposal regarding this incident**

As a clinical doctor:
- **Reviewed 13 of 15 divers who did a 235-273 msw sat in 2017**
- **One of the divers is an ongoing patient**

Some reports provided for insurers, lawyers for divers, NOPSEMA

Health sequelae of deep saturation diving

An incident based Medical Expert Report
including
Hypotheses regarding potential mechanisms of injury

Dr Ian Millar
Senior Specialist in Diving & Hyperbaric Medicine
Alfred Health
Melbourne, Australia
September 2019

AlfredHealth

Brain injury & neuro-degeneration research

Chronic neuro-pathology – e.g. early Alzheimer's

Recurrent mild concussions
- Soccer Football, American Football, boxing

Occasional mild to moderate concussions
- Rugby, Australian Rules Football

Military veteran concussive TBI (blast injury)

Major international collaborations
New AI / Imaging / biomarker technologies

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15 November 2019

Brain research in Melbourne, Australia

- Monash University – Alfred Health
- Department of Neuroscience
- >400 staff

- University of Melbourne - Florey Institute of Neuroscience
- Melbourne Brain Centre
- >500 staff

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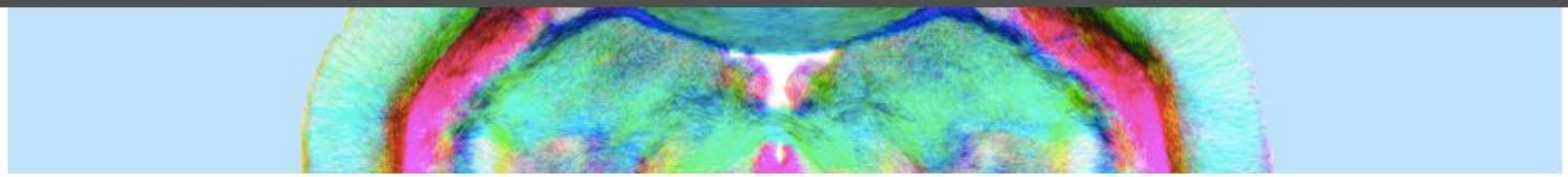

Central Clinical School home

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Neuroscience home

About us

Clinical services

Facilities

Research

Alpitsis group

Butzkueven group

Cloud group

Fielding/White group

Hutton group

Jokubaitis group

Jones group

Kwan group

Monif group

Research

The Department of Neuroscience has 17 research groups with over 140 staff and graduate research students. Thanks to infrastructure investments by Monash University and Alfred Health, during 2018 we will be opening new, purpose-built, state-of-the-art basic neuroscience laboratories, a preclinical imaging facility (with 9.4T MRI, PET-CT, FLECT and an MPI machine) and dedicated Neurological Clinical Trials Facility embedded in the Neurosciences Ward at the Alfred with capacity for overnight stays and a focus on early-stage trials.

Dr Rubina Alpitsis
Neuropsychology, neurological diseases
Alpitsis group

Prof Helmut Butzkueven
Clinical, translational neuroimmunology
Butzkueven group

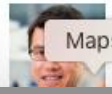
Prof Geoff Cloud
Stroke, cerebrovascular, vertebrobasilar
Cloud group

A/Prof Owen White
A/Prof Jo Fielding
Ocular Motor System, Human behaviour
Fielding/White group

Dr Elspeth Hutton
Peripheral neuropathy, pain, headache
Hutton group

Dr Vilija Jokubaitis
Multiple Sclerosis, Neuroimmunology, Genetics
Jokubaitis group

A/Prof Nigel Jones
Epilepsy, Behaviour research



Maps

Prof Patrick Kwan
Epilepsy, personalised

Dr Mastura Monif
Neurology, Neuroimmunology,

The start……

Rumours at EUBS 2017

- Some divers symptomatic after a sat dive

November 2017: Referral of “Index patient”

- Middle aged sat diver
- Severe HPNS during mid 2017 dive
- Severe persistent problems post sat
- Didn’t report problems until aborted entry into subsequent shallow sat dive
- Improving but substantially impaired

Symptoms at 4 months

Headaches
Anxiety
Lack of energy
Impaired:

- Working memory
- Long term memory
- Balance
- Coordination
- Judgement
- Emotional control
- Exercise tolerance

Examples

- Couldn’t hand a coffee cup across without spilling
- Damaged car backing out of garage
- Readily lost on familiar routes
- Tried to open house with wrong keys
- Tried to control TV with airconditioner remote
- Near misses with power tools
- Angered easily
- Couldn’t cope in crowds
- Word finding problems

Confirmed by partner

Evaluation at Hospital

MRI – normal

- High resolution DWI and TBI research protocol imaging acquired and archived

Blood tests – normal

- Plasma “bio-banked” in 10 aliquots

Neuropsychology testing

- Impairments in domains consistent with symptoms reported by patient and partner

Psychiatric evaluation

- Elements of depression, anxiety and PTSD but primarily consistent with persistent cognitive sequelae

Therapy and fitness for work

Unfit for any diving

Unfit for safety critical work, including sea-deck of working vessels, rigging and crane work, work at heights

Income support payments commenced subsequently

Prescribed anti-depressant medication

Trials of various anti-headache medications

Ongoing psychiatric and occupational medical review

And then, over the next 3 months

13 of 15 divers evaluated at Alfred / Monash Neurosciences

2 declined assessment (?OK)

12/13 reported prolonged cognitive impairment

11/13 still having some problems

8/15 subsequently certified “unfit for diving”

Now: at 28 months post exposure:

1 additional recovery and return to diving (at 18 months)

7/15 remain off work

Civil compensation cases pending

NOPSEMA investigation ongoing

Some more example problems

Can't surf any more (x 3 divers)

- Can't properly anticipate waves
- Can't balance on board

Can't multi-task

- During rigging on a workboat – safety failures / near misses

Can't remember instructions

- Shop for milk and bread – bring only milk home.
- 10 minute shopping trip – drive for 60 mins trying to find home
- Stare at workshop shelves and fail to see object

Sudden episodes of severe, suicidal depressive thoughts

Chattering teeth when quiet and relaxed

Vertiginous episodes / motion sickness susceptibility

Mild cognitive impairment

End result of many different type of injury

- Single point of time TBI, ischaemic, toxic, etc insult
- Repeated, cumulative minor injuries
- Cumulative or long duration toxic exposures
- Inflammatory or auto-immune injury
- Multi-embolic / ischaemic injury
- Hypoxic injuries

And also seen:

- After major surgery
- In “Functional” / psychiatric diseases
- and (mildy) during ”normal” life illness & stress……

So something went wrong……

What (operationally)?

- Quite a few things
- If “Best Practice” were followed, I wouldn’t be here

What (biologically)?

- Various injury thresholds were exceeded
- Brain injury resulted
- Nothing special (clinically) about the brain injury

- Research opportunities to look for “special features”
- Need money…….

Long Term Sequelae of Diving?

Modern diving is very safe

- Many confounding health risks
  - Non-diving work
  - Non reported injuries
  - Co-incident hazards
    - Gas contamination
    - Welding fume
  - Lifestyle (alcohol etc.)
  - Anecdotes ≠ evidence

BUT:

- Diving can cause sequelae

So is this something new?

Brain Injury concepts and research trends

Evolving Concepts of “Mild” Brain Injury

Differentiation between psychological and physical injury not appropriate

- Physical changes develop after “psychological” trauma
- Psychological changes result from traumatic brain injury

Physical disruption not required for injury
Excito-toxicity a critical element

- Can be triggered by concussive forces
- High stress (adrenaline, nor-adrenaline, cortisol) pre-disposes

NMDA receptors are key players in excito-toxicity

Oxidative stress is involved at many sites and stages of injury

There are **injury tolerant** patients
There are those **susceptible** to long term problems

- After a single event or an accumulation of events

Phases of brain injury

Primary event

- Trauma, lack of oxygen, biochemical or toxic event

Secondary brain injury

- **Blood flow dysfunction**
- **Inflammation**
- **Swelling**
- **Excito-toxicity - a critical element**

- Can be triggered by concussive forces
- High stress (adrenaline, nor-adrenaline, cortisol) pre-disposes

Oxidative stress is involved at many sites and stages of injury

Late / Persistent problems

- Apoptosis (cell death)
- Persistent neuro-inflammation
- Remodelling – good and bad

Outcomes of Neurological Injury

- Good recovery – hours to days
- Recovery after several weeks
- Set-backs due “overdoing it” but OK within a few months

- Prolonged but complete recovery (several years)

- Plateaued recovery and persistent problems

- Delayed neurological deterioration cases
- (e.g. delayed leuko-encephalopathy after some weeks, demyelination etc.)

- Late functional deterioration
  - gain seeking / malingering

  OR
  - compounding illnesses or injuries
  - disability stress / financial anxiety
  - depression
  - PTSD
  - compensation / litigation stress

Thresholds and Synergy

Some injurious events are single cause

Some involve multiple cumulative +/or synergistic factors

Most biological injury thresholds are not “tipping points”

Rather:
a spectrum of increasing injury level against increased severity and / or persistence of consequences

Neurotransmittors

Chemicals that “bridge the gap” between nerves

- Excitatory
- Inhibitory
- Modulatory

Released, act and re-absorbed in < 1 msec

Re-uptake / recycling / gain adjustments

Examples: Dopamine, Serotonin, NorAdrenaline, AcetylCholine
Glutamate

Excitatory transmitters

Glutamate chemical family - act on NMDA receptors
- Monosodium glutamate in food

Principal “activation” signalling mechanism
- Most anaesthetic drugs block these pathways

Excitatory can become excito-toxic

Excito-toxins
- Endogenous
- Exogenous

Excito-toxic “storm”

- Excito-toxic stimulus
- Releases calcium in cells
- Damages integrity of mitochondria
- Releases oxidative “free radicals”
- Causes inflammation, swelling,
- More excitability
- Stress response

Excito - toxicity

Response to acute primary injury:
- **Traumatic brain injury**
- **Hypoxic brain injury**

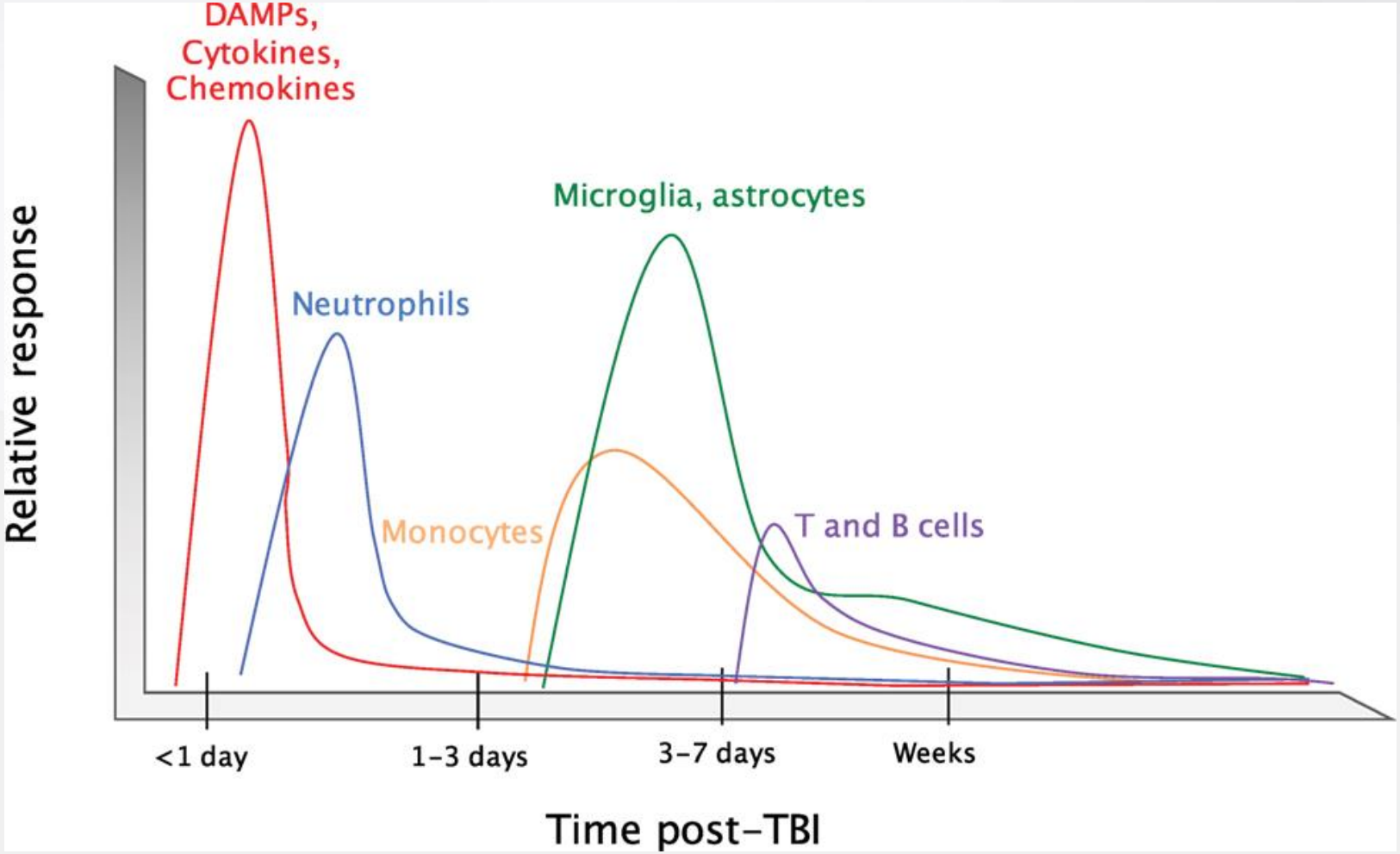
Stimulant drugs
- Amphetamines, cocaine, etc.

Status epilepticus

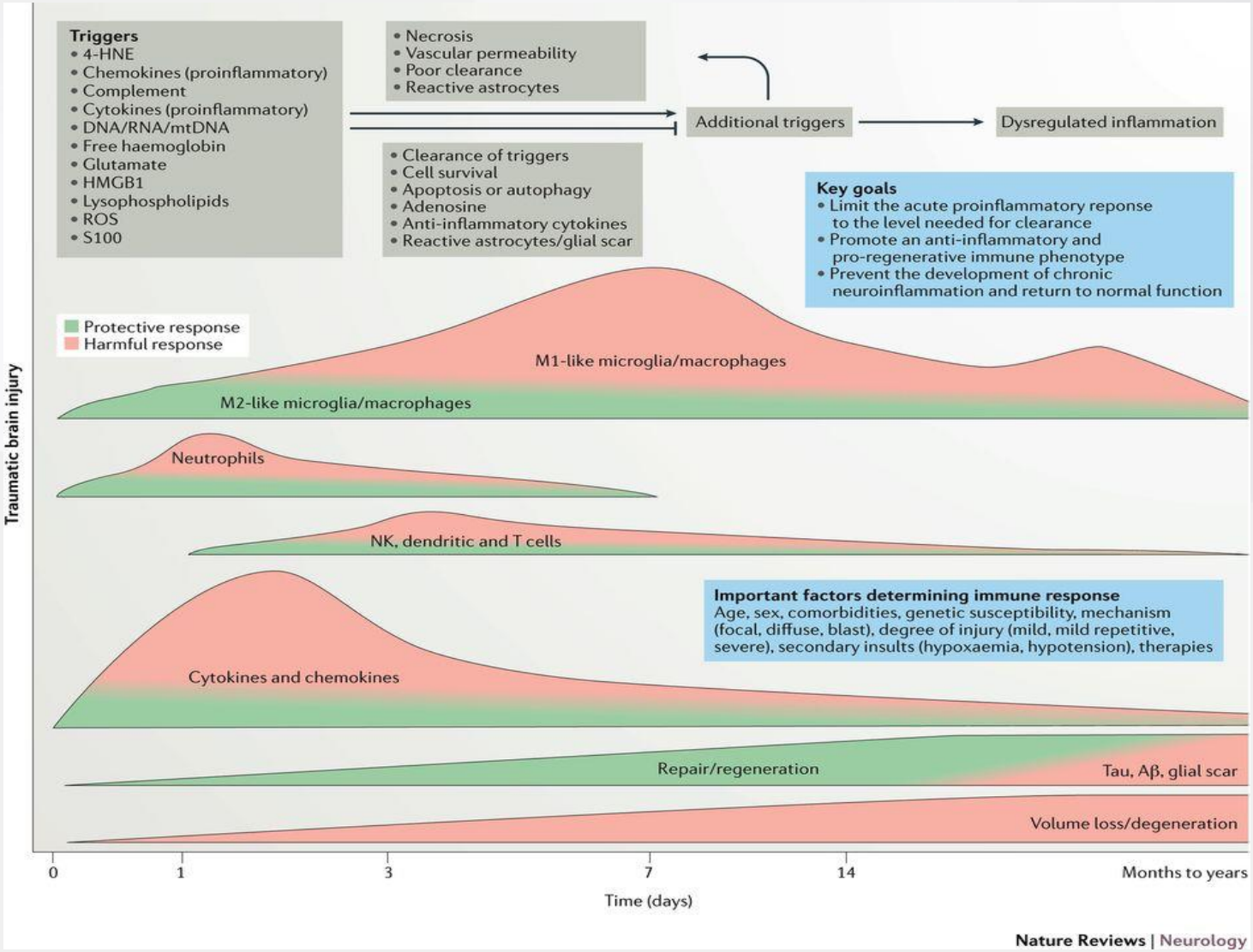
Domoic acid (shellfish) poisoning

High Pressure Neurological Syndrome
- **if severe enough**
- **if complicated by other excito-toxic stimuli**

Timeline of cellular inflammatory response



Protective vs harmful aspects of inflammation



Some important concepts

"Second hit" phenomenon (bad)

Stress ≠ damage

"Good stress" vs "bad stress"
Continuous stress ≠ intermittent stress

Oxidative stress can be good and bad

- HBOT – ppO_2 2500 mbar 2 hours BD = OK ("good")
- ICU ventilator - ppO_2 600 mbar 24/7 = toxic

Chronic / late brain effects
(weeks – months)

- Chronic neuro-inflammation
- Chronic oxidative stress
- Chronic neuro-vascular dysfunction (headaches)
- Demyelination
- Accumulation of toxic / damaged material
- Disordered functional settings
  - Over or under active; feedback loops
- Changes in volume of brain areas, fibre tracts

Recovery “set backs”

Days to weeks each time

Excessive physical or psychological stress

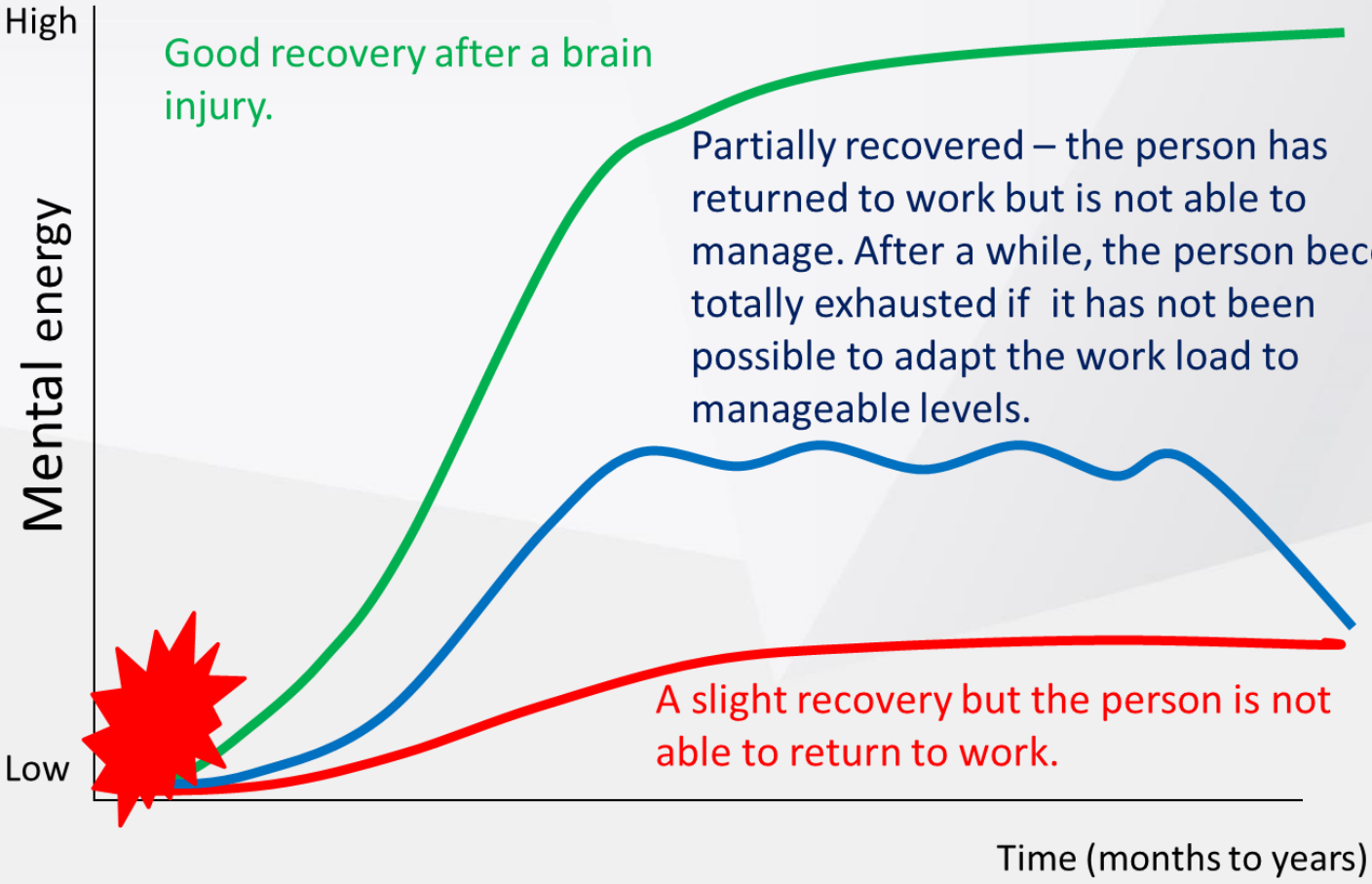
Exacerbation of:
- neuro-inflammation
- neuro-vascular dysfunction
- whole body inflammatory state
- Neuro-cognitive performance

Adversarial compensation is bad – inevitable, repeated stressors
- Uncertainty, anxiety
- Delayed / reduced income
- Disability / healthcare expenses

Impaired recovery, increased disability

Early settlement (regardless of amount) improves health outcomes

Timelines of decreased “mental energy”



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Variable susceptibility in response to injury

- Tolerance of Primary Injury
- Variable severity of secondary injury
- Susceptibility to chronic inflammation
- Susceptibility to lasting sequelae
  - Necrosis, apoptosis, demyelination
- Pre-disposition to psycho-pathology
- Capacity for neuroplasticity

Potential stressors during saturation diving

- Physical confinement – physical demands and limits
- Psychological – isolation and team dynamics
- Oxidative stress – high ppO_2
- (*Helium breathing / absence of nitrogen)*
- Inhaled breathing gas contaminants
  - In saturation living chamber, dive bell, diver's gas
  - Micro-contaminants in "tighter" systems?
  - Chemical exposures
- Upset diurnal rhythm – melatonin / cortisol etc.
- Lighting, noise, reduced sleep quality
- Thermal stresses – high, low, changed dynamics
- Altered microbiological flora

High Pressure Neurological Syndrome

An incompletely understood phenomenon

- Threshold 120 - 180msw – variable
  - Earlier onset with fast pressurisations
  - Deeper with slow pressurisation or with trimix
  - Significantly moderates with time at pressure
  - Initial settling of Sx within 1-2 hours
  - Adaptations / moderation over 24-48 hours
  - Symptoms can persist, but compatible with diving
  - Recurrences / exacerbations with
    - Downward excursions
    - Switch from trimix back to HeO_2
- Resolves completely with decompression

High Pressure Neurological Syndrome

Thermodynamically / cell function – slowed conduction
NMDA receptors / glutamate pathways activated

Clinically: slowed cognition but hyper-excitable

- "Feedback loop" concept (e.g. in tremor)

Critical frequency inputs may exacerbate HPNS
- VDU / movie visual flicker, sonic frequencies?

Hypothermia theoretically should exacerbate
Operational focus historically on avoiding heat stress

High Pressure Neurological Syndrome

Very variable individual susceptibility

- Minority of “HPNS” resistant
- Small number seem to be especially susceptible
- An enduring characteristic of each diver
- No significant habituation effects over time
- No predictive factors identified
- Only predictive test is test of symptoms and signs +/- EEG / ABR change with pressure test

?caution needed re: “unmasking” of underlying / old injuries

HPNS frequencies

- Slowed conduction, biochemical processes
- Compensatory increased “gain”
- More efficient? But “feedback looping”
- Tremor @ rate of 8 – 12 Hz
- Susceptibility to resonance ≤50Hz
- Screen flicker / video frame 25 – 30 Hz
- AC electricity 50 – 60 Hz

Thermal challenges

Dense helium – increased thermal flux

- Potential for heat loss or heat gain
- Insulation efficiency degraded

- Reduced thermal comfort zone
- Narrowed thermal safety limits
- Inevitable it won't be comfortable for all
  - Increased metabolism after diving, eating
  - Decreased metabolism during sleep
- Delay in diurnal rhythm adjustment of basal metabolic rate

Without gas heating

- Large heat loss from lungs – not sensed
- Heat gain required from hot water suit
- Cold brain / hot skin / blood temperature cycling…

And the oxidative stress question

Humans very tolerant of pO_2 @ 0.15 - 0.4 ATA

Normally

BUT

Once injured, brain is probably very susceptible to both hypoxia and hyperoxia

Current trials of oxygen therapeutics in acute injury:

- Stroke, post cardiac arrest, TBI….
- Is hyperoxia bad for the injured?

Vasodilator gases

CO_2 limit of 5000ppm = 10 x “normal”

- Breathlessness, impaired respiration, gas delivery systems reduce efficiency of CO_2 elimination
- Raises blood CO_2 level
- Increases brain blood flow,
  - lowers threshold for oxygen toxicity

Low level carbon monoxide also increases BBF

+/- cold gas on palate – “ice cream headache”

and Good Sleep……

- Sleep is “repair time” for the brain
- Toxic products eliminated
- Anti-oxidant levels restored
- Memories organized, filed
- Excess brain connections “pruned”

- Melatonin a potent anti-oxidant, experimental brain injury treatment agent
- Dark rest time, stable diurnal cycle important

Bright light in the morning, dim red/yellow light in the evening
Video screen embargo for 2 hours before sleep

So what if:

Deep dive research has involved "resistant" divers
Self selection of resistance applies strongly

HPNS is more of a problem than usually recognised for non-resistant divers
and….
Divers who have suffered moderate post sat. symptoms have "hidden" their symptoms

In the absence of complicating legal / compensation issues or new stressors, problems usually resolve

Dive medicals are too crude a tool to identify problems

The “bottom line” (the 2017 Australian event)

- A group of saturation divers **went to work**
- Their work was controlled by topsides
- In an environment controlled by others
- **They came home injured**
- Half have not yet recovered (2.5 years)
- Compensation processes still in process

The “bottom line” – deep saturation - IMO

Can it hurt you?
YES

Can it be done safely
Almost certainly YES – if everything is done right

BUT

- We are not sure of what “everything” is
- Maybe not for some susceptible individuals
- We are not measuring human outcomes well enough

Research aims

1. Recall of divers for repeat evaluation early 2020
Recruit comparator group of healthy sat divers
Analysis of biomarkers, MRI image data by an international group of expert brain research centres
(Research ethics approved already, but needs funding)

2. Use findings to select biomarkers +/- brain scan techniques to assess experienced divers for changes
3. Assess divers before, during and after dives
4. Combine quantitative electrophysiology and biomarkers with HPNS test dives to see if resistant divers can be identified