Barts and The London
School of Medicine and Dentistry

OMEGA-3 FATTY ACIDS FOR NEUROTRAUMA

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CENTRE LEAD

Centre for Neuroscience and Trauma

Blizard Institute

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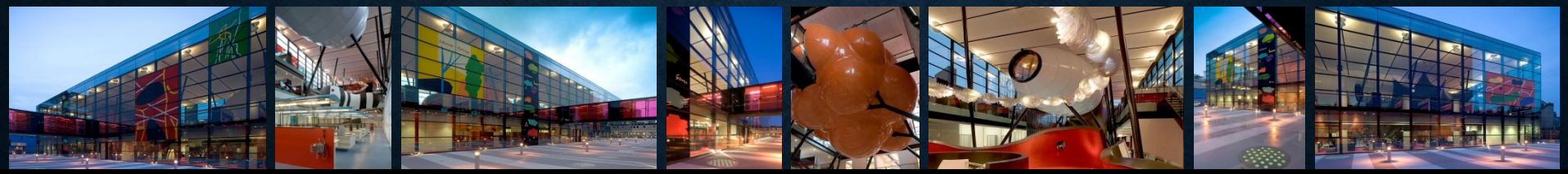


WHY ARE WE INTERESTED IN CLINICAL TRANSLATION IN NEUROTRAUMA?

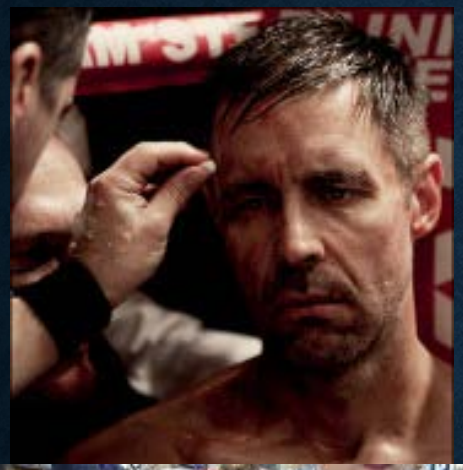
Level One Trauma Centre

Royal London Hospital - >2,000 trauma patients/year

Neurotrauma in a context of polytrauma

Intervention in the "golden hour"

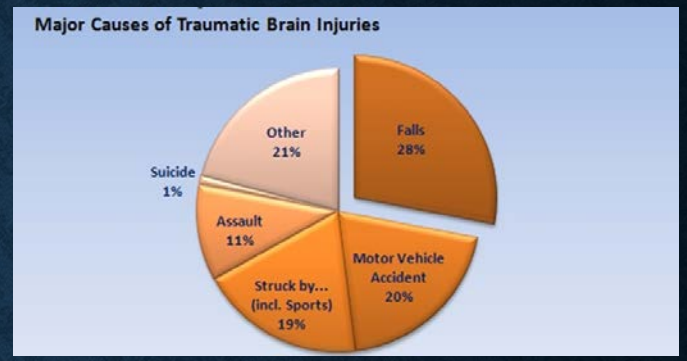
PRESENTATION OF TRAUMATIC BRAIN INJURY






Traumatic Brain Injury (TBI) is the leading cause of morbidity and mortality worldwide under the age of 45

THE IMPACT OF TBI



- In Europe:
  - 2.5 million people suffer a TBI each year
  - 1 million are admitted to hospital
  - 75.000 will die
- TBI is the leading cause of death and disability in young adults.
- The incidence in elderly patients is increasing.
- TBI can strike us all, but males are about twice as likely as females to experience a TBI.
- In younger patients Road Traffic Accidents are the most frequent cause of injury; in older patients falls.
- Moderate and severe head injury (respectively) are associated with a 2.3 and 4.5 times increased risk of Alzheimer's disease.

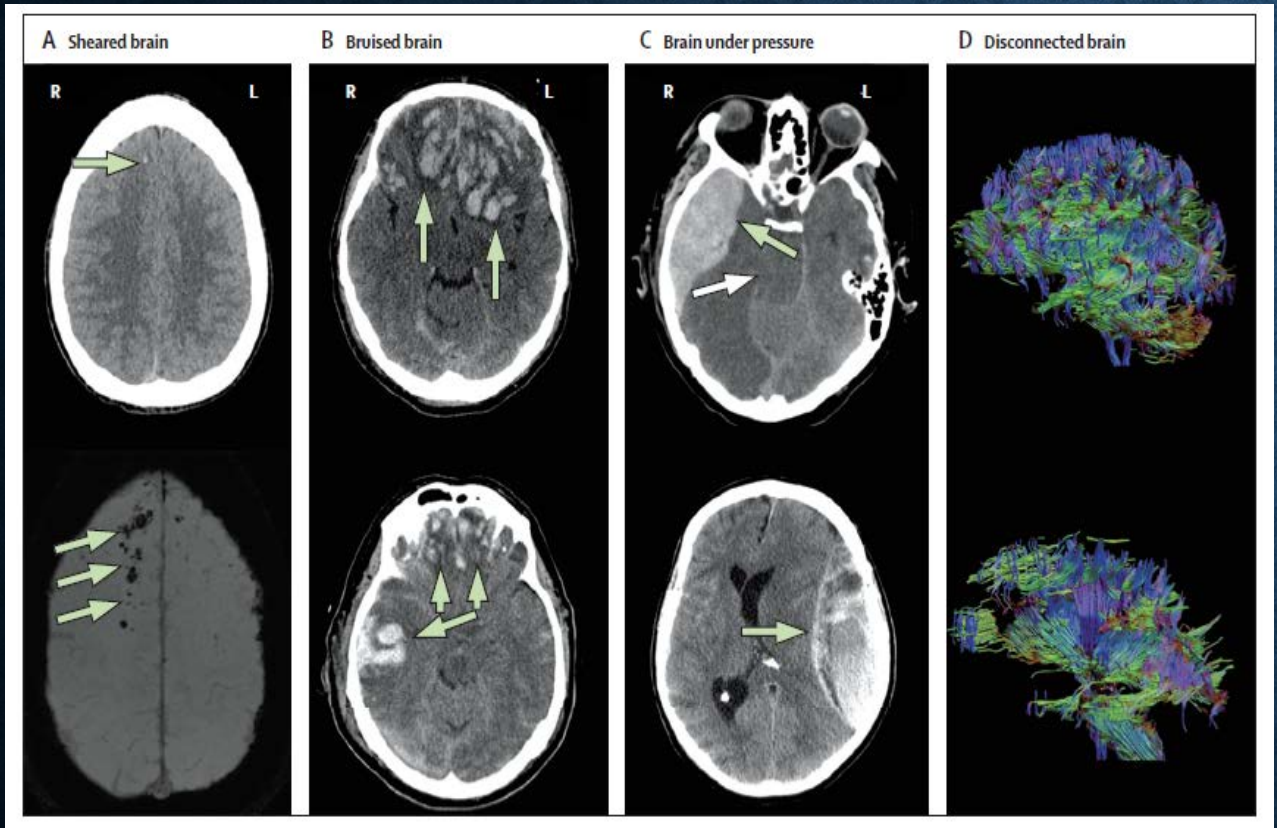
Having suffered a TBI, annual mortality remains increased up to seven fold for at least 13 years.

PUBLIC HEALTH IMPACT

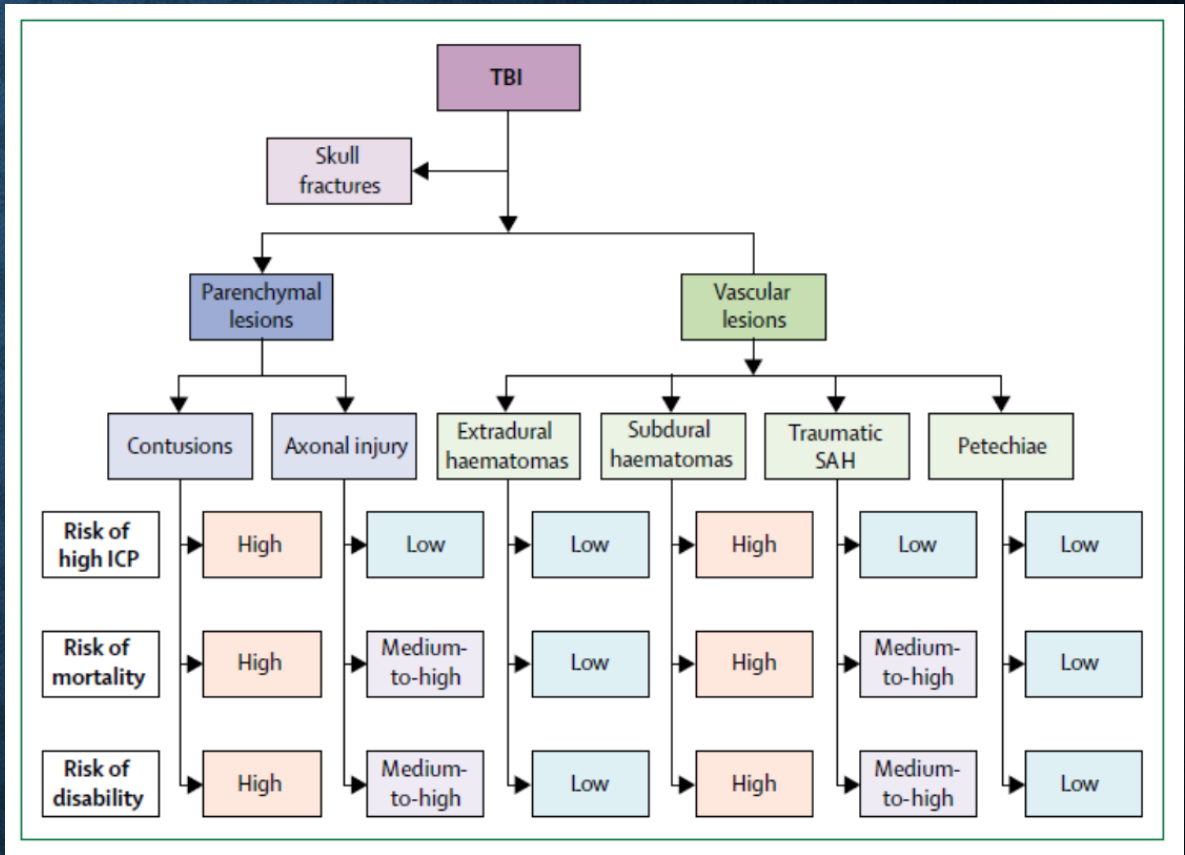
In the US, the annual burden of TBI has been estimated at over $ 70 billion.

In patients with severe TBI, the life time cost per case is estimated at over $ 400,000, with disability and lost productivity cost outweighing medical and rehabilitation costs by a factor of 4.

HUMAN TBI IS VERY HETEROGENEOUS



(Maas et al., 2017)

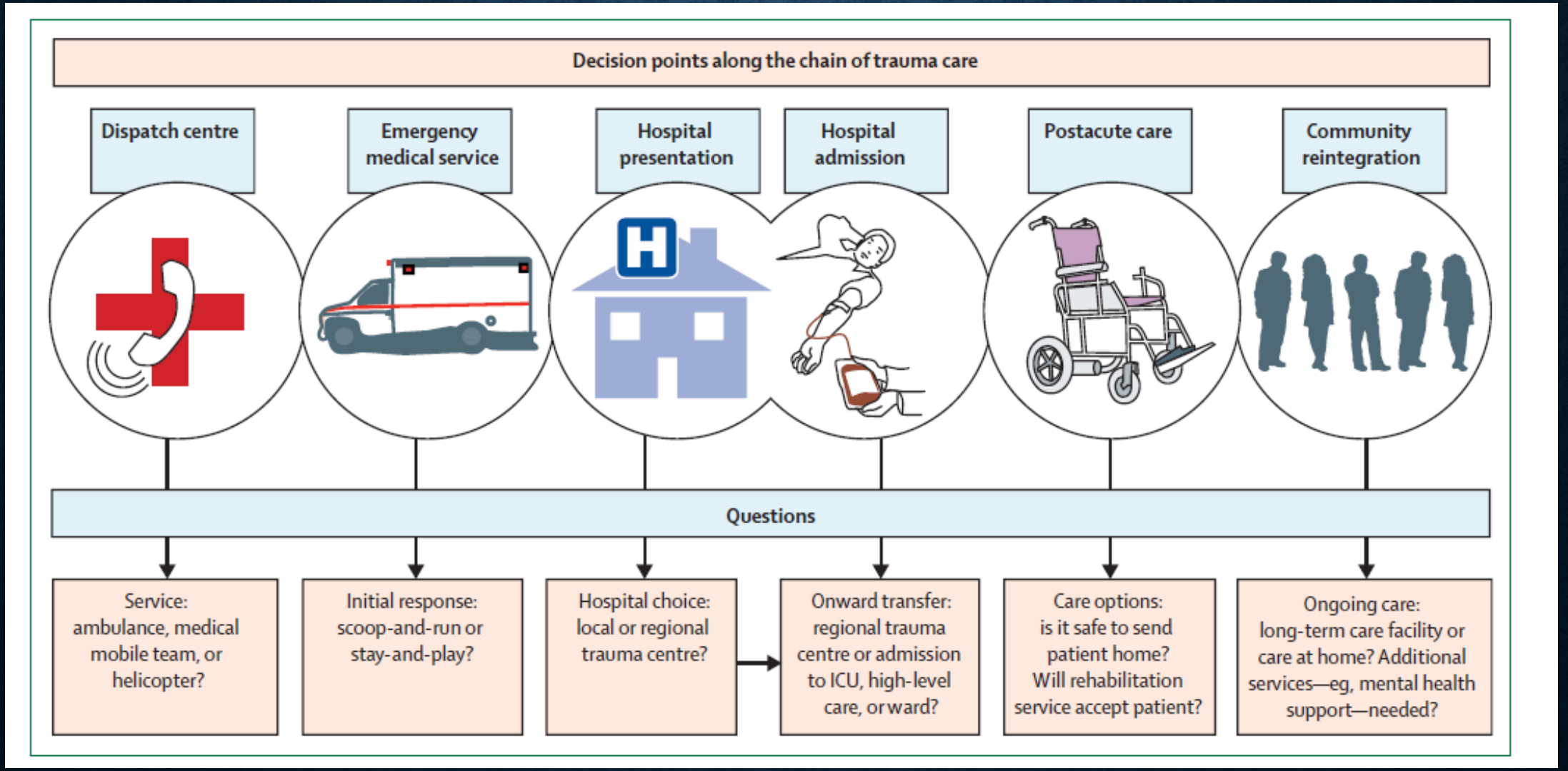


(Stocchetti et al., 2017)

What regime of treatment for what type of brain injury?

THE PATIENT CARE PATH IN TBI

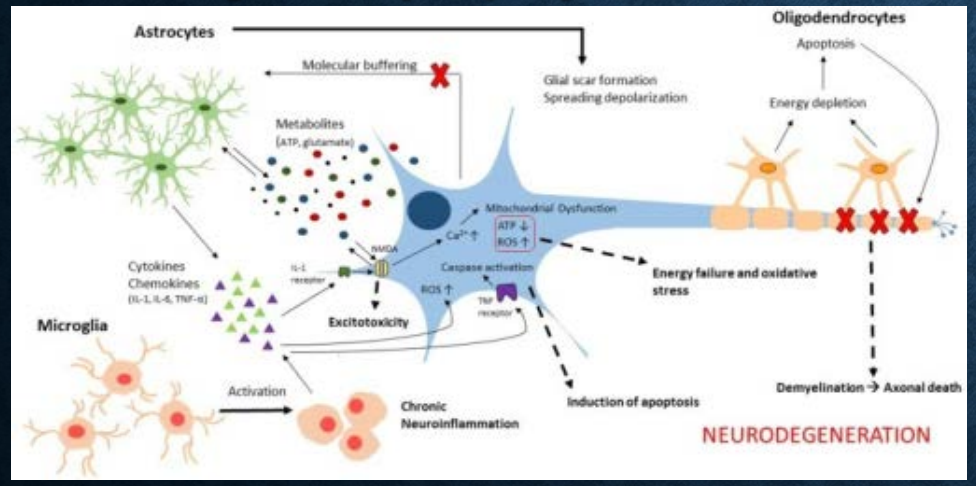
WHEN WOULD OMEGA-3 BE ADMINISTERED?

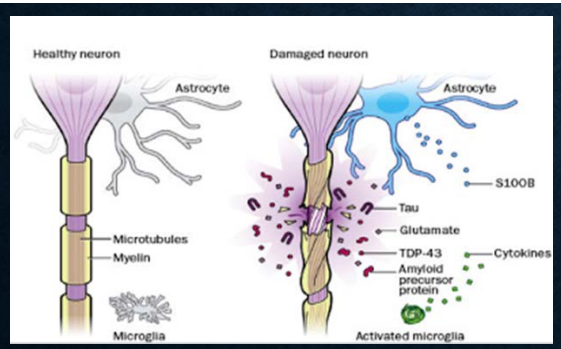


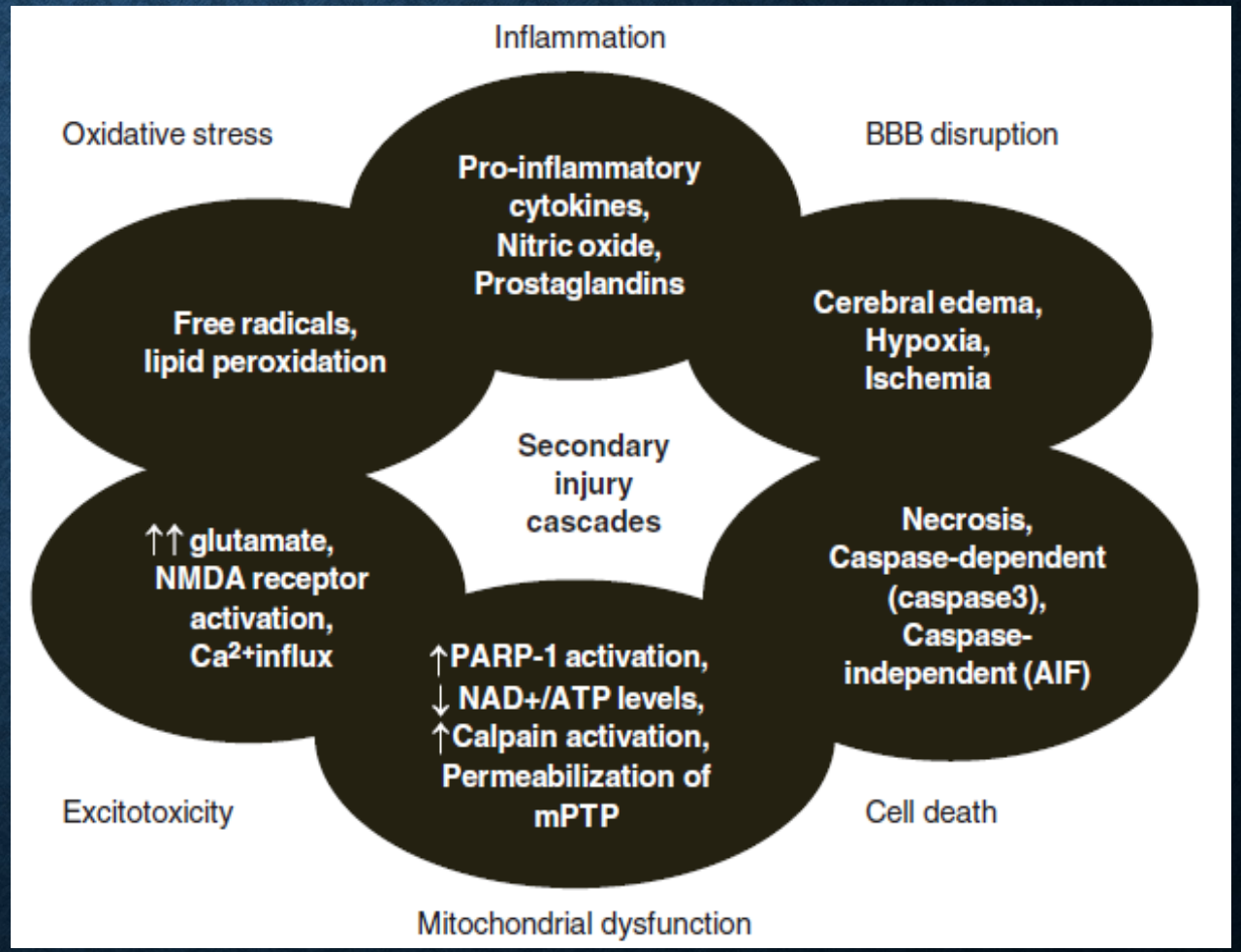
(Maas et al 2017)

SECONDARY INJURY PATHWAYS IN TBI

- Trauma affects neurons and non-neuronal cells and triggers a cascade of processes which continue for years after the primary injury event







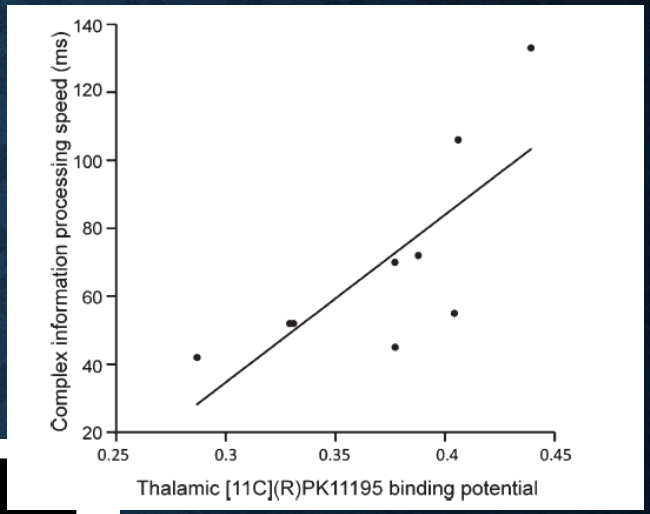
(Load and Faden 2010)

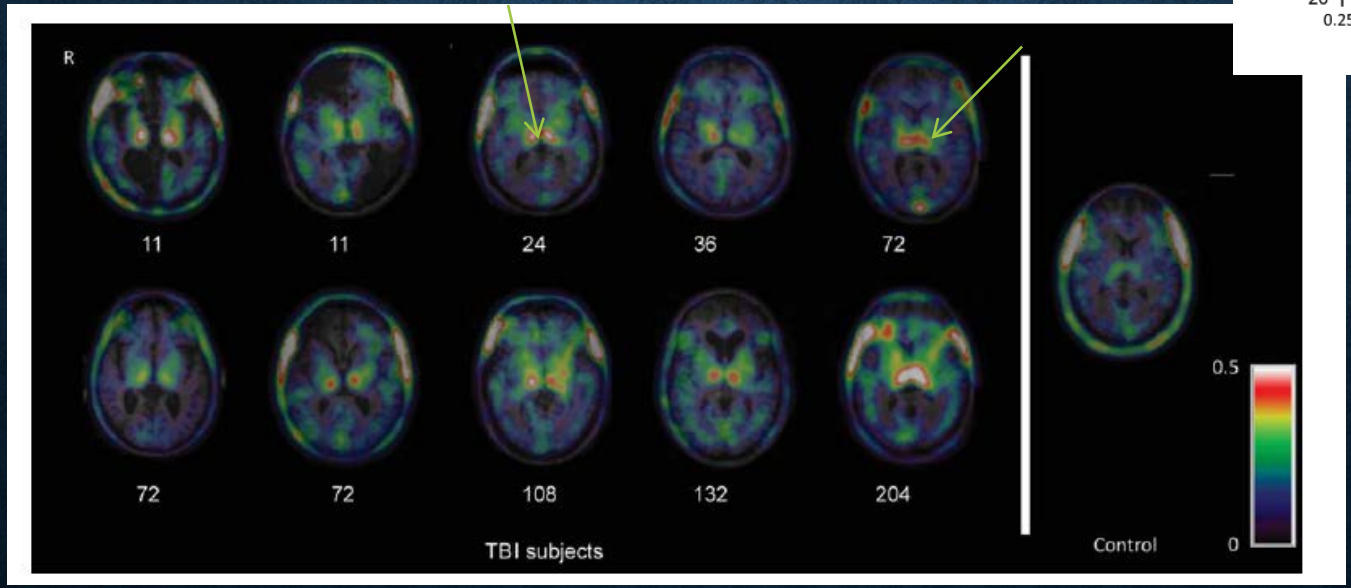
TBI AS A CHRONIC CONDITION

PERSISTENT NEUROINFLAMMATION SIGNAL

Inflammation after Trauma: Microglial Activation and Traumatic Brain Injury

Anil F. Ramlackhansingh, MRCP,[1] David J. Brooks, MD, DSc,[1] Richard J. Greenwood, FRCP,[2] Subrata K. Bose, PhD,[3] Federico E. Turkheimer, PhD,[1] Kirsi M. Kinnunen, PhD,[4] Steve Gentleman, PhD,[1] Rolf A. Heckemann, PhD,[1,5] Karen Gunanayagam, BSc,[1] Giorgio Gelosa, MD,[1] and David J. Sharp, MRCP, PhD[1]





Imaging of the translocator protein (TSPO) reveals neuroinflammatory changes more than a decade after injury

CHRONIC CONSEQUENCES OF TBI
THE TERTIARY INJURY

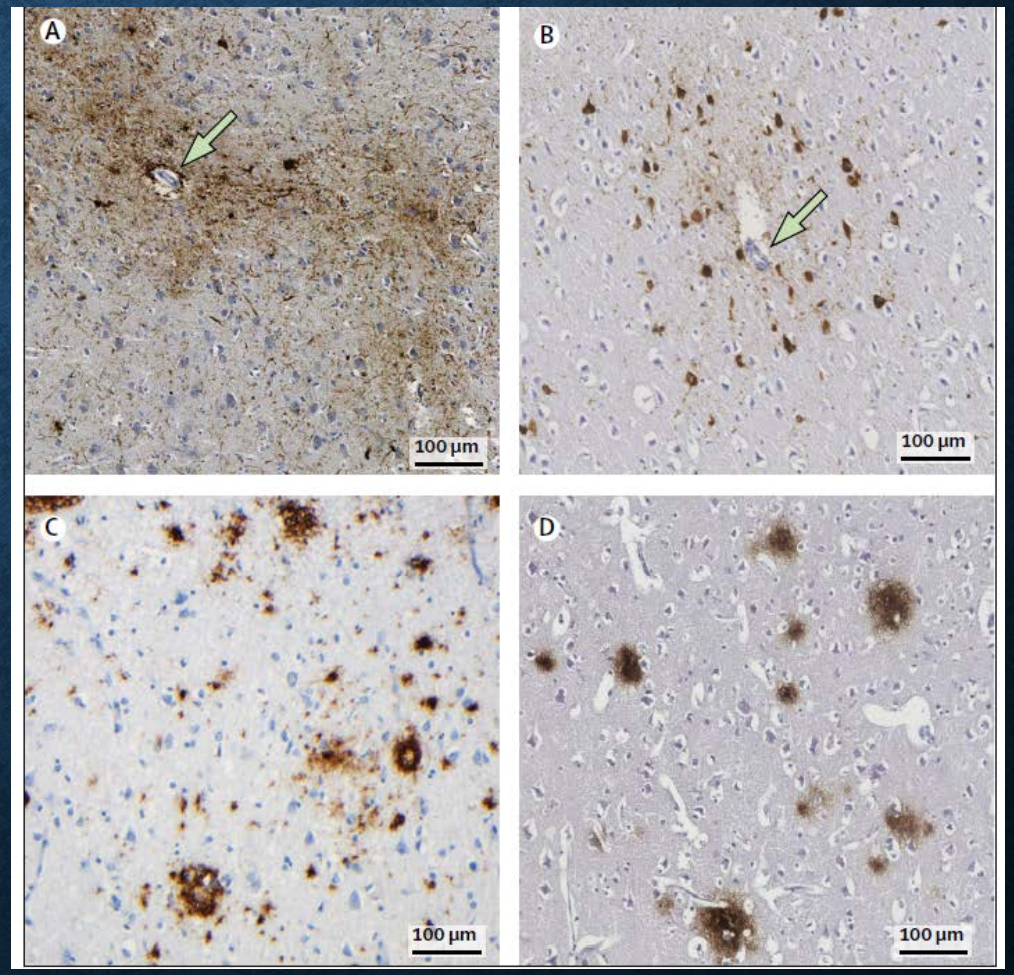
Function
- Disability or limitations to activity[3]
- Limitations to societal participation (eg, employment)[7]
- Cognitive deficits[8,9]
- Emotional problems[10]
- Behavioural change[11]

Disease
- Mild cognitive impairment[10,12]
- Neurodegenerative diseases
  - Alzheimer's disease or dementia[13,14]
  - Parkinson's disease or parkinsonism[10,15,16]
  - Dementia with Lewy bodies[16,17]
  - Frontotemporal dementia[17]
  - Amyotrophic lateral sclerosis[10,18]
  - Chronic traumatic encephalopathy[13,19]
- Post-traumatic epilepsy[20,21]
- Stroke[22,23]
- Neuroendocrine disorders[24,25]
- Psychiatric illness[10,26]

Mortality
- Mortality of any cause or reduced life expectancy[27,28]

(Wilson et al., 2017)

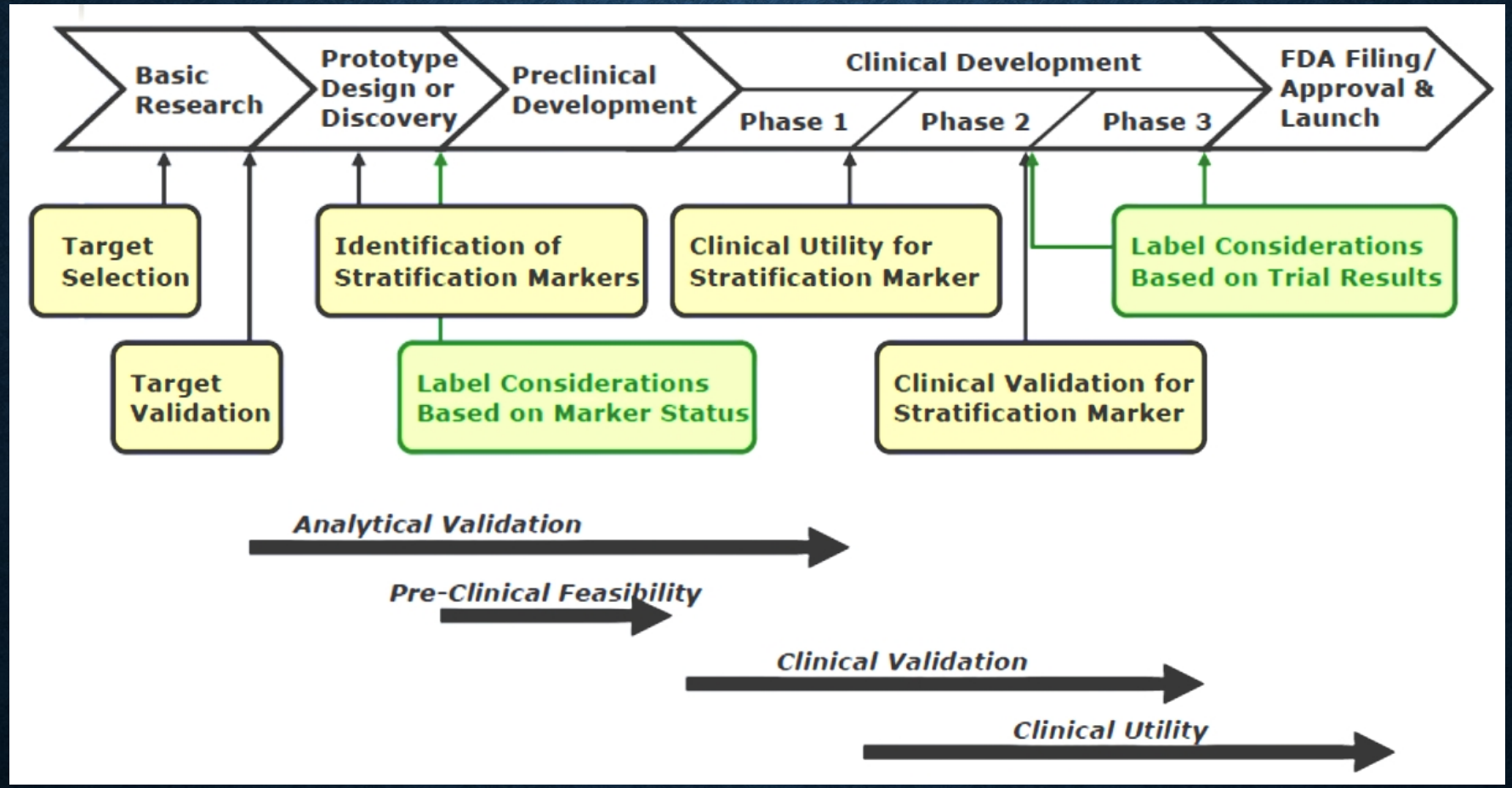
Chronic traumatic encephalopathy



PRIORITIES FOR TBI RESEARCH

- Neuroprotection in the acute phase
- Develop biomarkers predictive of severity and of response to treatment
- Regeneration and restoration of circuitry
- Prevent complications (e.g. post-traumatic stress disorder, personality changes, secondary epilepsy)

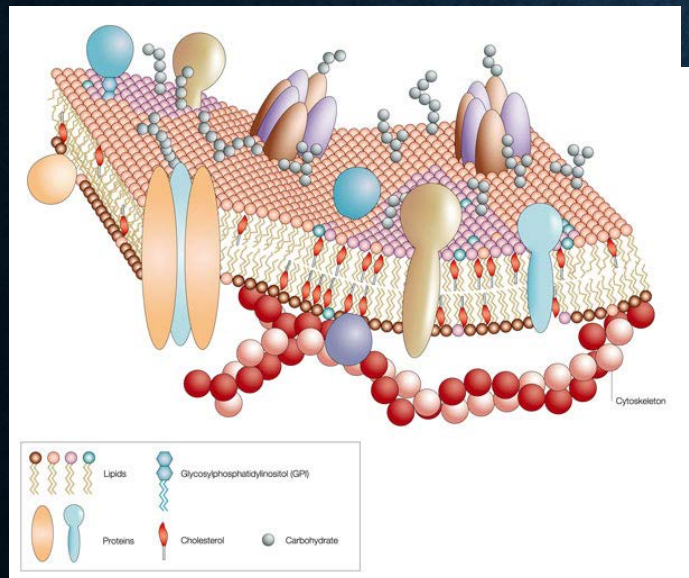
THE TRANSLATIONAL PATH FROM PRECLINICAL RESEARCH TO THE CLINIC

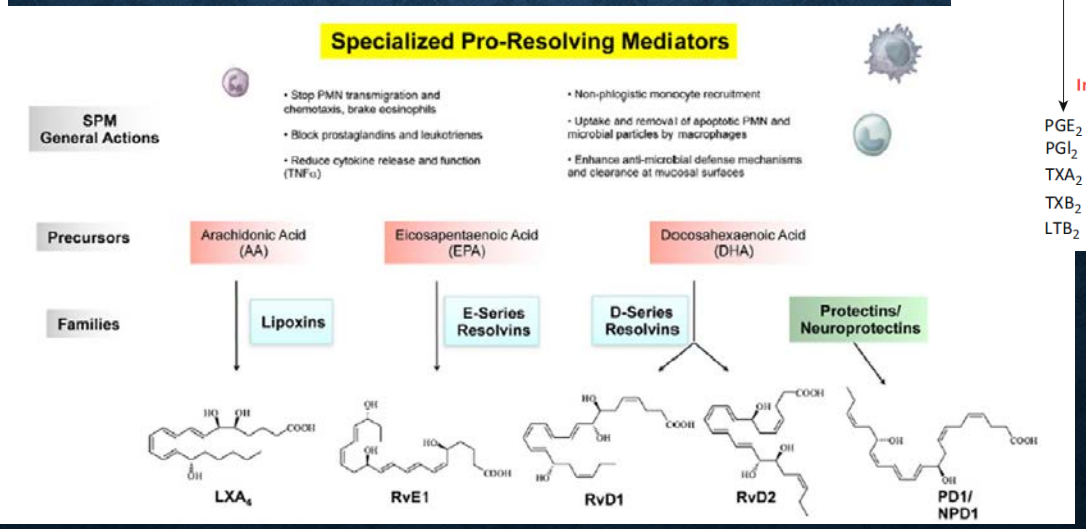


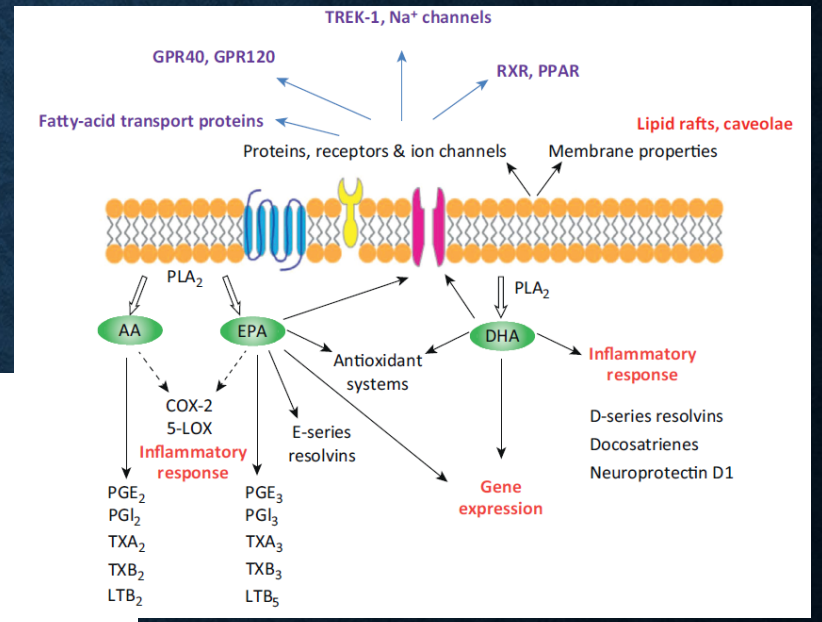
$2.5-3 billion; 10-15 years

DOCOSAHEXAENOIC ACID HAS MULTIPLE CELLULAR TARGETS AND ACTIVE METABOLITES

- Targets: ion channels (dual pore mechano-activated background potassium channels - TREK-1), voltage-gated sodium channels, retinoid receptors (RXR), peroxisome proliferator receptors (PPAR), GPCRs…
- Active metabolites (resolvins, protectins…)







(Michael-Titus and Priestley, 2013)

EXPERIMENTAL EVIDENCE OF EFFICACY OF OMEGA-3 FATTY ACIDS IN NEUROLOGICAL INJURY MODELS

doi:10.1093/brain/awm223 Brain (2007), 130, 3004–301

A combination of intravenous and dietary docosahexaenoic acid significantly improves outcome after spinal cord injury

W. L. Huang,* V. R. King,* O. E. Curran, S. C. Dyall, R. E. Ward, N. Lal, J. V. Priestley and A. T. Michael-Titus

Neuroscience Centre, Institute of Cell & Molecular Science, Queen Mary University of London, UK

Inflammation (© 2018)
DOI: 10.1007/s10753-018-0765-z

ORIGINAL ARTICLE

Docosahexaenoic Acid (DHA) Provides Neuroprotection in Traumatic Brain Injury Models *via* Activating Nrf2-ARE Signaling

peutic Regimen with Omega-3
ty Acids that Promotes White Matter
cial Microglial Responses

ORIGINAL ARTICLE

Omega-3 polyunsaturated fatty acid supplementation improves neurologic recovery and attenuates white matter injury after experimental traumatic brain injury

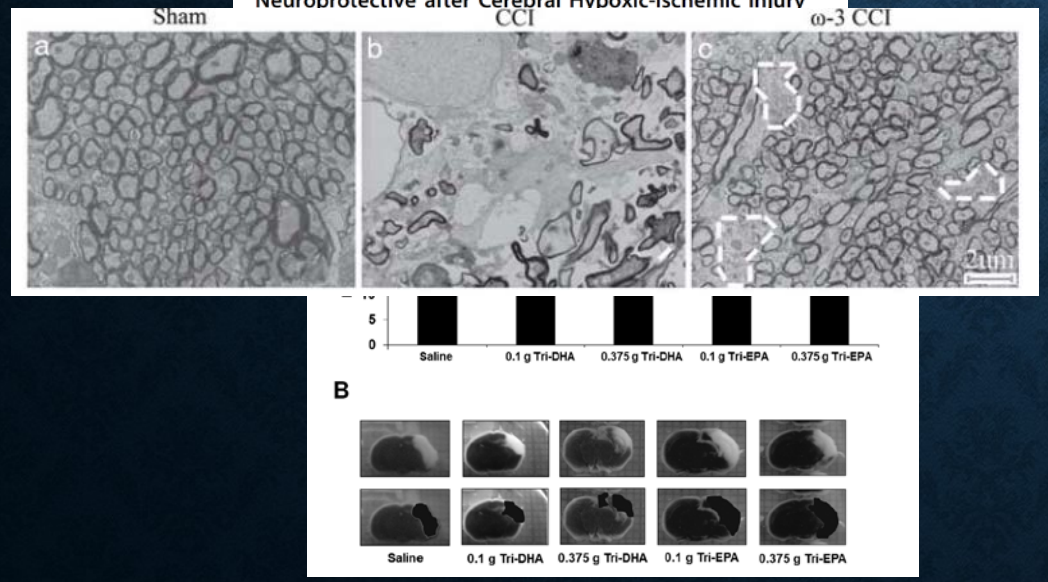
Hongjian Pu[1], Yanling Guo[1], Wenting Zhang[1], Lanting Huang[1], Guohua Wang[1], Anthony K Liou[2,3], Jia Zhang[1], Pengyue Zhang[1], Rehana K Leak[4], Yun Wang[1], Jun Chen[1,2,3] and Yanqin Gao[1,2]

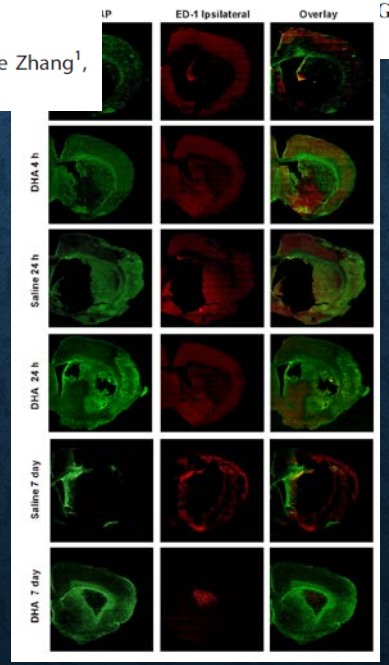
gguang Chen[1]

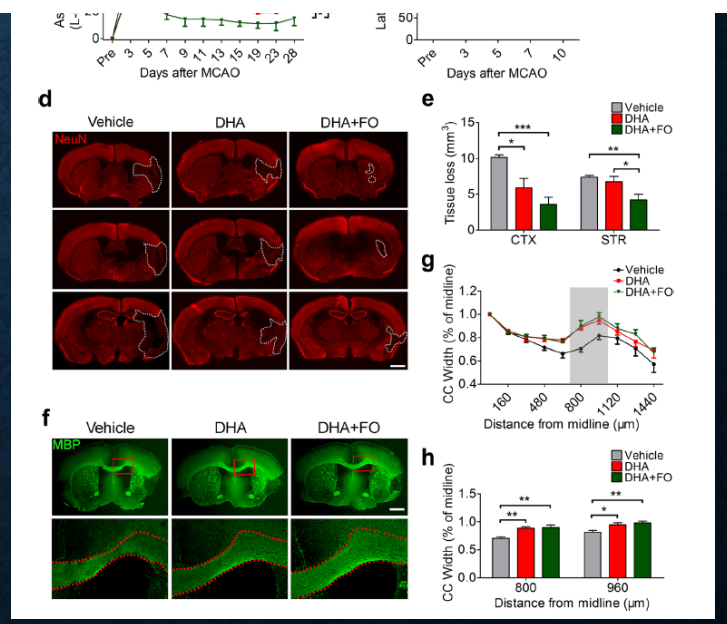
after Cerebral Ischemia

Xiaoyan Jiang[1,2] · Hongjian Pu[2] · Xiaoming Hu[1,2,3] · Zhishuo Wei[2] · Dandan Hong[2] · Gao[1,2] · Jun Chen[1,2,3] · Yejie Shi[2,3]

Neuroprotective after Cerebral Hypoxic-Ischemic Injury







SO, SHOULD OMEGA-3 FATTY ACIDS BE IN THE NEUROTRAUMA CLINIC NOW?

academics clinicians

THE TRANSLATIONAL FAILURE LESSONS

THE EXAMPLE OF PROGESTERONE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 25, 2014 VOL. 371 NO. 26

Very Early Administration of Progesterone for Acute Traumatic Brain Injury

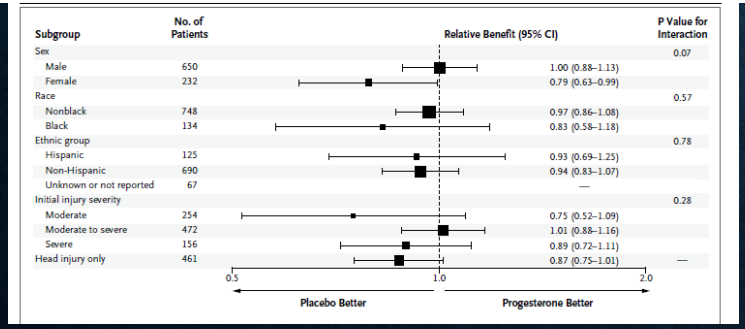
David W. Wrigh Ph.D.,
Vicki S. Hertzberg y, Ph.D.,
Harriet Howlett-Smith, R M.D., M.P.H.,
L. Scot

METHODS

We conducted a double-blind, multicenter clinical trial in which patients with severe, moderate-to-severe, or moderate acute TBI (Glasgow Coma Scale score of 4 to 12, on a scale from 3 to 15, with lower scores indicating a lower level of consciousness) were randomly assigned to intravenous progesterone or placebo, with the study treatment initiated within 4 hours after injury and administered for a total of 96 hours. Efficacy was defined as an increase of 10 percentage points in the proportion of patients with a favorable outcome, as determined with the use of the stratified

CONCLUSIONS

This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI. (Funded by the National Institute of Neurological Disorders and Stroke and others; PROTECT III ClinicalTrials.gov number, NCT00822900.)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Clinical Trial of Progesterone for Severe Traumatic Brain Injury

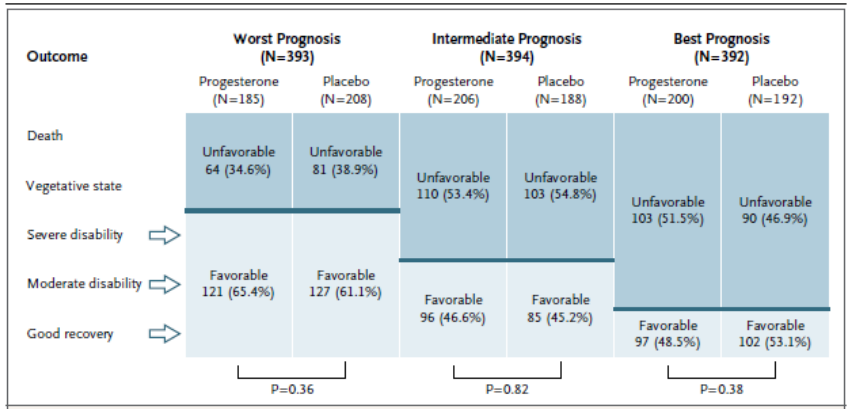


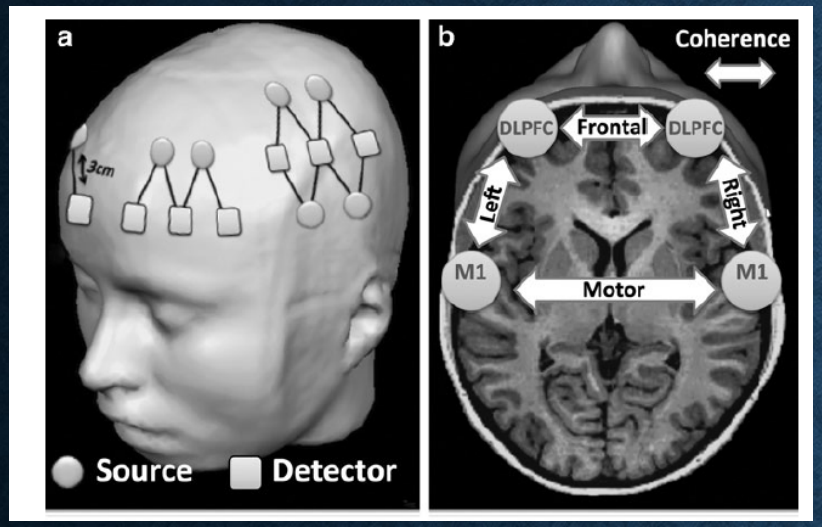
Figure 2. Efficacy Analysis with the Use of a Sliding Dichotomy Approach.

In the sliding dichotomy approach, the GOS was dichotomized for analysis, but the split for dichotomy was differentiated according to the baseline prognostic risk. Prognostic groups (based on worst, intermediate, and best prognosis)[22] were defined by baseline prognostic factors that included age, Glasgow Coma Scale motor score (1 or 2 vs. 3 vs. 4 vs. 5 or 6; scores range from 1 to 6, with lower scores indicating reduced motor response), pupillary response (bilateral response vs. unilateral response, no reactive pupils, or not testable), presence or absence of hypoxemia, presence or absence of hypotension, Marshall's classification (I or II vs. III vs. IV vs. V or VI), and presence or absence of traumatic subarachnoid hemorrhage. The Marshall classification is based on a review of CT scans; scores range from I to VI, with a score of II or higher indicating visible pathologic changes or worse. The arrow indicates the split for sliding dichotomy differentiated according to prognostic risk. P values were based on a Cochran–Mantel–Haenszel chi-square test with adjustment for geographic region (Asia, Europe, North America, and South America).

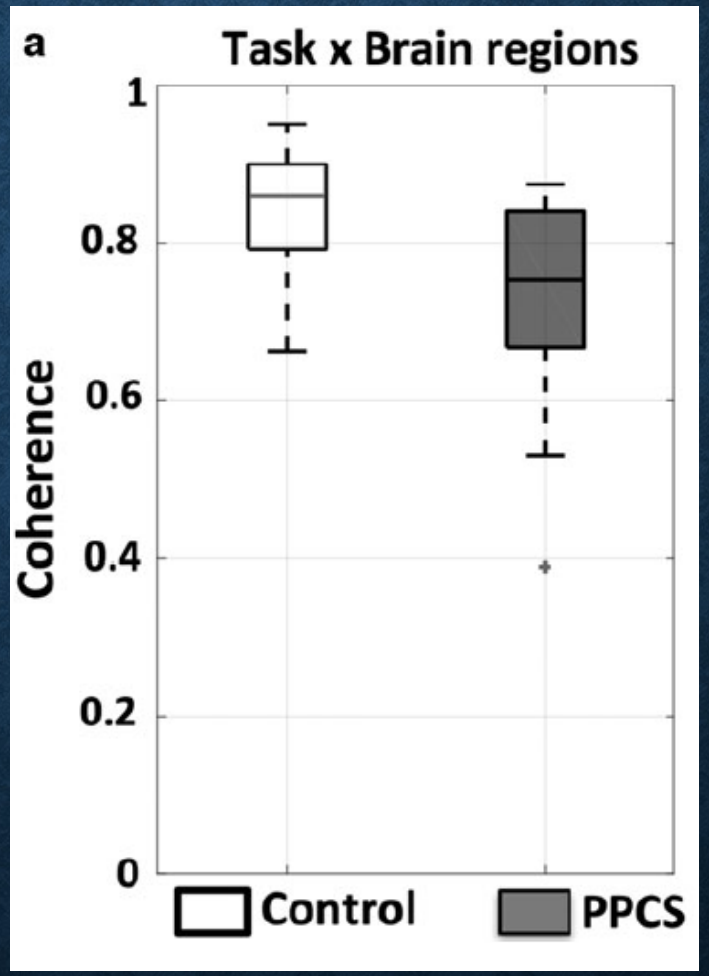
MILD TBI – CONCUSSION

FIRST STEPS TOWARDS THERAPEUTIC USE

CONCUSSION CHANGES BRAIN CONNECTIVITY



Connectivity evaluated using functional infrared spectroscopy



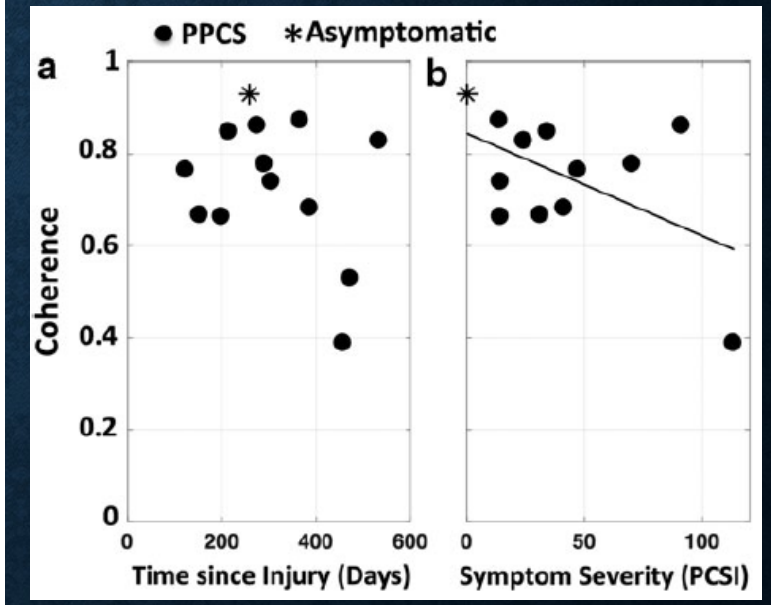


Table 1. Demographics

Condition	Age	Sex	Symptom score	Time post-injury (days)	Prior mTBI	Injury comment
PPCS	22	F	41	385	3	Hit front of head on counter
PPCS	37	F	-	470	0	Hit back of head when fell
PPCS	20	F	70	290	0	Hit head above right eye when biking
PPCS	24	M	14	195	2	Hit head on running track - LOC
PPCS	38	M	13.5	365	5	Sports related - LOC
PPCS	18	F	24	435	1	Hit back of head during skiing
PPCS	18	M	34	210	10	Hit head on right side on glass, after body-check from the left
PPCS	41	F	14	305	3	Head was hit on the right side with rock
PPCS	32	M	91	273	30	Elbow below the nose
PPCS	18	M	31	152	3	Hit to the left side of cerebrum during hockey (fell head first)
PPCS	41	F	47	124	0	Hit bottom right jaw on end of waterslide; LOC for 1 min
PPCS	42	F	113	456	0	Hit head on steering wheel during car accident (whiplash)
Asympt.	25	M	0	255	3	Sports-related during football

Demographics of PPCS patients included in the study as well as one asymptomatic patient, with age (second column); sex (third column); symptom score (fourth column) from the Post-Concussion Symptom Inventory (PCSI) with additional Sport Concussion Assessment Tool 3 (SCAT3) questions; the time since injury until fNIRS measurement (fifth column); how many mild traumatic brain injuries (mTBIs) were diagnosed before this injury (sixth column) and how the injury was acquired (last column).

PPCS, persistent post-concussion symptoms; LOC, loss of consciousness; Asympt., The participant who was symptomatic when recruited, but asymptomatic when data acquired. Not included in the statistical analysis.

(Hocke et al., 2018)

PPCS = persistent post-concussion symptoms

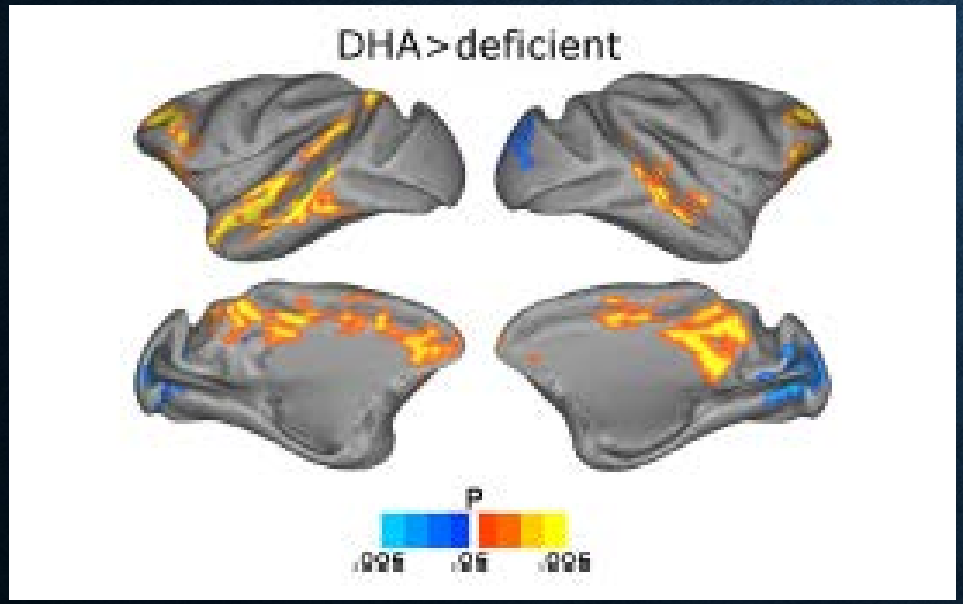
OMEGA-3 FATTY ACIDS AND NEUROPLASTICITY

THE RESTORATION OF CONNECTIVITY POST-NEUROTRAUMA

Behavioral/Cognitive

Dietary Omega-3 Fatty Acids Modulate Large-Scale Systems Organization in the Rhesus Macaque Brain

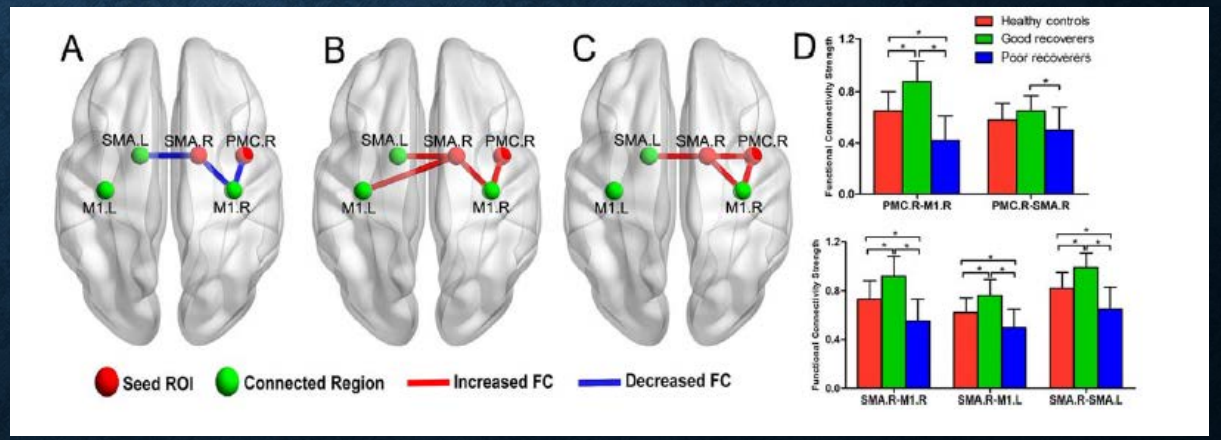
David S. Grayson,[1,2] Christopher D. Kroenke,[2,3,6] Martha Neuringer,[4,6] and Damien A. Fair[2,3,5]
[1]Center for Neuroscience, University of California, Davis, California 95616, [2]Department of Behavioral Neuroscience, [3]Advanced Imaging Research Center, [4]Casey Eye Institute, and [5]Department of Psychiatry, Oregon Health and Science University, Portland, Oregon 97239, and [6]Division of Neuroscience, Oregon National Primate Research Center, Beaverton, Oregon 97006



◆ Human Brain Mapping 37:2195–2209 (2016) ◆

Motor Recovery at 6 Months After Admission Is Related to Structural and Functional Reorganization of the Spine and Brain in Patients With Spinal Cord Injury

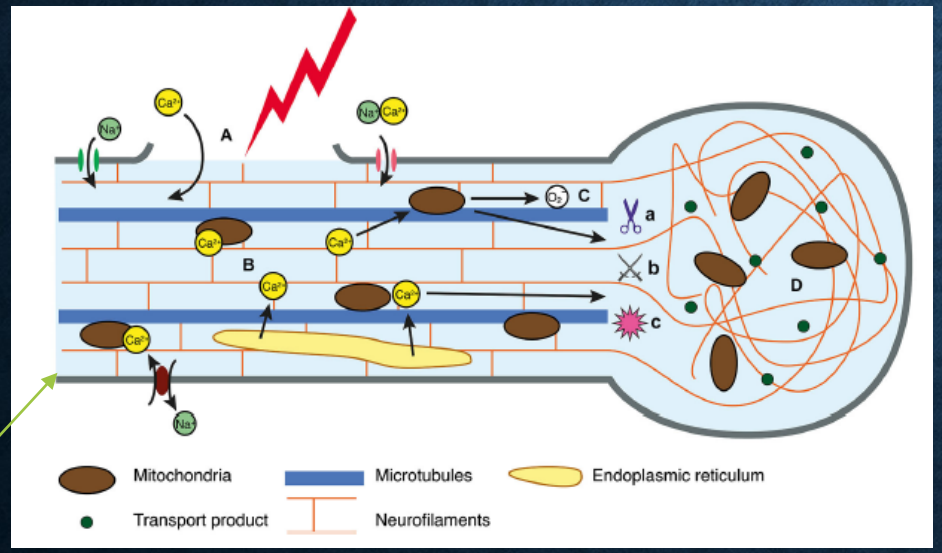
Jingming Hou,[1] Zimin Xiang,[2,3] Rubing Yan,[1] Ming Zhao,[4] Yongtao Wu,[1] Jianfeng Zhong,[2] Lei Guo,[2] Haitao Li,[4] Jian Wang,[4] Jixiang Wu,[1] Tiansheng Sun,[2]* and Hongliang Liu[1]*

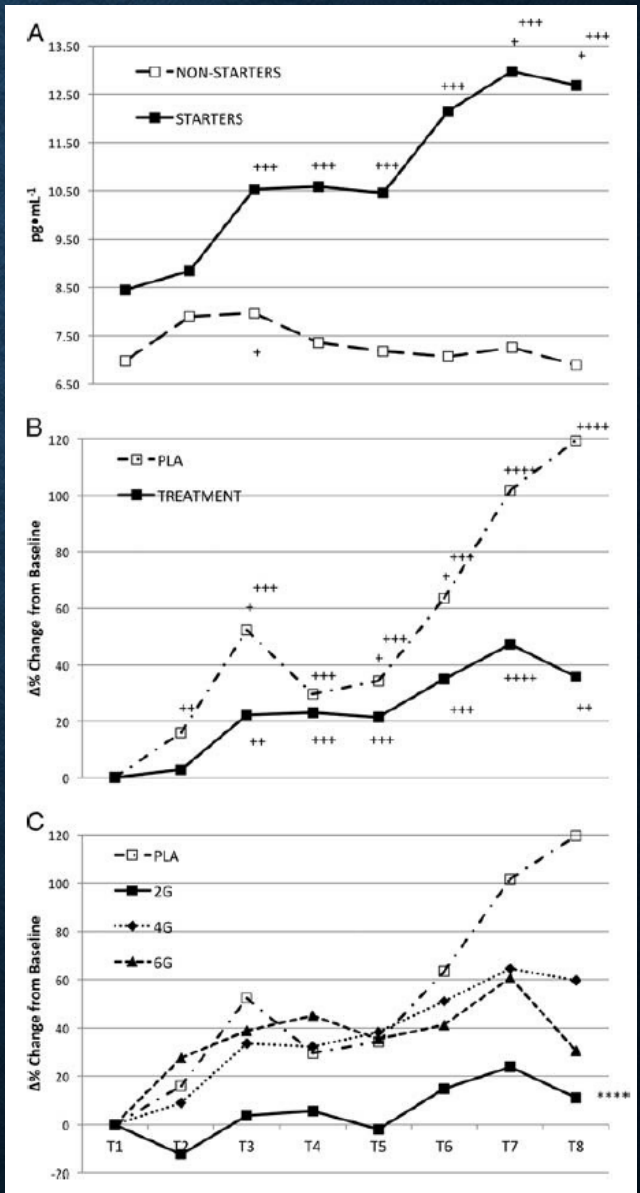


PROTECTION BY DHA IN SPORTS CONCUSSION

Effect of Docosahexaenoic Acid on a Biomarker of Head Trauma in American Football

JONATHAN M. OLIVER[1], MARGARET T. JONES[2], K. MICHELE KIRK[1,3,4], DAVID A. GABLE[1,3], JUSTIN T. REPSHAS[1]
TORIE A. JOHNSON[1], ULF ANDRÉASSON[6], NIKLAS NORGREN[5], KAJ BLENNOW[6], and HENRIK ZETTERBERG[6,7]



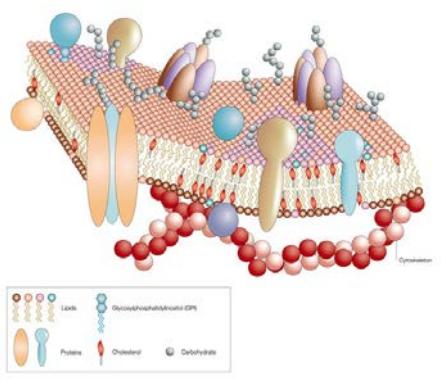


Disruption of the axonal cytoskeleton post-injury
Release of Neurofilament L reflects the neuronal damage

DHA ONLY OR DHA PLUS …?

PHOSPHOLIPIDS DECREASE IN TBI

SIMILAR OBSERVATIONS IN EXPERIMENTAL AND HUMAN TBI

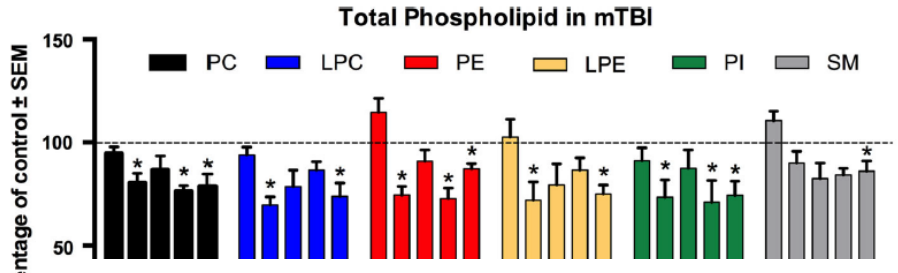


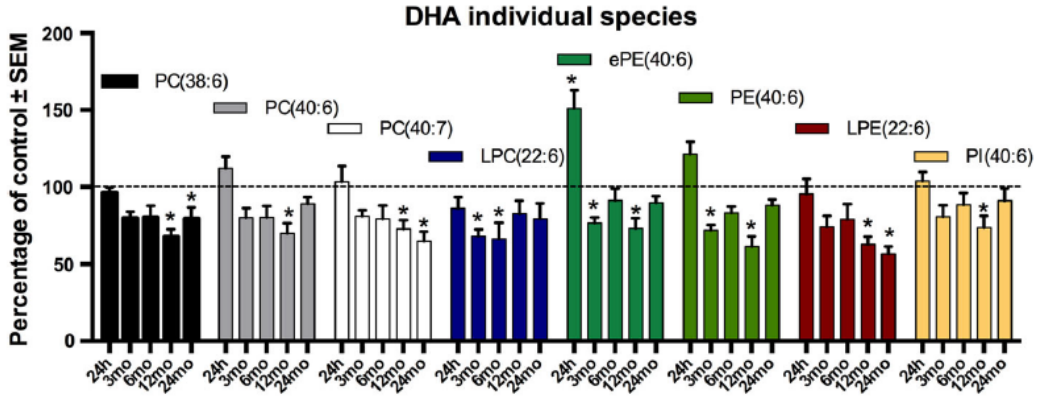
017-016-8436-4

ORIGINAL PAPER

Mild TBI Results in a Long-Term Decrease in Circulating Phospholipids in a Mouse Model of Injury

Tanja Emmerich[1,2,3] · Laila Abdullah[1,2,3] · Joseph Ojo[1,2] · Benoit Mouzon[1,2,3] · Thinh Nguyen[1] · Gary S. Laco[1] · Gogce Crynen[1,2] · James E. Evans[1,3] ·



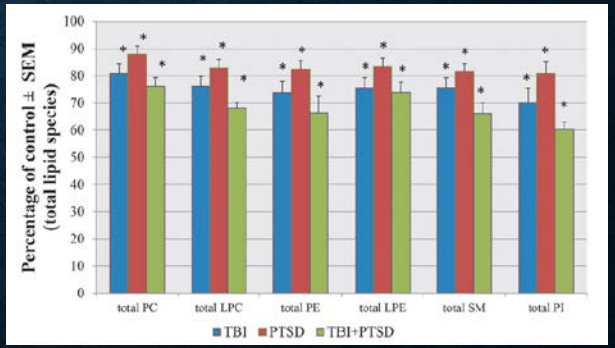


JOURNAL OF NEUROTRAUMA 33:1331–1348 (July 15, 2016)

DOI: 10.1089/neu.2015.4061

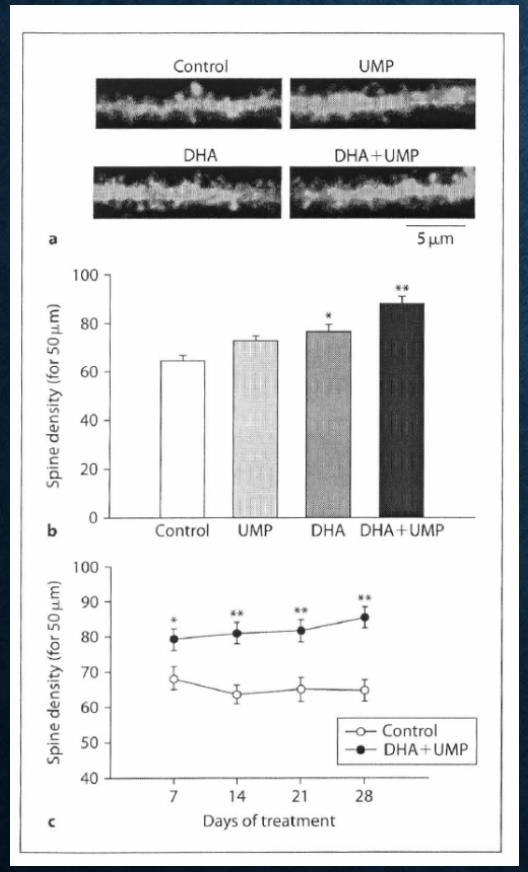
Plasma Lipidomic Profiling in a Military Population of Mild Traumatic Brain Injury and Post-Traumatic Stress Disorder with Apolipoprotein E ε4–Dependent Effect

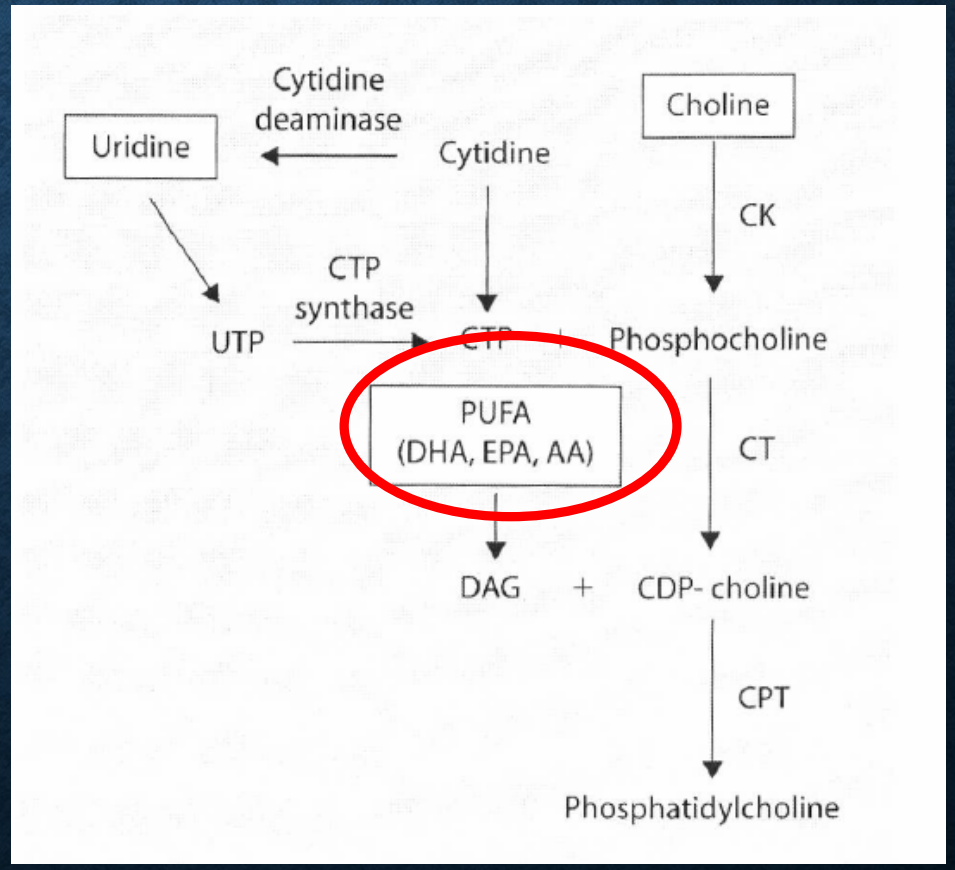
Tanja Emmerich,[1–3] Laila Abdullah,[1–3] Gogce Crynen,[1,2] Michael Dretsch,[4,5] James Evans,[1] Ghania Ait-Ghezala,[1–3] Jon Reed,[1,3] Hannah Montague,[1] Helena Chaytow,[1] Venkatarajan Mathura,[1–3] Justin Martin,[1] Robert Pelot,[1–3] Scott Ferguson,[1–3] Alex Bishop,[1] John Phillips,[1] Michael Mullan,[1,2] and Fiona Crawford[1–3]



Administration of Docosahexaenoic Acid, Uridine and Choline Increases Levels of Synaptic Membranes and Dendritic Spines in Rodent Brain

Richard J. Wurtman[a] · Mehmet Cansev[a,b] · Toshimasa Sakamoto[a] · Ismail H. Ulus[a,b]





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PLOS ONE

The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer's Disease: A Randomised Controlled Study

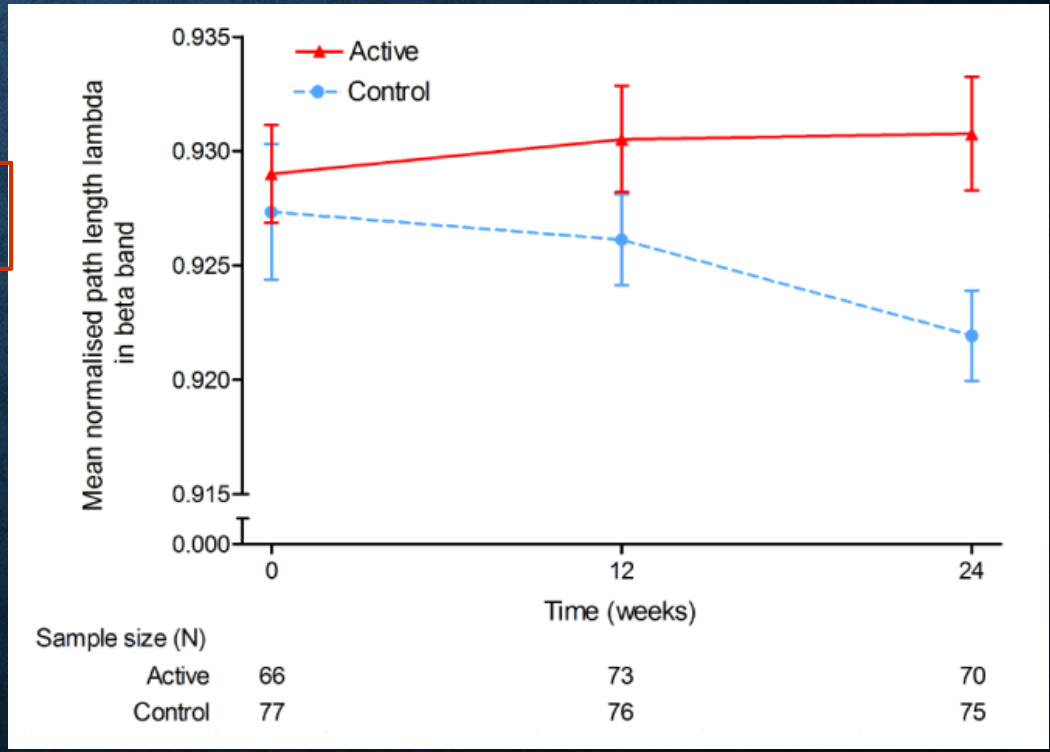
Hanneke de Waal[1]*, Cornelis J. Stam[2], Marieke M. Lansbergen[3], Rico L. Wieggers[3], Patrick J. G. H. Kamphuis[3], Philip Scheltens[1], Fernando Maestú[4], Elisabeth C. W. van Straaten[2,3]

(2014)

Table 1
Nutritional composition of Fortasyn™ Connect, the nutrient combination in Souvenaid

Component	Amount per daily dose*
Eicosapentaenoic acid, mg	300
Docosahexaenoic acid, mg	1200
Phospholipids, mg	106
Choline, mg	400
Uridine monophosphate, mg	625
Vitamin E (alpha-tocopherol equivalents), mg	40
Vitamin C, mg	80
Selenium, µg	60
Vitamin B12, µg	3
Vitamin B6, mg	1
Folic acid, µg	400

*Souvenaid (125 mL [125 kcal] daily dose) contains Fortasyn Connect. Souvenaid is a registered trademark of Nutricia N.V. Fortasyn is a trademark of Nutricia N.V.



TBI AND DEMENTIA

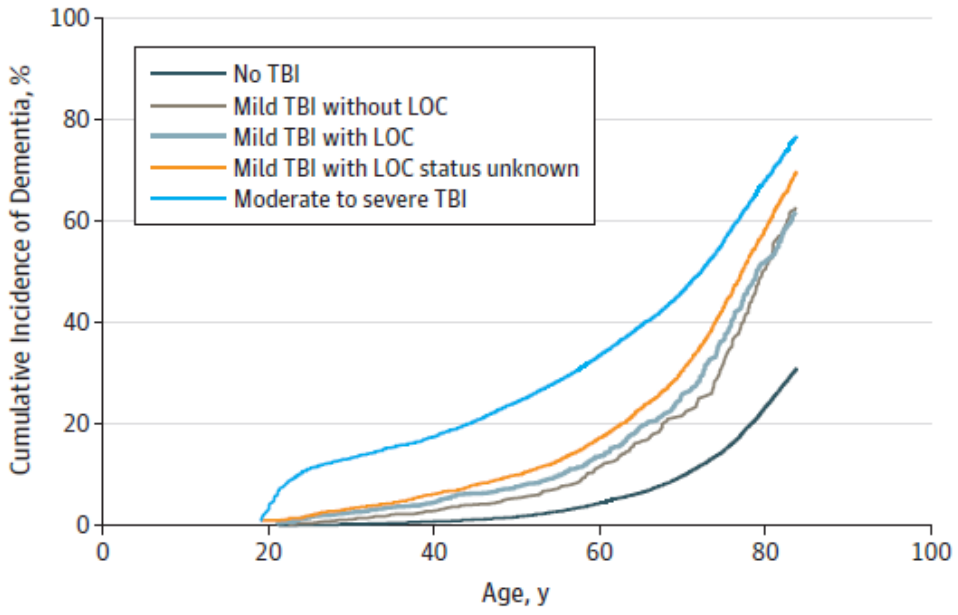
SPECIALISED NUTRITION CONTAINING OMEGA-3 FATTY ACIDS AS PROPHYLAXIS

JAMA Neurology | Original Investigation

Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans

Deborah E. Barnes, PhD, MPH; Amy L. Byers, PhD, MPH; Raquel C. Gardner, MD; Karen H. Seal, MD, MPH; W. John Boscardin, PhD; Kristine Yaffe, MD

Figure. Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity



24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial

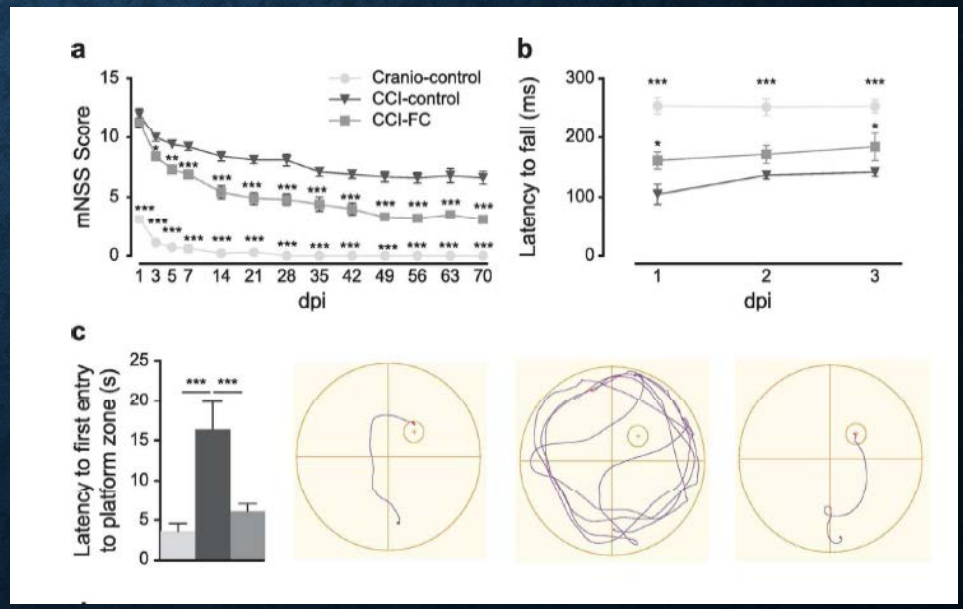
Hilkka Soininen, Alina Solomon, Pieter Jelle Visser, Suzanne B Hendrix, Kaj Blennow, Miia Kivipelto, Tobias Hartmann, on behalf of the LipiDiDiet clinical study group*

Summary

Background Nutrition is an important modifiable risk factor in Alzheimer's disease. Previous trials of the multinutrient Fortasyn Connect showed benefits in mild Alzheimer's disease dementia. LipiDiDiet investigated the effects of Fortasyn Connect on cognition and related measures in prodromal Alzheimer's disease. Here, we report the 24-month results of the trial.

Lancet Neurol 2017
Published Online October 30, 2017
http://dx.doi.org/10.1
S1474-4422(17)3033

Multinutrient in Mouse Experimental TBI

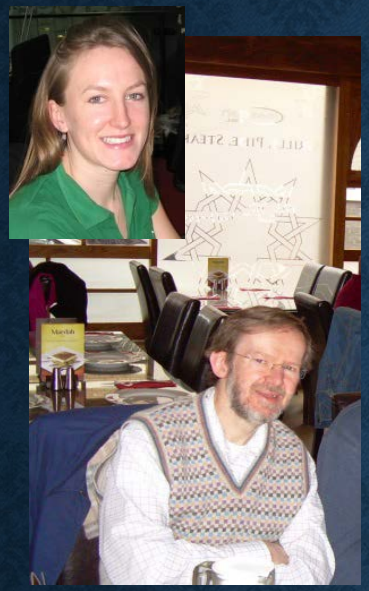


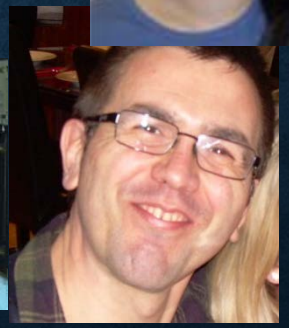
(Thau-Zuchman et al., 2018)

NEXT STEPS FOR OMEGA-3 FATTY ACIDS IN TBI

LOOKING INTO THE FUTURE

- TBI is increasingly recognised as a public health issue with massive impact
- There have been significant advances in the characterization of omega-3 fatty acids as neuroactive substances with unique structural and signalling roles
- There is increasing evidence of therapeutic potential of omega-3 fatty acids from the acute to the chronic phase post-trauma
- There are promising steps towards generation of clinically relevant data in pilot studies





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