Traumatisk Hjärnskada (TBI)

Datainsamling och register

Ett historiskt och framtidsperspektiv

Dr David Nelson MD PhD
Karolinska University Hospital
Stockholm Sweden

Tsunamivåg av dataregistrering på gång !

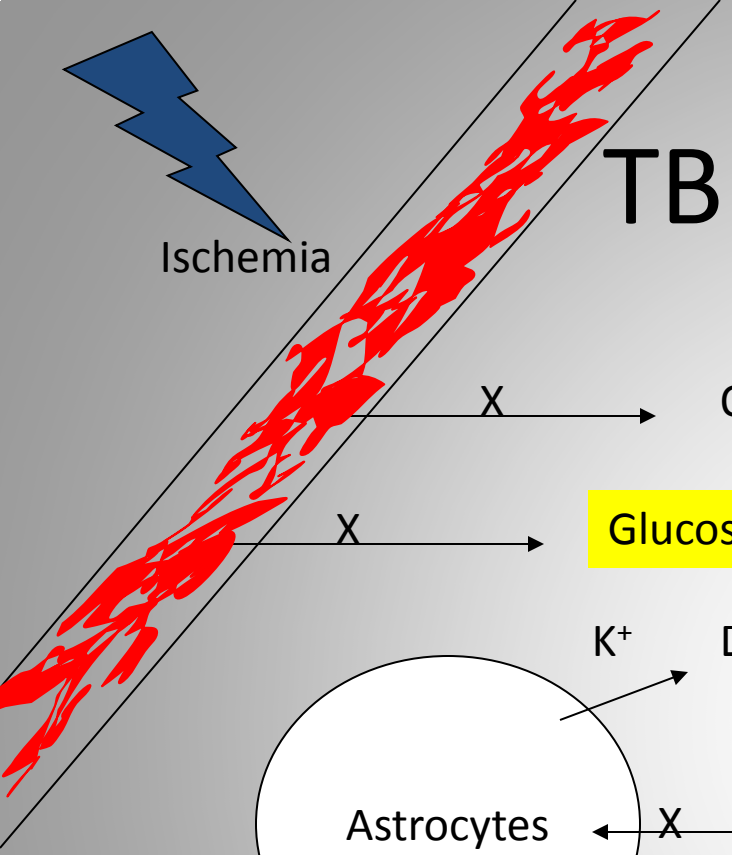
Bakgrund- kliniska läkemedelsprövningar på 90-talet… alla negativa

International Mission for Prognosis and Analysis of Clinical Trials in TBI

(IMPACT) arbetet – vad gick fel ?

Blicka framåt- Center-TBI, TRACK-TBI

TBI pathophysiology



Lactate ↑ Pyruvate ↓

X → O_2 → Anaerobic metabolism

X → Glucose ↓

K^+

Neurons

K^+ Disturbed ionic balance

Ca^{2+}

Astrocytes ← X Glutamate ↑

Excitotoxicity

Proteolytic enzymes
Phospholipases
Membrane degredation

Glycerol ↑

Astrocyte swelling
Edema
Blood brain barrier disrupture
0_2 diffusion barrier

Free radical formation
Inflammation
(cytokines, PMNs,NO)

Table 1. *Overview*

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Unpublished: tiriliazad-domestic (Upjohn)	Tirilazad (lipid peroxidation)	36	GCS ≤8: 72% GCS 9–12: 28%	1155	1991–1994	Terminated	No sign. Tx. effect reported
Marshall et al.,[31] 1998 Tirilazad-International (Upjohn)	Tirilazad (lipid peroxidation)	50	GCS ≤8: 85% GCS 9–12: 15%	1120	1992–1994	Completed	No sign. Tx. effect
Young et al.,[21] 1996 (Sanofi-Winthrop)	PEGSOD (free radical damage)	29	GCS ≤8	1562	1993–1995	Completed	No sign. Tx. effect
Unplublished (SyntheLabo)	Eliprodil (glutamate exitotoxicity)	20+	GCS 4–8	452	1993–1995	Completed	No sign. Tx. effect
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Robertson et al.,[32] 1999 (Inv. initiated, NIH NS27616)	CBF vs. ICP directed management (cerebral ischemia)	1	Motor score ≤5	189	1994–1997	Completed	No difference in neurologic outcome. Decrease in episodes of jugular desaturation
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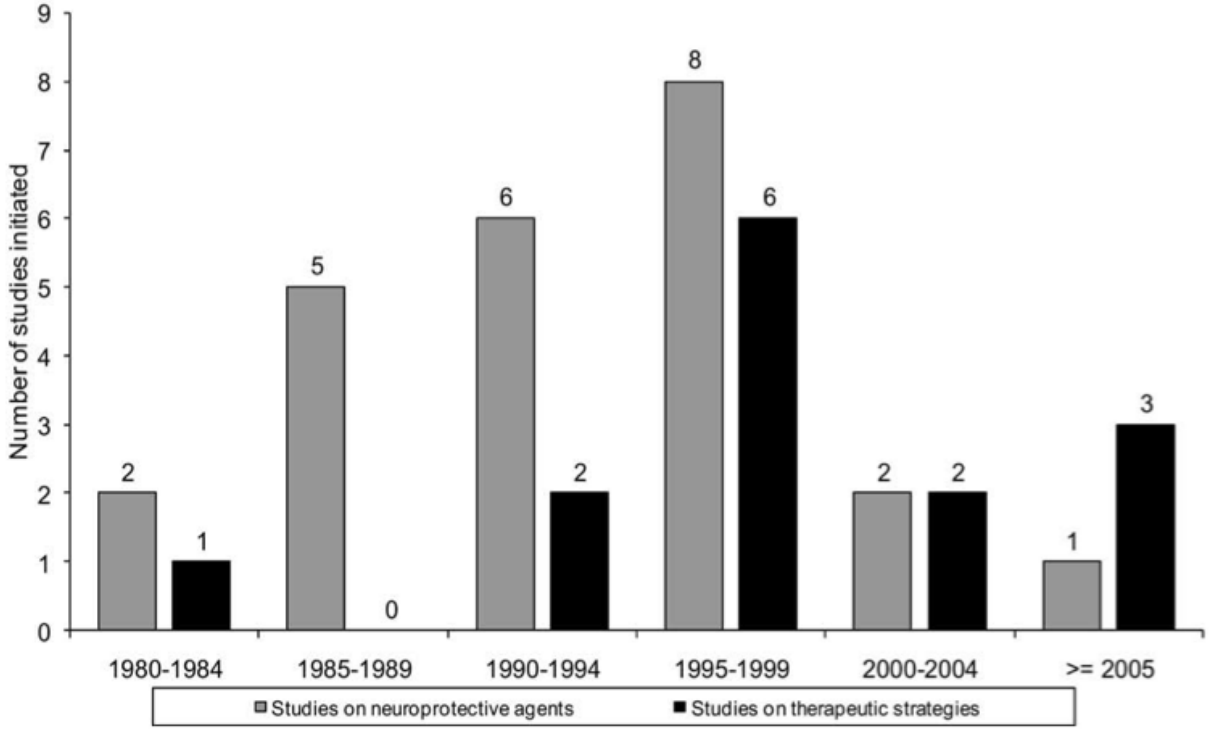

FIG. 1. Numbers of initiated randomized controlled trials on moderate to severe traumatic brain injury per 5-year time periods. Trials were grouped by studies on neuroprotective agents and studies on therapeutic strategies.

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Varför hittar man inga effekter?

- Alla testade droger var utan effekt ?
- Effekten drunknar I brusig data ?
- Metodiska problem med studierna
- Är drogen given till rätt patient i rätt fönster
- Ingen “magic bullet” dvs kanske inte finns en drog ?
- Orealistiska förväntningar (power analyses)
- För små studier ?

IMPACT

International Mission for Prognosis and Analysis of Clinical Trials in TBI

Search: OK

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You are here: TBI-IMPACT.org » IMPACT » Mission & Aims

IMPACT

Mission & Aims

The global aim is to optimize clinical trial methodology in the field of TBI to maximize the chance of demonstrating benefit of effective new therapies.

The IMPACT project will critically examine the methodological challenges posed by TBI trials, and investigate the application of conventional and innovative methods for design and analysis of trials in TBI. Data sets from completed randomized controlled trials (RCTs) and observational studies will be used as "culture media" in which to develop and test these methods. The insight obtained from these investigations will lead to informed recommendations for future clinical trials in TBI, and are expected to also be of relevance to RCT's in other fields.

IMPACT was initially funded from 2003-2006 (IMPACT I). IMPACT I focused on methodology to deal with the heterogeneity of the population and included extensive prognostic analyses.

IMPACT I established the IMPACT database and development of prognostic models necessary for relating final outcome to initial prognostic risk. We found that a relative trial size reduction of up to 50% can be achieved with covariate adjustment and by applying innovative statistical approaches, which exploit the ordinal nature of the Glasgow Outcome Scale (GOS). These include proportional odds analysis and applying the concept of the sliding dichotomy, in which the split for dichotomizing the GOS is differentiated according to baseline prognostic risk (Murray et al 2005).

Continuation funding (IMPACT II) was obtained for the period 2007-2011. In IMPACT II, we expanded the IMPACT database, including data from a mega trial and from more recent studies which contain the Extended GOS (GOSE), an endpoint of presumed increased sensitivity.

Impact II focuses on:

- center effects and variations in patient management (specific aim 2)
- sensitivity of outcome measures (specific aim 3) as related to statistical power
- the choice (specific aim 4) between a mega trial (with large numbers of patients, substantial heterogeneity, and simple outcome measures) and a conventional trial (with fewer patients, less heterogeneity among centers, and more complex outcome measures)

List of subpages

- Background
- Mission & Aims
- Collaboration
- Investigators
- Advisory Board
- IMPACT database
- Prognostic calculator
- IMPACT recommendations
- Common Data Elements (Draft)
- Data Sharing
- Acknowledgements

IMPACT

The IMPACT Project is focused on advancing knowledge of prognosis, trial-design and treatment in TBI.

IMPACT has

- developed and validated prognostic models for classification and characterization of TBI series
- participated in the development of standardization of data collection in TBI studies (common data elements).
- provided evidence based recommendations for improving sensitivity and efficiency of trials in TBI

IMPACT will

- continue its research efforts towards provision of further evidence in support of efforts to improve treatment.
- Advise and assist in the development of clinical research programmes, investigating new treatments for TBI which could lead to better patients outcomes.

http://www.tbi-impact.org/

Andrew I.R. Maas (Principal Investigator)

Unselected Prospective series published in past decade

	N	*Study Years*	*Publication plus year*
TCDB	746	1984-1987	Foulkes et al. 1991
EBIC core data study*	847	1995	Murray et al. 1999
UK 4	988	1986-1988	Murray et al. 1999
Total:	**2581**		

Therapeutic trials published or conducted in past decade (N>300)

	N	*Study Years*	*Publication plus year*
HIT I Nimodipine	351	1987-1989	Bailey et al. 1991
HIT II Nimodipine	852	1989-1991	EUR Study Group 1994
Tirilazad trials (2)*	2269	1991-1994	Marshall et al. 1998
Saphir	924	1995-1997	-
International Selfotel trial	409	1994-1996	Morris et al. 1999
PEGSOD	1574	1993-1995	Young et al. 1996**
SKB	139	1996	Marmarou et al. 1999
Total:	**6518**		

Datasets added in IMPACT II

(APOE, NABIS hypothermia, Cerestat, Pharmos dexanabinol)

	N	Description
APOE 1996-1999 *Teasdale et al. 2005*	351	This cohort study investigated the relation between ApoE genotype and outcome across all injury severities, includes many patients with mild injuries, accurate details on treatment and 8-point GOSE.
NABIS hypothermia 1994-1998 *Clifton et al. 2001*	392	We had originally planned to include this dataset in the current grant period, but received the full dataset too late to include in IMPACT I. Considerable center effects and variations in patient management have been reported for this dataset.
CERESTAT 1996-1997	532	Is an unpublished RCT investigating the effect of Aptiganel HCl, a non competitive NMDA blocker in severe TBI.
The Pharmos Dexanabiol Trial 2001-2004 *Maas et al. 2006*	861	Investigated safety and efficacy of dexanabinol, and is the most recent conventional Phase III trial in TBI. Dexanabinol is a non-psychotropic cannibinoid agonist with demonstrated neuroprotection in preclinical studies. Both the Principal Investigator and Professor Gordon Murray are well acquainted with this study as they have been closely involved in the design and analysis of the trial (Maas et al 2006). The Pharmos study includes extensive data on patient management and outcome assessed by the 8 -point GOSE together with Quality of Life scores (SF 36 and CIQ).

Datasets in collaboration with CRASH & TARN investigators

(CARSH, TARN)

	N	Description
CRASH 1999-2004 *Edwards et al. 2005* *Roberts et al. 2004*	10008	Aimed to resolve the uncertainty concerning the use of steroids in TBI and represents the only mega trial conducted in the field of TBI. The dataset is typical of a mega trial with large numbers, limited information and simple outcome assessment. The CRASH investigators recruited 10008 patients in 239 centers from 49 countries. We greatly appreciate the permission granted by the CRASH management group to provide us with the raw data and consider it especially relevant to include this study in the IMPACT dataset because it contains a large number of patients with mild injury and allows us to evaluate the relative merits of a mega trial based on actual data rather than simulations studies.
TARN-TBI 1989- ongoing *Patel et al. 2005*	22000	TARN represents a large dataset of the Trauma Audit and Research Network, and includes over 22000 patients with TBI. Although it is not a clinical trial, the methodology of data collection (large numbers, simple data) is very similar to that which would be applied in a mega trial. We therefore consider it an asset to include the TARN data on TBI within our analysis, particularly in specific aim 4.

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Panel: Recommendations for design and analysis of randomised controlled trials in traumatic brain injury[8]

- Details of the major baseline prognostic characteristics should be provided in every report of a study; in trials they should be differentiated per treatment group. We also advocate the reporting of a summary of the baseline prognostic risk as determined by validated prognostic models.
- Inclusion criteria should be as broad as is compatible with the current understanding of the mechanisms of action of the intervention being evaluated. This approach will maximise recruitment rates and improve the generalisability of the results.
- The statistical analysis should incorporate (prespecified) covariate adjustment to mitigate the effects of heterogeneity.
- The statistical analysis should use an ordinal approach, based on either sliding dichotomy or proportional odds methods.

Lärdomar från IMPACT

Vi måste veta vilka vi studerar ! Populationen är allt !

- Registrera rätta parametrar för riskjustering
- Behövs standardiserad datainsamling
- Breda inklusionskriterier i studier men TBI är inte ett tillstånd! Komplext och heterogent. Måste finnas ett urval som motiveras mekanistisk eller patofysiologiskt (GCS tveksamt !)

Vi måste utvärdera i förhållande till en outcome variabel där vi väntar oss behandlingseffekt !

Vi gör väldigt olika idag !

Konsekvenser av IMPACT

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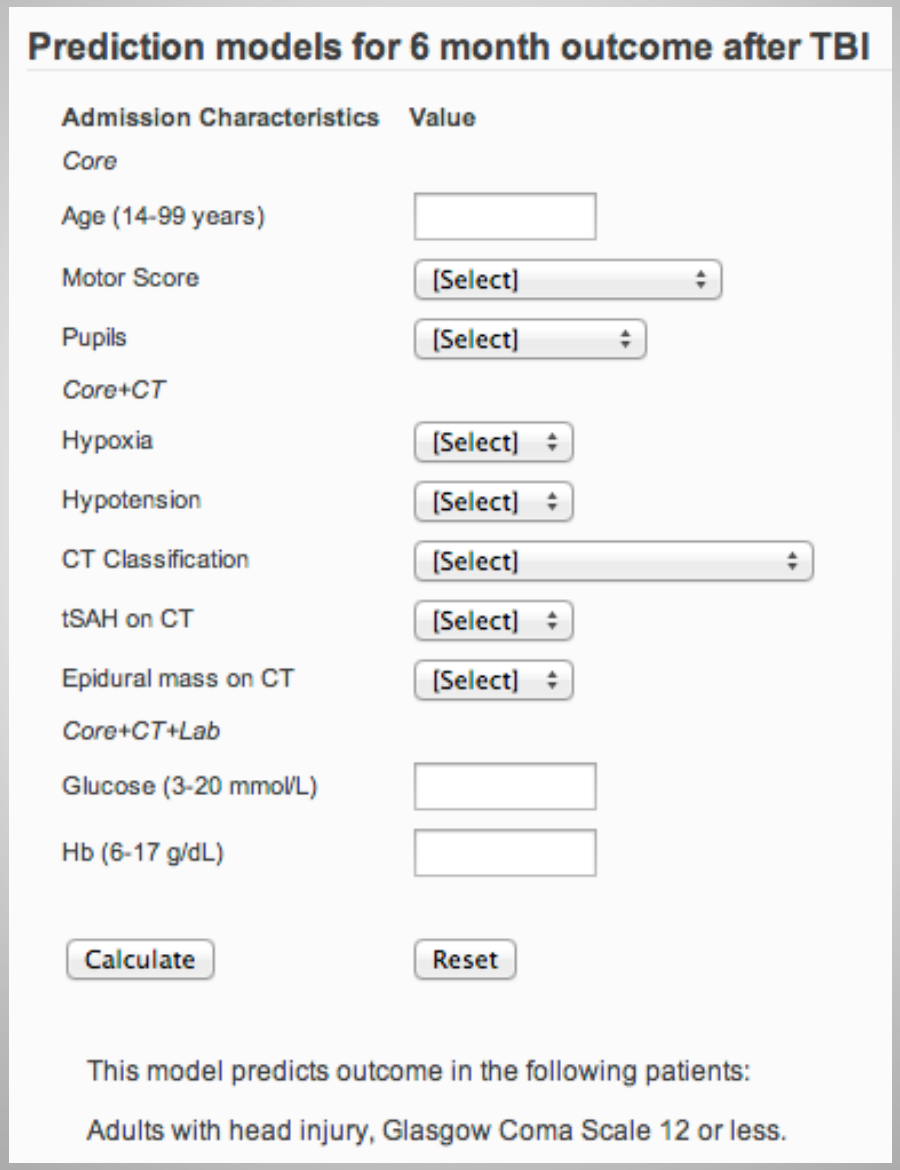
IMPACT Kalkylatorn



Prediction models for 6 month outcome after TBI

Admission Characteristics	Value
Core	
Age (14-99 years)	
Motor Score	[Select]
Pupils	[Select]
Core+CT	
Hypoxia	[Select]
Hypotension	[Select]
CT Classification	[Select]
tSAH on CT	[Select]
Epidural mass on CT	[Select]
Core+CT+Lab	
Glucose (3-20 mmol/L)	
Hb (6-17 g/dL)	

Calculate Reset

This model predicts outcome in the following patients:

Adults with head injury, Glasgow Coma Scale 12 or less.

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Common Data Elements

Common Data Elements (β-version)

The Common Data Elements were initially developed by the Working Group 'Demographics and Clinical Assessment' as part of the interagency initiative towards 'an integrated approach to Research in Psychological Health and Traumatic Brain Injury'. (NIH-NINDS; The National Institute on Disability and Rehabilitation Research; the department of Veterans Affairs; the Defense and Veterans Brain Injury Center and the Defense Centers of Excellence). The development of CDEs was further supported by a supplemental grant from NIH-NINDS (NS 042691).

International input has been incorporated in this version.

Refining and validation of Common Data Elements is a continuing proces. Any kind of feedback or comments are very welcome and will be highly appreciated.

Andrew I.R. Maas
Contact: andrew.maas@uza.be
Last update: 11th January 2011

Information

Modular Data Elements for TBI
The proposed modules contain all essential data elements for development of a case report form in TBI studies. The elements and modules can be used as 'building blocks' and used as 'plug-in' elements that can be used multiple times in various sections when building your CRF. The elements are presented at three levels of detail: basic, intermediate and advanced with the greatest level of detail in the advanced version. Thus, the common data elements offer optimal flexibility and basic, intermediate and advanced versions can be used interchangeably when designing your CRF.

Sponsors

- Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury
- Department of Veterans Affairs (VA)
- National Institute on Disability and Rehabilitation Research (NIDRR)
- National Institutes of Health – National Institute of Neurological Disorders and Stroke (NINDS)

Basic = Intermediate

Baseline risk assessment

Age:

☐☐ yr.

Pre-enrollment secondary insults:

Hypoxia ○ No ○ Yes

Hypotension ○ No ○ Yes

Pupillary reactivity:

○ Both pupils reactive

○ One non-reacting pupil

○ Both pupils non-reactive

CT parameters:

CT class ☐ (1-5)

tSAH ○ No ○ Yes

Qualifying Motor Score For study admission: ☐ (1-6)

Time of Assessment:

○ Post-stabilization

○ Admission

○ First hospital

○ Scene of accident

○ Other

Conditions of Assessment:

○ No sedation/paralysis

○ After stopping sedation

○ After pharmacologic reversal

○ Under sedation

Perspectives on future research

Standards for data collection and prognostic research

The IMPACT studies illustrate how international and multidisciplinary collaboration can accelerate research and how methodological research can lead directly to improved clinical research. The recent institution of the International Initiative for Traumatic Brain Injury Research (InTBIR) as a collaboration between funding agencies (the European Commission, NIH-NINDS, and CIHR) represents a milestone accomplishment and provides a platform for global collaboration in TBI research.[50,51]

The concepts developed by the IMPACT study group are being taken forward. Use of common data elements is currently required in all observational studies and trials in TBI that are funded by NIH-NINDS. A recent call by the European Commission also mandated use of core common data elements.[52] This adoption of common data elements by funding agencies might be expected to assist with comparisons between studies, meta-analyses of individual patient data across studies,

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NIH EU CIHR

The International Initiative for Traumatic Brain Injury Research (InTBIR)

Working together to improve outcomes and lessen the global burden of traumatic brain injury by 2020

InTBIR is a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). It was set up in October 2011 to advance clinical traumatic brain injury (TBI) research, treatment and care.

NIH EU CIHR

Data wharehouse och Data sharing

EU

CENTER-TBI

Collaborative European NeuroTrauma Effectiveness Research in TBI

A 2020 vision: Generating knowledge for improving TBI outcomes

USA

TRACK-TBI Multicenter Initiative

Kina

Indien ?

Vad är syftet ?

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Vad är syftet ?

- Bättre ” multi-dimensionell” karakterisering av TBI

- Utnyttja skillnader mellan Centra för att se vad vi gör olika idag som spelar mest roll

  Comparative Effectivness Research (CER)

CENTER-TBI

Collaborative European NeuroTrauma Effectiveness Research in TBI

A 2020 vision: Generating knowledge for improving TBI outcomes

- Multi-dimensional characterization of TBI
- Utilize differences in outcomes to identify best practice today (Comparative effectiveness research- CER)
- www.center-tbi.eu

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- 65 centra, 20 länder in europa , tot. 5400 patienter
- Standardiserad datainsamling (Common data elements)
- Bred inklusion av TBI patienter- tre strata (akuten, Inlagda, IVA)
- 20 centra med högupplöst IVA data (200 Hz)
- Data: epidemiologisk, fysiological, biomarkörer, radiologi, genetik, multipla outcome score
- International Neuroinformatics Coordinating Facility (INCF-KI)

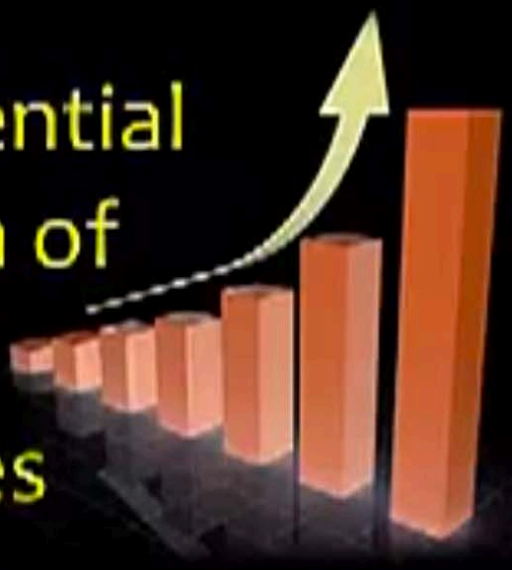
Prof. George Djorgovski: Big Data Science in the 21st Century

Caltech

Föreläsningserie NIH

Finns på YouTube

Exponential Growth of Data Volumes

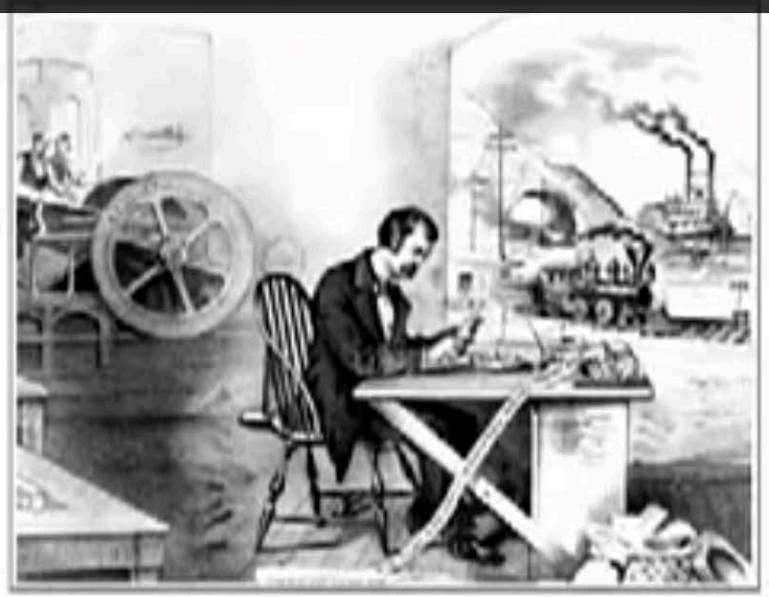


... and Complexity

on Moore's law time scales

Understanding of complex phenomena requires complex data!

From data poverty to data glut
From data sets to data streams
From static to dynamic, evolving data
From anytime to real-time analysis and discovery
From centralized to distributed resources
From ownership of data to ownership of expertise



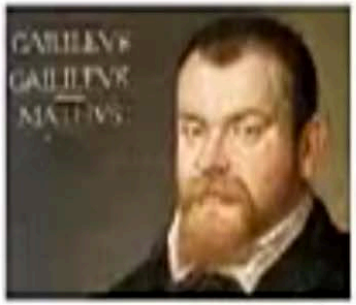
Information technology revolution is historically unprecedented - in its impact it is like the industrial revolution and the invention of printing combined

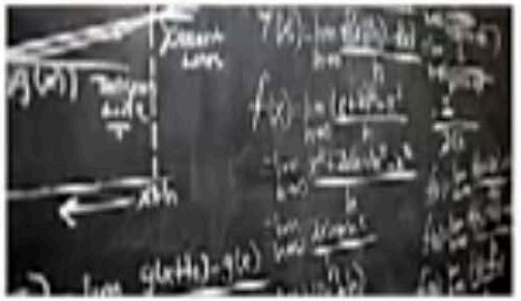
Science and scholarship are slowly adopting the new tools and technologies and there are great scientific and leadership opportunities in this arena

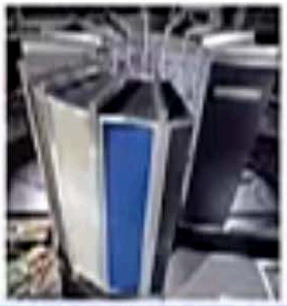
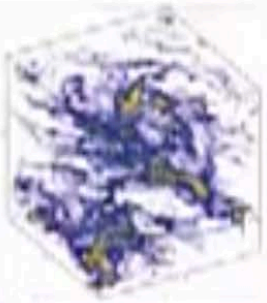
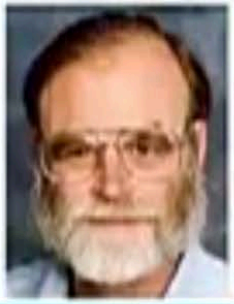
We are effectively developing a new methodology of science and scholarship for the 21st century

The Evolving Paths to Knowledge

- The First Paradigm: Experiment/ Measurement
- The Second Paradigm: Analytical Theory
- The Third Paradigm: Numerical Simulations
- The Fourth Paradigm: Data-Driven Science

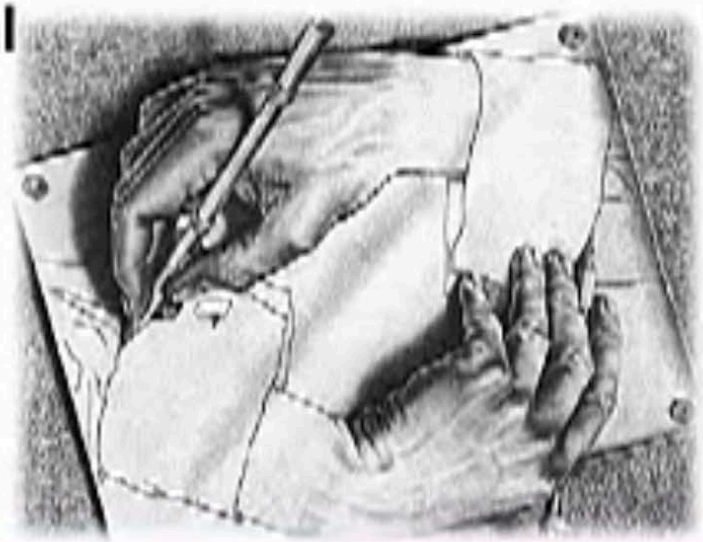


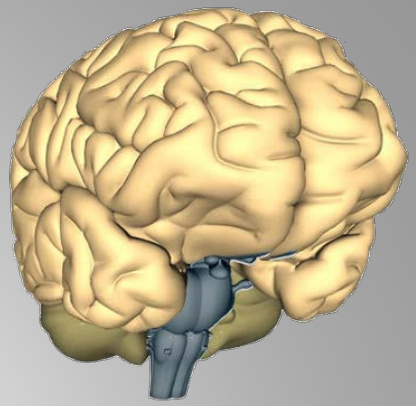



Transformation and Synergy

- ***All science*** in the 21st century is becoming cyber-science (e-Science) - and with this change comes the need for ***a new scientific methodology***
- The challenges we are tackling:
  - Management of large, complex, distributed data sets
  - Effective exploration of such data → new knowledge
  - **These challenges are universal**
- A great synergy of the computationally enabled science, and the science-driven technology





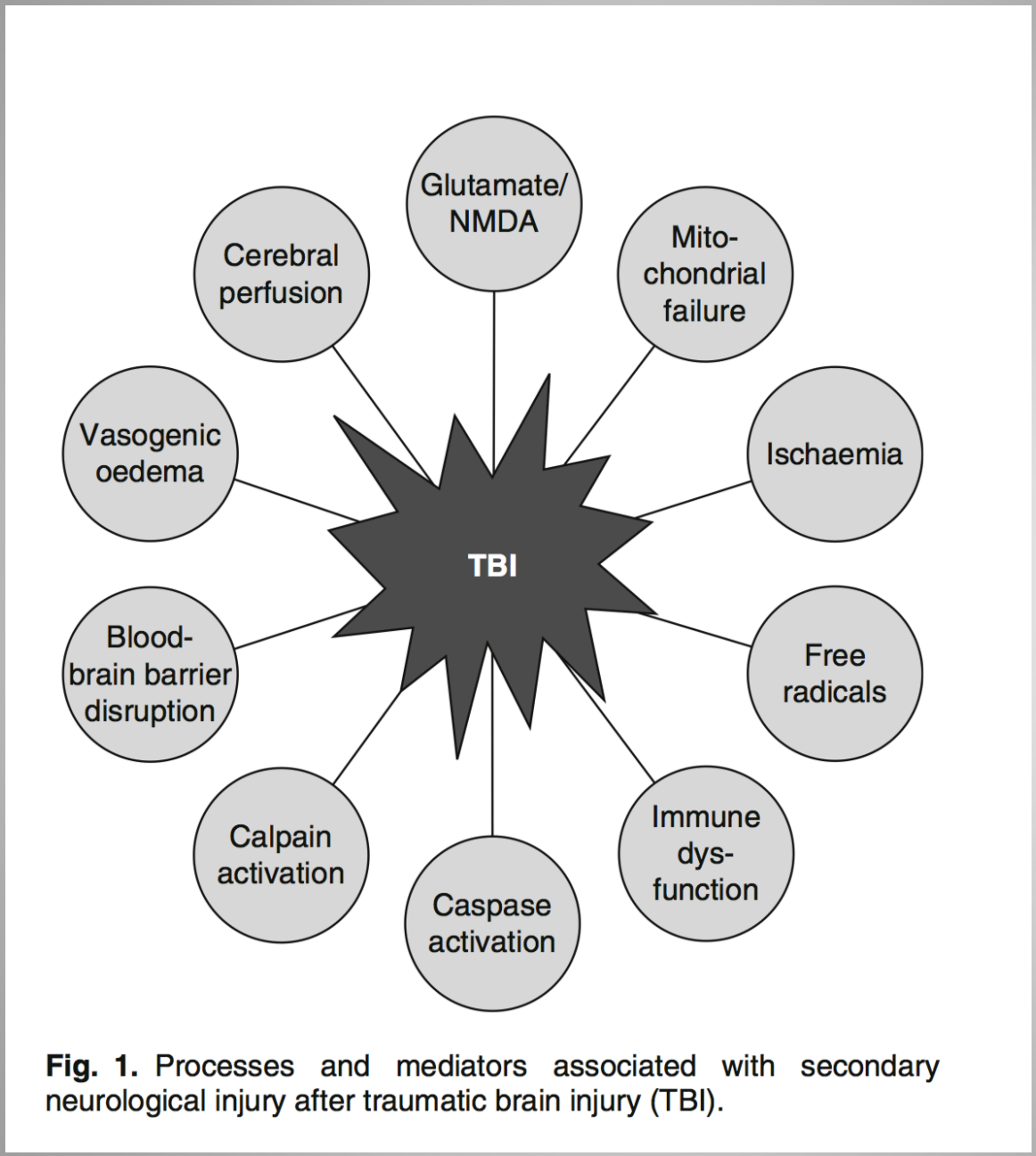
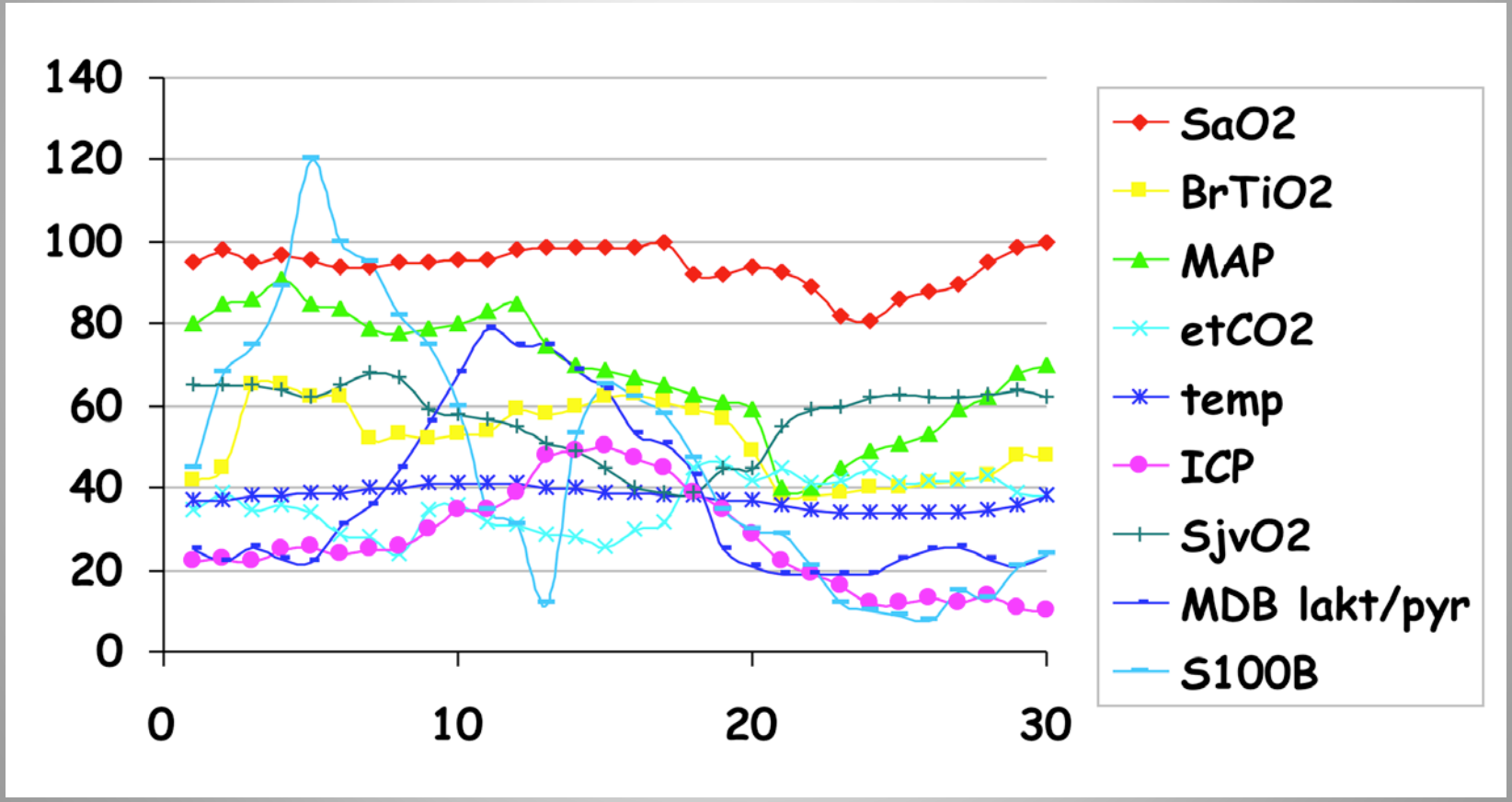


Fig. 1. Processes and mediators associated with secondary neurological injury after traumatic brain injury (TBI).

Multi-modal monitoring



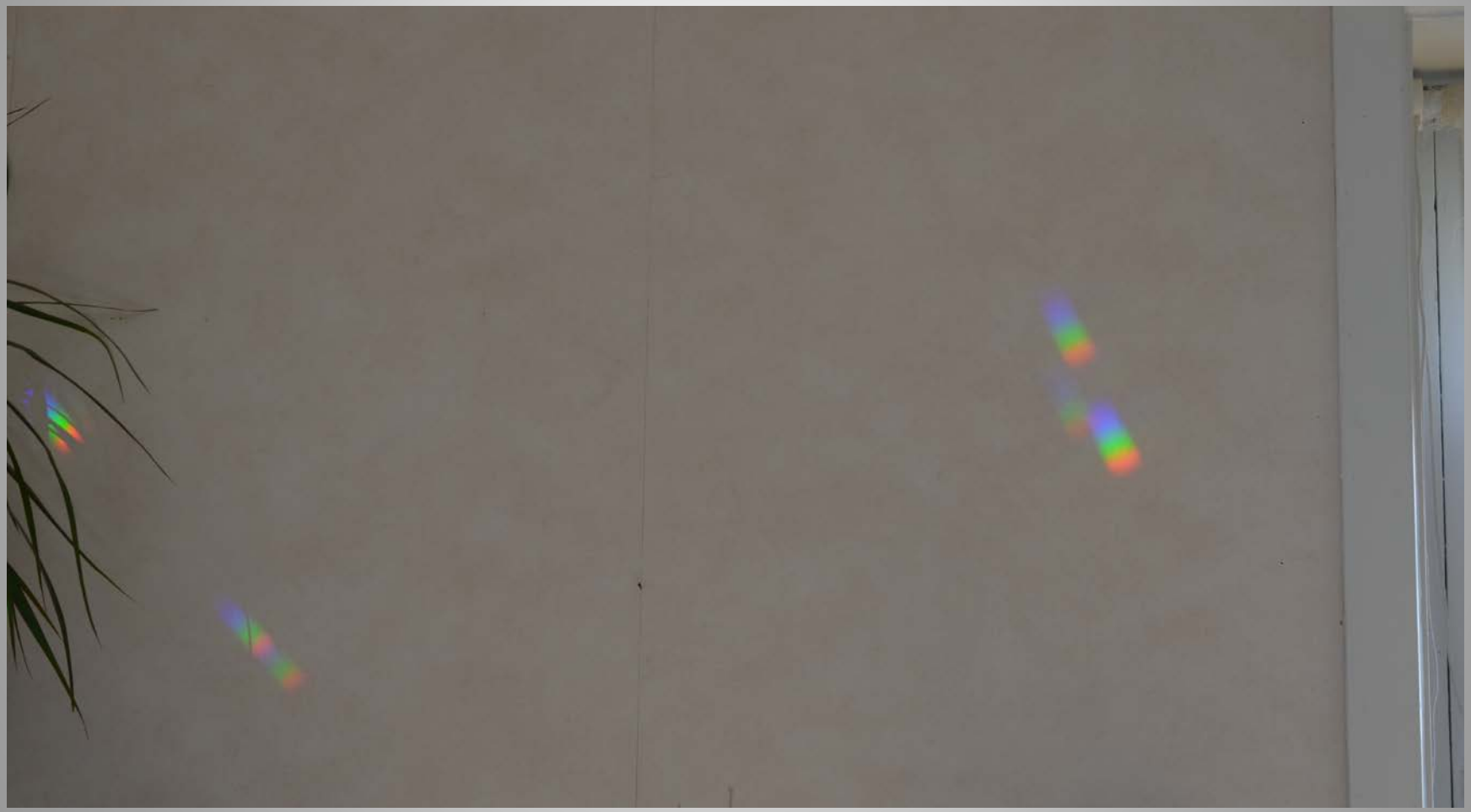
Brain Trauma Foundation

Guidlines 2007

1 level-A rekommendation !!


ONE WAY
ONE WAY
ONE WAY
SPEED LIMIT 40
ONE WAY
ONE WAY
ONE WAY
ONE WAY
ONE WAY

- Biologiska komplexa system-TBI komplext system
- Titta på enstaka parametrar till synes planlöst med det kan finnas regelbundenhet
- ”states”-> ”state” changes
- Ett mindre antal parametrar för att ” övervaka" sådana system
- Kräver nya sätt att titta på data



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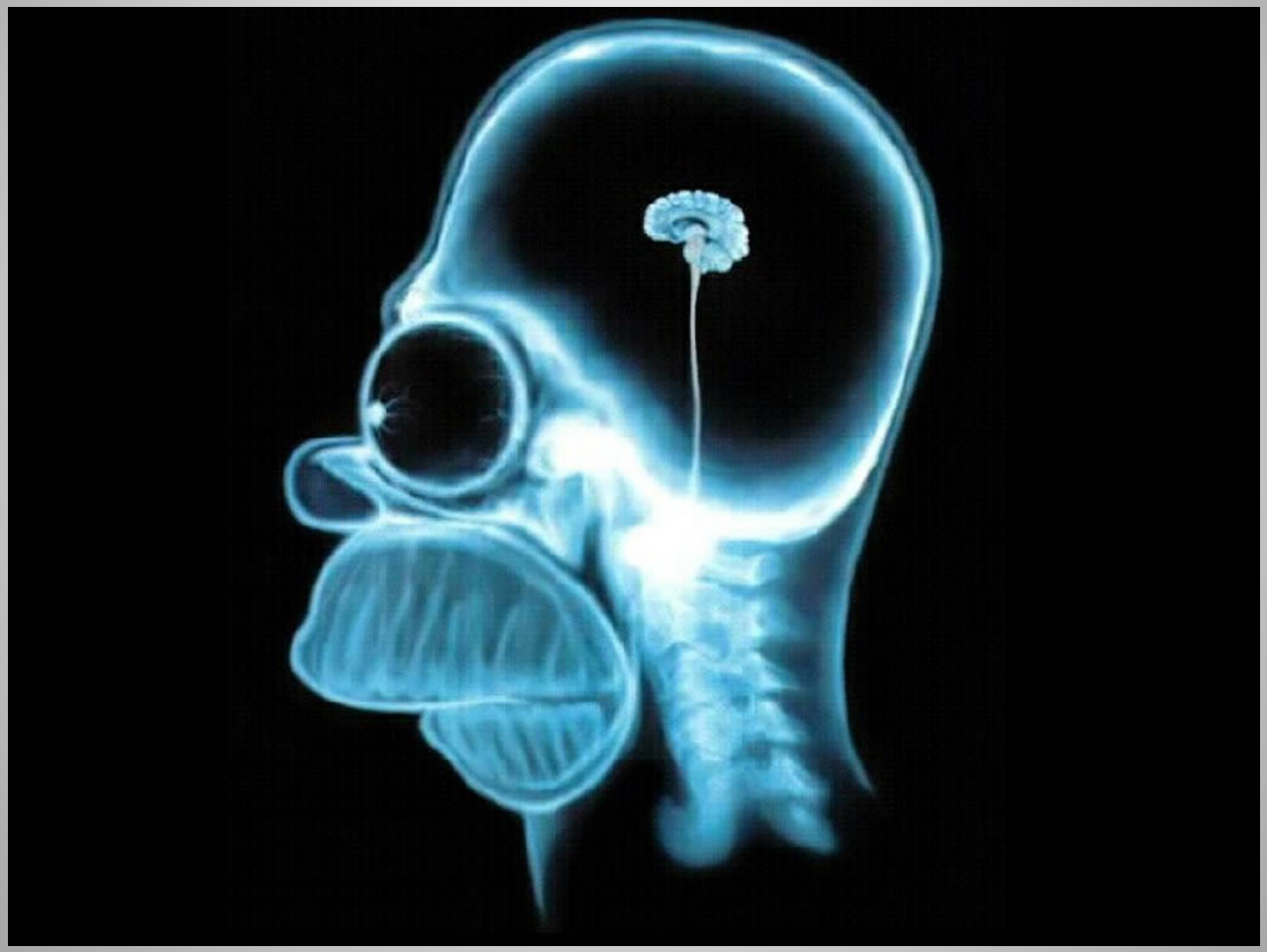
- Identifying verifiable complex patterns and states with machine learning techniques could help to improve are understanding of the complex pathophysiology of TBI
- Dimensionality reduction . What causes state changes and transitions !
- Pattern recognition methods could help identify subgroups/injuries/states that need be targeted with specific treatments .
- Use of machine learning for on-line monitoring could in the future help us interpret raw data streams

Och SIR då ?



Basic = Intermediate

Baseline risk assessment

Age:

☐☐ yr.

Pre-enrollment secondary insults:

Hypoxia ○ No ○ Yes

Hypotension ○ No ○ Yes

Pupillary reactivity:

○ Both pupils reactive

○ One non-reacting pupil

○ Both pupils non-reactive

CT parameters:

CT class ☐ (1-5)

tSAH ○ No ○ Yes

Qualifying Motor Score For study admission: ☐ (1-6)

Time of Assessment:

○ Post-stabilization

○ Admission

○ First hospital

○ Scene of accident

○ Other

Conditions of Assessment:

○ No sedation/paralysis

○ After stopping sedation

○ After pharmacologic reversal

○ Under sedation

Glasgow Outcome Scale (GOS)

GOOD RECOVERY (5)

(Able to return to work or school)

MODERATE DISABILITY (4)

(Able to live independently but unable to return to work or school)

SEVERE DISABILITY (3)

(unable to live independently)

VEGETATIVE STATE (2)

DEAD (1)

Jennett, Bond: Lancet 1975

Often grouped as 1-3 (unfavorable) & 4-5 (favorable)

GOS-Extended (GOSE)

1 = Dead	
2 = Vegetative State	Condition of unawareness with only reflex responses but with periods of spontaneous eye opening.
3 = Low Severe Disability 4 = Upper Severe Disability	Patient who is dependent for daily support for mental or physical disability, usually a combination of both. If the patient can be left alone for more than 8h at home it is upper level of SD, if not then it is low level of SD.
5 = Low Moderate Disability 6 = Upper Moderate Disability	Patients have some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but are able to look after themselves. They are independent at home but dependent outside. If they are able to return to work even with special arrangement it is upper level of MD, if not then it is low level of MD.
7 = Low Good Recovery 8 = Upper Good Recovery	Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some patients have minor neurological or psychological deficits. If these deficits are not disabling then it is upper level of GR, if disabling then it is lower level of GR.

TACK

Frågor?