Concussions:
How Doctors Diagnose and Treat Traumatic Brain Injury
(And Why Is It So Difficult?)

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9/18/2018

Disclosures

- Intellectual Property related to concussion and brain injury assessment
- Intellectual Property related to assessment of dementia after brain injury
- Intellectual Property related to treatment of intracranial hemorrhage

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Abbott Diagnostic Laboratories
Continuing Legal Education in MN, NY
Hennepin County Medical Center
Hennepin Health Foundation
Integra Corporation
Islamic Medical Association of North America
Medtronic Corp
Minnesota Brain Injury Alliance
Minnesota, Texas, Louisiana, Wisconsin High School Coaches Association
National Football League
National Neurotrauma Society
North American Brain Injury Society
Oculogica Inc
OssDsign
Steven and Alexandra Cohen Foundation for Veteran Post Traumatic Stress and Traumatic Brain Injury
United States Veterans Administration and Office of Research and Development
USA Football

Table 4. Estimated average annual numbers of traumatic brain injury-related emergency department (ED) visits, hospitalizations, and deaths, by external cause, United States, 2002–2010

Mechanism of injury	ED visits	Hospitalizations	Deaths
Falls	658,668	66,291	10,944
Struck by or against an object	304,797	6,808	372
Motor vehicle traffic	232,240	53,391	14,795
Assault/Homicide	179,408	15,032	5,665
Self-inflicted/ Suicide	*	*	14,713
Other	122,667	25,478	4,990
Unknown	97,018	113,172	0

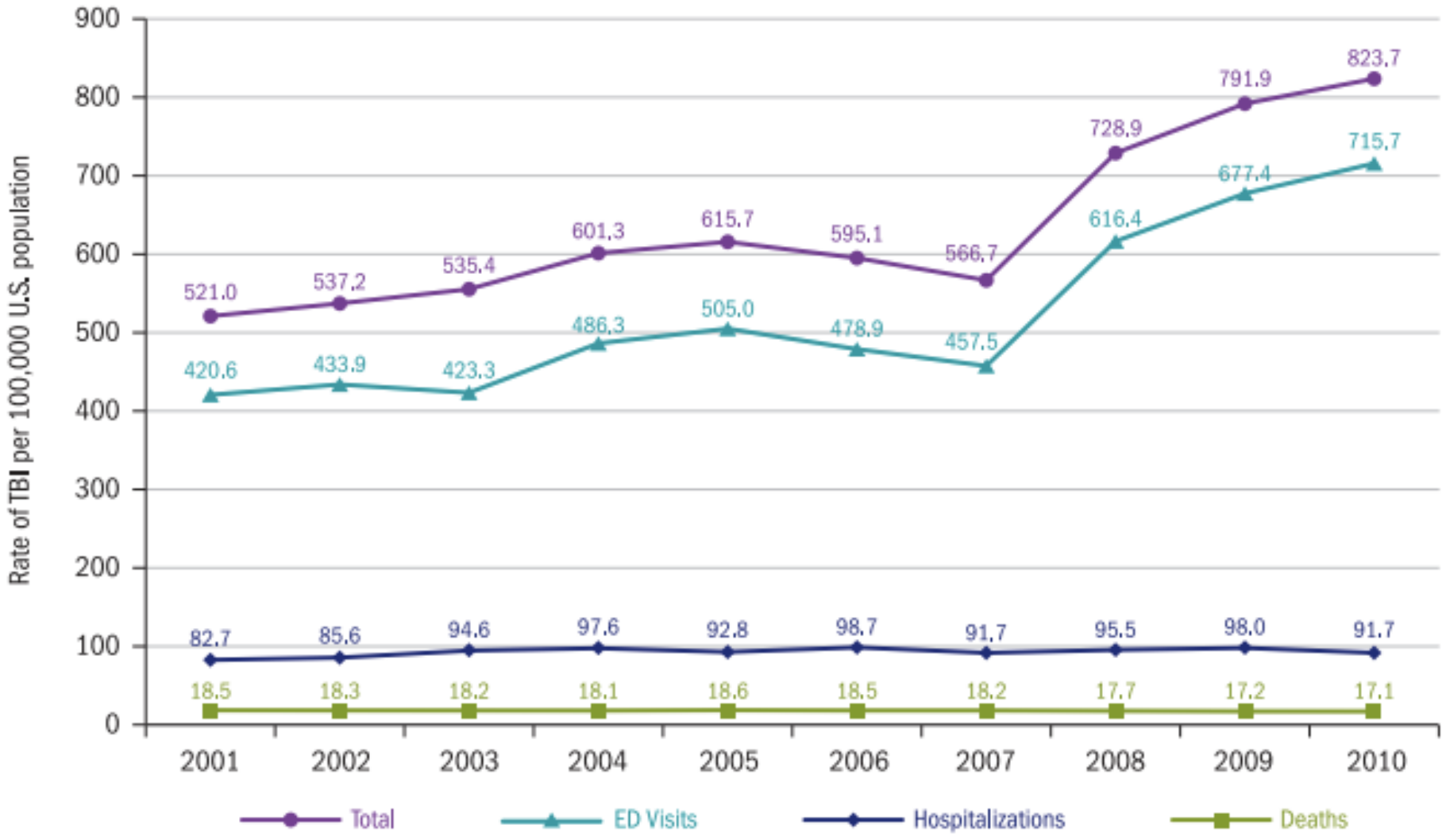
*Estimate not reported because of small numbers

#1 cause of death and disability in Americans under age 35

#1 cause of premature death and disability in the world

https://www.cdc.gov/traumaticbraininjury/pdf/tbi_report_to_congress_epi_and_rehab-a.pdf

Figure 1. Annual age-adjusted rates of TBI-related Emergency Department (ED) visits, hospitalizations, and deaths—United States, 2001–2010



https://www.cdc.gov/traumaticbraininjury/pdf/tbi_report_to_congress_epi_and_rehab-a.pdf

JAMA Pediatrics

Online First >

Original Investigation | May 31, 2016

Point of Health Care Entry for Youth With Concussion Within a Large Pediatric Care Network

FREE ONLINE FIRST

Kristy B. Arbogast, PhD[1,2]; Allison E. Curry, PhD[1]; Melissa R. Pfeiffer, MPH[1]; Mark R. Zonfrillo, MD, MSCE[1,2]; Juliet Haarbauer-Krupa, PhD[3]; Matthew J. Breiding, PhD[3]; Victor G. Coronado, MD, MPH[3]; Christina L. Master, MD[2,4]

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JAMA Pediatr. Published online May 31, 2016. doi:10.1001/jamapediatrics.2016.0294

Text Size: A A A

80% of concussed children do not present to an Emergency Dept and thus would not be included in CDC numbers

At least 30 failed multicenter randomized prospective clinical trials since 1992:

Hennepin County Medical Center

Hypothermia/Temperature Control: 13 (Eurotherm)

Pharmacology: 10 (PROTECT III, Synapse)

Surgical Intervention: 3 (DECRA)

Hyperbaric Oxygen: 2

Hypertonic Saline: 1 (ROC)

ICP Monitoring: 1 (BEST-TRIP)

RESCUE ICP (hypothermia stage 2 - decompressive craniectomy stage 3)

1.1 billion dollars has been spent on failed clinical trials for TBI

THERAPEUTIC AREA	PHASE 1	PHASE 2	PHASE 3	PHASE 1, 2, & 3 SUBTOTAL [D]	FDA NDA/BLA REVIEW PHASE [C]	PHASE 4	TOTAL [D]
Anti-Infective	$4.2 (5)	$14.2 (6)	$22.8 (5)	$41.2 (3)	$2.0	$11.0 (12)	**$54.2 (10)**
Cardiovascular	$2.2 (9)	$7.0 (13)	$25.2 (3)	$34.4 (10)	$2.0	$27.8 (4)	**$64.1 (6)**
Central Nervous System	$3.9 (6)	$13.9 (7)	$19.2 (7)	$37.0 (6)	$2.0	$14.1 (11)	**$53.1 (11)**
Dermatology	$1.8 (10)	$8.9 (12)	$11.5 (13)	$22.2 (13)	$2.0	$25.2 (7)	**$49.3 (12)**
Endocrine	$1.4 (12)	$12.1 (10)	$17.0 (9)	$30.5 (12)	$2.0	$26.7 (6)	**$59.1 (7)**
Gastrointestinal	$2.4 (8)	$15.8 (4)	$14.5 (11)	$32.7 (11)	$2.0	$21.8 (8)	**$56.4 (8)**
Genitourinary System	$3.1 (7)	$14.6 (5)	$17.5 (8)	$35.2 (8)	$2.0	$6.8 (13)	**$44.0 (13)**
Hematology	$1.7 (11)	$19.6 (1)	$15.0 (10)	$36.3 (7)	$2.0	$27.0 (5)	**$65.2 (5)**
Immunomodulation	$6.6 (1)	$16.0 (3)	$11.9 (12)	$34.5 (9)	$2.0	$19.8 (9)	**$56.2 (9)**
Oncology	$4.5 (4)	$11.2 (11)	$22.1 (6)	$37.8 (5)	$2.0	$38.9 (2)	**$78.6 (3)**
Ophthalmology	$5.3 (2)	$13.8 (8)	$30.7 (2)	$49.8 (2)	$2.0	$17.6 (10)	**$69.4 (4)**
Pain and Anesthesia	$1.4 (13)	$17.0 (2)	$52.9 (1)	$71.3 (1)	$2.0	$32.1 (3)	**$105.4 (2)**
Respiratory System	$5.2 (3)	$12.2 (9)	$23.1 (4)	$40.5 (4)	$2.0	$72.9 (1)	**$115.3 (1)**

https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development

Hennepin County Medical Center

30 Failed Trials Since 1992

Inclusion Criteria

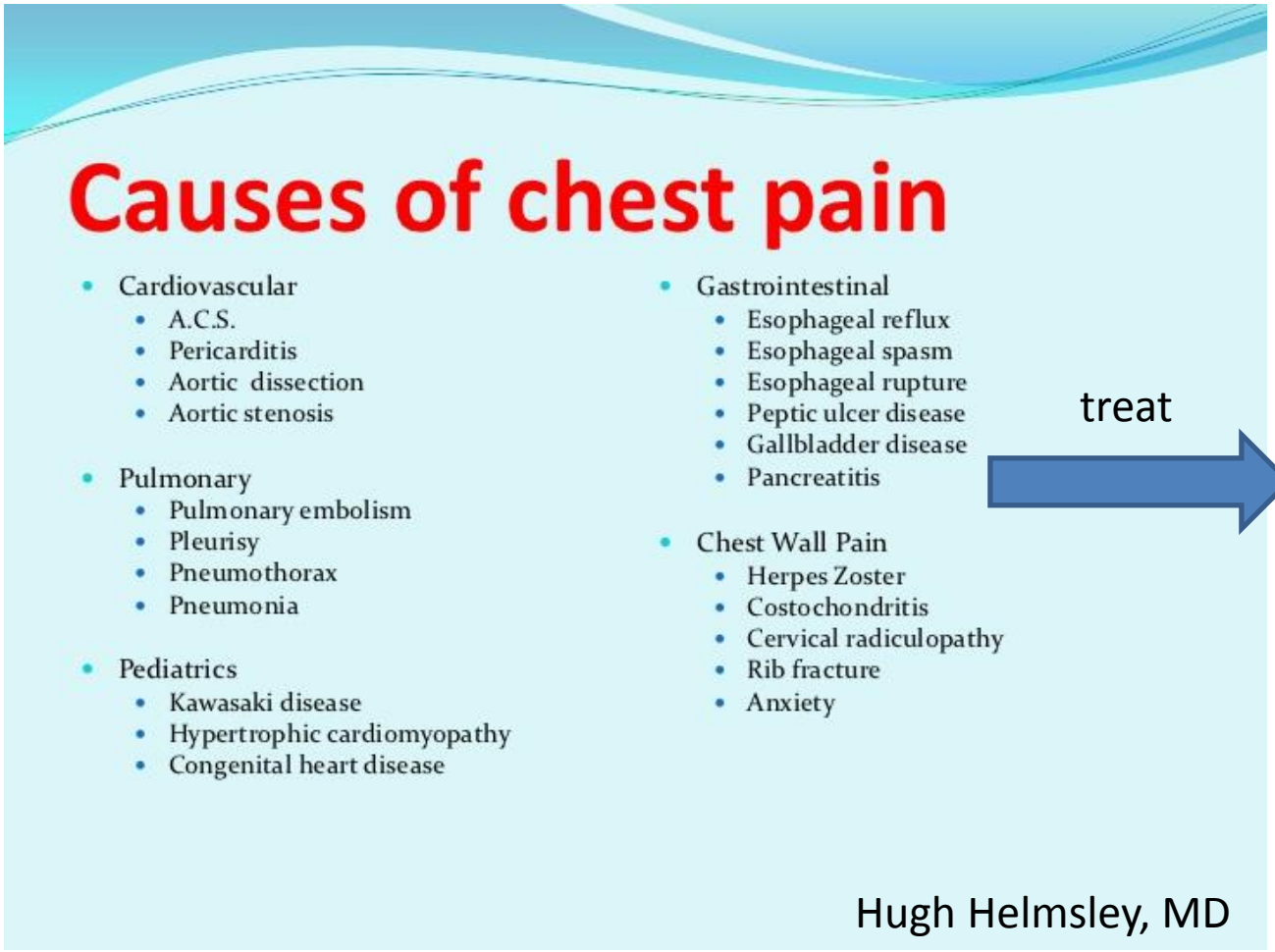
- GCS: 20
- GCS with +CT: 4
- GCS Motor Score: 1
- AIS Range: 1
- 'Head trauma': 2
- ICP values: 1
- Traumatic SDH: 1

Outcome Measures

- GOS: 11
- GOS as primary measure: 14
  - LOS, DRS, ICP, SAE's, Neuropsych, Quality of Life, CPP, GOAT, ect.
- PCPC: 1 (Pediatric GOS)
- Temperature Gradient: 1
  - GOS as Secondary Measure
- IMPACT: 1
- Neurobehavioral Rating Scale: 1
- Bayley-III: 1

Hennepin County
Medical Center

Would you run a clinical trial for "chest pain" with history and exam as your classifier? And an 8 pt outcome measure?



treat

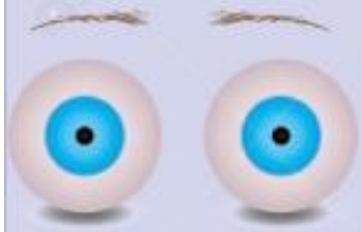
1 Death
2 Vegetative state
3 Lower severe disability
4 Upper severe disability
5 Lower moderate disability
6 Upper moderate disability
7 Lower good recovery
8 Upper good recovery

How do we assess a brain injured patient?

History of the Present Illness (get it from the EMT)
type of accident (single car/multiple)
restrained/unrestrained
helmeted/not
duration of extrication
what meds already given
where intubated
hemodynamic stability
how are the other victims

ROS, meds, allergies, PMHx:
check for medical bracelets/wallet cards
"unable to obtain" (but not "none")

Glasgow Coma Scale (Physical Exam)

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

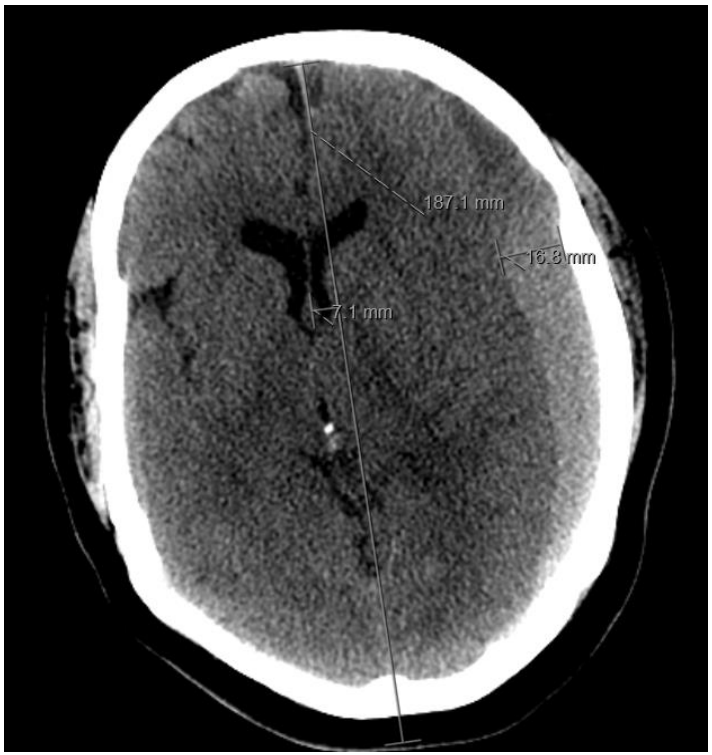

SOMATOM Spirit

Our current classification scheme for TBI:

Mild
GCS 13-15
Amnesia<30 min
short LOC

Moderate
GCS 8 -13
amnesia >30 min <7d
middle LOC

Severe
GCS<8
amnesia>7d
long LOC



37 yo woman who fell 2 weeks prior and had a SDH – She was GCS 15. Went to the OR two weeks after the fall…

Loss of consciousness can occur for many reasons! (intoxication, polytrauma)
Lack of LOC does not equate with milder injury (either short or long term)

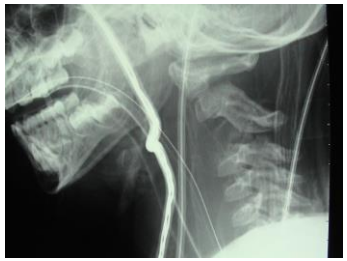
Hennepin County Medical Center

Why is concussion/brain injury so hard to diagnose and define?

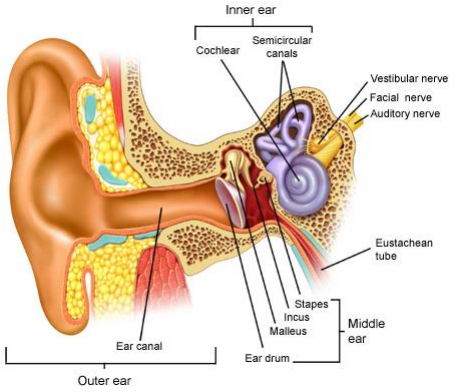
No two brain injuries are the same!

Similar symptoms can have multiple causes

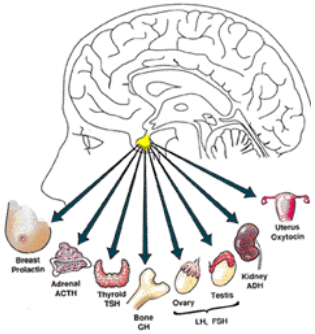
Neck injury



Inner ear injury



Endocrine Dysfunction



Cortical Spreading Depression

Scalp Injury

Skull Injury

Compressive Lesions
Epidural / Subdural

Subarachnoid Hemorrhage/IVH

Diffuse Axonal Injury

Anoxic Brain Injury

Prognosis

Best

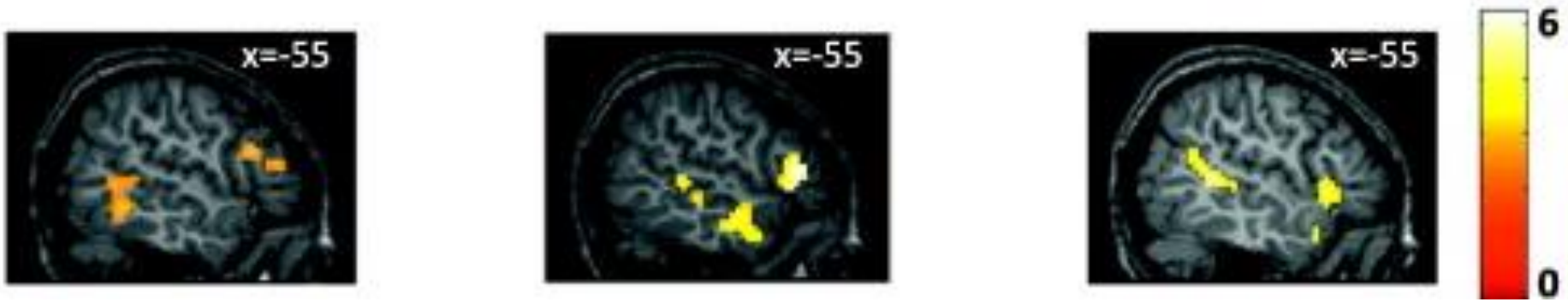
Worst

Why is concussion/brain injury so hard to diagnose and define?

The brain is not simple -

no two brains are the same

no one brain is the same over time



tests that require baselines are not ideal

baselines vary from person to person

vary in the same person over time

Monzalvo et al. Brain and Language, Volume 127, Issue 3, 2013, 356 - 365

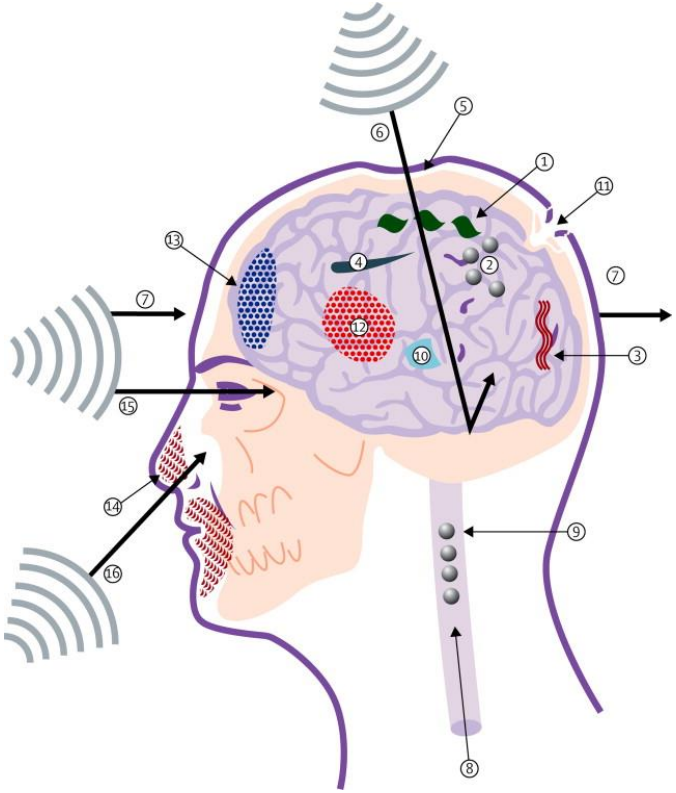
Why is concussion/brain injury so hard to diagnose and define?

No two recoveries are the same (functional plasticity, resilience)

Genetic and environmental contributors to recovery (COMT, BDNF, ApoE, RAR)

Why is concussion/injury so hard to diagnose and define?

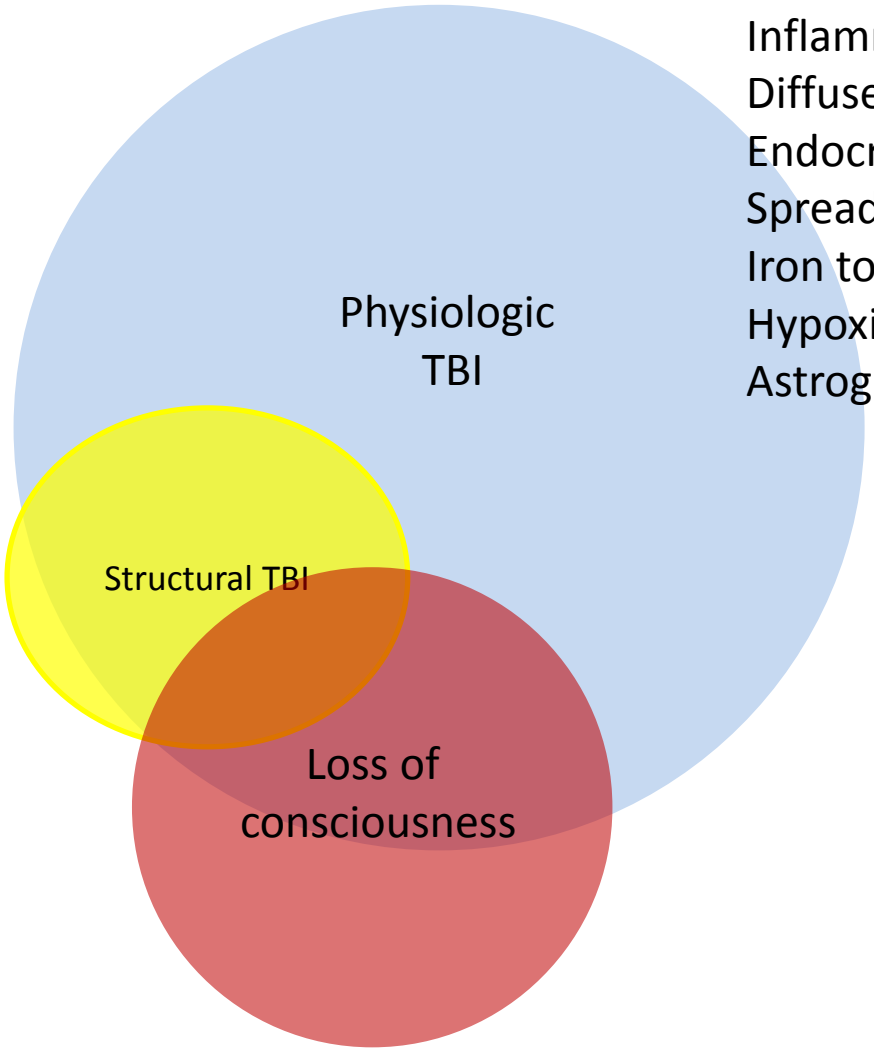
Some people with brain injury were never “hit” in the head…



- Primary blast injury: transmission of the blast pressure wave to the brain.
- Secondary blast injury: penetration of projectiles through the skull and into the brain.
- Tertiary blast injury: acceleration and deceleration effects, for example, if the casualty is thrown against fixed surfaces.
- Quaternary blast injury: thermal, chemical, and other injuries to the head, including the face, scalp, and respiratory tract.

Schematic diagram of the mechanisms of blast-related traumatic brain injury. Figure shows local effects (1–7) and systemic effects (8, 9) of primary blast injury, secondary blast injury (10–12), tertiary blast injury (13), quaternary blast injury (14), and portals for blast wave transmission to the brain (15, 16). (1) Acoustic impedance mismatch causes spallation. (2) Shock–bubble interaction. (3) Shear stress causing diffuse axonal injury. (4) Cavitation. (5) Skull deformation with elastic rebound. (6) Reflection of the blast wave within the skull. (7) Bobblehead effect of acceleration–deceleration. (8) Blood surge from the torso damages the microvasculature. (9) Air embolism from blast lung injury.(10) Penetrating fragments. (11) Compound fractured skull. (12) Intracerebral haemorrhage. (13) Contrecoup contusion. (14) Burns. (15) Blast wave transmitted through the orbits. (16) Blast wave transmitted through the nasal sinuses. Rosenfeld et al. Lancet Neurology Blast-related traumatic brain injury, 2013-09-01Z, Volume 12, Issue 9, Pages 882-893

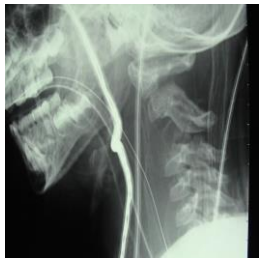
Neither imaging nor LOC tell the whole story



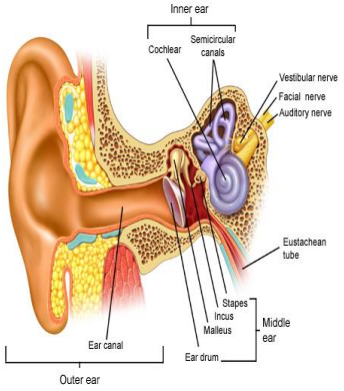
Inflammation/edema
Diffuse axonal injury
Endocrine dysfunction
Spreading depolarization (CSD)
Iron toxicity
Hypoxic/anoxic Injury
Astroglial scarring (blast)

Yet we accept mixed pathophysiology for brain injury and put everyone in the same trial…

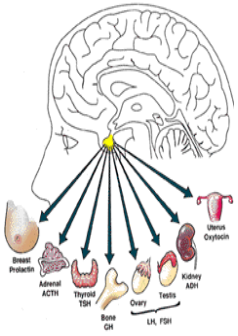
Neck injury



Inner ear injury



Endocrine Dysfunction



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Anoxic Brain Injury

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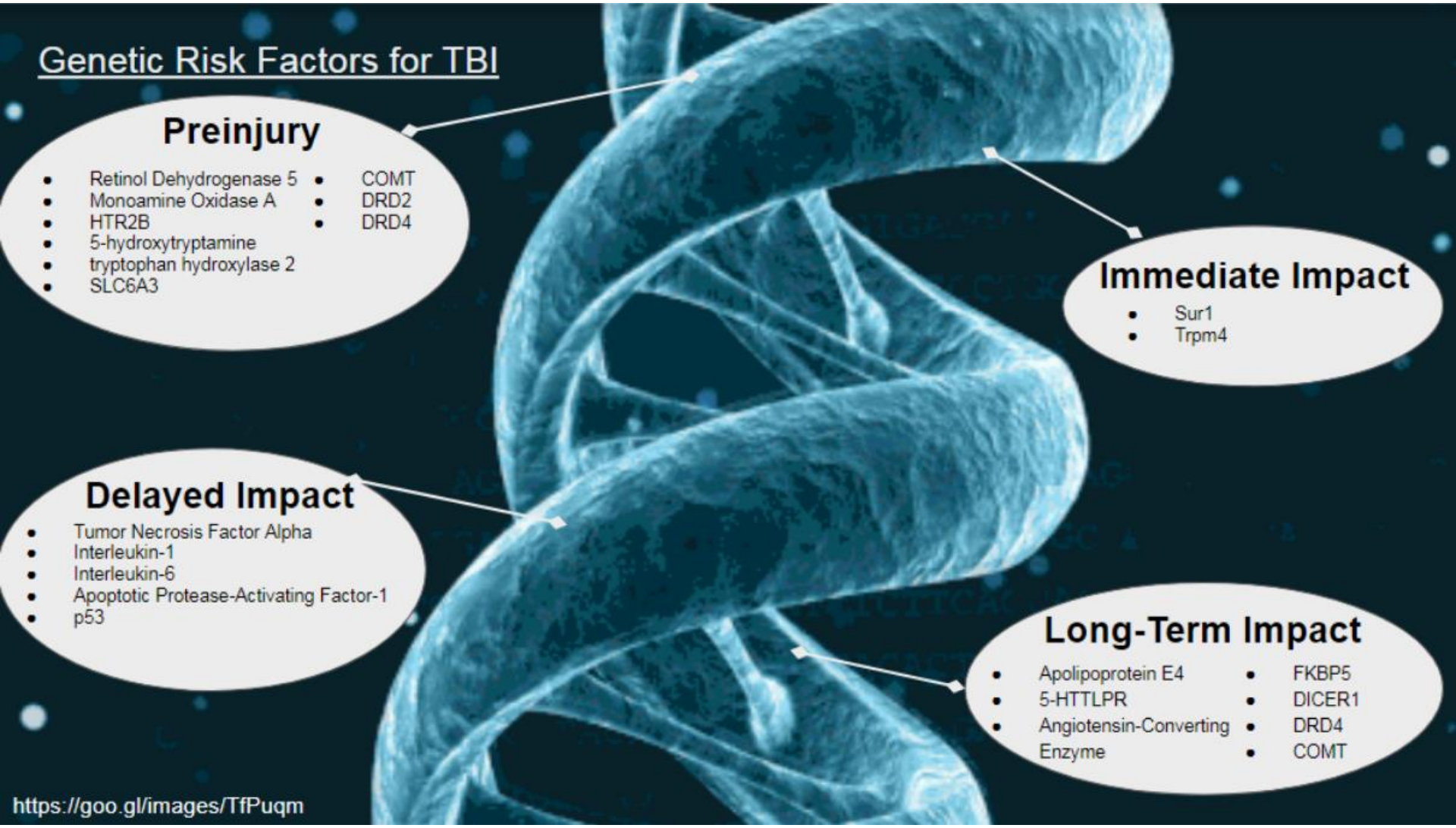
Better Classification of Brain Injury Begins With Objective Assessment

genetics

radiographic measures

serum markers

eye tracking


Genetic Risk Factors for TBI
Preinjury
Retinol Dehydrogenase 5
Monoamine Oxidase A
HTR2B
5-hydroxytryptamine
tryptophan hydroxylase 2
SLC6A3
COMT
DRD2
DRD4
Immediate Impact
Sur1
Trpm4
Delayed Impact
Tumor Necrosis Factor Alpha
Interleukin-1
Interleukin-6
Apoptotic Protease-Activating Factor-1
p53
Long-Term Impact
Apolipoprotein E4
5-HTTLPR
Angiotensin-Converting Enzyme
FKBP5
DICER1
DRD4
COMT
https://goo.gl/images/TfPuqm

SCIENCE

University of Minnesota is nerve center of brain-mapping research

The U's expertise in high-tech medical imaging led to the first detailed mapping of the functions and neural activities of brains in ordinary middle-aged adults.

By **Jeremy Olson** Star Tribune | MAY 26, 2017 — 12:55AM

ELIZABETH FLORES, STAR TRIBUNE

The University of Minnesota was chosen as a leader of the Connectome project because of its Center for Magnetic Resonance Research, shown in 2013. There, it

FOCUS ON THE NEUROSCIENCE TOOLBOX REVIEW

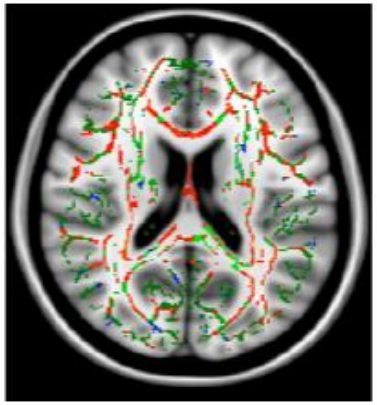
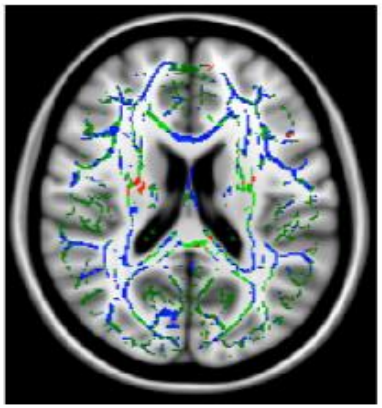
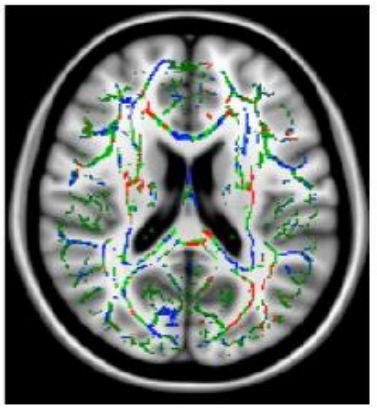
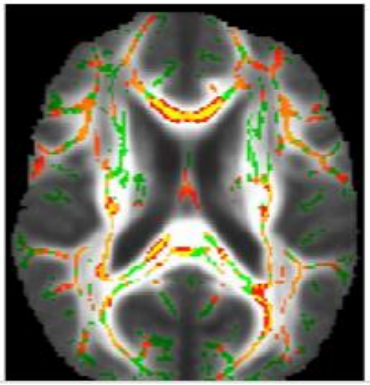
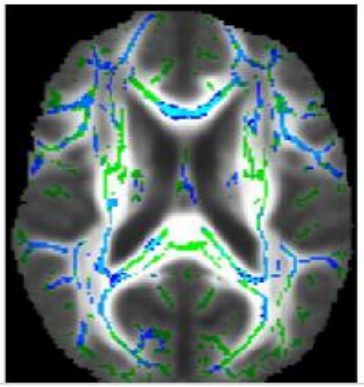
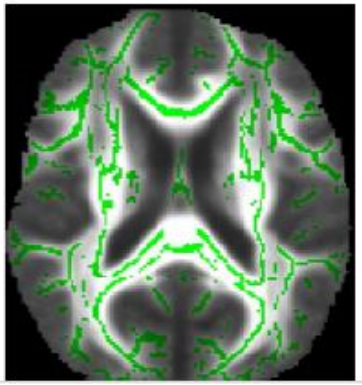
nature neuroscience

The Human Connectome Project's neuroimaging approach

Matthew F Glasser[1], Stephen M Smith[2], Daniel S Marcus[3], Jesper L R Andersson[2], Edward J Auerbach[4], Timothy E J Behrens[2], Timothy S Coalson[1], Michael P Harms[5], Mark Jenkinson[2], Steen Moeller[4], Emma C Robinson[6], Stamatios N Sotiropoulos[2], Junqian Xu[7], Essa Yacoub[4], Kamil Ugurbil[4] & David C Van Essen[1]

Noninvasive human neuroimaging has yielded many discoveries about the brain. Numerous methodological advances have also occurred, though inertia has slowed their adoption. This paper presents an integrated approach to data acquisition, analysis and sharing that builds upon recent advances, particularly from the Human Connectome Project (HCP). The 'HCP-style' paradigm has seven core tenets: (i) collect multimodal imaging data from many subjects; (ii) acquire data at high spatial and temporal resolution; (iii) preprocess data to minimize distortions, blurring and temporal artifacts; (iv) represent data using the natural geometry of cortical and subcortical structures; (v) accurately align corresponding brain areas across subjects and studies; (vi) analyze data using neurobiologically accurate brain parcellations; and (vii) share published data via user-friendly databases. We illustrate the HCP-style paradigm using existing HCP data sets and provide guidance for future research. Widespread adoption of this paradigm should accelerate progress in understanding the brain in health and disease.

The Human Connectome Project (HCP) began in 2010 when the National Institutes of Health (NIH) awarded ~$40 million to two consortia to develop improved neuroimaging methods and to acquire a data set of unprecedented size and quality for mapping the normal human macroscale connectome[1,2]; that is, the long-distance connections between all of the brain's areas. Better maps of the brain's areas and their connections will deepen our understanding of healthy brain function and may improve our ability to understand and treat neurological and psychiatric disorders. The 'WU-Minn-Ox' HCP consortium has developed broadly useful MRI acquisition protocols, consisting of thoroughly tested and optimized pulse sequences and image reconstruction algorithms; (ii) a collection of exceptionally high-quality, freely shared neuroimaging data; (iii) numerous publicly available neuroimaging software and informatics tools; (iv) a growing number of discoveries emerging from analyses of HCP data; (v) the emergence of an HCP-style paradigm for neuroimaging data acquisition, analysis and sharing; and (vi) a growing number of HCP-style projects that will study different age ranges and brain disorders.

DIFFUSION PROPERTY	Fractional Anisotropy	Mean Diffusivity	Axial Diffusivity
Definition	Scalar value describing degree of diffusion asymmetry (isotropic = 0 where λ1 = λ2 = λ3 to anisotropic = 1).	Total diffusion within a voxel. Also known as the apparent diffusion coefficient (ADC).	Diffusion along the main axis of the ellipsoid.
Biological Meaning	Decreased FA may reflect loss of microstructural integrity (i.e. degeneration).	Increased MD may reflect cellular breakdown , brain bleeds, or lesions.	Decreased axial diffusivity but no change in radial diffusivity suggestive of axonal damage without myelin injury.
Equation	$\sqrt{\frac{3}{2}}\frac{\sqrt{(\lambda_1-\tilde{\lambda})^2+(\lambda_2-\tilde{\lambda})^2+(\lambda_3-\tilde{\lambda})^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$	(λ1 + λ2 + λ3) / 3	λ (parallel) = λ1
Contrast 1 (red-yellow) gives the control > TBI *Contrast 2 (blue-lightblue) gives the control < TBI* *Green = mean_FA_skeleton*			
Enhanced thresholded p-value images fully corrected for multiple comparisons across space			

Differences in Diffusion Properties of White Matter Tracts in Patients with Acute Traumatic Brain Injury

Tessneem Abdallah, BA[1,2,3], Margaret Y. Mahan, MS[1,2,3,4], Hannah Casey[1,2,3], Mark Oswood, MD, PhD[2,5], Charles Truwit, MD[2,5], Chad Richardson, MD[1,2,3], Uzma Samadani, MD, PhD[1,2,3,6]
[1]Brain Injury Research Lab; [2]Hennepin County Medical Center, Minneapolis, MN; [3]Minneapolis Medical Research Foundation, Minneapolis, MN; [4]Department of Biomedical Informatics and Computational Biology, University of Minnesota, Minneapolis, MN; [5]Department of Radiology, University of Minnesota, Minneapolis, MN;
[6]Department of Neurosurgery, University of Minnesota, Minneapolis, MN

Methods

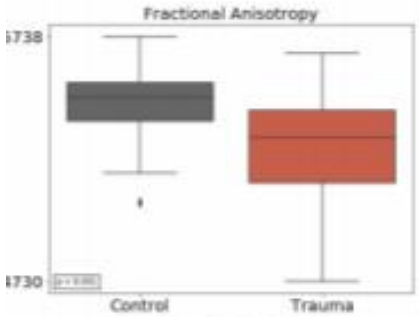
- Patients with suspected head trauma recruited from level I trauma center; healthy controls from community
- Inclusion criteria: ages 20-70, present to emergency department within 24 hours of injury, scanned within 4.22 +/- 2.55 days from injury
- Exclusion criteria: neurocognitive abnormalities, psychiatric disorders, contraindications to MRI

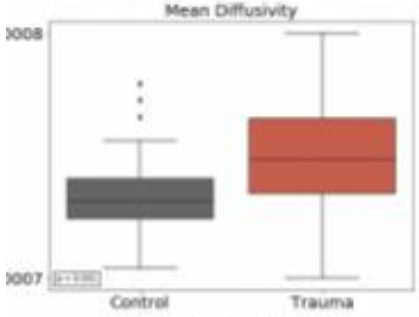
	Trauma (n=58)	Control (n=42)
Female	18	20
Male	40	22
Age (years)	43.5 [20.4-70.2]	37.3 [20.7-67.2]

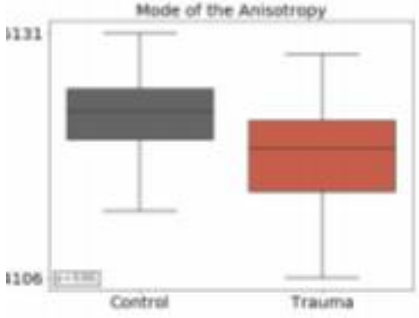
Table 1: Subject Demographics

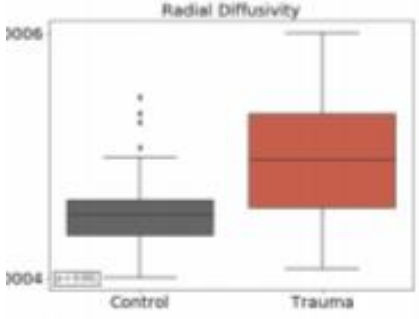
Mechanism of Injury	N
Assault	2
Bicyclist	7
Incidental Fall	21

Mechanism of Injury	N
Assault	2
Bicyclist	7
Incidental Fall	21
Motor Vehicle Crash	23
Pedestrian struck by vehicle	3
Other	2



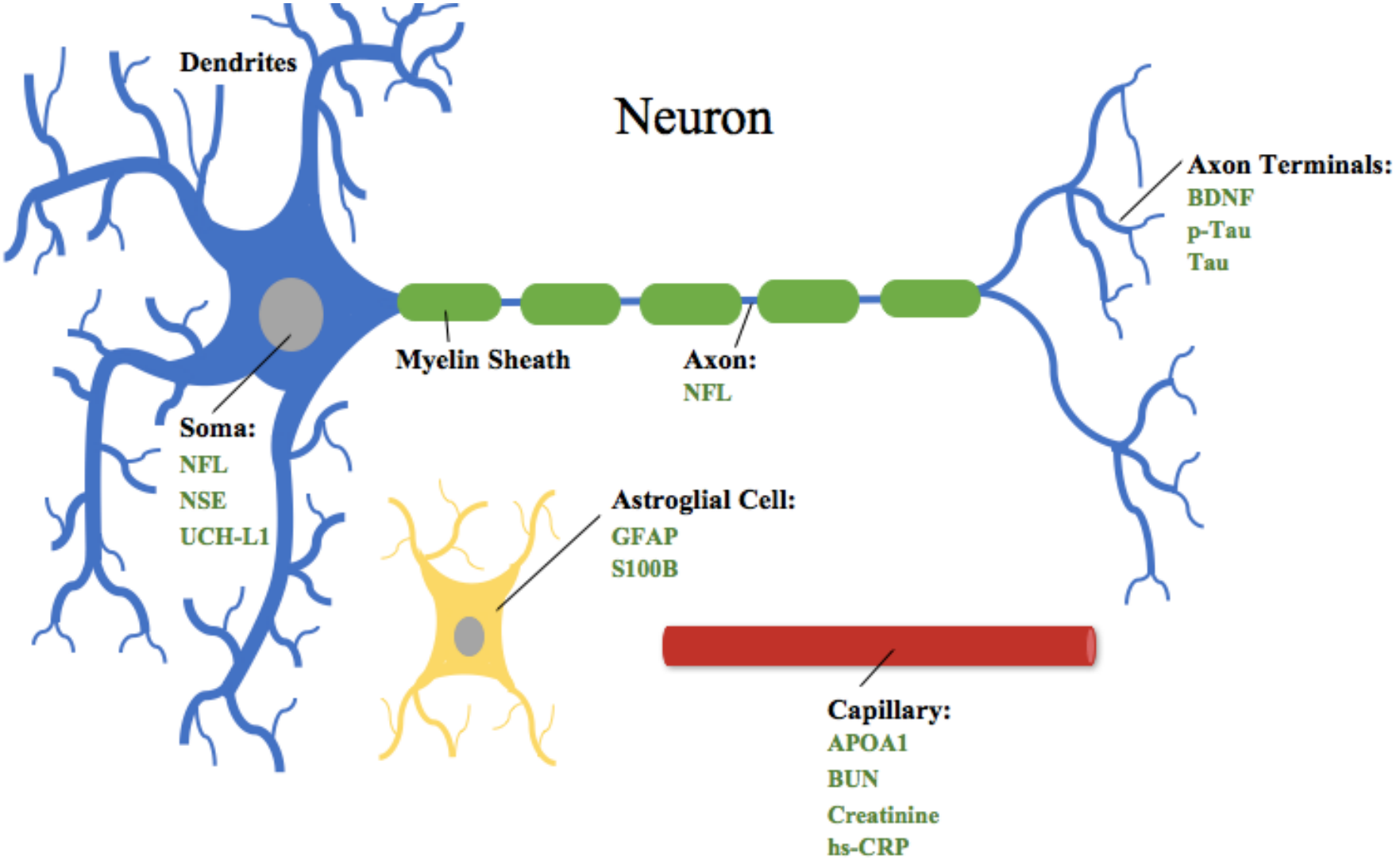






Definition	Biological Significance
Fractional Anisotropy	
Scalar value describing degree of diffusion asymmetry	FA is an overall measure of microstructural integrity
Mean Diffusivity	
Total diffusion within a voxel; also known as the apparent diffusion coefficient (ADC)	MD is a measure of membrane density and is sensitive to cellular breakdown and lesions
Mode of Anisotropy	
Measures whether anisotropy is planar or linear	MO detects abnormalities in crossing fibers affecting brain connectivity
Radial Diffusivity	
Scalar value measuring motion perpendicular to axon	RD increases with demyelination in white matter or with changes in axonal diameter

Blood-based Biomarkers



Biomarkers “Specific” to Brain Injury

- Neuronal Injury
  - Neuron Specific Enolase (NSE)- Neuron-specific isoform of the glycolytic enzyme Enolase
  - Ubiquitin C-terminal Hydrolase (UCTHL-1)- Cytoplasmic protease - histological marker of neurons
- Axonal Injury
  - Myelin Basic Protein (MBP)- Major component of CNS myelin sheath
  - Tau Protein- Forms microtubule bundles in axons
- Glial Injury
  - S100B- low-affinity calcium-binding protein found in astrocytes
  - Glial Fibrillary Acidic Protein (GFAP)- concentrated in cytoskeleton of astrocytes
- Auto-antibodies
  - Specific Markers- S100B, GFAP, Glutamate

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Biomarker Concentrations

Type	Time	UCH-L1	GFAP	S100B
TBI	0-6 hours post-injury	**9498**	23	**3380**
TBI	24 hours post-injury	738	**498**	201
TBI	2 weeks post-injury	178	20	66
Average Control		91	12	71

Spontaneous Bleed

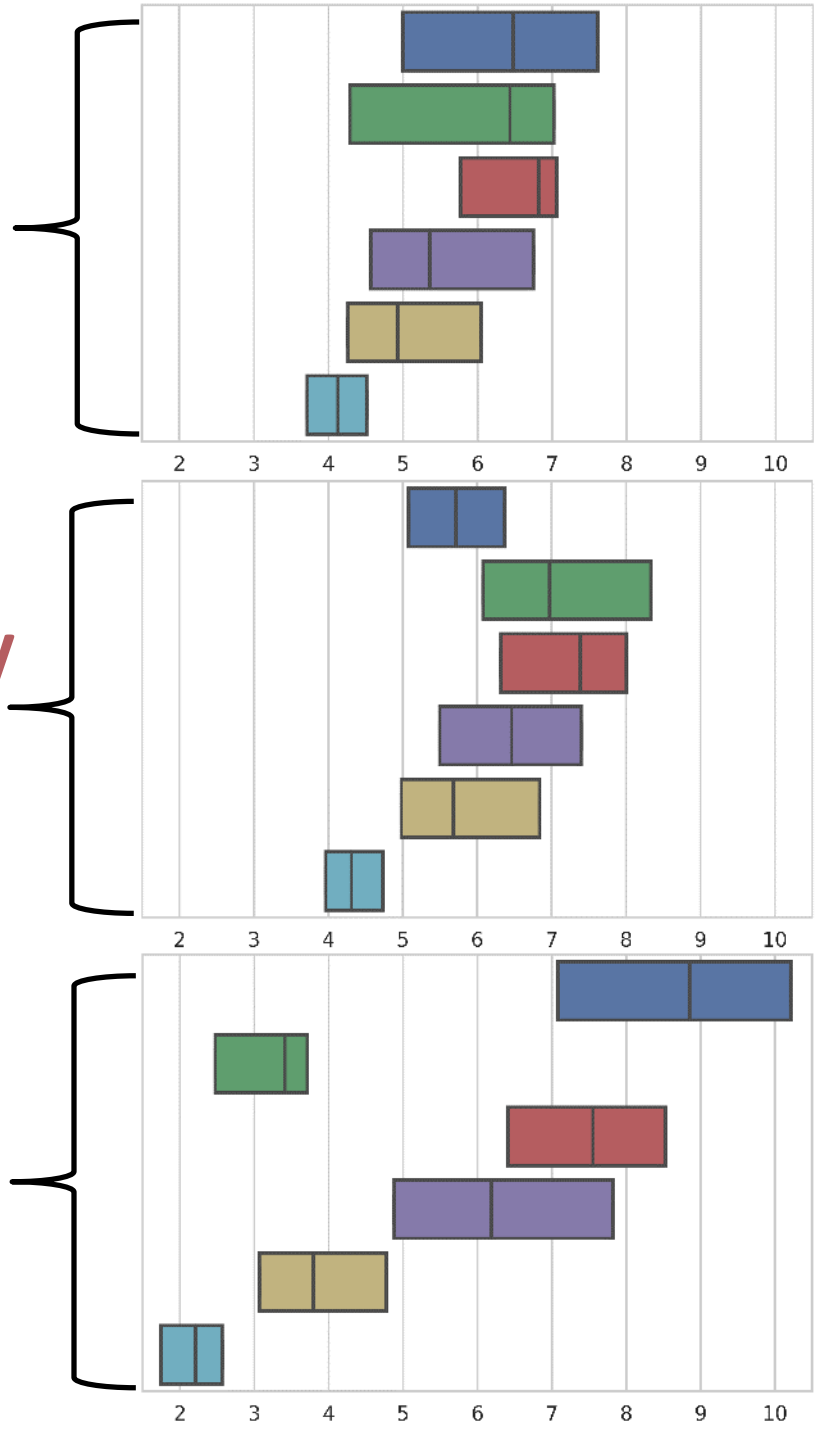
Anoxia

Diffuse Axonal Injury

CT-positive TBI

CT-negative TBI

Control



S100B

UCH-L1

GFAP

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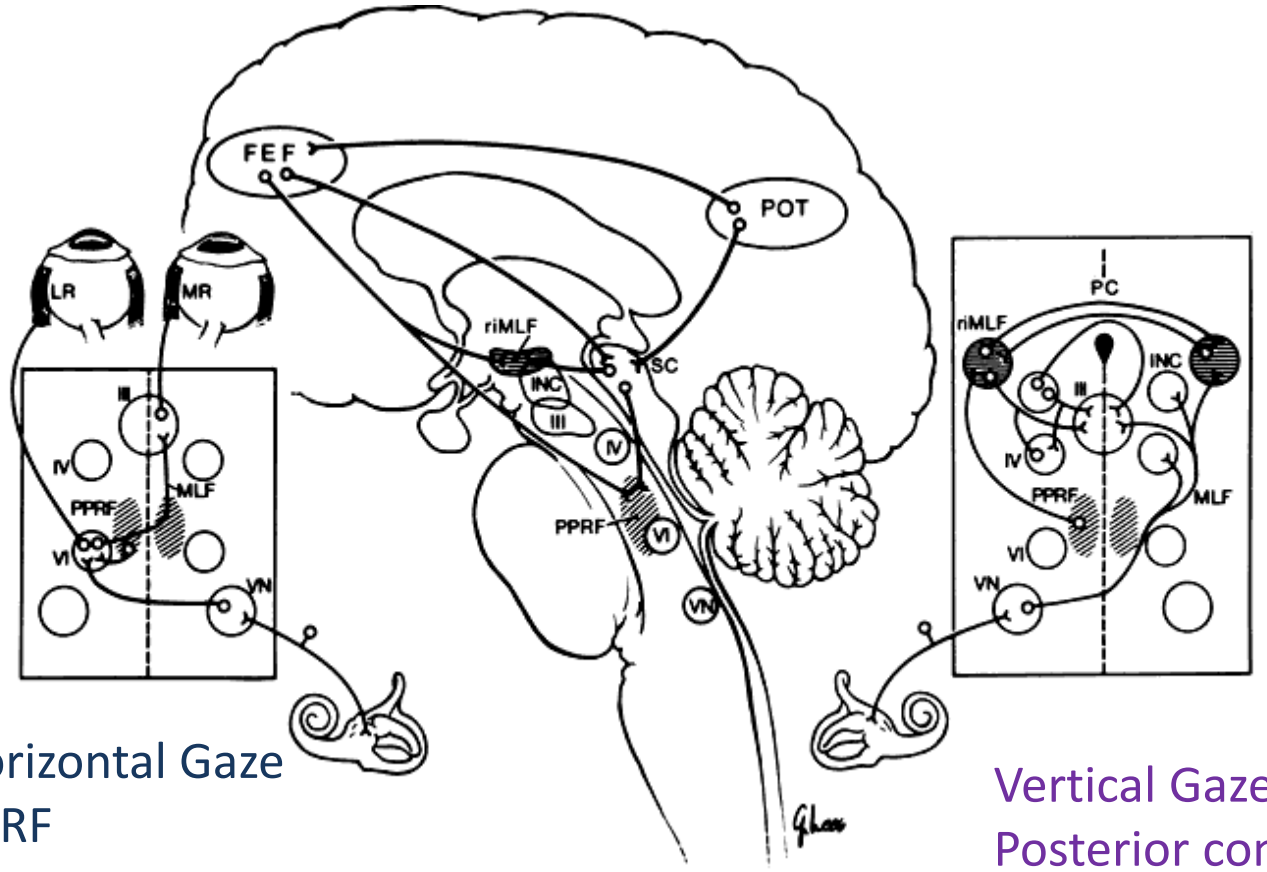


Horizontal Gaze
PPRF

Vertical Gaze
Posterior commisure
riMLF

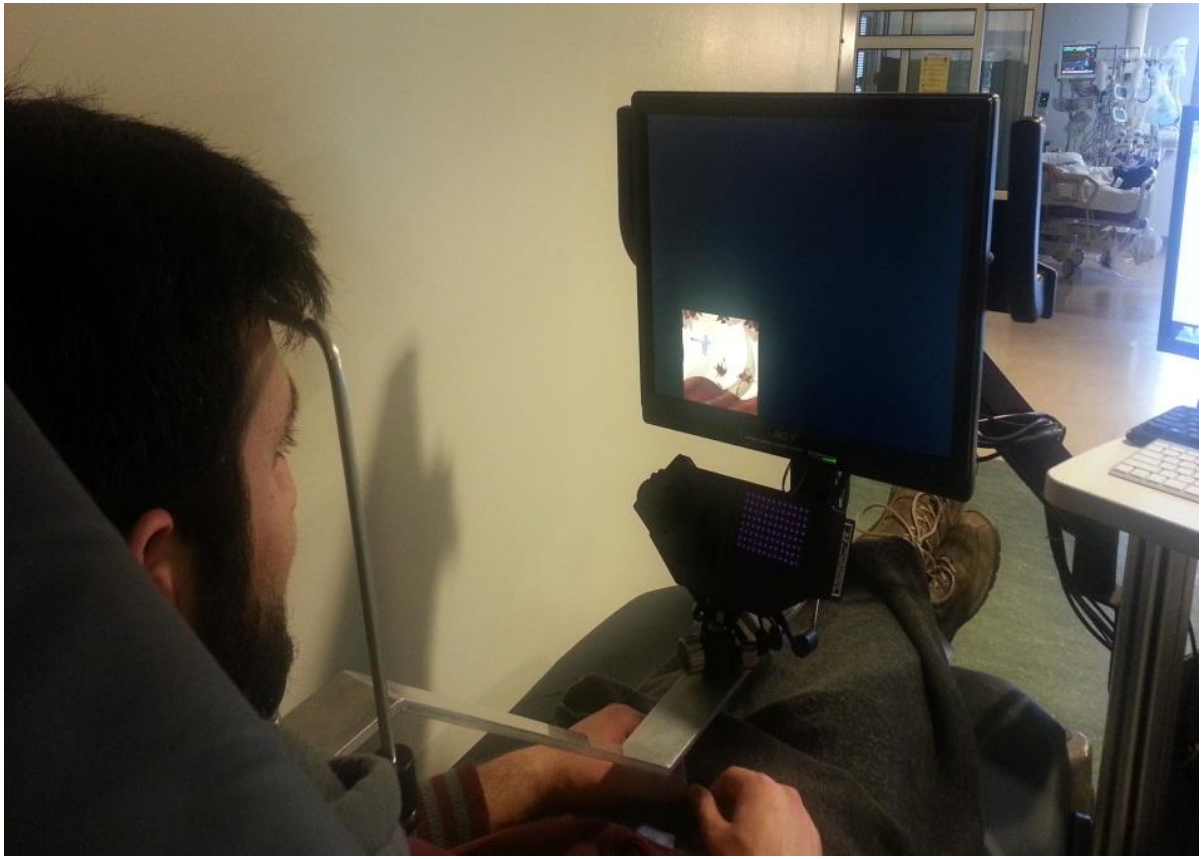
Supranuclear control of eye movements
http://oculist.net/downaton502/prof/ebook/duanes/pages/v1/ch004/002f.html

Edwin Smith

- Edwin Smith kept the ancient treatise
- In 1905, Mr Smith's daughter donated the artefact to New York Historical Society
- The medical treatise was written around 1700 B.C., but most of the information based on texts written around .3000B.C

Method:

The subject watches a 220 second video playing inside of an aperture moving around the perimetry of a video monitor while a camera records eye movements.



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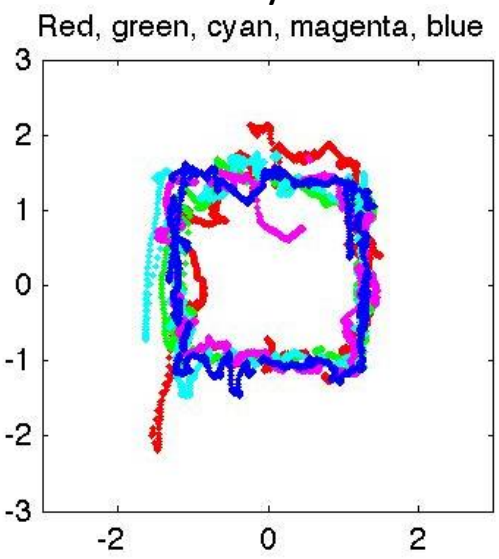
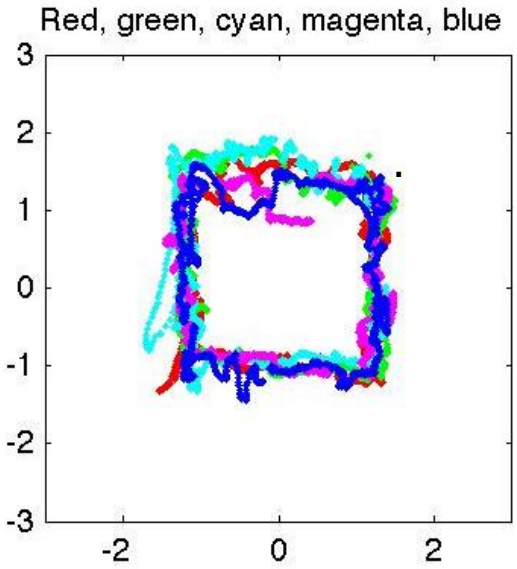
Binocular Tracking of A Normal Subject:

Left eye



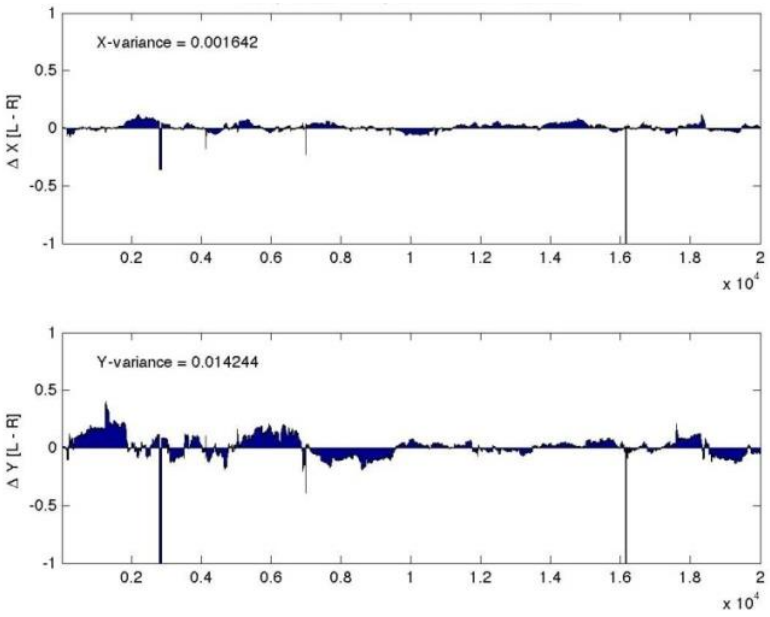
Aspect Ratio
0.97516

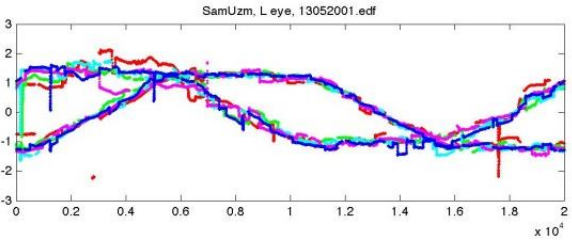
Right eye

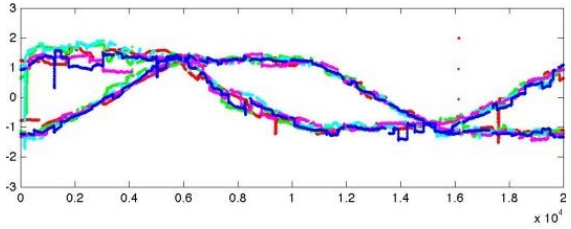


Aspect Ratio
0.99314

Conjugacy







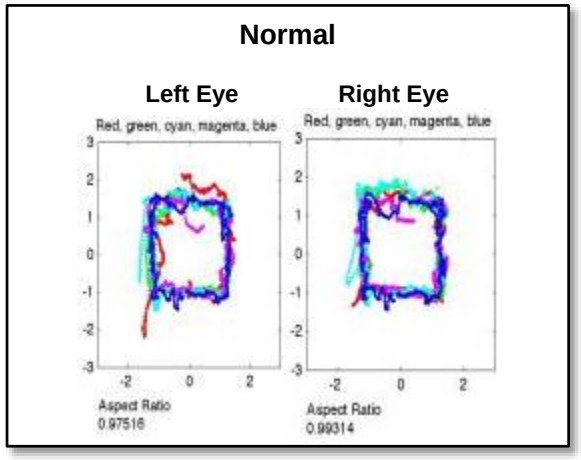
total var.015885

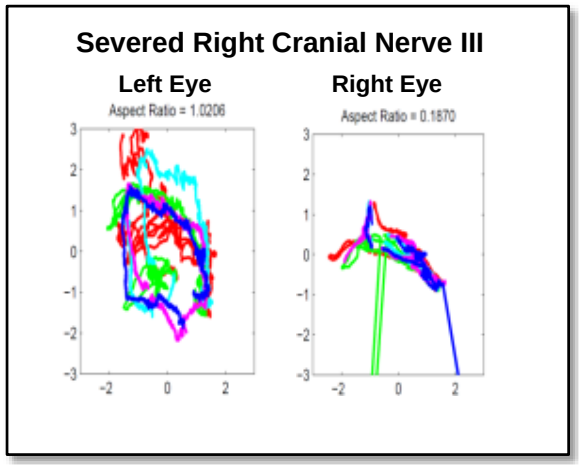
JNS
CLINICAL ARTICLE
J Neurosurg 122:707–720, 2015

Detection of third and sixth cranial nerve palsies with a novel method for eye tracking while watching a short film clip

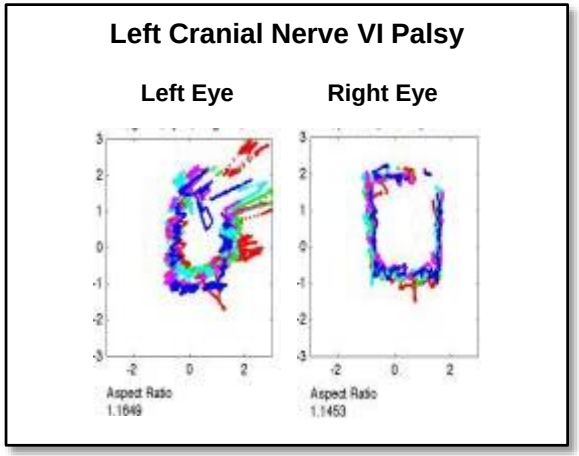
Uzma Samadani, MD, PhD,[1,2] Sameer Farooq,[2] Robert Ritlop, MEng,[2] Floyd Warren, MD,[1,3] Marleen Reyes, BA,[1,2] Elizabeth Lamm, BA,[2,4] Anastasia Alex, BS,[3] Elena Nehrbass, BS,[1,2] Radek Kolecki, MS,[2] Michael Jureller, BS,[2] Julia Schneider,[2] Agnes Chen, BA,[2] Chen Shi, BS,[1,2] Neil Mendhiratta, BA,[1,2] Jason H. Huang, MD,[5] Meng Qian, PhD,[6] Roy Kwak, MD,[1] Artem Mikheev, MS,[7] Henry Rusinek, PhD,[7] Ajax George, MD,[7] Robert Fergus, PhD,[4] Douglas Kondziolka, MD,[2] Paul P. Huang, MD,[2] and R. Theodore Smith, MD, PhD[3]

[1]New York Harbor Health Care System, Manhattan Veteran's Administration; Departments of [2]Neurosurgery, [3]Ophthalmology, [6]Psychiatry, and [7]Radiology, New York University School of Medicine; [4]Department of Computer Science, Courant Institute, New York University, New York, New York; and [5]Department of Neurosurgery, Scott and White Health Care, Temple, Texas





Cranial nerve III palsy
Impacts box height



Cranial nerve VI palsy
Impacts box width

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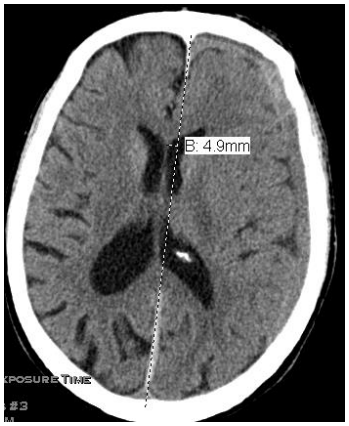
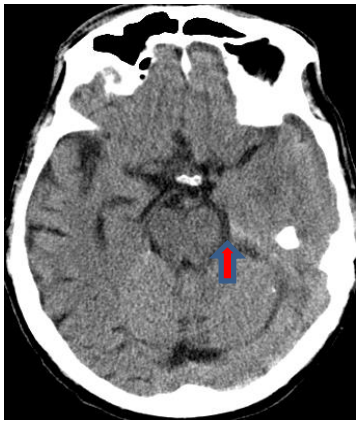
Supratentorial

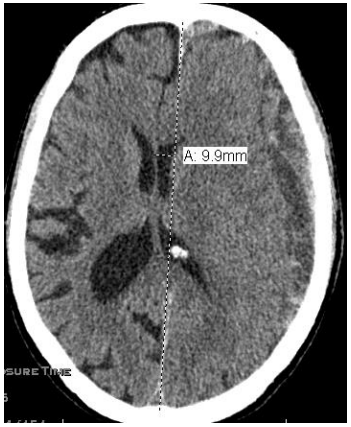
Mass Lesions

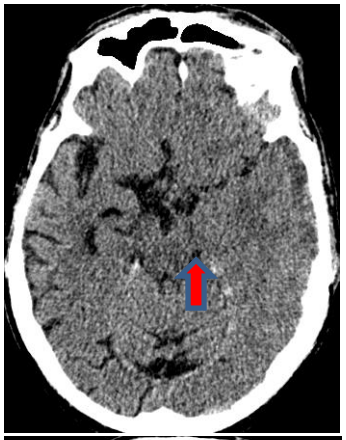
subdural, epidural, other hemorrhage, focal edema
can be present in concussion

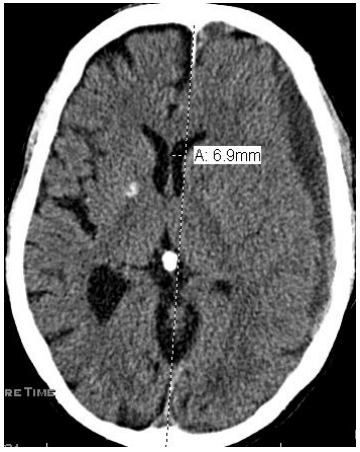
HEIGHT of box

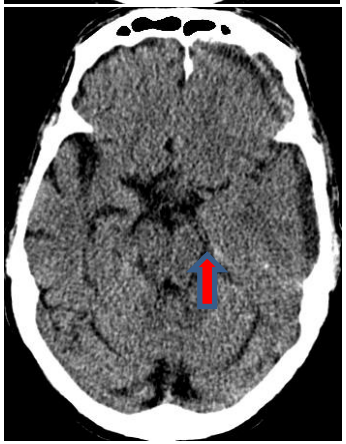








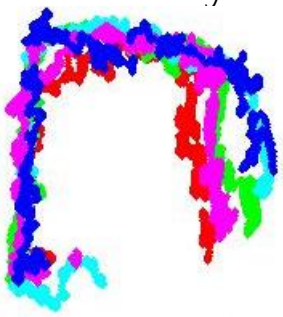




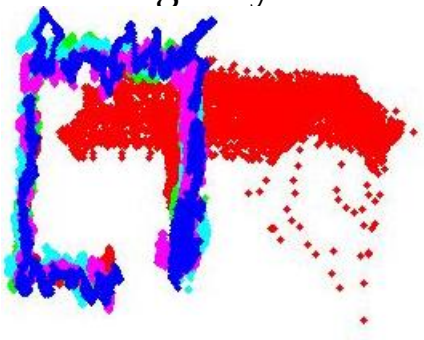
86 year old

At presentation, complaining of a headache

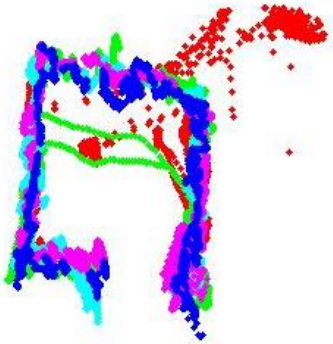
Left eye

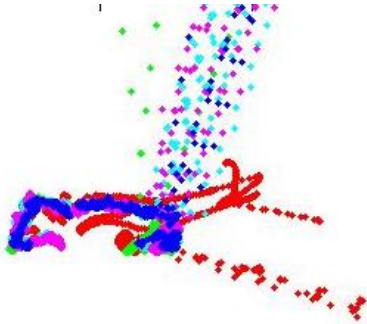


Right eye

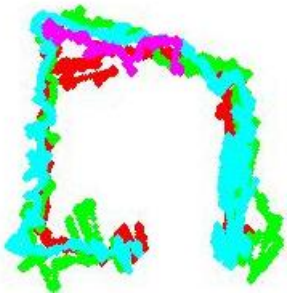


8 days later, the headache had resolved but then recurred

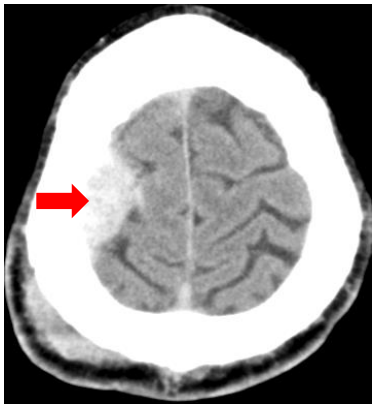


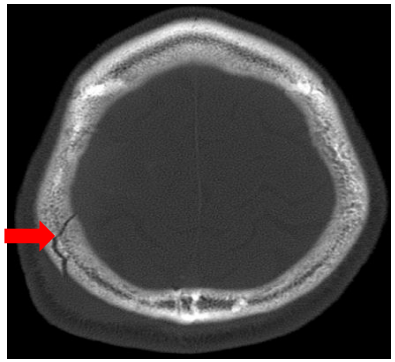


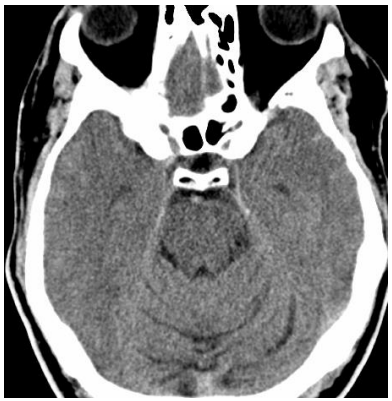
After 100 cc of subdural hematoma was evacuated



Hypertension, hyperlipidemia mild chronic renal insufficiency ophthalmologic history of bilateral cataract surgery (2 years and 8 years prior), pseudophakia and scleral buckling. He had a baseline visual acuity of 20/25 (right eye) and 20/30 (left eye)

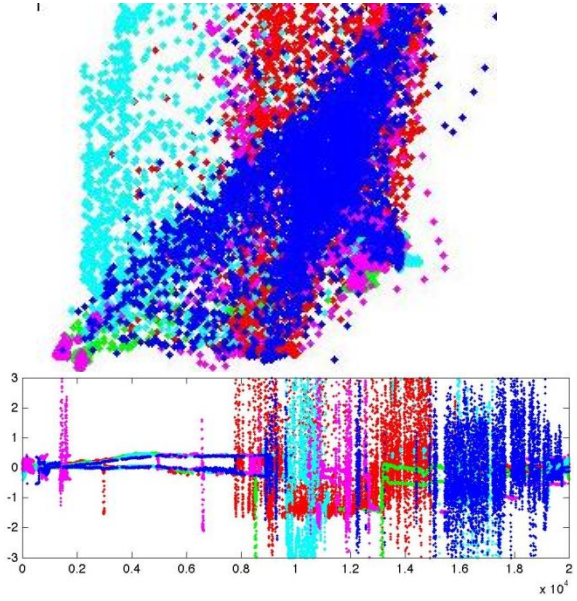




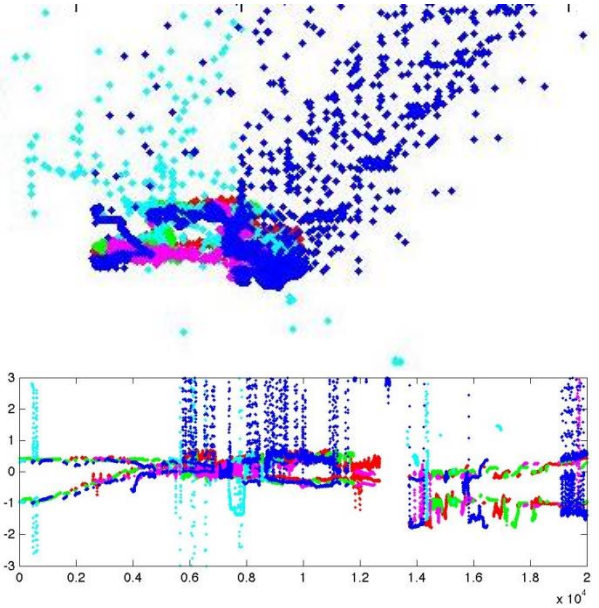


Preoperative CT images

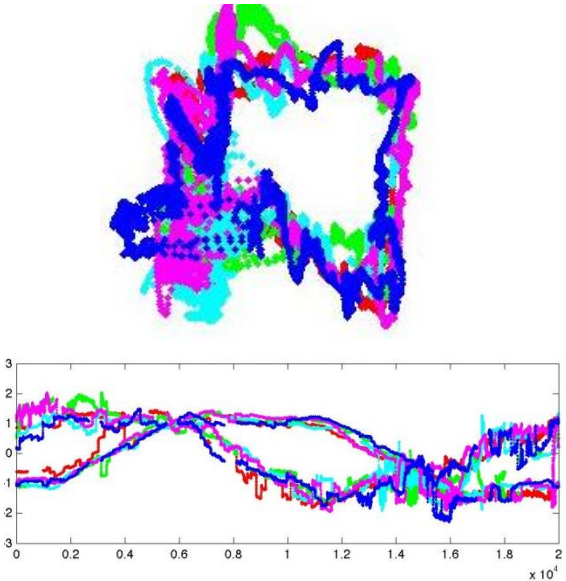
Preop Left Eye



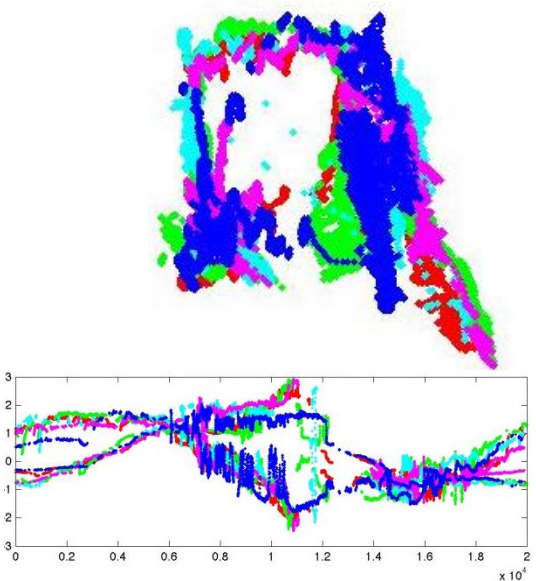
Preop Right Eye



7 Days Postop Left Eye

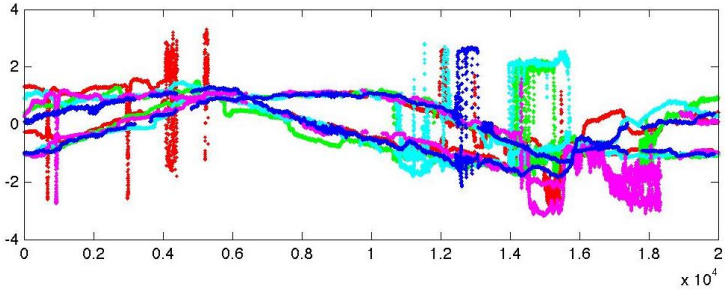


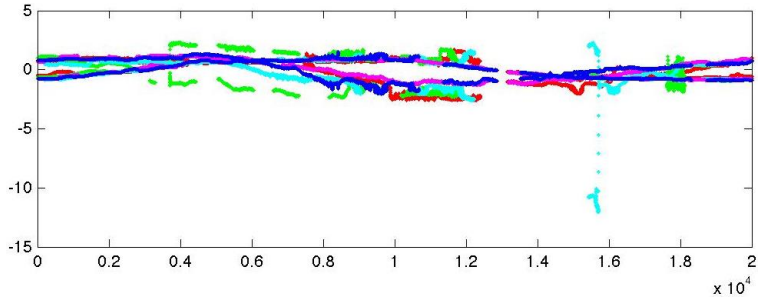
7 Days Postop Right Eye



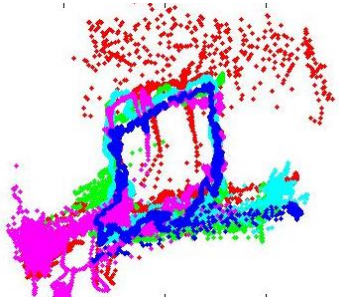
Left eye

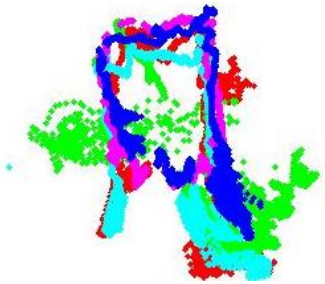
Right eye

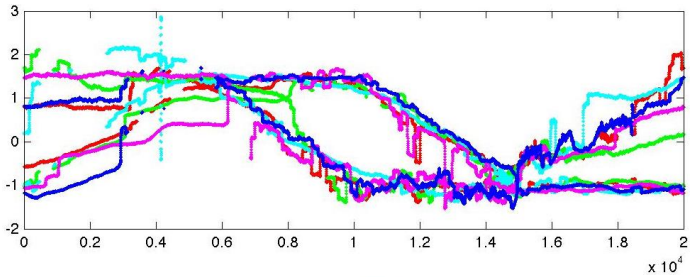


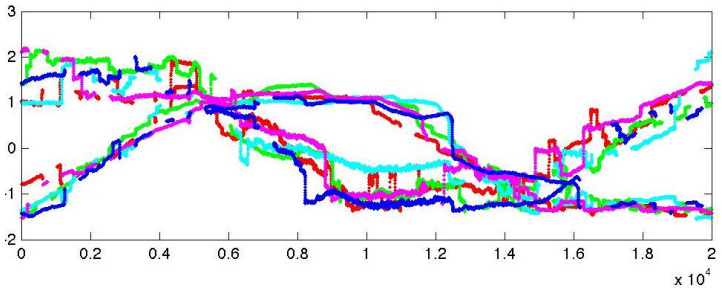


11 days postop

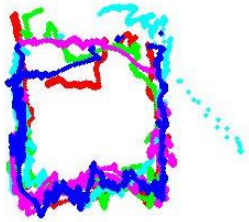








35 days postop



The subject returned to work 2 months after the ictus, and has not been eye tracked again.

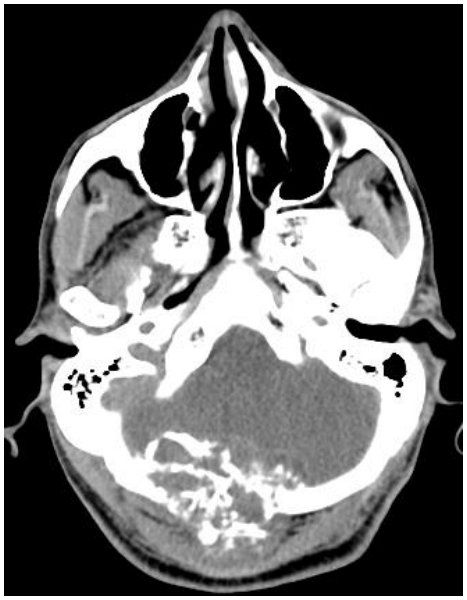
Infratentorial

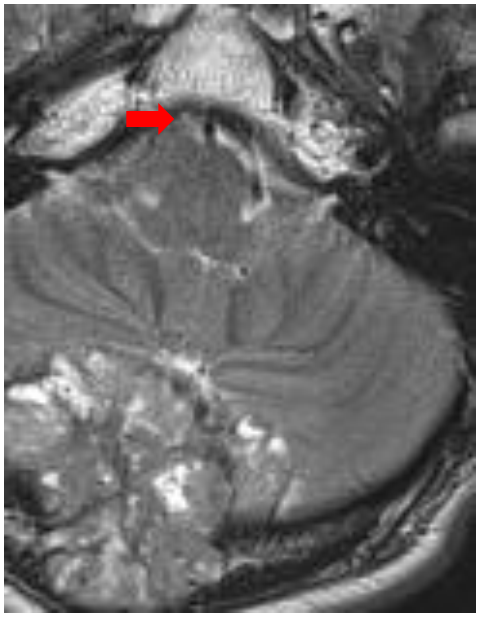
Mass Lesions

subdural, epidural, other hemorrhage, focal edema
can be present in concussion

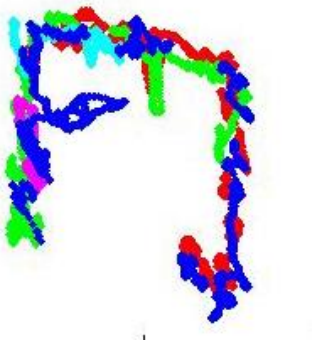
WIDTH of box

54 yo male with poorly differentiated papillary carcinoma, presented with a tender mass on the back of his head and a progressive headache

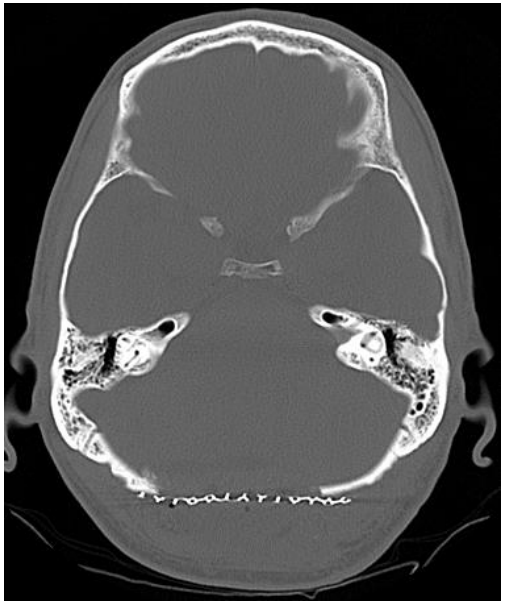


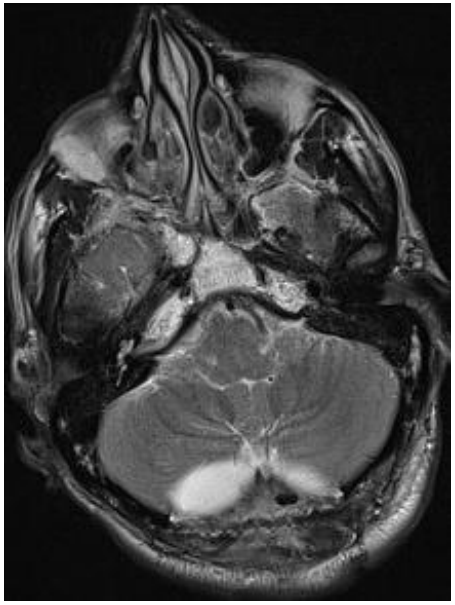


Preoperative

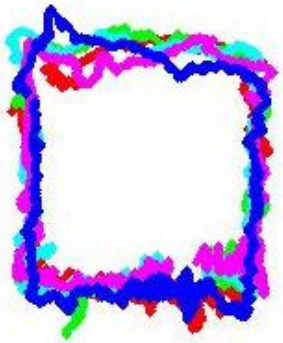


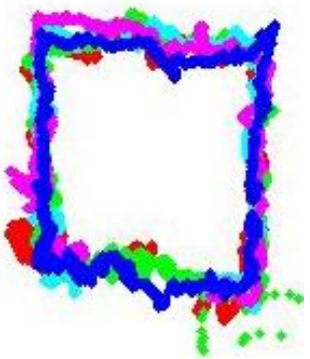
Aspect ratio 1.84 1.14





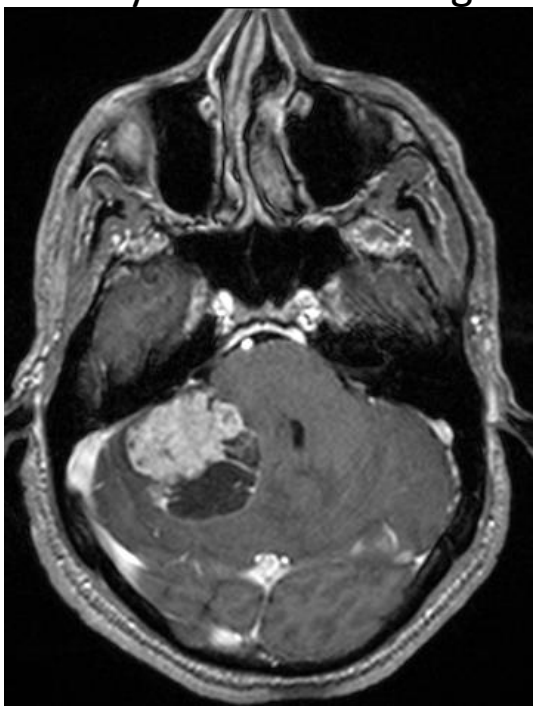
Left eye Right eye

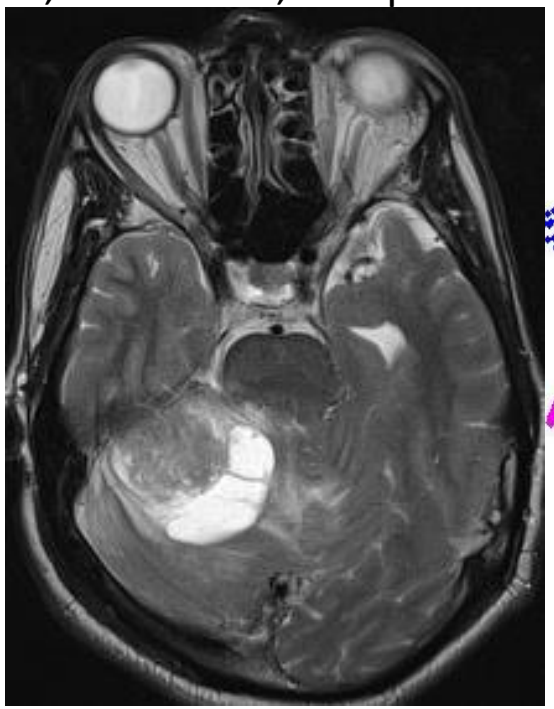


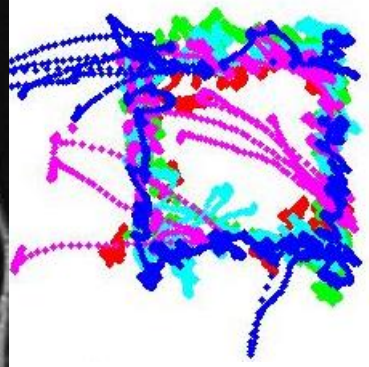


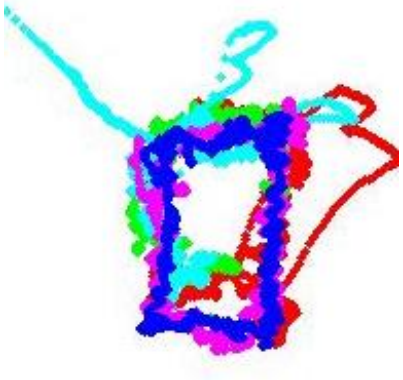
Aspect ratio 1.03 1.13

56 yo male with lung mass, headaches; Ophthalmology: no evidence of papilledema

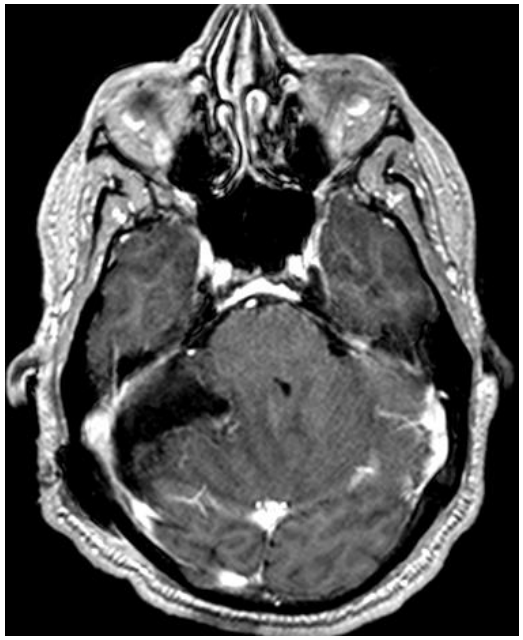








Left eye AR 1.03 Right eye AR 1.44



Left eye 0.97 Right eye 1.02

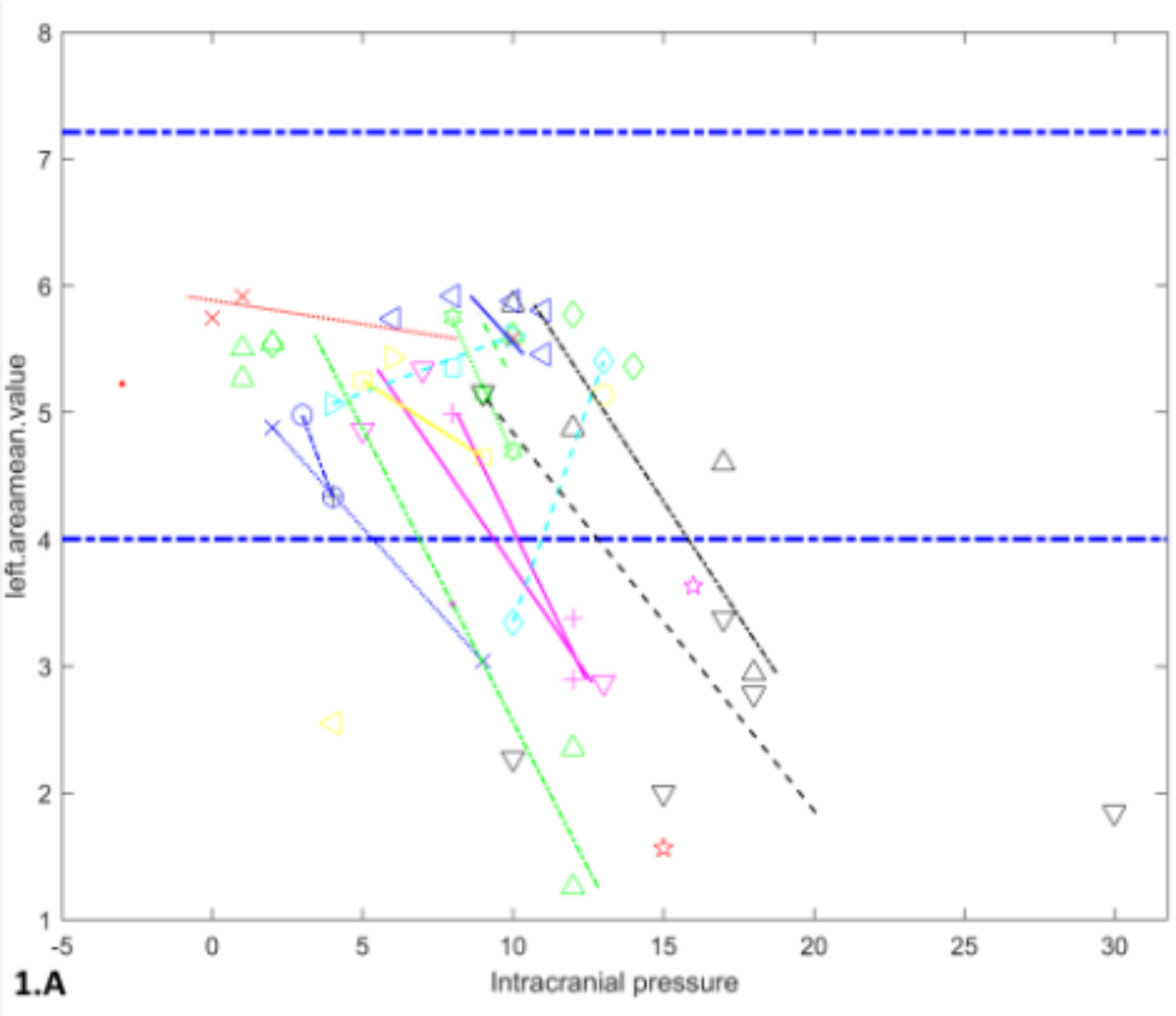
Postoperative Day 1

Elevated Intracranial Pressure

focal injury in a young person, typically diffuse injury, edema can be present in concussion

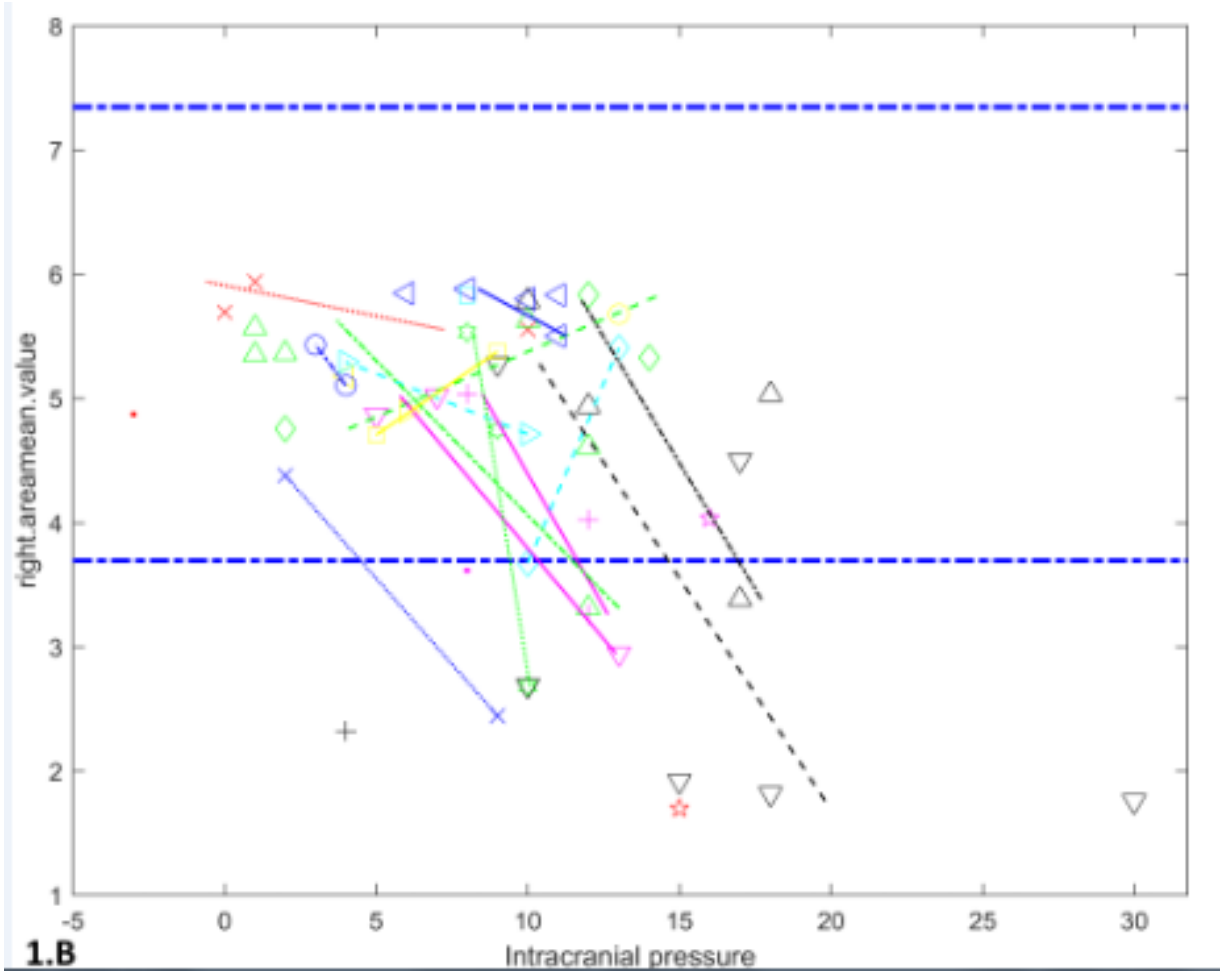
AREA of box

24 patients tracked on 55 occasions – Left area (HxW of box) vs ICP



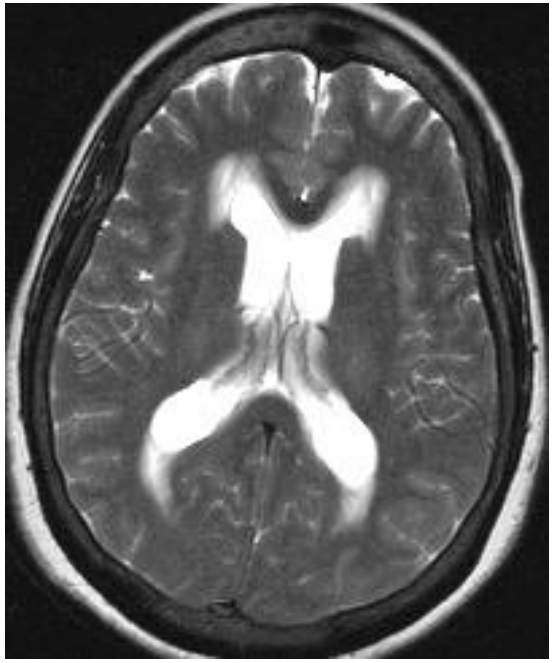
Linear regression with generalized estimating equations; p<.001

24 patients tracked on 55 occasions – right area (HxW of box) vs ICP

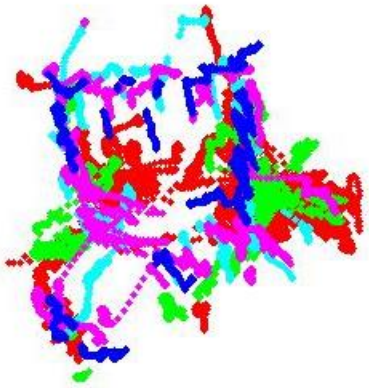


Linear regression with generalized estimating equations; p=.006

59 yo female one year history of progressive intermittent vertigo, biparietal headache and imbalance. She reported intermittent horizontal diplopia. Ophthalmologic examination revealed full ocular motility, and no evidence of papilledema or neurosarcoidosis.
CSF ACE1 level was 4.8 U/l (reference range 0 to 2.5 U/l) and biopsy of a pulmonary mass revealed sarcoidosis.

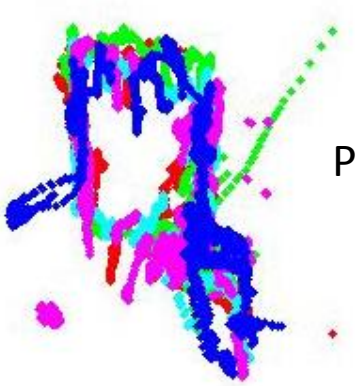


Aspect ratio 0.81



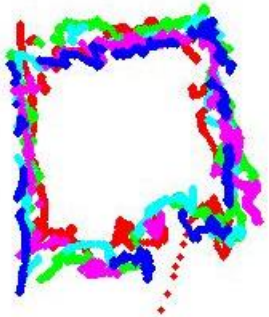
Left eye

1.34

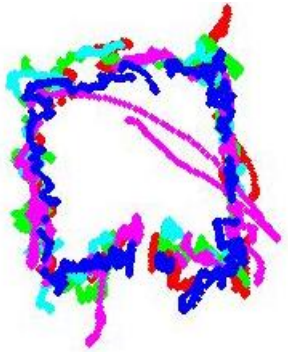


Preoperative

Right eye



Aspect ratio 1.04



1.00

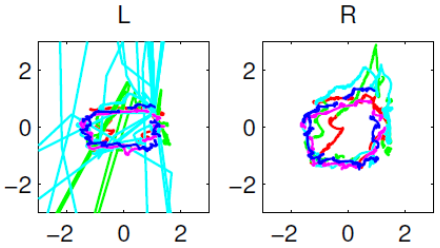
Postoperative Day 2

Concussion

as diagnosed by its symptoms and signs

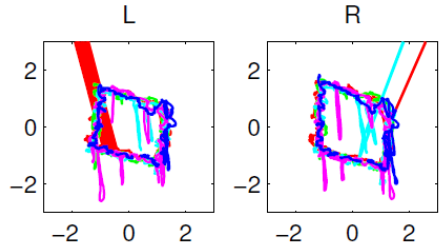
BOX score – sum of z-score of metrics (impacted by mass effect, ICP and other oculometric measures)

23 year old right-handed male fell from height of 30 feet. Patient was awake and alert in the field. GCS 14 in ER. Reported diffuse pain including in head. No vomiting. Neuro examination was non-focal but patient was admitted for orthopedic injuries. No ophthalmic history other than optometric visit 6 months prior. Wears corrective lenses for astigmatism. Reports a learning disability. Medications administered within 24hours prior to eye tracking: albuterol, vancomycin hydrochloride, piperacilin tazobactam, aztreonam, pentacel. Patient was tracked 8 days after injury. No SCAT performed initially.
Follow-up at 16 days after injury:
Positive for 16/22 SCAT3 symptoms with a severity score of 18/132 and GCS of 15/15. Total SAC score of 22/30.
Follow-up at 34 days after injury:
Positive for 10/22 SCAT3 symptoms with a severity score of 27/132 and GCS of 15/15. Total SAC score of 22/30
Follow-up at 75 days after injury:
Positive for 13/22 SCAT3 symptoms with a severity score of 39/132 and GCS of 15/15. Total SAC score of 26/30



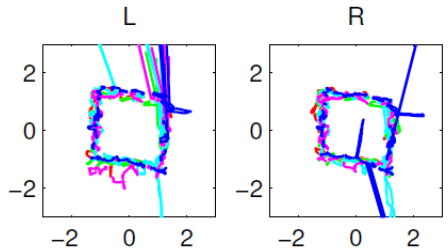
L.Area: 2.062*	R.Area: 4.636	Conj.varXrit: 0.057*
L.varXrit: 0.281*	R.varXrit: 0.025	Conj.varXbot: 0.013*
L.varXlef: 0.074*	R.varXlef: 0.090*	Conj.varXlef: 0.015*
L.varTotal: 1.027*	R.varTotal: 0.481	Conj.varYlef: 0.109*
		SCORE: 21

8 days after fall



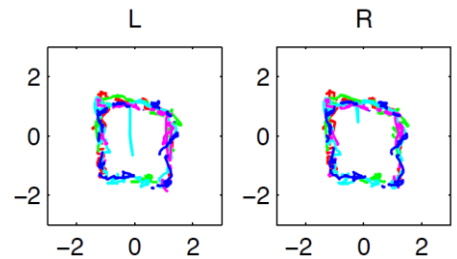
L.Area: 4.441*	R.Area: 5.369	Conj.varXrit: 0.003
L.varXrit: 0.022	R.varXrit: 0.017	Conj.varXbot: 0.028*
L.varXlef: 0.018	R.varXlef: 0.010	Conj.varXlef: 0.006*
L.varTotal: 0.784*	R.varTotal: 0.587	Conj.varYlef: 0.014
		SCORE: 8

16 days after fall



L.Area: 5.688	R.Area: 5.390	Conj.varXrit: 0.003
L.varXrit: 0.017	R.varXrit: 0.020	Conj.varXbot: 0.013*
L.varXlef: 0.009	R.varXlef: 0.009	Conj.varXlef: 0.002
L.varTotal: 0.558*	R.varTotal: 0.596	Conj.varYlef: 0.004
		SCORE: 2

34 days after fall



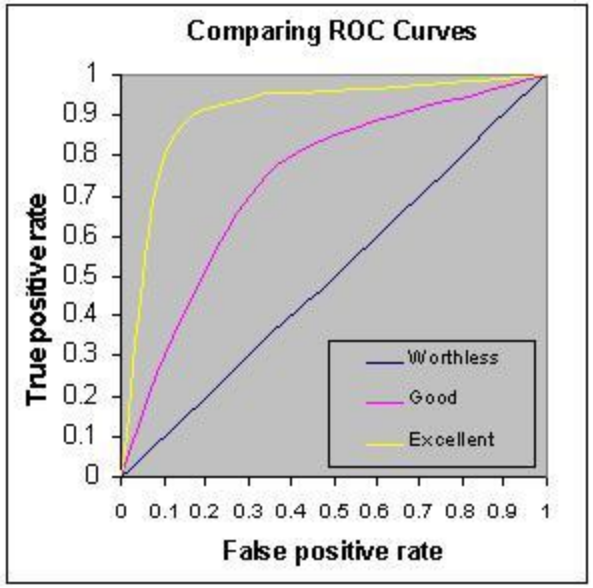
L.Area: 5.9389	R.Area: 5.8832	Conj.varXrit: 0.0036
L.varXrit: 0.0118	R.varXrit: 0.0096	Conj.varXbot: 0.0027
L.varXlef: 0.0082	R.varXlef: 0.0115	Conj.varXlef: 0.0015
L.varTotal: 0.4287	R.varTotal: 0.4161	Conj.varYlef: 0.0011
		SCORE: 0

75 days after fall

Creating a biomarker

Hennepin County Medical Center

Generate a receiver operating characteristic curve by plotting
the true positive rate (sensitivity) versus the false positive rate (1-specificity):



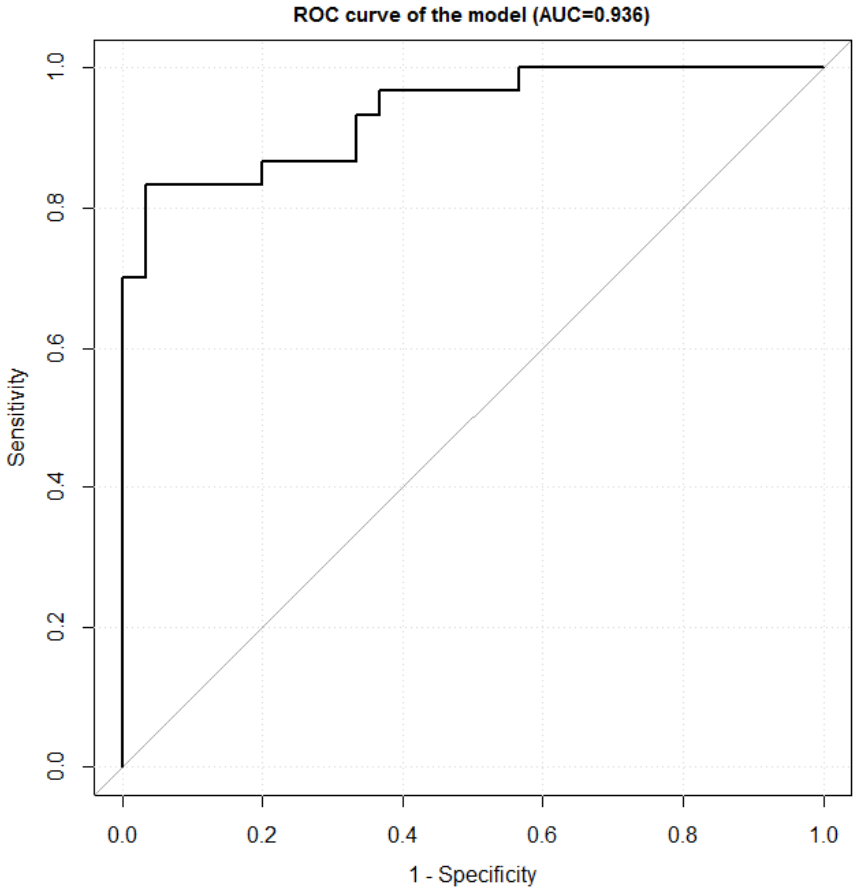
The AUC (area under curve) indicates the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one (assuming 'positive' ranks higher than 'negative')

For comparison: AUC of PSA for prostate cancer is 0.801
Of mammography for breast cancer 0.74 to 0.88 (depending on subject age)

How Effective is Eye Tracking as a Biomarker for Concussion?

Generate a ROC curve and calculate AUC:

Define “true positive” concussion as SSS>40 and **SAC<=27** (30 males met criteria)



Method	Variables	AUC	Cross-validated AUC	misclassification rate
Best subset	conj_boxscore_value, conj_varX_value, conj_varXtop_value, left_areamean_value, left_distTop_value, left_widthmean_value, right_widthmean_value	0.936	0.814	10%

Hennepin County Medical Center

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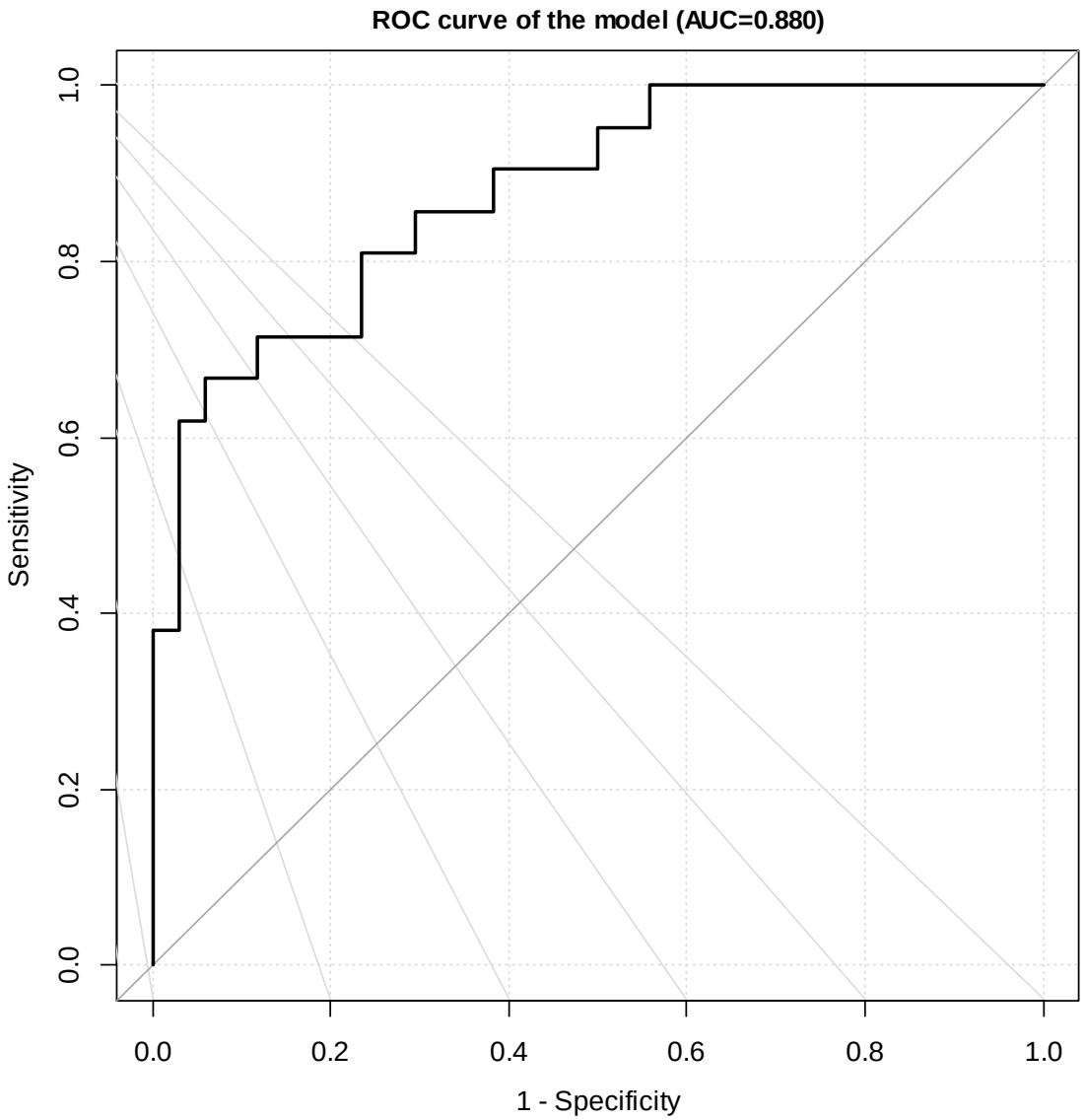
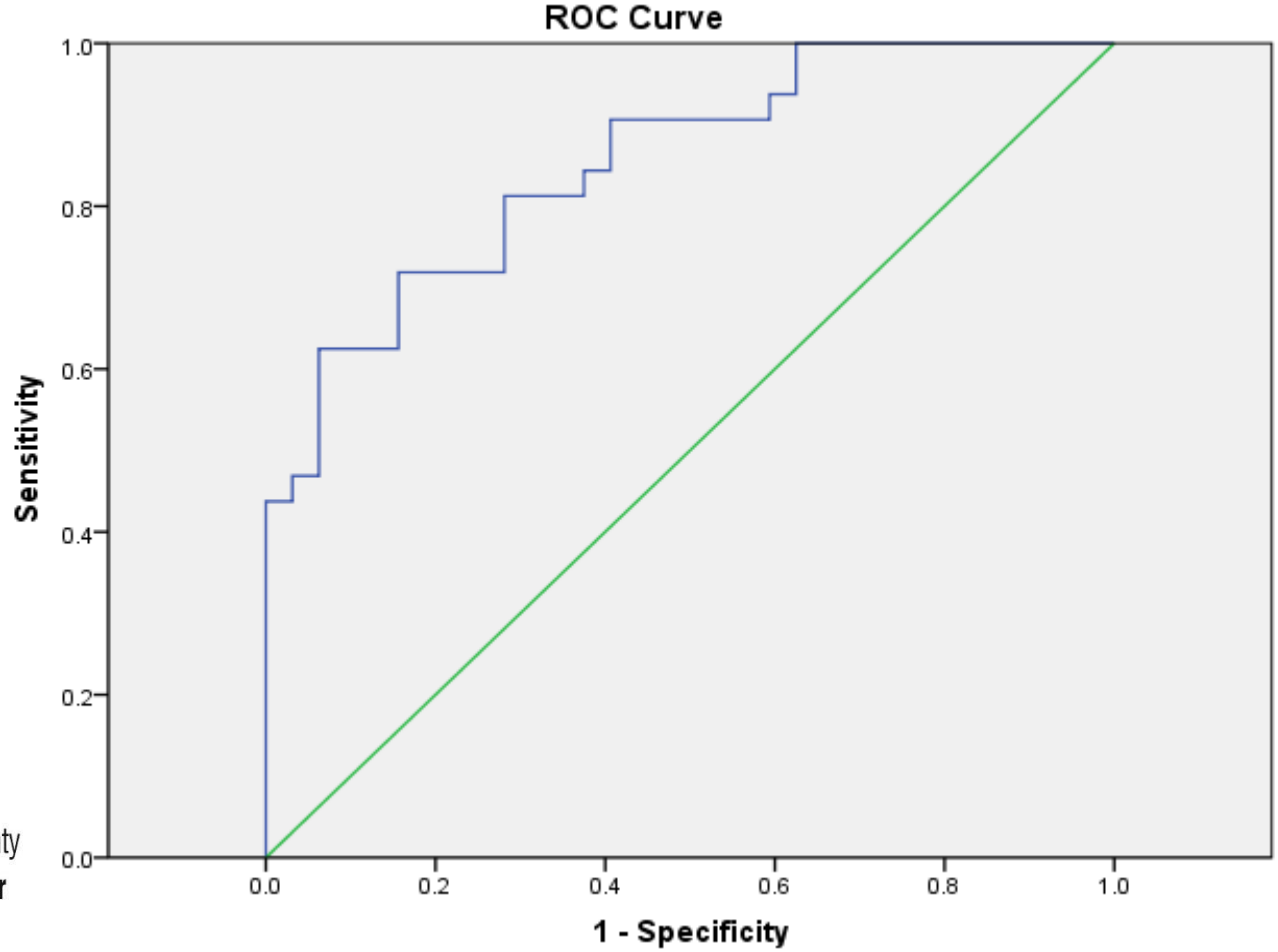


255 subjects (controls and concussions), in a non-balanced ED study

Receiver operating curve for eyetracking as a method of diagnosing concussion in the balanced sample of 64 pediatric subjects
a mean of 22 weeks post injury (range 1 to 109 weeks);
15 females, 17 males in each category. Mean of 13.4 years old.

The area under the curve was 0.854.



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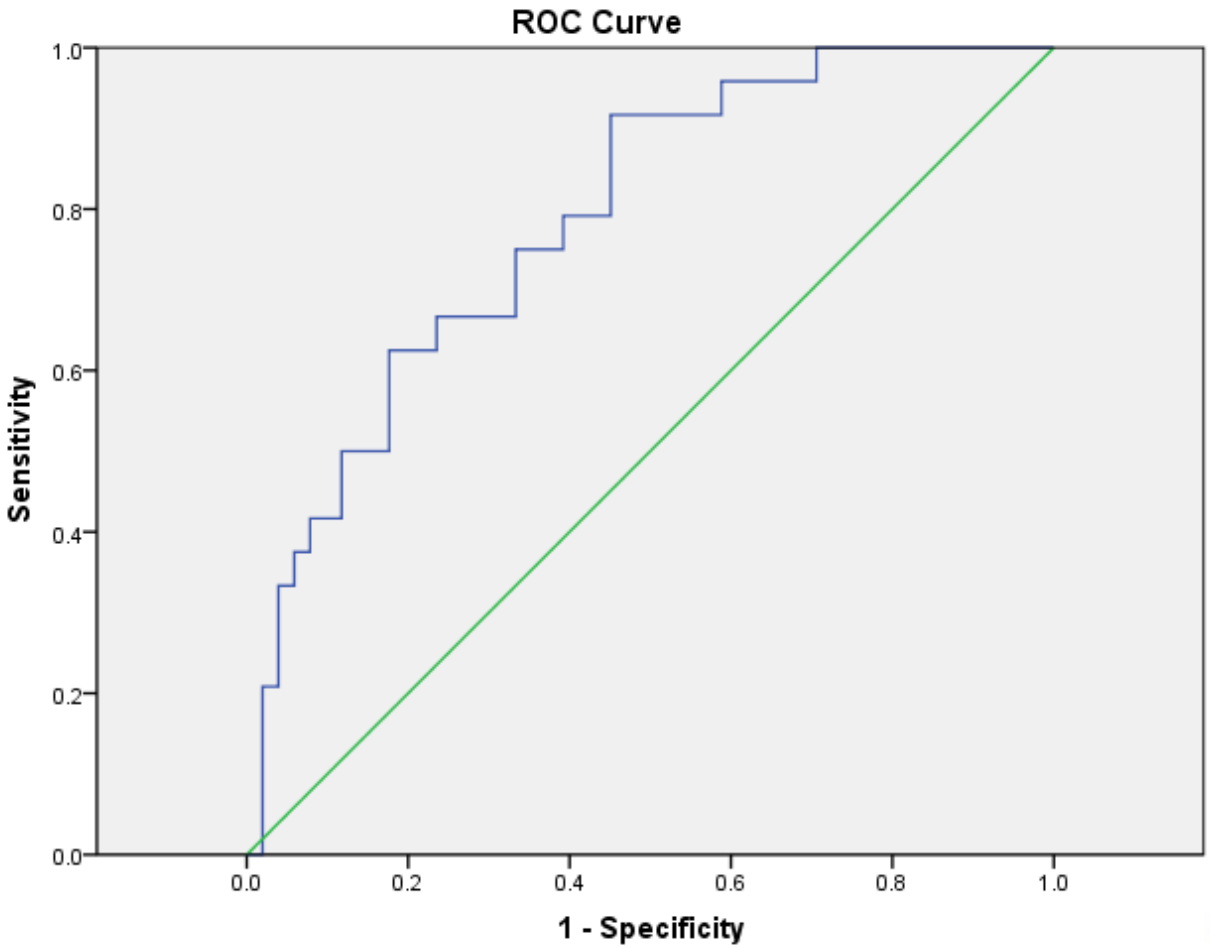
Receiver operating cure for eyetracking as a method of diagnosing concussion in a cross-validation sample of 75 subjects (24 cases mean 14.7 years, 51 controls mean 18.3 years)

The area under the curve was 0.789.



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Vergence Dysfunction
(in patients with concussion)

Velocity of eye movement in the right eye alone and comparing right to left eyes, across bottom of box

OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

Ophthalmic & Physiological Optics ISSN 0275-5408

REVIEW

Vergence dysfunction in mild traumatic brain injury (mTBI): a review

Preethi Thiagarajan, Kenneth J Ciuffreda and Diana P Ludlam

SUNY State College of Optometry, Department of Vision Sciences, New York, USA

Citation information: Thiagarajan P, Ciuffreda KJ & Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. *Ophthalmic Physiol Opt* 2011, **31**, 456–468. doi: 10.1111/j.1475-1313.2011.00831.x

Keywords: accommodation, acquired brain injury, eye movements, oculomotor rehabilitation, traumatic brain injury, vergence, vergence dysfunction, vision rehabilitation, vision therapy, visual system plasticity

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Received: 5 November 2010; Accepted: 31 January 2011

Abstract

Vergence eye movements are used to track objects that move in depth in one's binocular visual field to attain and maintain a fused and single percept. The mechanism and control of vergence eye movements involves complex neurological processes that may be compromised in individuals with traumatic brain injury, thus frequently resulting in a wide range of vergence dysfunctions and related near-work symptoms, such as oculomotor-based reading problems. This paper presents a review of the vergence system and its anomalies in mild traumatic brain injury, as well as their diagnostic and therapeutic clinical ramifications. Implications related to brain imaging and human neuroplasticity are also considered.

Table 1. Summary of data from the retrospective studies showing frequency of occurrence (%) of the different types of oculomotor dysfunctions

	Ciuffreda *et al.*[5]	Goodrich *et al.*[28]		Lew *et al.*[29]	Stelmack *et al.*[30]	Brahm *et al.*[31]	
Sample size (*n*)	160	Non-blast 25	Blast 21	62	88	Non-blast 12	Blast 112
Percent of war fighters	0	100	100	94	88	100	100
Reading problem	75 (est)	60	62	70	50	83.3	87.5
Vergence	56	36	24	46	28	63.6	46.8
Version	51	32	5	25	6	16.7	24.1
Accommodation	41	20	24	21	47	71.4	45.7
Strabismus	26	50 (est)	30 (est)	11	8	8.3	7.1
CN palsy	7	50 (est)	30 (est)	Not listed	0	–	–
Nystagmus	0.6	4	0	5	Not listed	0	7.1
General oculomotor dysfunction	90	At least 50 (est)	At least 50 (est)	70	50 (est)	40 (est)	40 (est)

est, estimate; –, data not available. Actual percentages are rounded off for simplicity. Nystagmus - includes unidentified fixation instability.

Research

Original Investigation

Association of Football Subconcussive Head Impacts With Ocular Near Point of Convergence

Keisuke Kawata, MS; Leah H. Rubin, PhD, MPH; Jong Hyun Lee; Thomas Sim; Masahiro Takahagi, MEd; Victor Szwanki, MS; Al Bellamy, MS; Kurosh Darvish, PhD; Soroush Assari, BS, MS; Jeffrey D. Henderer, MD; Ryan Tierney, PhD; Dianne Langford, PhD

IMPORTANCE An increased understanding of the relationship between subconcussive head impacts and near point of convergence (NPC) ocular-motor function may be useful in delineating traumatic brain injury.

OBJECTIVE To investigate whether repetitive subconcussive head impacts during preseason football practice cause changes in NPC.

Invited Commentary page 770

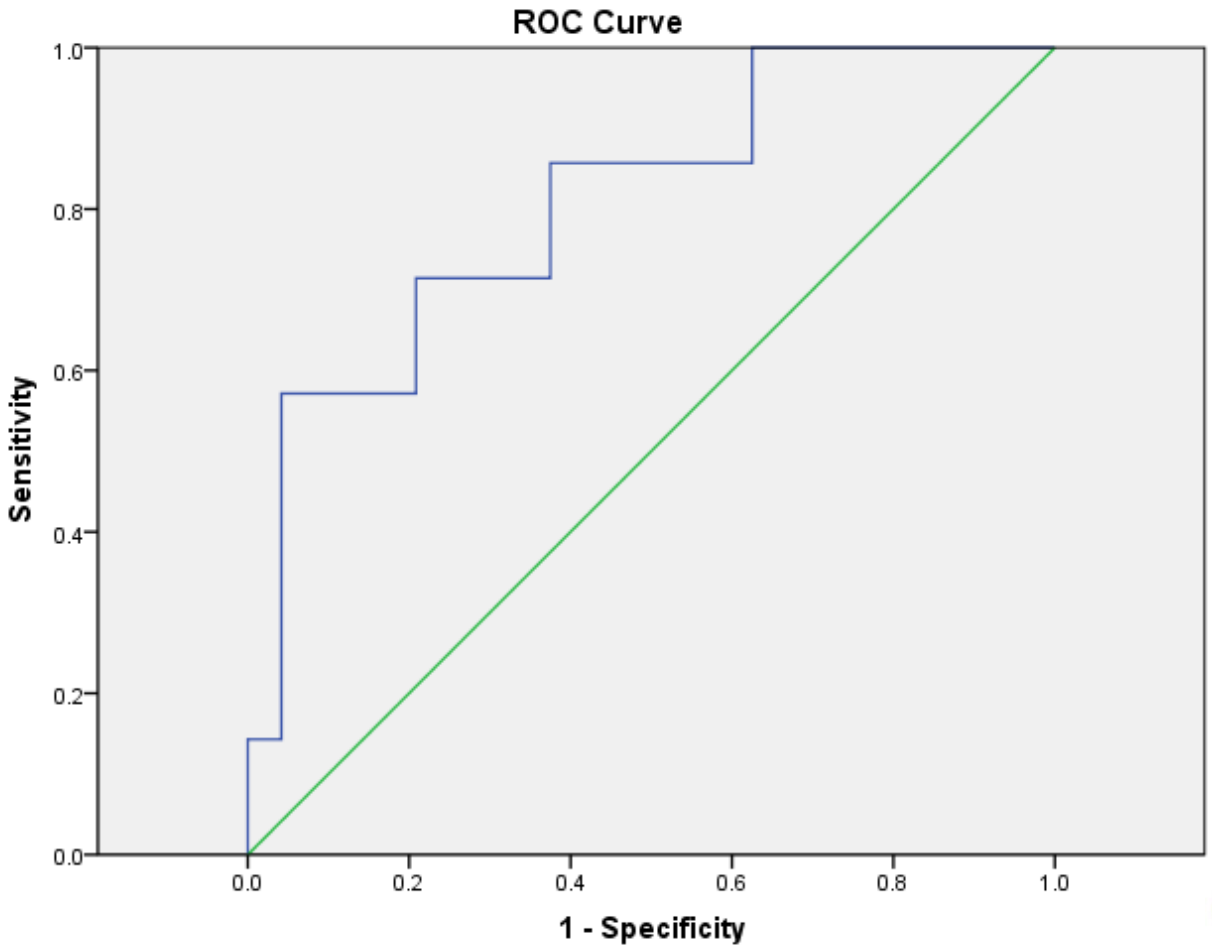
Supplemental content at jamaophthalmology.com

29 football players studied

Among 22 subjects with more hits (measured by accelerometer) there was disordered NPC compared to 7 subjects with fewer hits

Receiver operating cure for eyetracking as it correlates to abnormality in near point of convergence (as defined by NPC > 6 cm) in 32 concussed pediatric subjects.

The area under the curve was 0.81.



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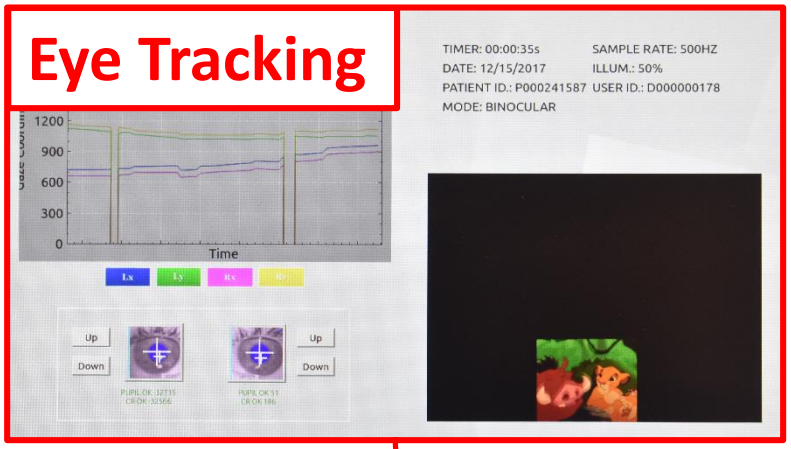
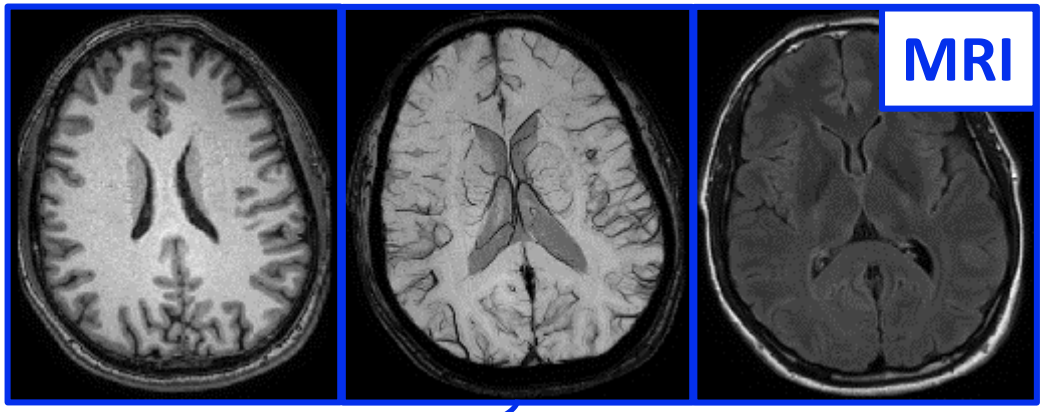
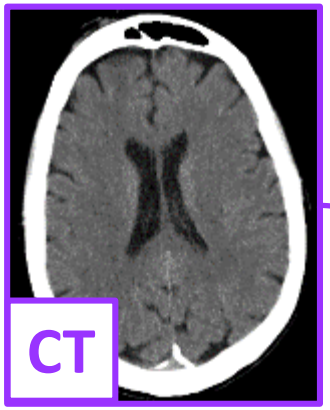
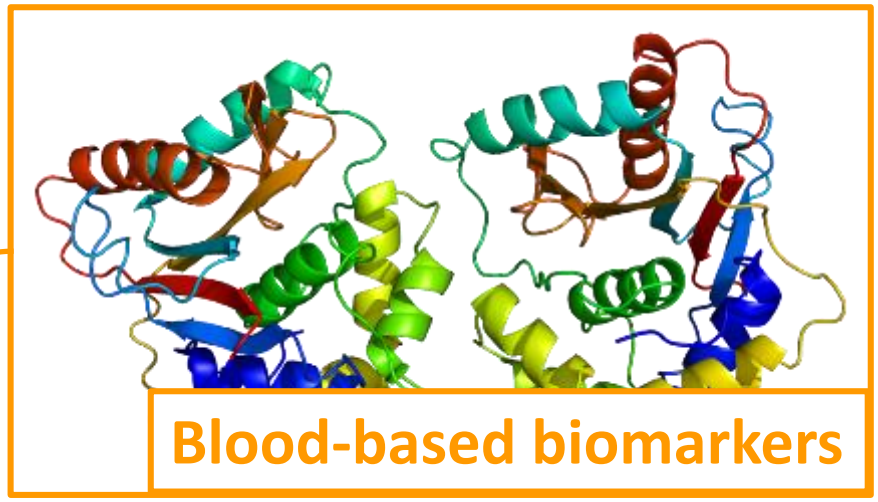
Hierarchical Approach to Classification







Algorithm



Molecule: https://commons.wikimedia.org/wiki/File:Protein_UCHL1_PDB_2etl.png

- Conventional approach

= Pathophysiology / understanding based

Pathophysiology in stats

= Stochastic (some variables + some random error = Outcome)

= an understandable equation

- Testing:
  - P-value
  - R-squared
  - Other goodness of fit metrics

- Machine learning

= Observation based / we usually don't understand model fully

Machine comes up with complex explanation of data

= very complex equation

= Humans don't get to understand fully

- Testing
  - Accuracy on an independent dataset

- Conventional approach

- Examples
  - Regular papers in medicine
  - Associating factors with poor or good outcome based on p-value

- Everyday example
  - Using American College of Surgeons surgical risk calculator

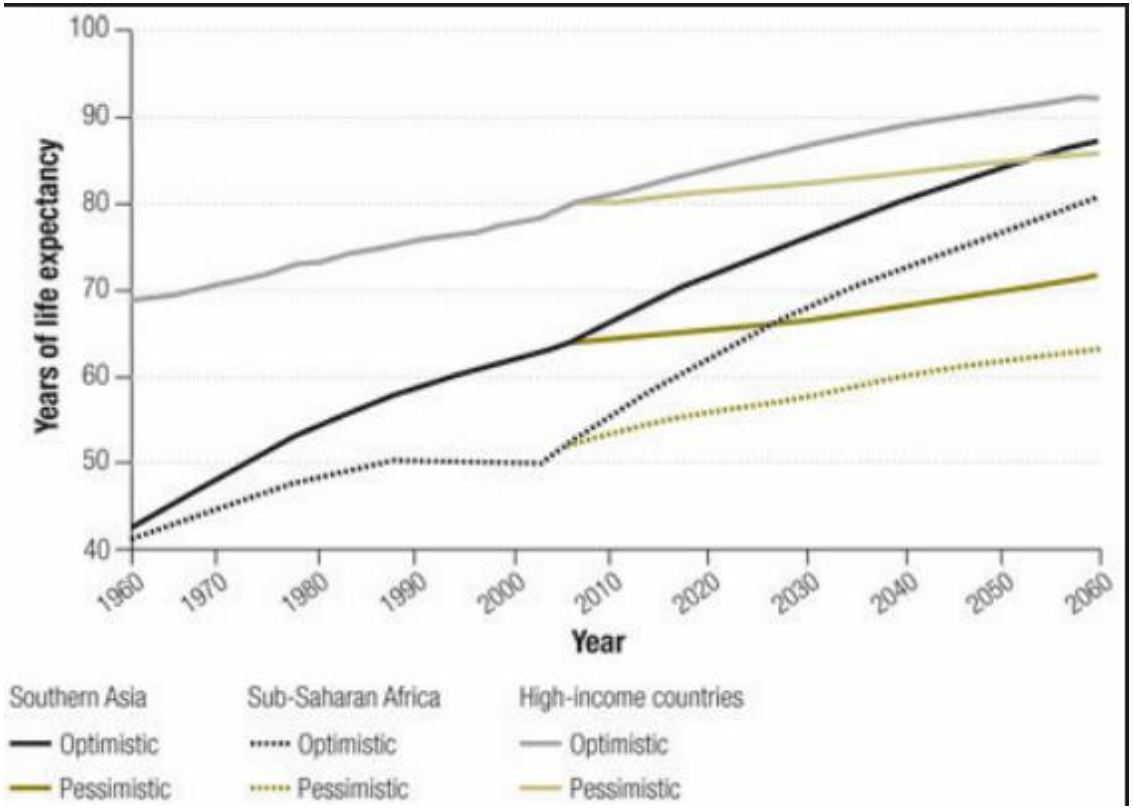
- Machine learning

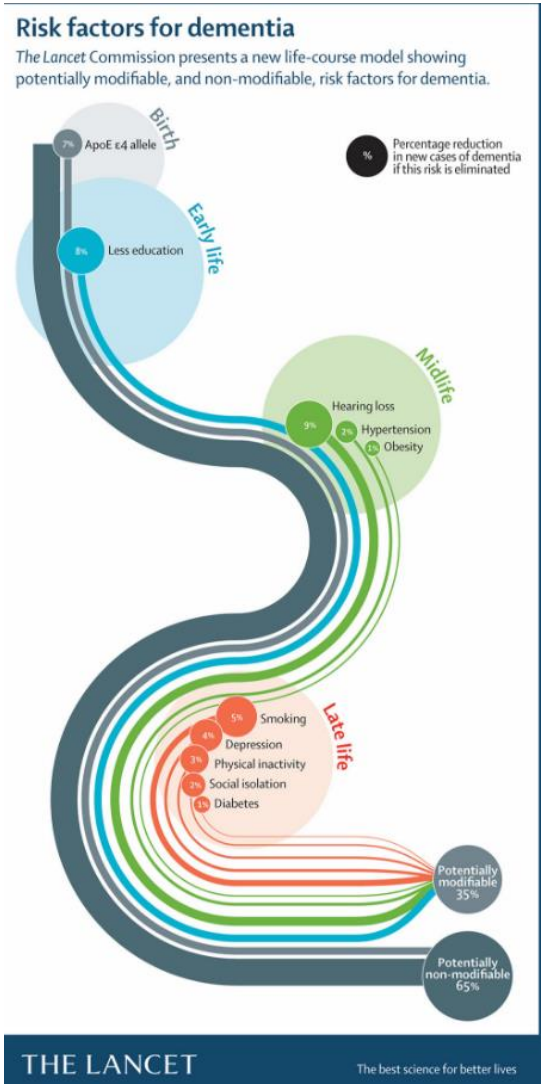
Automated car driving
Image analysis
Face recognition
Voice recognition
Multiple other complex forms of data …

Everyday example (in 2025)

A calculator in Epic that analyzes 100s of patient factors (including e.g. # of missed appointments) to give you a score. You don’t know exactly what!

Big data will be needed to solve
the big problems





Certain common medications tied to 30% higher dementia risk, study finds

By Mark Lieber, CNN

Updated 6:31 PM ET, Wed April 25, 2018

More from CNN


Dwayne Johnson is now a doting dad of three girls


Turkish court sentences journalists to years in prison for...

41,000 patients
284,000 controls

Those who took anticholinergics used for depression (e.g. amitriptyline), urinary incontinence (e.g. oxybutynin) and Parkinson's disease (e.g. procyclidine) had a 30% increased risk of developing dementia

Anticholinergic drugs and risk of dementia: case-control study

Kathryn Richardson,[1] Chris Fox,[2] Ian Maidment,[3] Nicholas Steel,[2] Yoon K Loke,[2] Antony Arthur,[1] Phyo K Myint,[4] Carlota M Grossi,[1] Katharina Mattishent,[2] Kathleen Bennett,[5] Noll L Campbell,[6] Malaz Boustani,[7] Louise Robinson,[8] Carol Brayne,[9] Fiona E Matthews,[10] George M Savva[1]

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[2]Norwich Medical School, University of East Anglia, Norwich, UK
[3]School of Life and Health Sciences, Aston University, Birmingham, UK
[4]School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK
[5]Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland
[6]Department of Pharmacy Practice, College of Pharmacy, Purdue University, West Lafayette, IN, USA
[7]School of Medicine, Indiana University, Indianapolis, IN, USA
[8]Institute for Ageing, Newcastle University, Newcastle upon Tyne, UK
[9]Cambridge Institute of Public Health, University of Cambridge, Cambridge, UK
[10]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

Correspondence to:
K Richardson
k.richardson@uea.ac.uk

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVES
To estimate the association between the duration and level of exposure to different classes of anticholinergic drugs and subsequent incident dementia.

DESIGN
Case-control study.

SETTING
General practices in the UK contributing to the Clinical Practice Research Datalink.

PARTICIPANTS
40 770 patients aged 65-99 with a diagnosis of dementia between April 2006 and July 2015, and 283 933 controls without dementia.

INTERVENTIONS
Daily defined doses of anticholinergic drugs coded using the Anticholinergic Cognitive Burden (ACB) scale, in total and grouped by subclass, prescribed 4-20 years before a diagnosis of dementia.

MAIN OUTCOME MEASURES
Odds ratios for incident dementia, adjusted for a range of demographic and health related covariates.

RESULTS
14 453 (35%) cases and 86 403 (30%) controls were prescribed at least one anticholinergic drug with an ACB score of 3 (definite anticholinergic activity) during the exposure period. The adjusted odds ratio for any anticholinergic drug with an ACB score of 3 was 1.11 (95% confidence interval 1.08 to 1.14). Dementia was associated with an increasing average ACB score. When

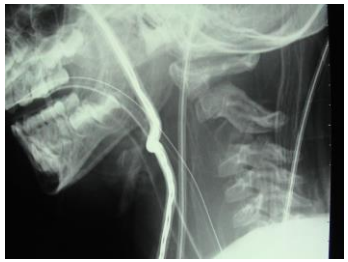
CONCLUSIONS
A robust association between some classes of anticholinergic drugs and future dementia incidence was observed. This could be caused by a class specific effect, or by drugs being used for very early symptoms of dementia. Future research should examine anticholinergic drug classes as opposed to anticholinergic effects intrinsically or summing scales for anticholinergic exposure.

TRIAL REGISTRATION
Registered to the European Union electronic Register of Post-Authorisation Studies EUPAS8705.

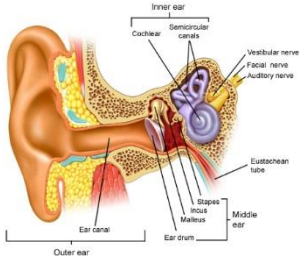
Introduction

Dementia is a leading cause of disability and death,[1] and its prevention is a global public health priority. Dementia is caused by a number of different neurodegenerative processes that contribute to irreversible cognitive decline and associated symptoms, such as the progressive loss of independence and daily functioning. Mixed dementias are more prevalent than is often recognised, with symptoms often more closely linked to overall pathological burden as opposed to any specific disease process.[2 3] No disease modifying treatments for dementia exist, however, age specific dementia incidence across populations is declining, suggesting that changing lifestyles or environment may lead to a meaningful change in the prevalence of dementia.[4] Hence identifying and reducing the exposure to risk factors that can affect any aspect of long term brain health is important for dementia

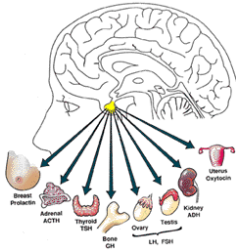
What does this mean for acute and chronic effects of neurotrauma?



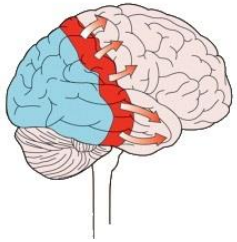
Spinal Cord Injury = Paralysis



Inner Ear Injury - Dizziness



Endocrine Dysfunction=
Depression, Suicidality



Cortical Spreading Depression=
Headache, Seizures, Stroke

Scalp Injury

Skull Injury

Compressive Lesions
Epidural / Subdural

Subarachnoid
Hemorrhage/IVH

Diffuse Axonal Injury=CTE

Anoxic Brain Injury=
Permanent Neuro Deficit

Prognosis
Best

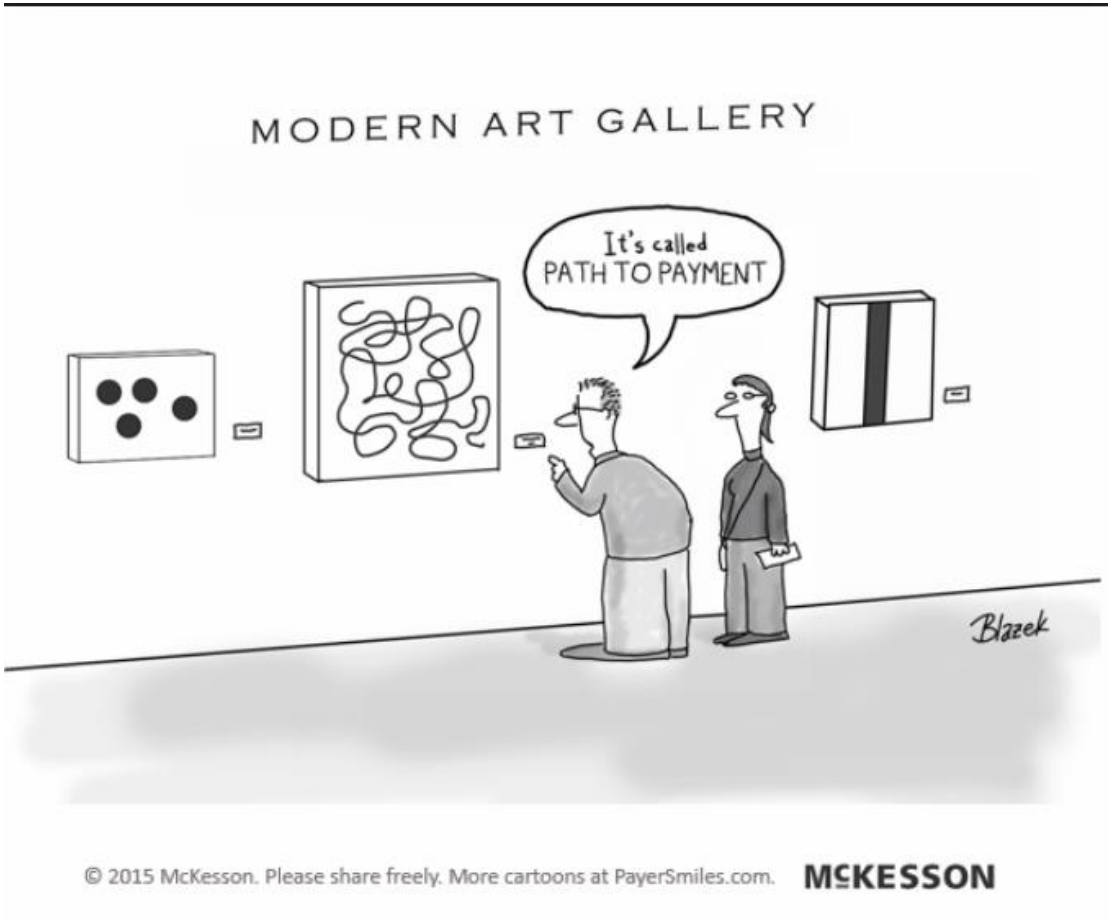
Worst

https://www.newscientist.com/article/dn28571-dr-google-will-see-you-now/

LIVING HEALTH 30 November 2015

Dr Google will see you now

Will Big Data End Reimbursement Woes?



Disruption in the Administration of HealthCare

Home › Thought Leadership › DRG Blog › Titans of Business Unite to Take on...

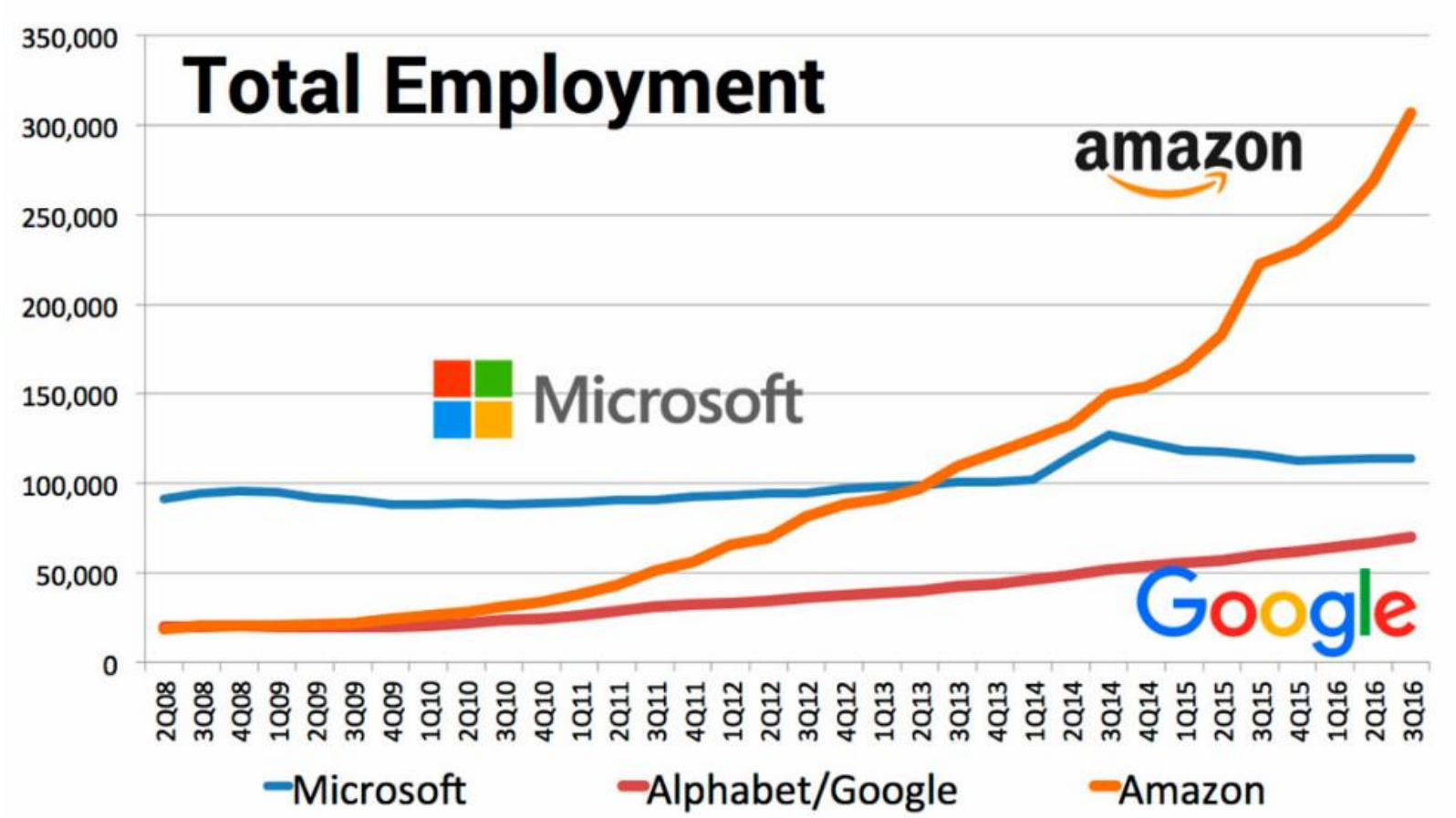
Titans of Business Unite to Take on Healthcare

Amazon, Berkshire Hathaway, and JPMorgan Chase Collaboration Points to Disruption in Healthcare Industry

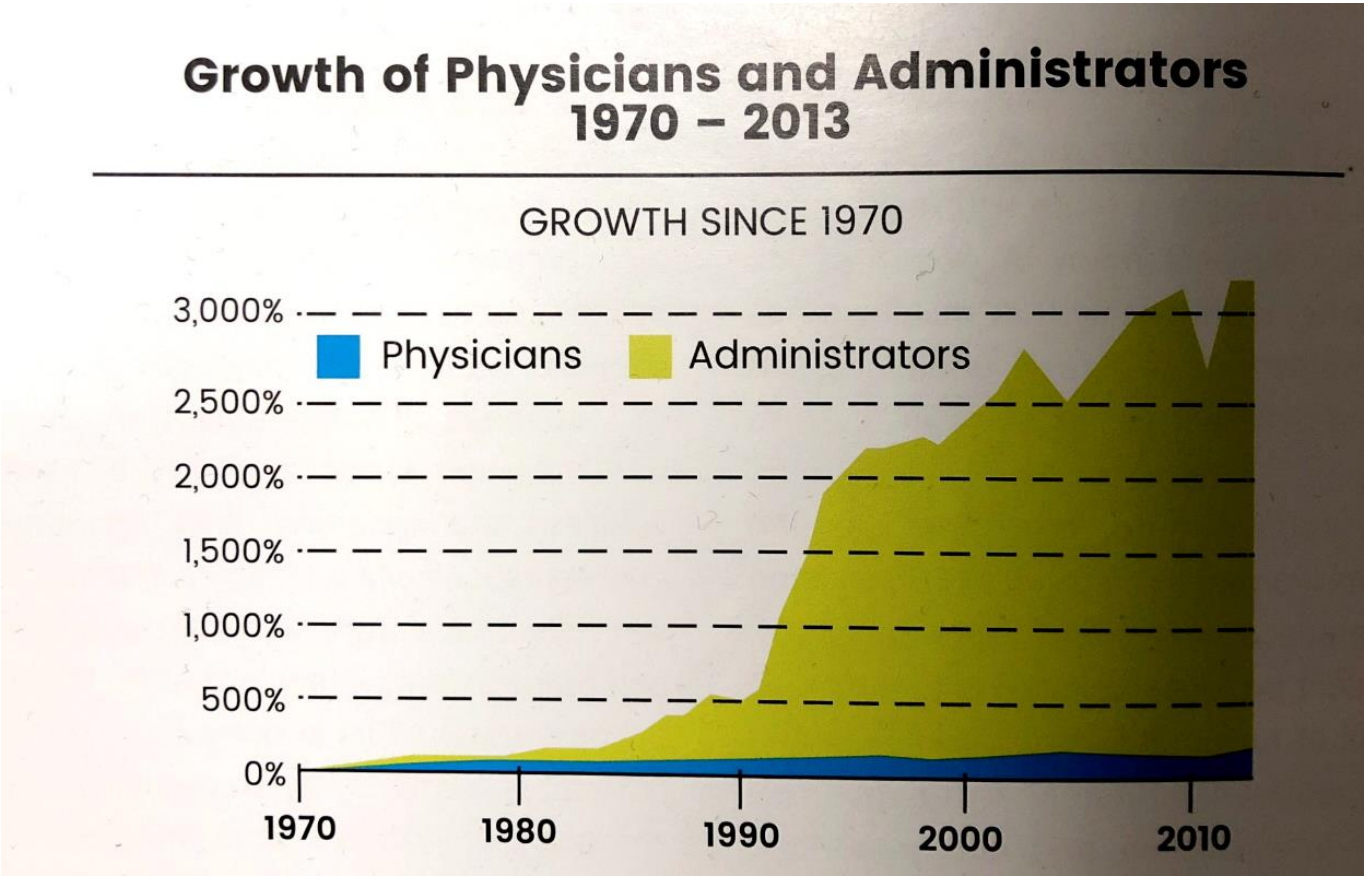
It's the business equivalent of a superhero movie when Warren Buffett (The Oracle of Omaha), Jeff Bezos (Amazon), and Jamie Dimon (JPMorgan Chase) unite to form a new healthcare

'the independent company would be "free from profit-making incentives and constraints."'

Axios.com


Total Employment
amazon
Microsoft
Google
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
2Q08
3Q08
4Q08
1Q09
2Q09
3Q09
4Q09
1Q10
2Q10
3Q10
4Q10
1Q11
2Q11
3Q11
4Q11
1Q12
2Q12
3Q12
4Q12
1Q13
2Q13
3Q13
4Q13
1Q14
2Q14
3Q14
4Q14
1Q15
2Q15
3Q15
4Q15
1Q16
2Q16
3Q16
Microsoft
Alphabet/Google
Amazon

The End of the FDA/Hospital/Clinic System/Insurance/CMS As We Know It!



We will have a trial that succeeds when

"He can go back in the game. It's just a bruise."

-we can classify the injury appropriately using objective assessors

-we have sensitive outcome measures

Hennepin County Medical Center

Hennepin County Medical Center

That's All Folks!

Wile E. Coyote created 1948-1963
(note anisocoric and disconjugate gaze)