Rapture of the deep / Inertgasnarcosis (IGN)

- *new insights and questions* -

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COLUMBIA UNIVERSITY

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My disclosures…

History…

Einer der ersten Berichte über die Inertgasnarkose (IGN) wurde von Colladon, einem französischen Arzt, verfasst. Dieser tauchte 1826 mit einer Taucherglocke auf 20 m hinab und beschrieb „...einen Zustand der Aufregung als ob ich etwas Alkoholisches getrunken hätte...“ (Unsworth 1966).

Junod (1835) beobachtete „Hirnaktivitätssteigerung, lebhaftes Vorstellungsvermögen und Symptome einer Vergiftungserscheinung“.

Später berichtete Green (1861) über „Schläfrigkeit, Halluzinationen und beeinträchtigtes Urteilsvermögen“.

Das Auftreten von gefährlichen Symptomen wie Euphorie, Vergiftungserscheinungen und Narkose wurde auch bei vielen Tunnelarbeitern und Tauchern beschrieben, die einer komprimierten Luft von mehr als 4 bar (30 m) ausgesetzt waren (Hill & McLeod 1903, Hill & Greenwood 1906).

Im 20. Jahrhundert gab es eine Anzahl von Berichten über gesunde Taucher, die sich „mental oder emotional abnormal“ verhielten, wenn sie tiefer als etwa 30 m tauchten. Diese Symptome wurden jedoch oft fälschlicherweise mit Verunreinigungen ihrer Atemgase erklärt oder einem erhöhten pCO_2 oder pO_2 zugeschrieben (Levett 2008).

Im Laufe der Zeit wurden diese Anzeichen und Symptome von vielen Forschern beobachtet und schließlich 1935 von Behnke et al auf das narkotische Potential von Stickstoff zurückgeführt. Behnke untersuchte die mentalen Veränderungen von Tauchern auf verschiedenen Tauchtiefen und stellte dabei euphorische Stimmungsänderungen und eine Beeinträchtigung der mentalen Funktionen sowie der neuromuskulären Koordination ab einer Tiefe von 20 m fest. Mit zunehmender Tauchtiefe intensivierten sich die Symptome bis schließlich auf etwa 90 m Tiefe narkotische Bewusstseinsstörungen auftraten.

Hartig F, Köhler A., Tauchmedizin 2019, GF. Verlag

Table 1 Signs and symptoms of nitrogen narcosis at different depths [2,29]

Depth (msw)	Atmospheric pressure (atm)	*p*N2 (atm)	Signs and symptoms of narcosis
0–10	1–2	0.79–1.58	Unnoticeable/minor symptoms such as subtle changes in behaviour
10–30	2–4	1.58–3.16	Mild impairment of unpractised tasks
			Impaired reasoning
30–50	4–6	3.16–4.74	Delayed response to visual and auditory stimuli
			Calculation errors and poor choices
			Mild amnesia
			Overconfidence, idea fixation and a sense of well-being
			Laughter (chambers) or anxiety (cold water)
50–70	6–8	4.74–6.32	Impaired judgement and confusion
			Hallucinations
			Delay in response to signals, instructions and other stimuli
			Uncontrolled laughter, hysteria (in chamber)
			Feelings of terror (in some)
70–90	8–10	6.32–7.90	Mental confusion
			Loss of memory
			Stupefaction and loss of judgement
90+	10+	7.90+	Hallucinations, increased intensity of vision and hearing
			Unconsciousness
			Death

Clarke JE, 2015 Extreme Physiology & Medicine

Tabelle 1. Anzeichen und Symptome einer Stickstoffnarkose auf verschiedenen Tiefen mit Druckluft

Tauchtiefe	pN_2 (bar)	Narkoseschwelle	Anzeichen und Symptome
0 – 10 m	0,8 - 1,6		Keine oder geringe Anzeichen wie subtile Verhaltensänderungen
10 – 30 m	1,6 - 3,2		Milde Beeinträchtigung ungewohnter Tätigkeiten
30 – 50 m	3,2 - 4,7	25% (3 bar)	Verzögerte Reaktionen auf visuelle und auditive Stimuli, Rechenfehler und Fehlentscheidungen, milde Amnesie, übermäßiges Selbstvertrauen, Euphorie oder Beklemmung/Ängstlichkeit
50 – 70 m	4,7 - 6,3		Konfusion und beeinträchtigtes Urteilsvermögen, Halluzinationen, verzögerte Reaktionen auf Anweisungen, Signale oder Stimuli, unkontrolliertes Gelächter (Druckkammer) und Hysterie, Todesangst
70 – 90 m	6,3 - 7,9	75% (8 bar)	Geistesverwirrung, Gedächnisverlust, Betäubung und Verlust des Urteilsvermögens
> 100 m	> 8,7	100% (12 bar)	Bewusstlosigkeit, Reflexverlust, Tod

Achtung: die Symptomassoziation mit den Tiefenangaben sind nur allgemeine Werte und können im Einzelfall erheblich abweichen.

Hartig, Köhler 2018

NITROGEN NARCOSIS IN MAN
Temporo - spatial disorientation
Memory troubles
Euphoria
Hallucinations
Mood changes
Impaired neuromuscular coordination
Psychomotor and intellectual decrements

Table 1. Signs and symptoms of nitrogen narcosis in man from 0.3MPA (3 bars, 4 ATA).

Contributing factors

sein kann. Darüber hinaus beeinflussen und verstärken folgende Faktoren eine IGN:

- Alkohol, Drogen, Medikamente
- Müdigkeit, Schlafmangel,
- Anstrengung,
- Stress, Angst und Beklemmung,
- Kälte
- Dunkelheit, schlechte Sicht
- sowie jeglicher Anstieg von exogenem oder endogenem Kohlenstoffdioxid.

Vor allem Alkohol, Drogen oder Medikamente beeinflussen das Auftreten und die Symptomatik einer IGN sehr stark. Medikamente oder Drogen wie Scopolamin oder Methamphetamine verstärken die Symptomatik der IGN (Bennett 1962-1972). Besonders Scopolamin ist problematisch, da dieses Medikament gerne von Tauchern gegen die Seekrankheit eingenommen wird. Scopolamin wirkt bei niedriger Dosierung leicht beruhigend und hemmend auf das Brechzentrum im Gehirn.

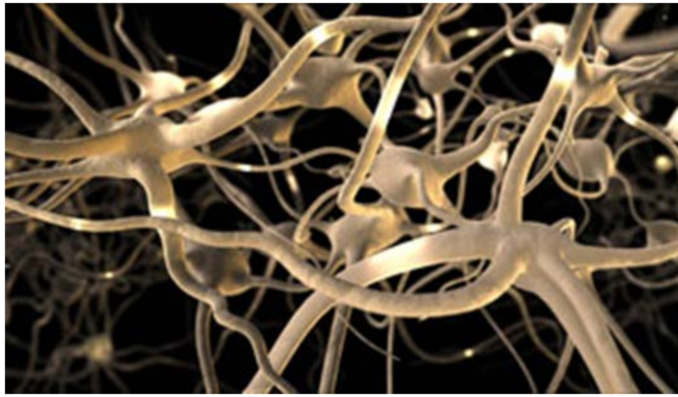
Hartig F, Köhler A., Tauchmedizin 2019, Feuchter Verlag

2 ½ big hypotheses

Appendix
Summary table of the major hypotheses as to the mechanism(s) of gas anaesthesia and inert gas narcosis

	Hypothesis	Mechanism of anaesthesia	Evidence
	Physical models		
1	Critical volume	Physical expansion of plasma membrane	Increasing partial pressures of anaesthetic gases increase the volume of various lipids.[13] Gas anaesthesia can be reversed by hydrostatic pressure.[12,14]
	Multi-site expansion	Physical expansion of discrete sites in the plasma membrane	Slope of anaesthetic potency vs. pressure found to be non-linear and different for various agents.[16,17]
	Changes in ion permeabilities	Anaesthetic agents alter plasma membrane permeabilities to various ions	Application of inert and anaesthetic gases alters ion content on either side of various lipid membranes.[19–23]
	Modified multi-site expansion	Anaesthetic gases and pressure have separate actions at separate membrane sites	All light anaesthetic gases interact with the membrane at a common hydrophobic site.[24] Narcosis and HPNS can coexist in the same individual at the same time.[24]
	Biochemical models		
	Altered synaptic conduction	Changes in neurotransmitter release at CNS synapses affect consciousness	Hyperbaric exposure and breathing gas mix alter the release of various CNS neurotransmitters.[25–28]
2	Single-protein interactions	Anaesthesia results from the interaction of anaesthetic molecules with certain specific functional proteins	Various anaesthetics alter conduction through specific post-synaptic inotropic and metabotropic ion channels.[31–35]
	Multi-protein interactions	Anaesthesia results from the specific interaction of anaesthetic molecules with multiple functional proteins	Many anaesthetic gases have been found to bind selectively with multiple different target proteins.[42,43] Halothane binds in a competitive, saturable, stoichiometric manner to multiple proteins throughout the brain.[44] Protein tertiary structures contain small hydrophobic cavities with weak polarity. Occupation of these cavities by small molecules reduces protein motion.[45–47]

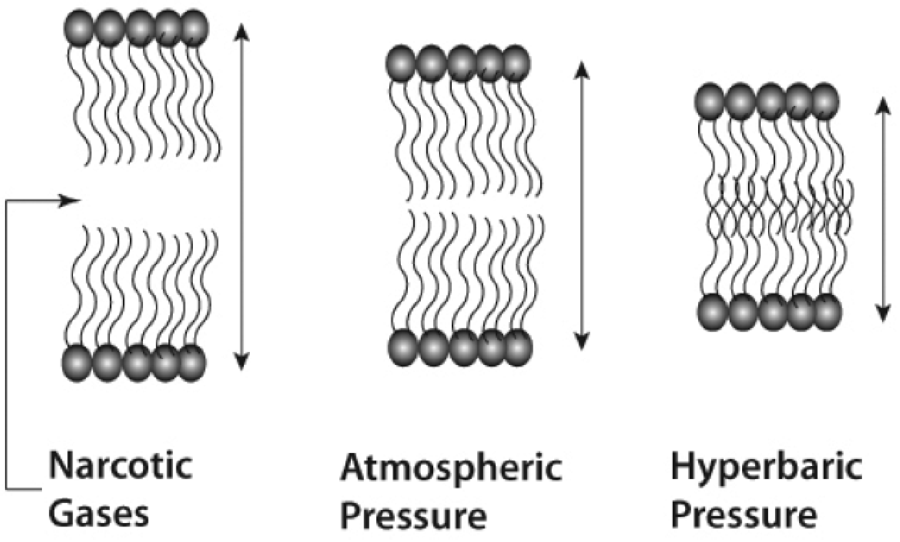
½ ?



C.Smith et al., 2010. DHM

Meyer Overton hypothesis = critical volume concepts = physical hypothesis

Figure 1
The critical volume hypothesis. Molecules of narcotic gases dissolve in the cell membrane and cause it to swell. When the membrane reaches a certain volume narcosis is produced. Pressure reverses this narcotic effect by compressing the membrane.



Meyer 1899, Overton 1901

C.Smith et al., 2010. DHM

Table 1
Narcotic potencies and physical properties of simple gases[4,6]

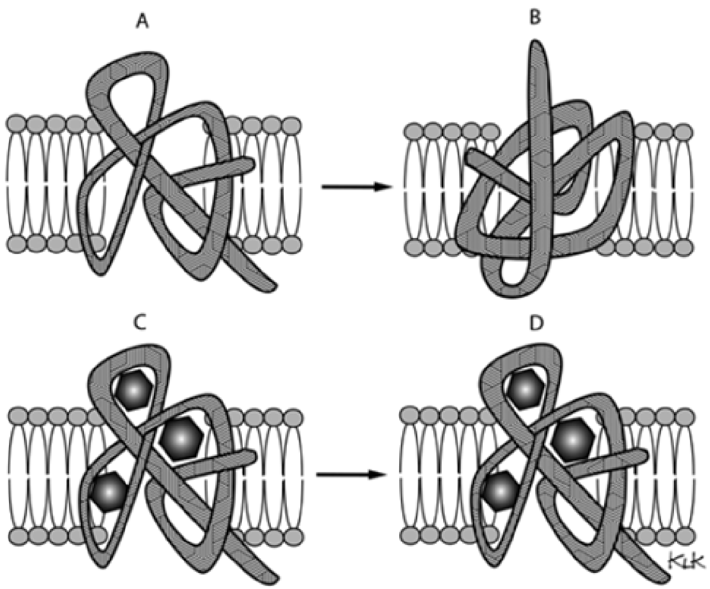
Gas	Molecular mass (g/mol)	Van der Waals radius (pm)	Anaesthetic pressure (Ata)	Oil:gas partition coefficient (at 37°C)	Relative narcotic potency
Helium	4	140	190.546	0.016	0.23
Neon	20	154	87.096	0.019	0.28
Hydrogen	2	120	138.038	0.05	0.55
Nitrogen	28	155	33.113	0.069	1.00
Argon	40	188	15.136	0.13	2.33
Krypton	83.7	202	4.467	0.4	7.14
Xenon	131.3	216	0.955	1.8	25.64

Some Trimixdivers are concerned about oxygen...

C.Smith et al., 2010. DHM

Biochemical 3D hypothesis = protein based concept

Figure 3
Anaesthetic gases may exert their effects through the occupation of small cavities in proteins.
A depicts a protein in its resting, inactive state. When activated (B), the protein undergoes a conformational change. C depicts a protein in its inactive state with molecules of an anaesthetic or narcotic gas occupying cavities within the tertiary structure of the protein. In D, the protein is unable to undergo conformational change, and thus remains inactive.

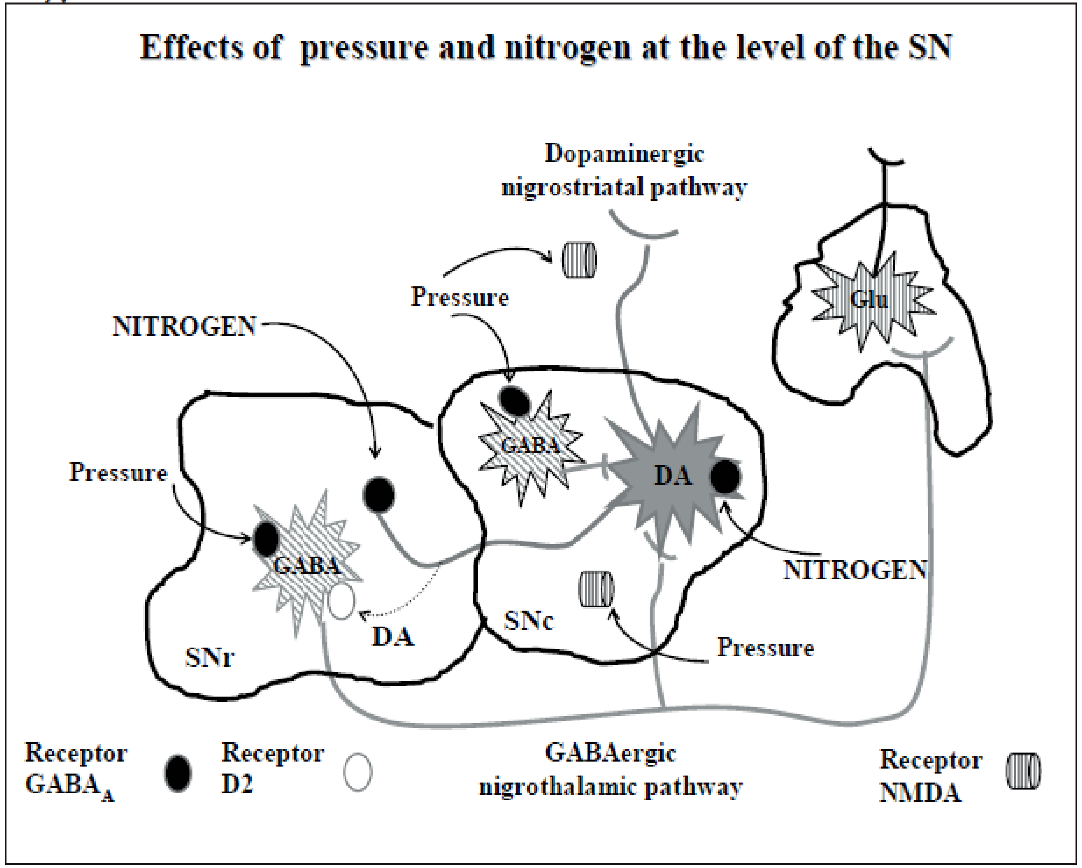


Eckenhoff 2001
Rostain 2016
Lavoute 2018, 2012
Nicoll 1982
Balon 2003
Bennett 1989
Brauer 1987

C.Smith et al., 2010. DHM

Inert gas + pressure …

Fig. 3



Rostain JC et al, UHM 2006

CFFF and dementia cards…

Balestra 2012
Hamilton 1995
Monteiro 1996
Hobbs 2008
Lafere 2016
Germonpre 2017
Hartig 2019 i.p.
Köhler 2019 i.p.
…

The trigger role of pO2?

Statistical bias?

Contributing factors?

The role of NBO

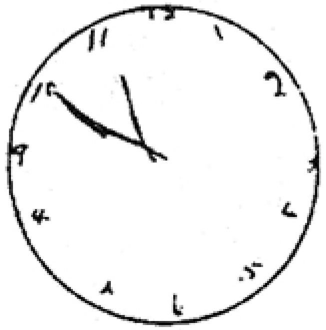
The role of psychocognitive stress?

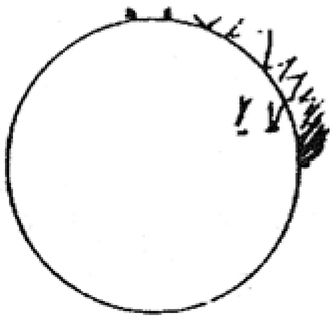
Concordant in AIR, discordant in TMX, unknown in Nitrox…

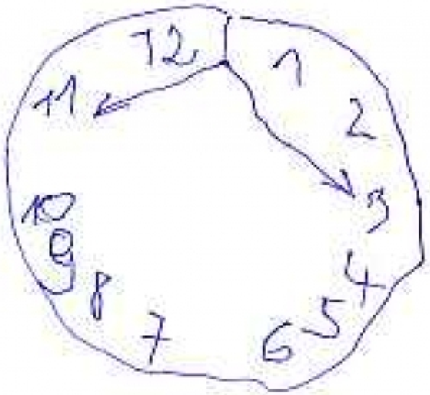
The clock drawing test

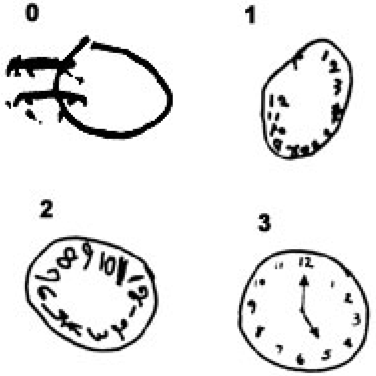
- IGN
- Hypoglycemia
- Carbon monoxide
- Dementia/Alzheimer
- DNS
- …

„half past one“



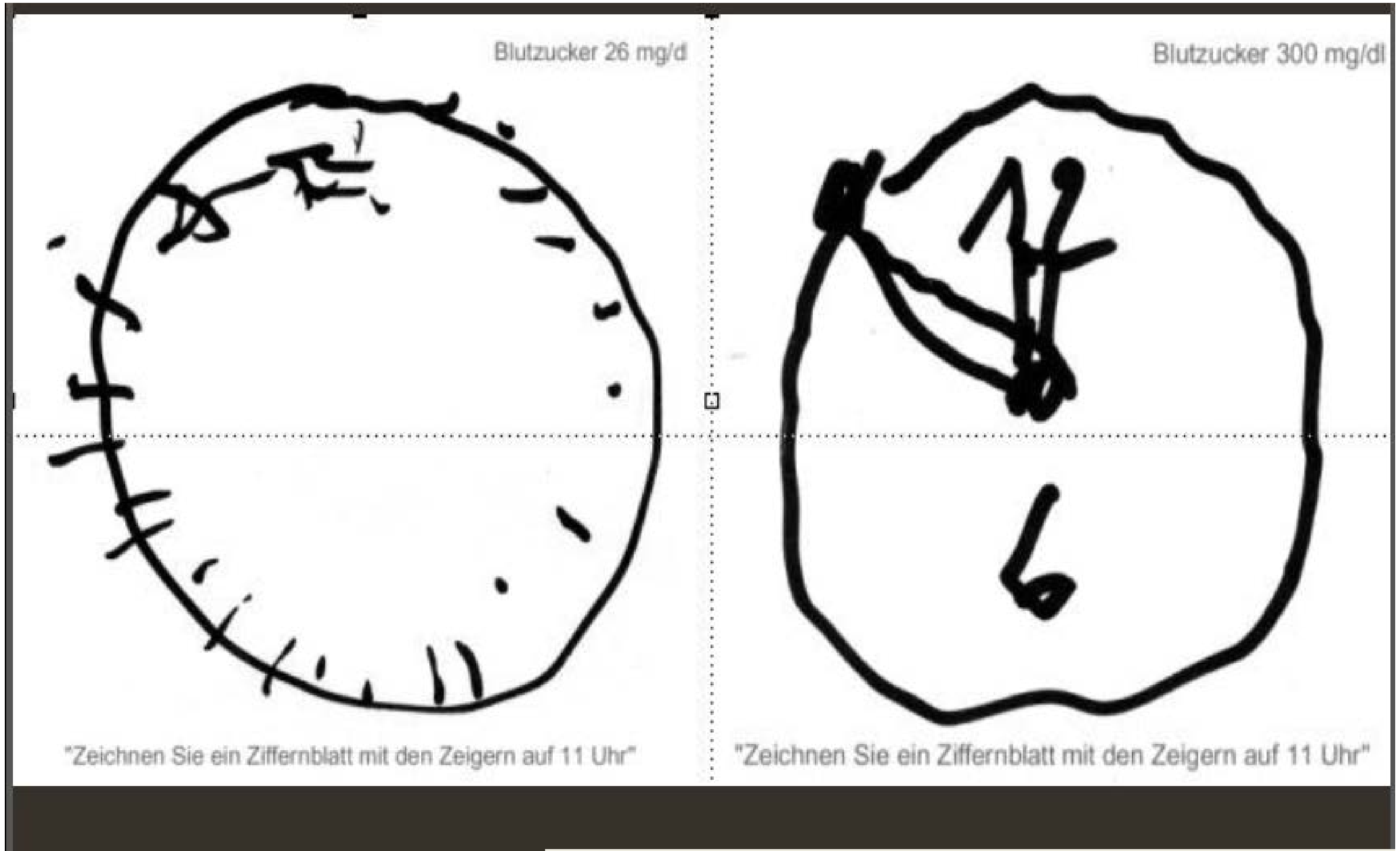






Hartig, Sojer et al, 2013

This might be your dive buddy …

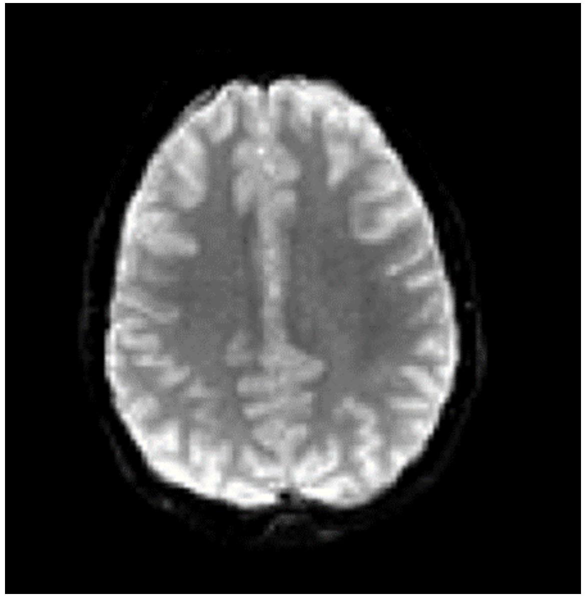


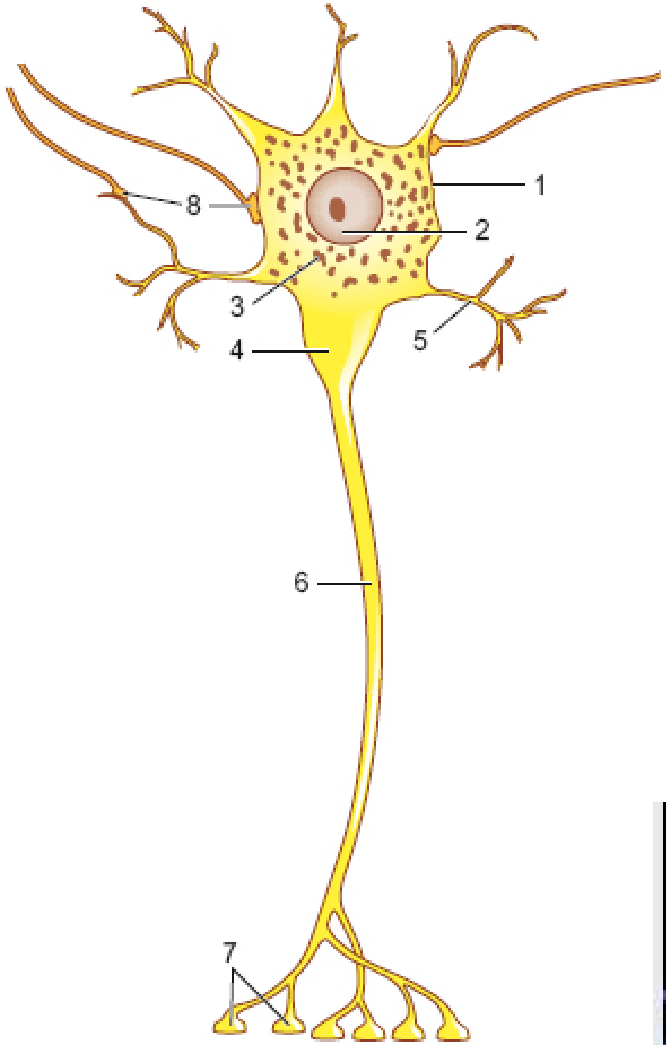
A Funny Patient, Sojer, Hartig, Pechlaner 2007 JRSM

Blockbuster BBB

- 600 km brainvessels
- >100 billions Neurones, >1000 billions gliacells
- At 6 locations fenestrated
- 98% of all substances can not pass BBB
- 3 different barrier versions
- Amazingly publish rate in the past years

- Missing link in hyperbaric conditions?
- 3bar rule…





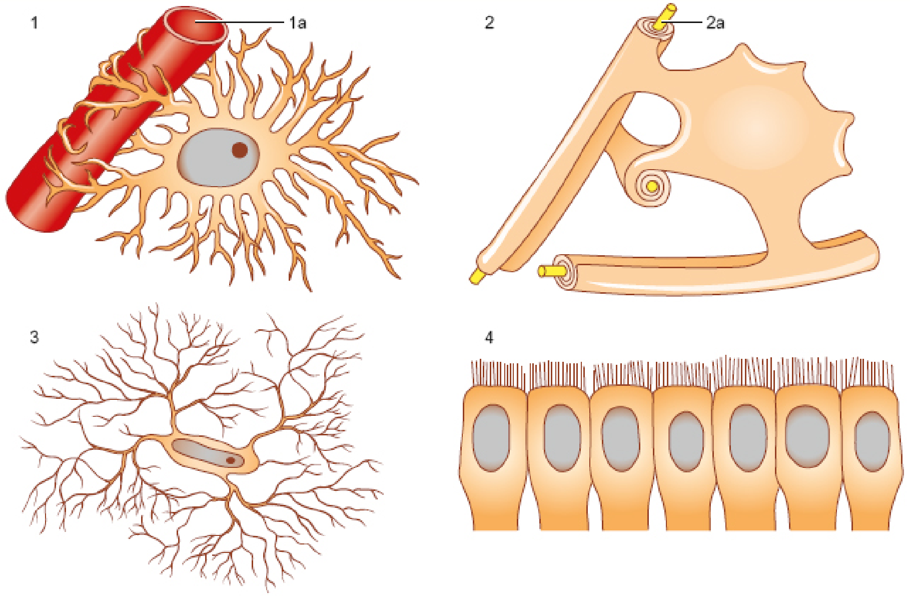
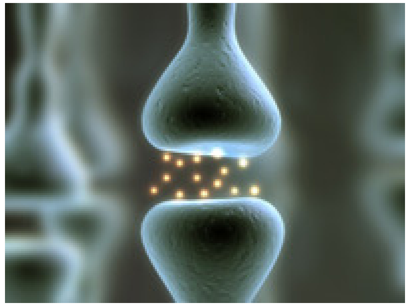
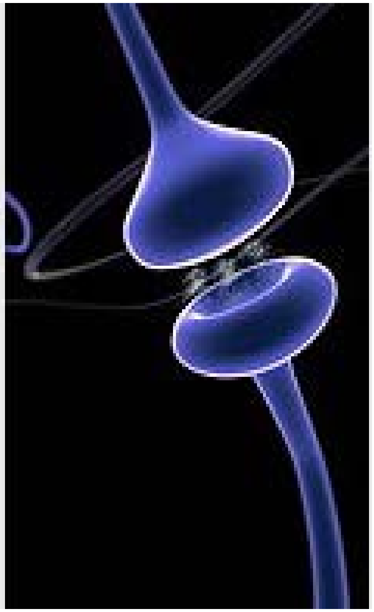
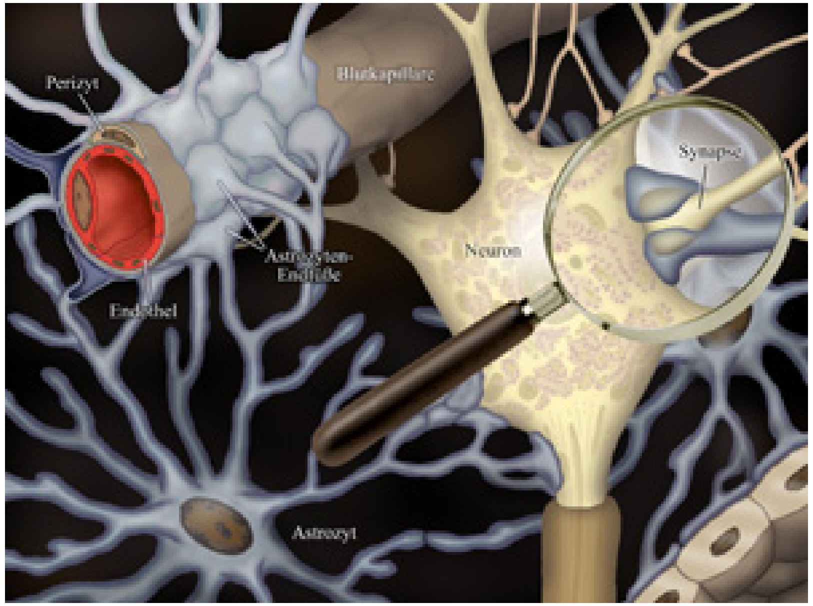


Abb. 1.6 Gliazellen des Zentralnervensystems.
1 Astrozyt (hier: protoplasmatischer Astrozyt; umgreift mit seinen Fortsätzen eine **1a** Hirnkapillare), **2** Oligodendrozyt (bildet mit seinen Fortsätzen Markscheiden um **2a** Axone), **3** Mikroglia (spezielle Form von Makrophagen), **4** Ependymzellen.
Trepel: Neuroanatomie, 5. A., Elsevier GmbH 2011



Glutamat
GABA
NMDA
…

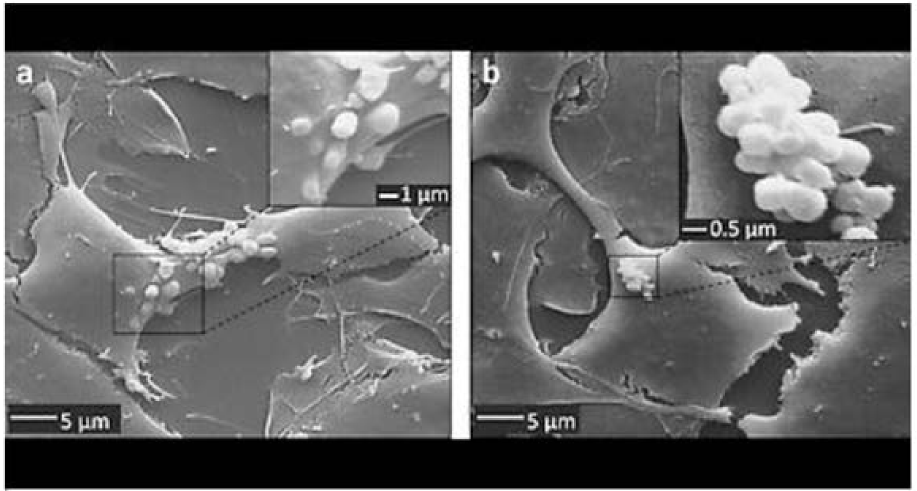




First time BBB breakthrough in 2015, Canada

Neuer Mechanismus der Blut-Hirn-Schranke entdeckt

Donnerstag, 11. Oktober 2018



Rasterelektronenmikroskopische Aufnahme der Barrier Bodies. Auf Foto a werden die Barrier Bodies von der Zelle abgeschnürt. Foto b zeigt die traubenförmige Anhäufung der Barrier Bodies. /Birthe Gericke, Ingo Gerhauser

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Biomaterials
Volume 161, April 2018, Pages 129-143

Reversible opening of the blood-brain barrier by claudin-5-binding variants of *Clostridium perfringens* enterotoxin's claudin-binding domain

Winfried Neuhaus [a, 1] ... Jörg Piontek [c]

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CSF-Biomarkers in Olympic Boxing: Diagnosis and Effects of Repetitive Head Trauma

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Abstract

Background: Sports-related head trauma is common but still there is no established laboratory test used in the diagnostics of minimal or mild traumatic brain injuries. Further the effects of recurrent head trauma on brain injury markers are unknown. The purpose of this study was to investigate the relationship between Olympic (amateur) boxing and cerebrospinal fluid (CSF) brain injury biomarkers.

Methods: The study was designed as a prospective cohort study. Thirty Olympic boxers with a minimum of 45 bouts and 25 non-boxing matched controls were included in the study. CSF samples were collected by lumbar puncture 1–6 days after a bout and after a rest period for at least 14 days. The controls were tested once. Biomarkers for acute and chronic brain injury were analysed.

Results: NFL (mean ± SD, 532±553 vs 135±51 ng/L p = 0.001), GFAP (496±238 vs 247±147 ng/L p<0.001), T-tau (58±26 vs 49±21 ng/L p<0.025) and S-100B (0.76±0.29 vs 0.60±0.23 ng/L p = 0.03) concentrations were significantly after boxing compared to controls. NFL (402±434 ng/L p = 0.004) and GFAP (369±113 ng/L p = 0.001) remained elevated after the rest period.

Conclusion: Increased CSF levels of T-tau, NFL, GFAP, and S-100B in >80% of the boxers demonstrate that b and the cumulative effect of head trauma in Olympic boxing may induce CSF biomarker changes that suggest nervous injuries. The lack of normalization of NFL and GFAP after the rest period in a subgroup of boxers ongoing degeneration. The recurrent head trauma in boxing may be associated with increased risk of chron brain injury.

Leaky BBB

Same to similar pathways in

- Trauma
- Hypoxia

What about diving?

„Imagine you could open BBB under pressure and applicate chemotherapies…"

E.Hametner, Innsbruck

2019:
116 Neuropeptides

„Imagine what would happen if 116 neuropeptides would pass in the peripheral blood...“

M.Sojer, Innsbruck

highly active and pluripotent…

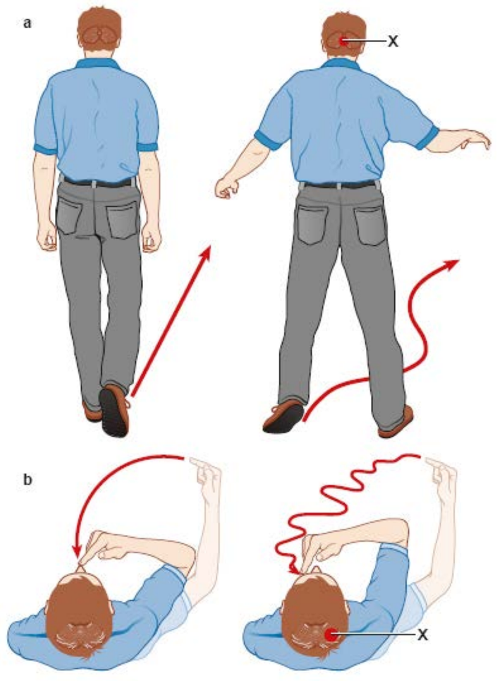
Courtesy of Sojer M., exact source unknown

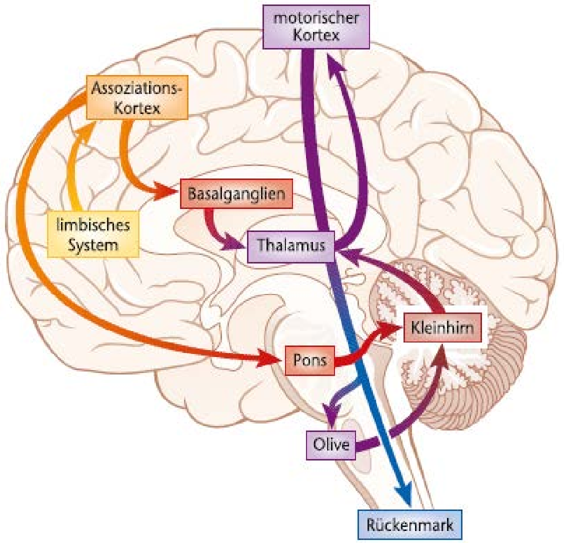
A possible link to other controversial theories?

Mitchell/Dollette hypothesis (2003) of inner ear ICD, „ear-lymphe as helium pool“

vs.

Klingmann et al, others
Gas embolic hypothesis

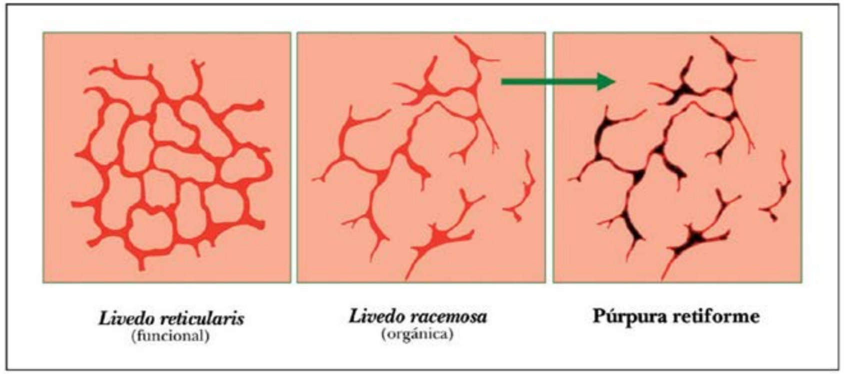




Skin bends
Local tissue supersaturation

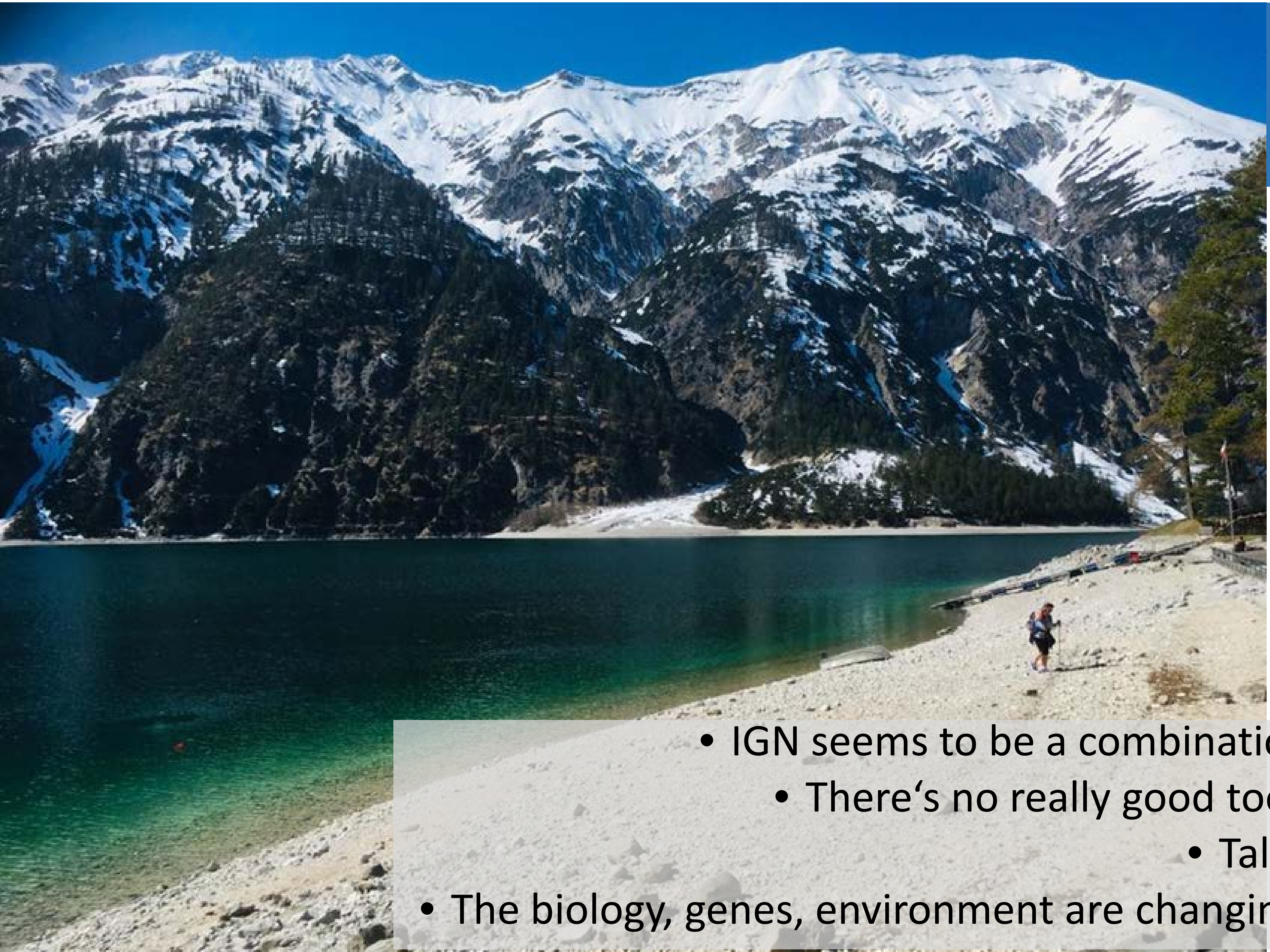
vs.

Arterial bubble embolism



Put both together or postulate something complete new

Arieli vs. Harvey …



conclusion

- IGN seems to be a combination of 2 ½ hypothesis?
- There‘s no really good tools for measuring IGN
- Talk about funnel chests
- The biology, genes, environment are changing – the physics never

„Man muss erst wissen, wenig zu wissen!“

„First you have to know, that you‘re knowing nothing!“