Behandlung und Pathophysiologie des Delirs

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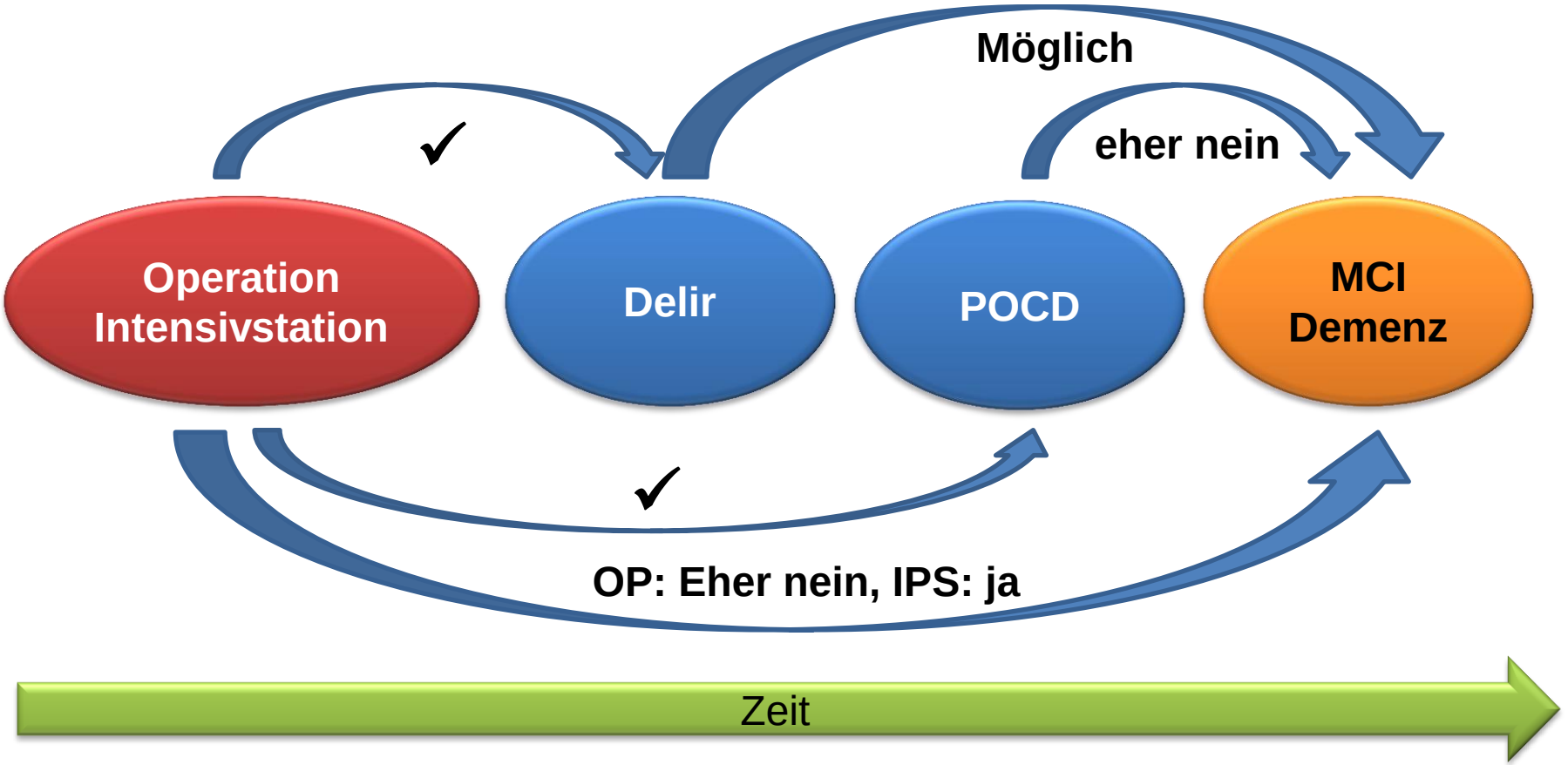
Übersicht

- Eine kurze Einführung
- Pathophysiologie
- Therapie

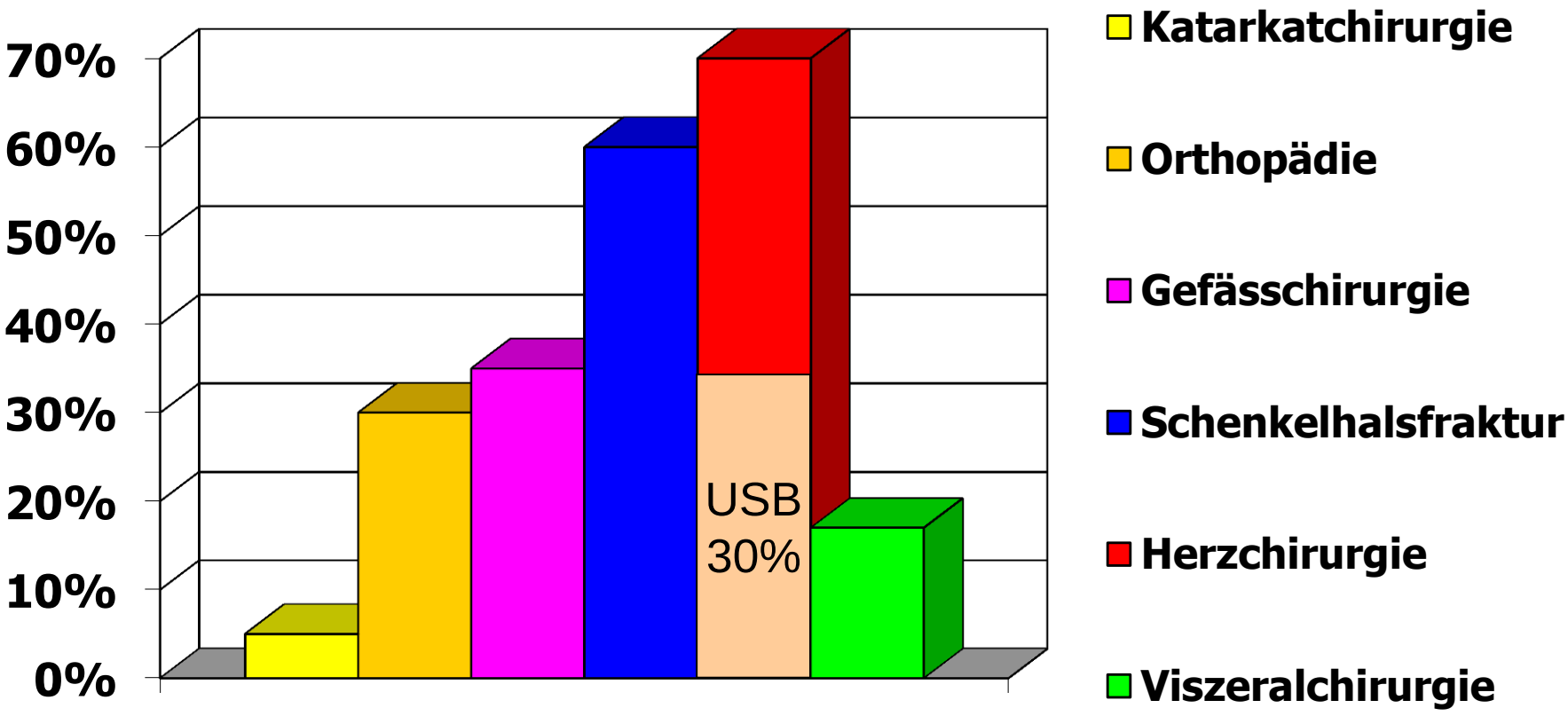
- Interessenskonflikte:
  - Honorare für Referate von
    - Orion Pharma (Dexdor®)
    - Covidien (BIS® Anästhesietiefenmonitoring)
    - Lilly

Kognitive Störungen nach Operationen



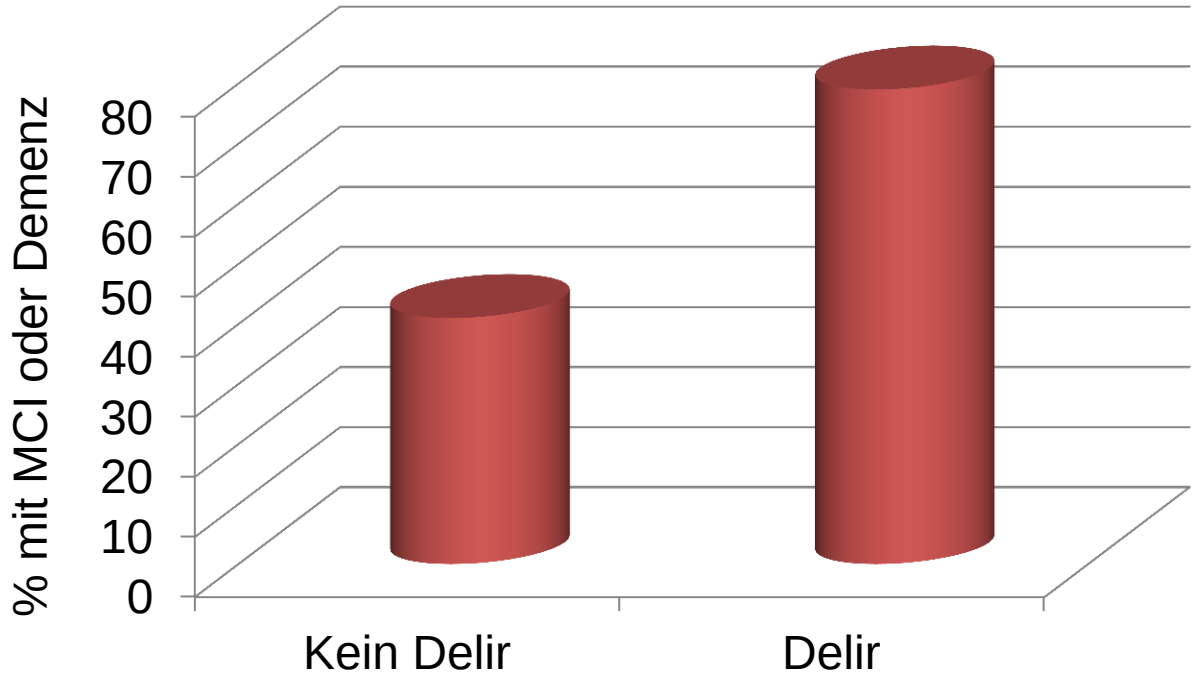
Postoperatives Delir

Patienten > 65 Jahre



Delir und MCI oder Demenz

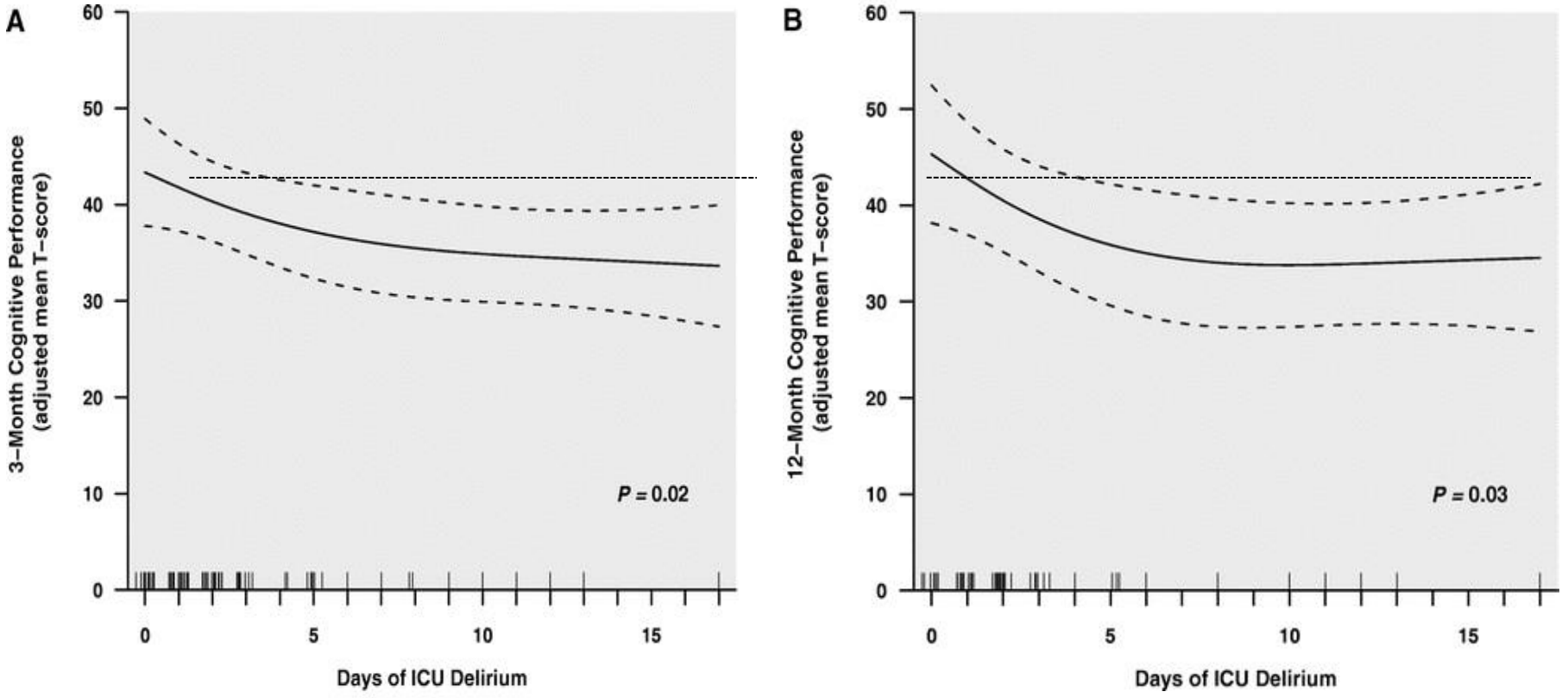
Hüftchirurgie elektiv und notfallmässig, Alter > 70 Jahre



“Patients who developed delirium after surgery during their hospital stay had a 170% increased risk of dementia or MCI in the 30-month follow-up period.”

Kat MG et al. Dement Geriatr Cogn Disord 2008;26:1–8

Delir und protrahierte kognitive Defizite



Girard T et al. Crit Care Med 2010;38:1513

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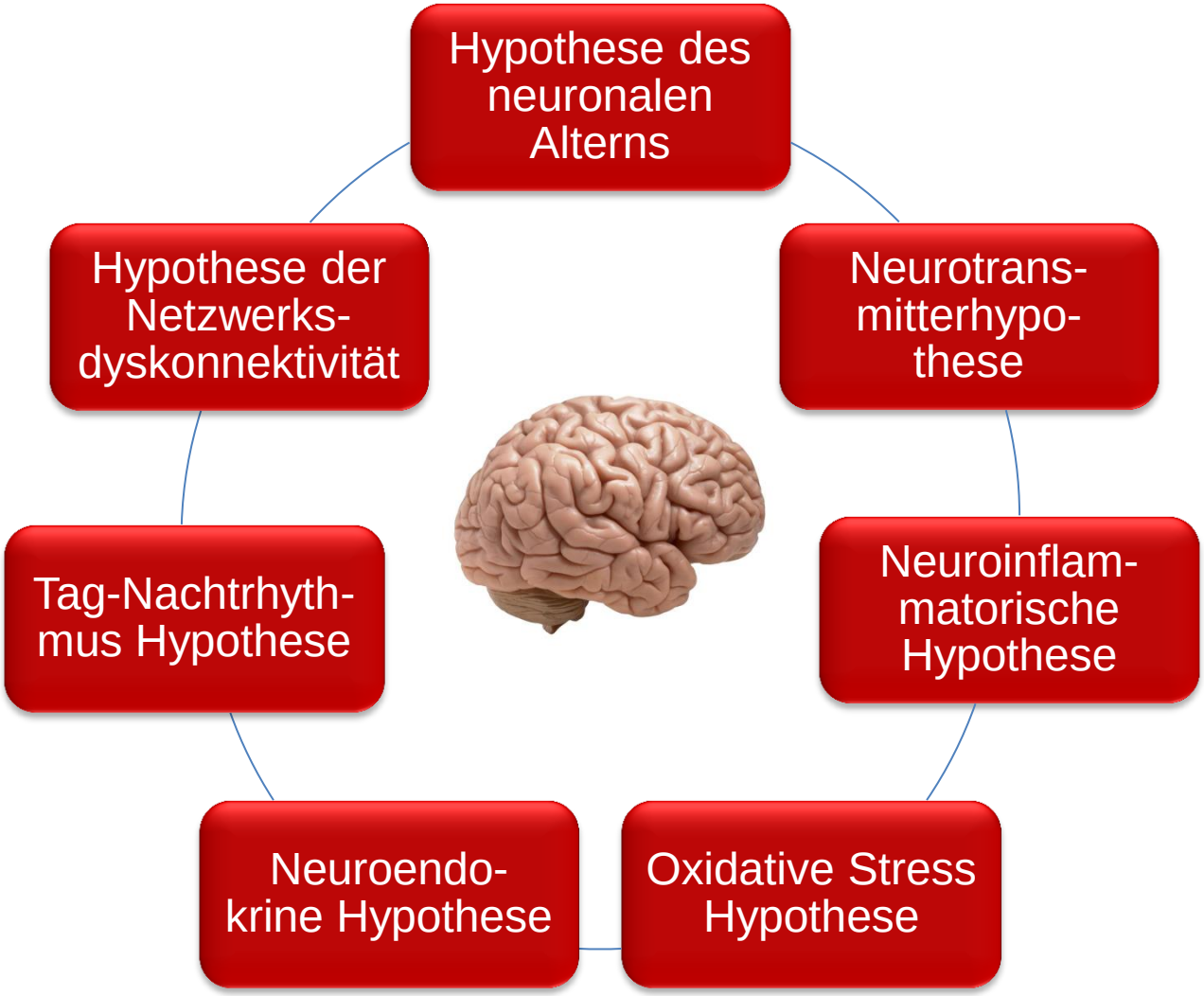
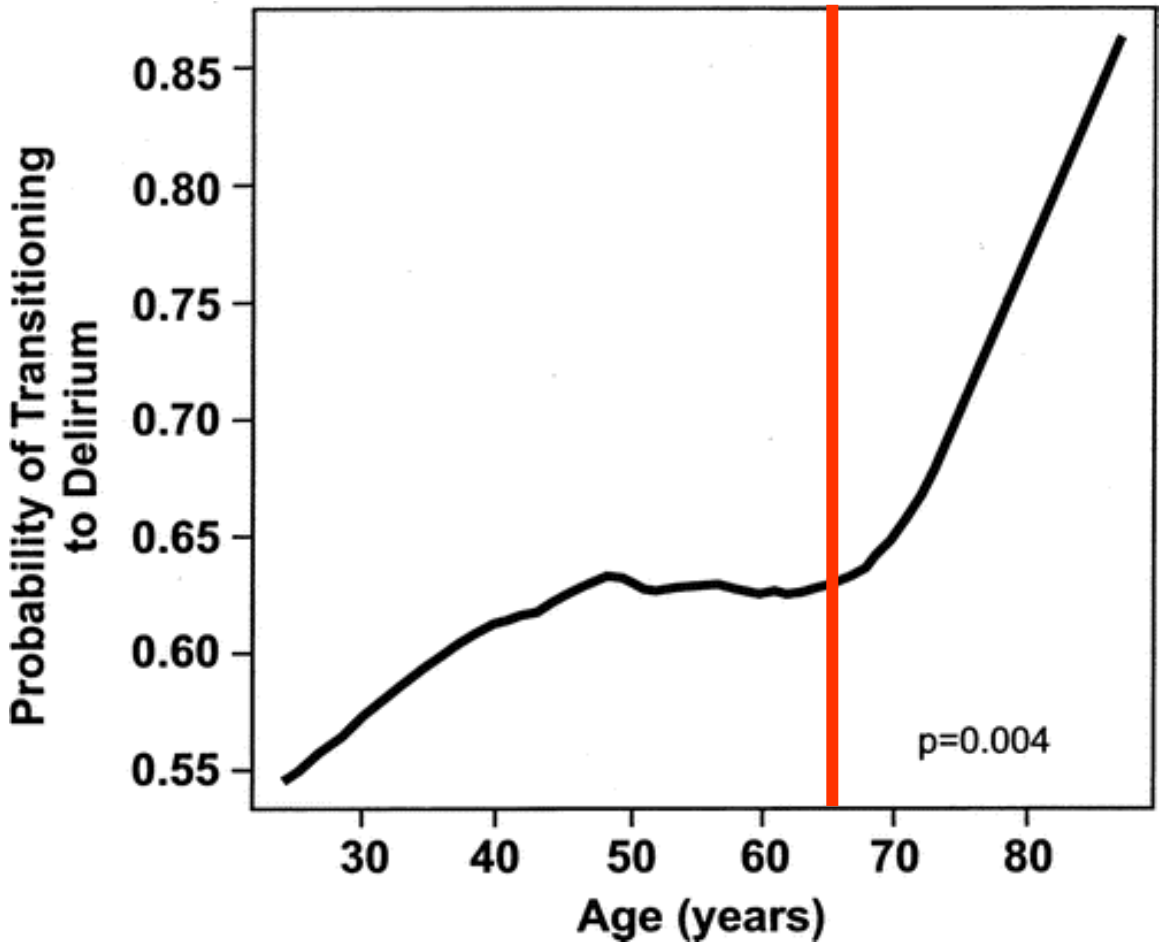
Pathophysiologie des Delirs



Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013 Dec;21(12):1190-222.

Hypothese des neuronalen Alterns



Pandharipande P et al. Anesthesiology 2006;104:21

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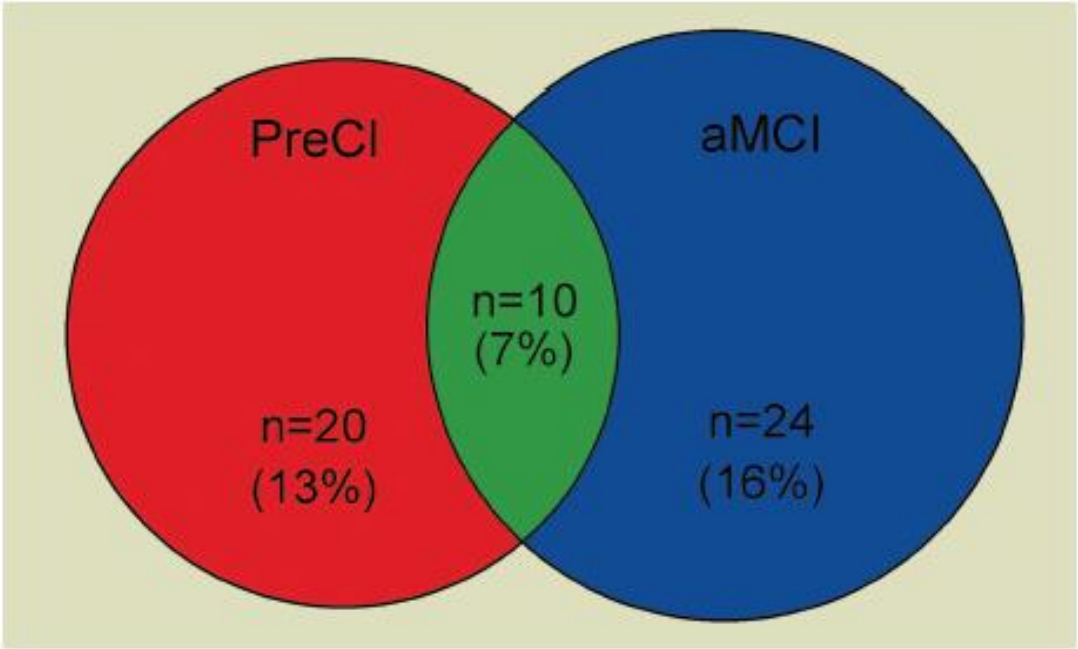
Präoperative kognitive Funktion

Preexisting Cognitive Impairment and Mild Cognitive Impairment in Subjects Presenting for Total Hip Joint Replacement

Lisbeth A. Evered, B.Sc., M.Biostats.,* Brendan S. Silbert, M.B., B.S., F.A.N.Z.C.A.,†
David A. Scott, M.B., B.S., F.A.N.Z.C.A., Ph.D.,‡ Paul Maruff, Ph.D.,§
David Ames, B.A., M.D., F.R.C.Psych., F.R.A.N.Z.C.P.,‖
Peter F. Choong, M.B., B.S., M.D., F.R.A.C.S.#



Evered LA et al. Anesthesiology 2011;114:1297

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Neurotransmitterhypothese

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Phe	His	Cytok	HPA axis	NMDA activity	Changes in RBF	EEG	Mel	Inflam	Cort
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↑	↑,↓	⇊↑	⇊	↑	⇊	↓	↓	↑	↑
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	⇊↑	⇊	↓	⇊	↓	↓	↑	↑
TBI	↑	↑	↑	↑	↑	↑	↑	↑	↓	↑⇊	↑	↑	↑	↓	↓	↑⇊	↑
CVA	↓	↑	↑	↑	↑	↑	↑	↑	↓	↑⇊	↑	↑	⇊	↓	↓	↑⇊	↑
Hepatic Failure (encephalopathy)	⇔	↓	↑	↑	↑	↓	↑	↑	↑	↑⇊	⇊	↑	⇊	↓	↓	↑	↑
Sleep deprivation	↓	↓	⇊	↑	↑	↑	↓	↑	↑	↑	⇊	↑	↑	↓	↓⇊	↑⇊	↑
Trauma, Sx, & Post-op	↓	↑	↑	↑	↓	↑	↓	↑	↑	↑	↑	↑	⇊	↓	↓	↑	↑
ETOH & CNS-Dep Withdrawal	↑	↑	↑	↓	↑	↑	↓	↑	↑	↑	↑⇊	↑	↓	↑	↓	↑	↑
Infection/Sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↑	↑⇊	↑⇊	⇊	↓	↓	↑	↑
Dehydration & Electrolyte Imbalance	⇔	↑	↑	↑	↓	↑	?	?	↑	↑	⇊	↑	↓	⇊	↓	⇊↑	↑
Medical Illness	↓	↑	↑	⇊	↓	↑	↓	↑	↑	↑	↓	↑	⇊	⇊	↓	⇊	↑

Maldonado JR. Am J Geriatr Psychiatry. 2013;21:1190-222.

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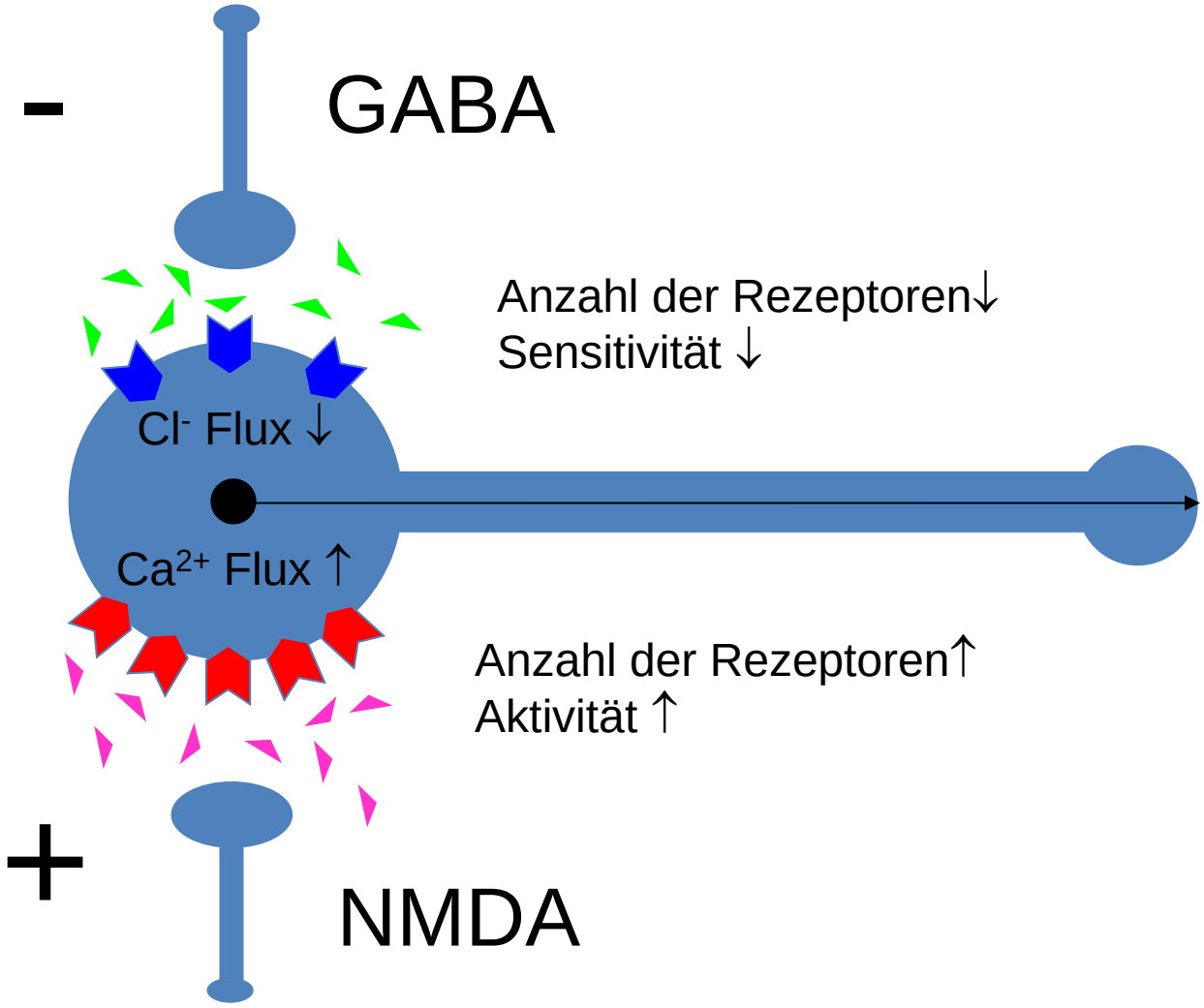
Alkoholentzugsdelir



DeBellis R et al. J Intensive Care Med 2005;20:164

„Anticholinergika“

Keine anticholinerge Wirkung

- Aspirin
- Nitroglyzerin
- Betablocker
- Insulin
- Ibuprofen

Anticholinergika

- Antivertiginosa (alte Antiemetika)
- Spasmolytika (Buscopan®)
- Atropin/Scopolamine
- Ipratropium
- Oxybutinin, Tolterodin

Anticholinerge NW

- Trizyklische Antidepressiva
- Neuroleptika
- Antihistaminika
- Antiarrhythmika (Klasse I)
- **Pethidin**

Atropine-like activity

- Prednisolon
- Digoxin
- Nifedipin
- Furosemid
- Ranitidin

Mintzer J, Burns A. J R Soc Med 2000; 93:457

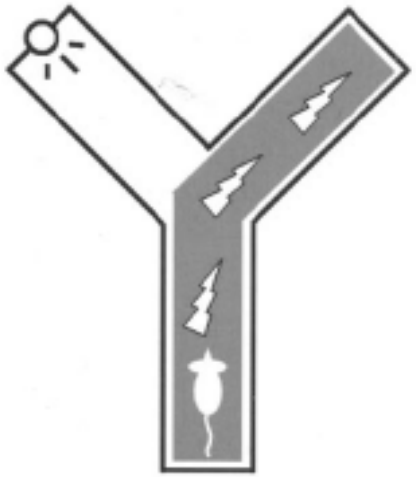
SIRS and Brain?

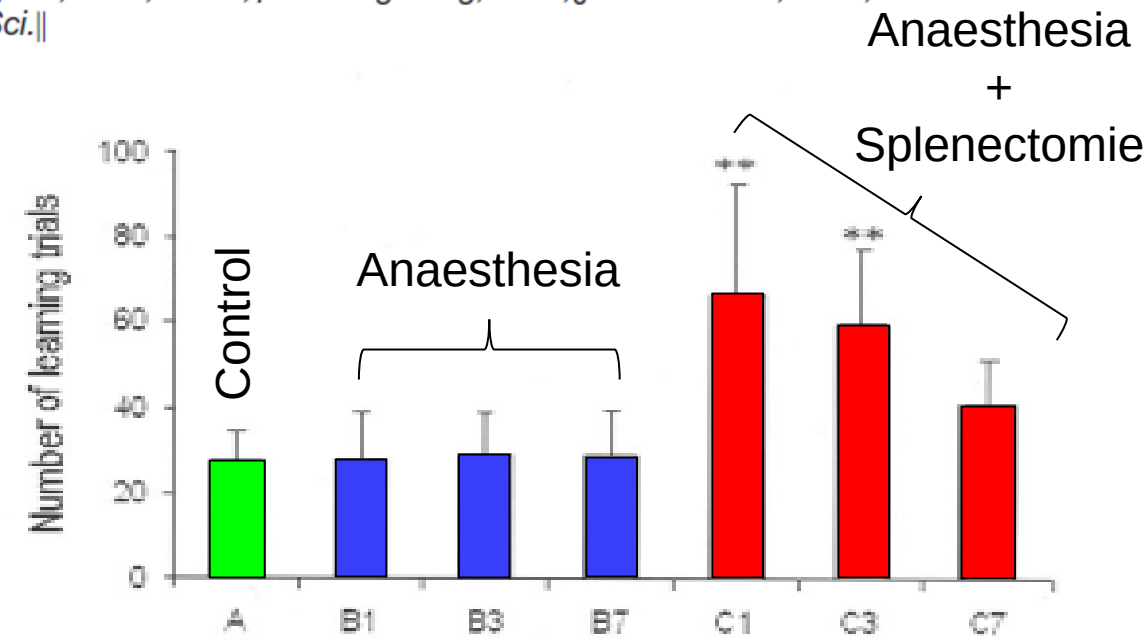
Anesthesiology 2007; 106:436–43

Postoperative Impairment of Cognitive Function in Rats

A Possible Role for Cytokine-mediated Inflammation in the Hippocampus

Yanjie Wan, M.D., Jing Xu, M.D.,† Daqing Ma, M.D., Ph.D.,‡ Yinming Zeng, M.D.,§ Mario Cibelli, M.D.,# Mervyn Maze, F.R.C.P., F.R.C.A., F.Med.Sci.‖*

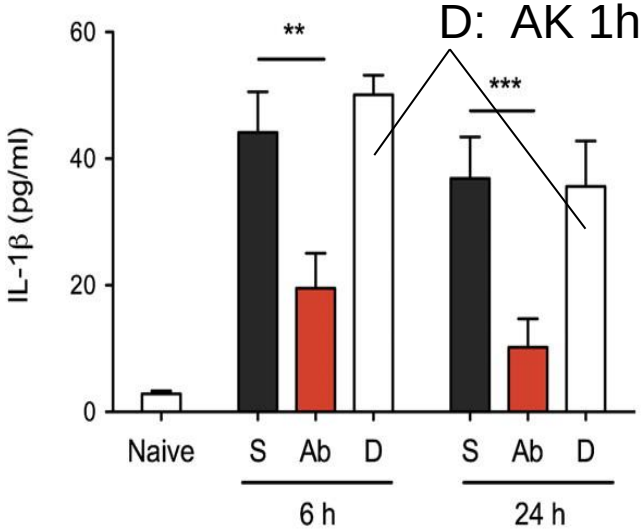


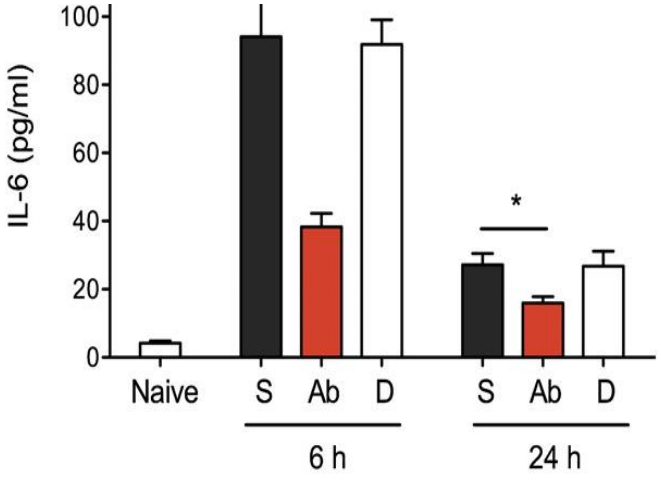


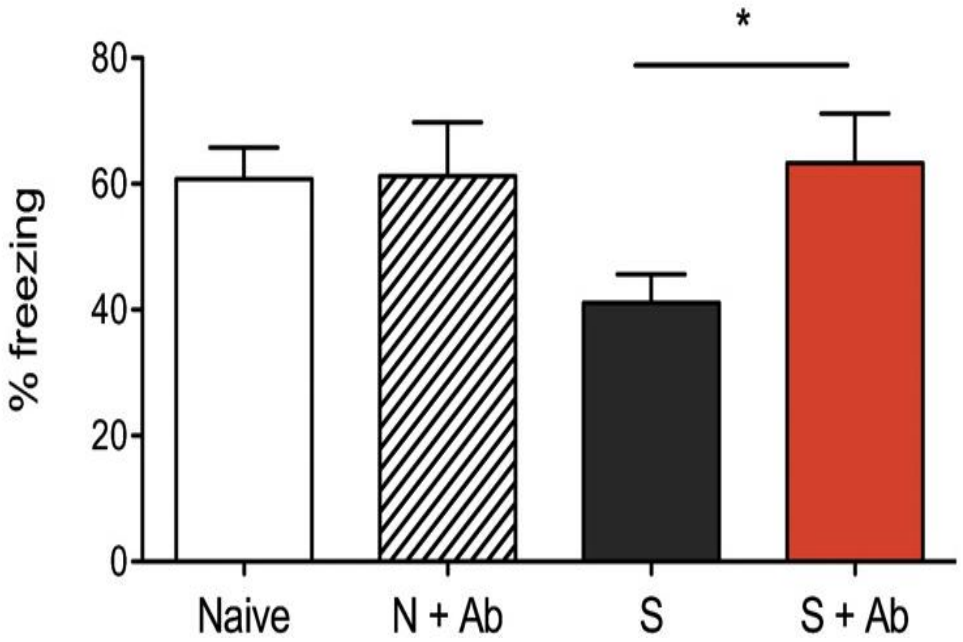
TNF-α

A

D: AK 1h nach Chirurgie







Terrando N et al. Proc Natl Acad Sci USA 2010;107:20518

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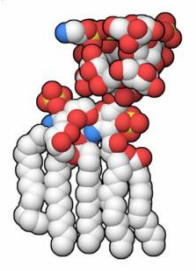
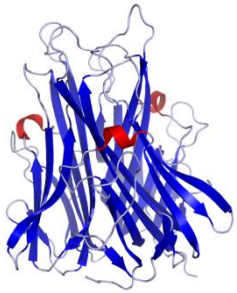
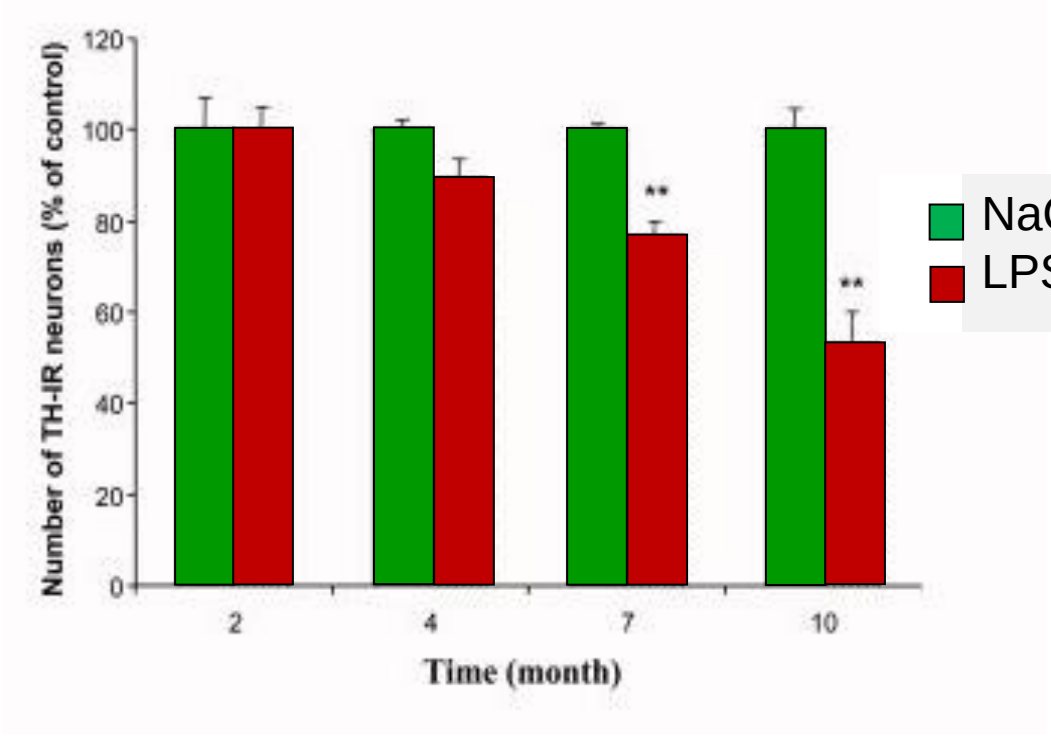
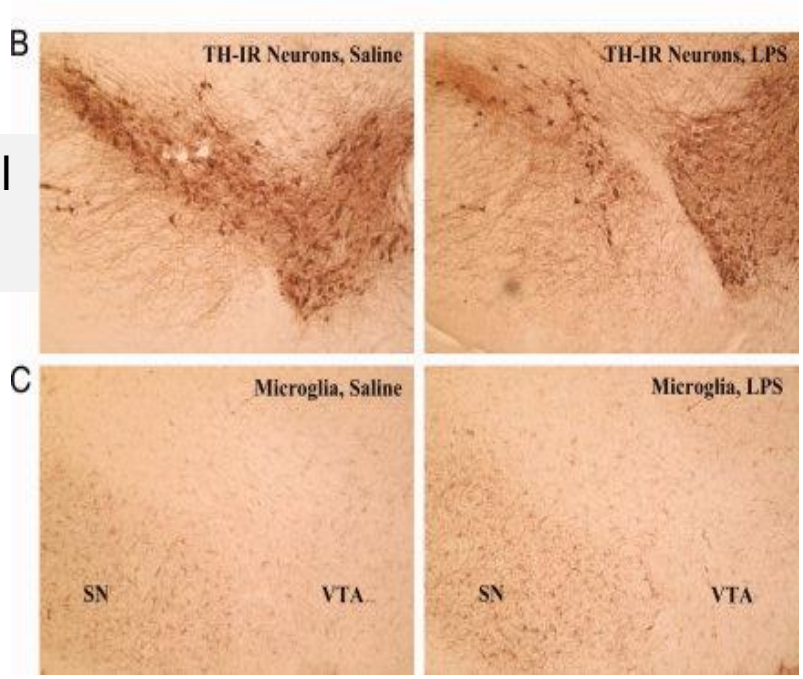
LPS und Neurotoxizität



LPS → TNF-α







Qin L et al. Glia 2007;55:453

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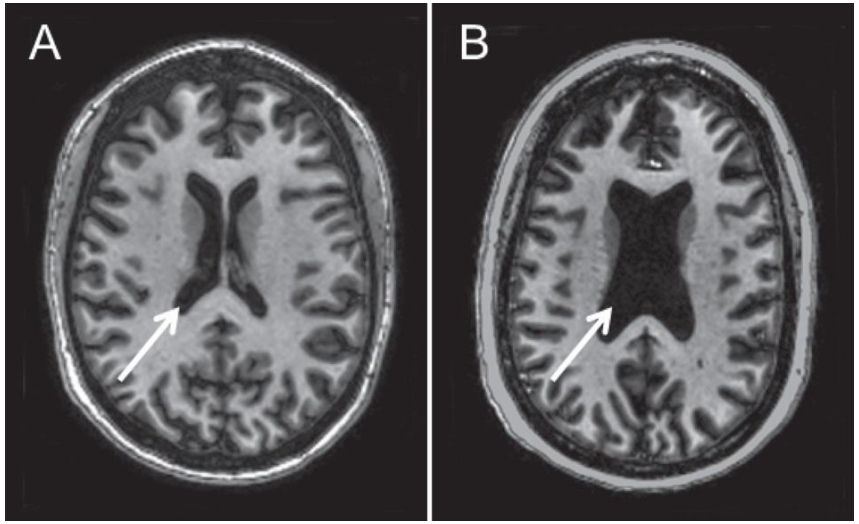
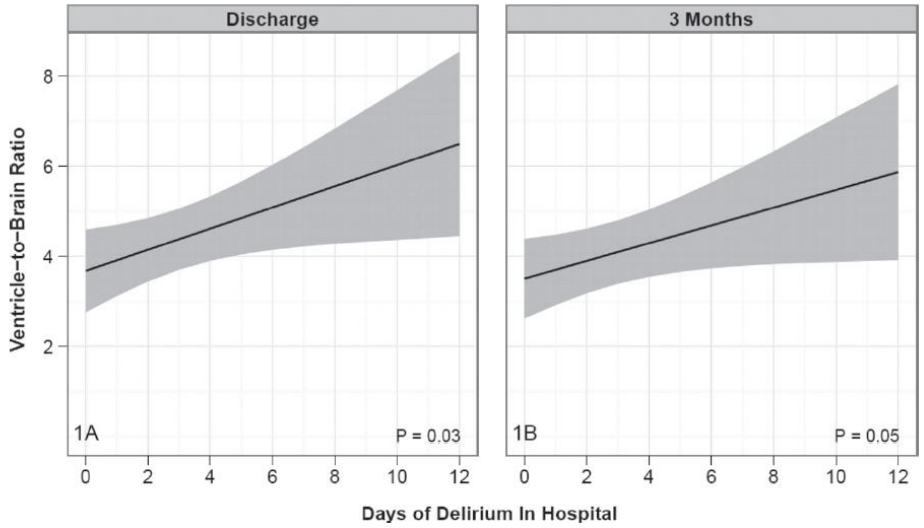
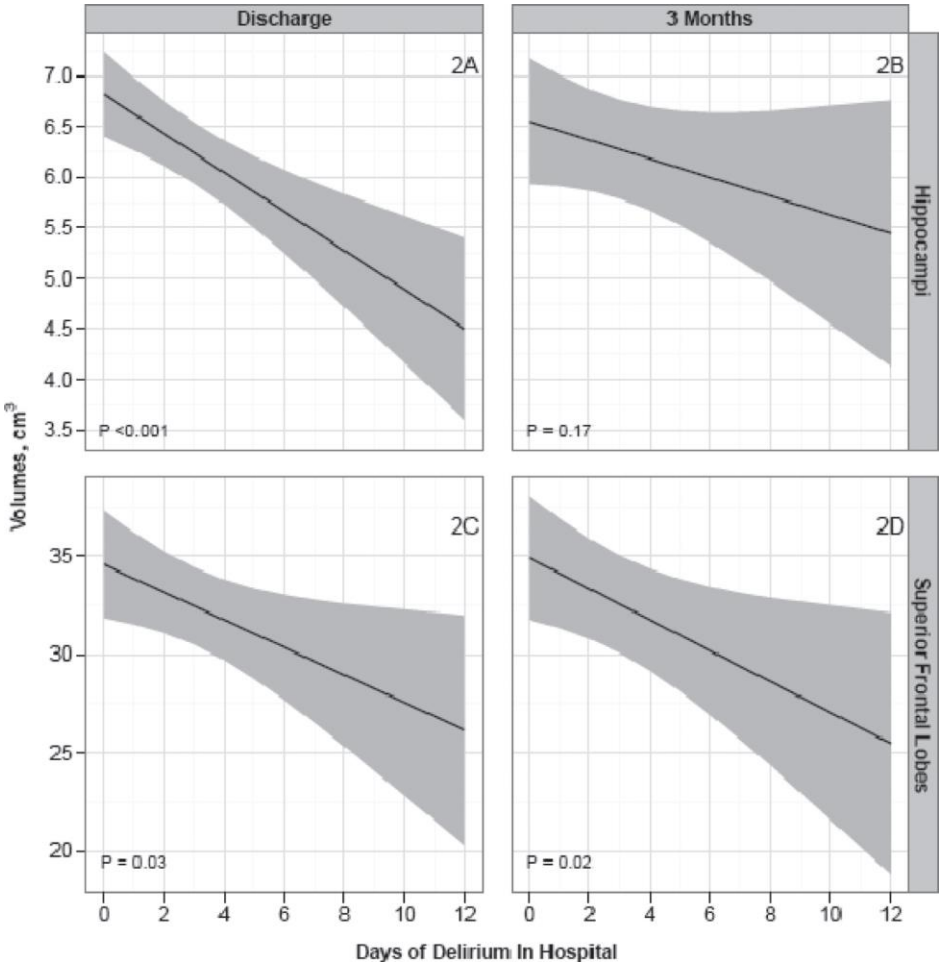
Hirnvolumen und Delir







Gunther Ml et al. Crit Care Med. 2012;40:2022-32

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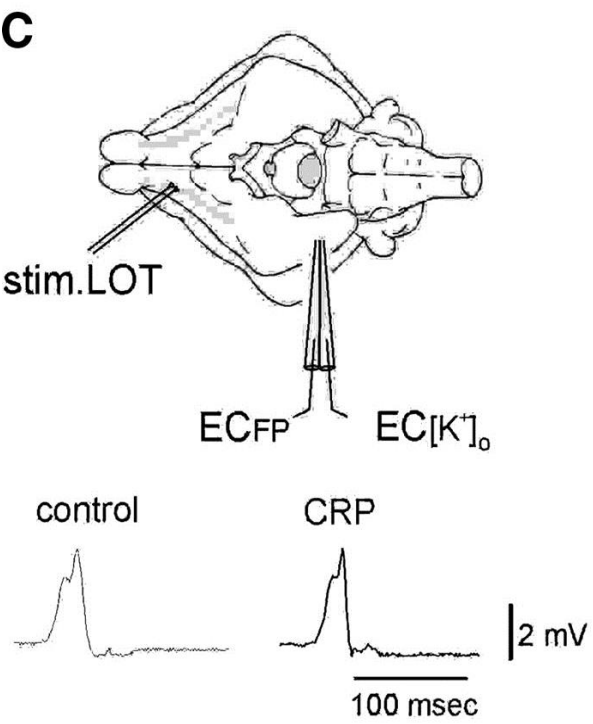
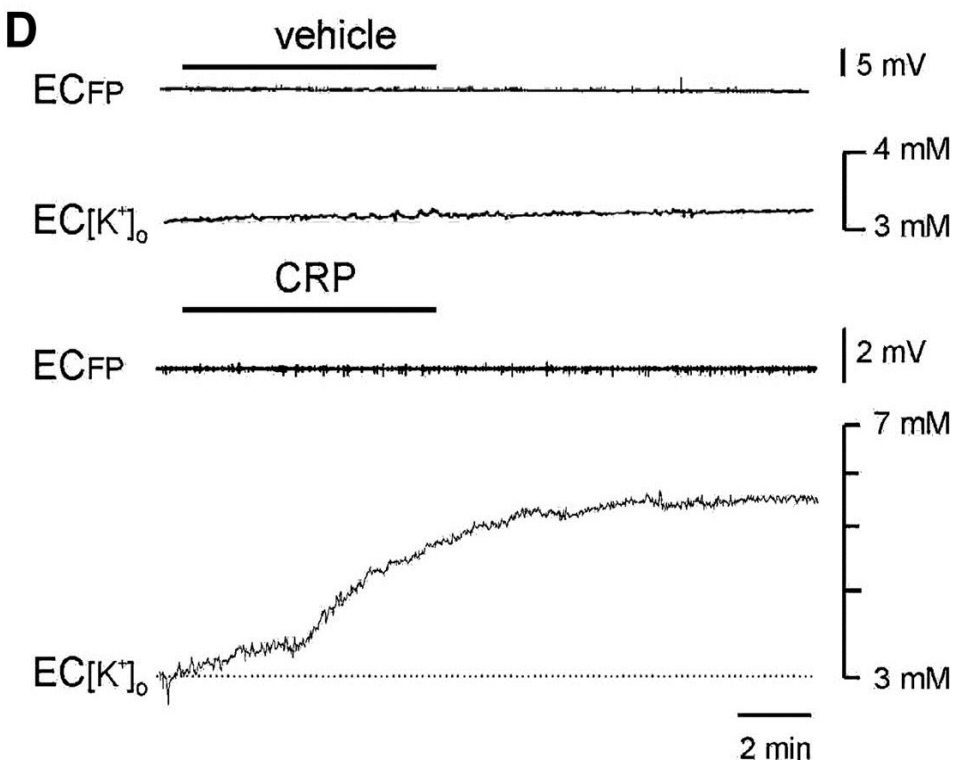
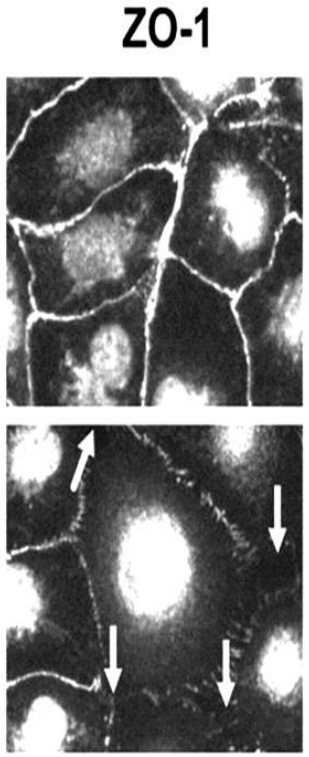
CRP und Bluthirnschranke







Kuhlmann CRW et al. Stroke 2009;40:1458

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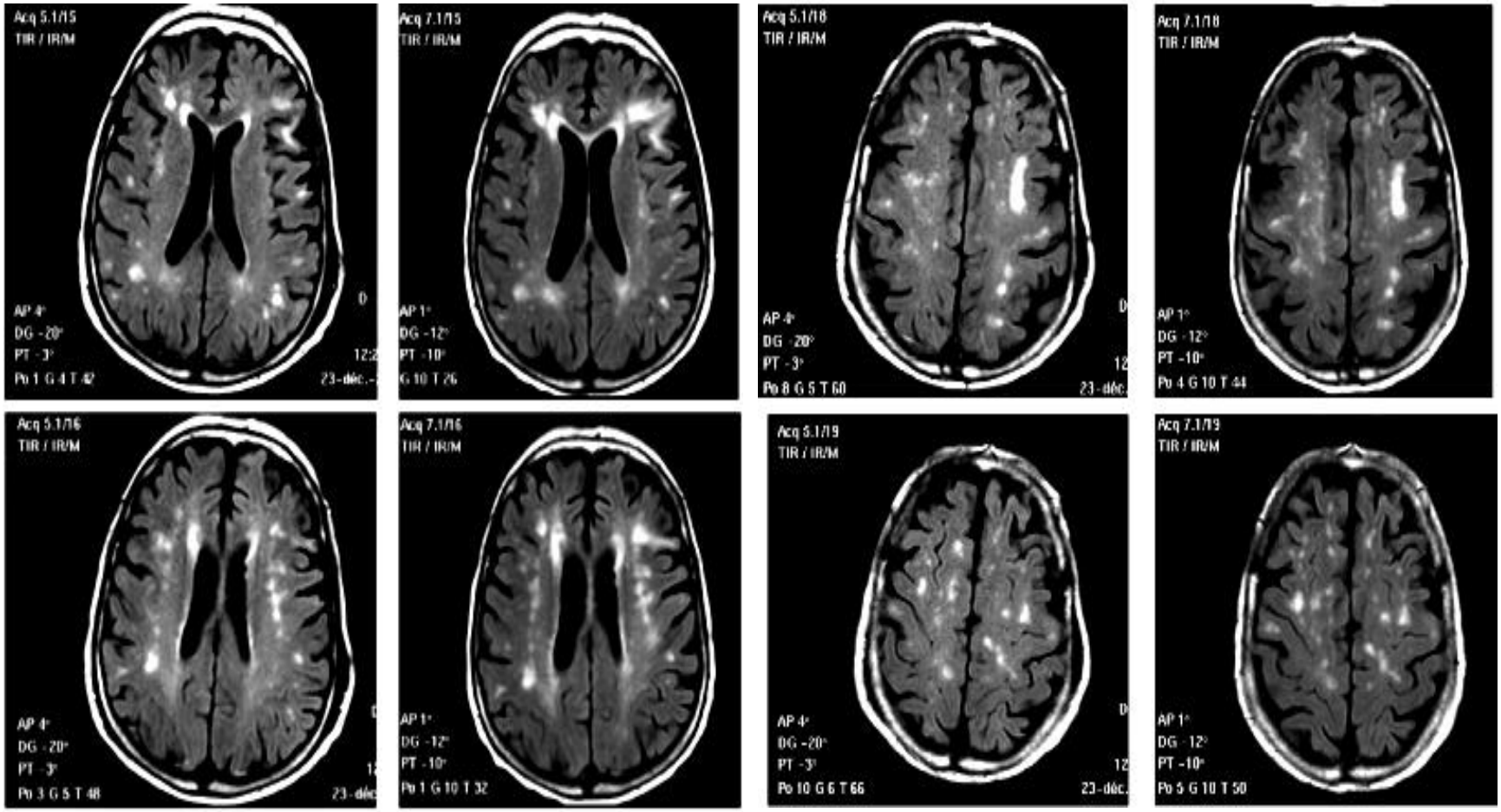
Klinische Assoziationen?



Sharshar T et al. Intensive Care Medicine 2007

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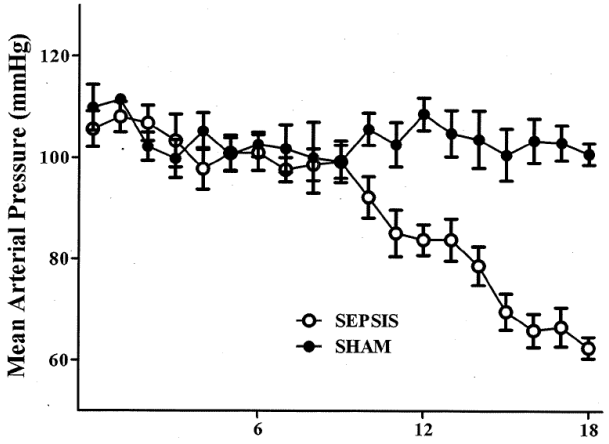
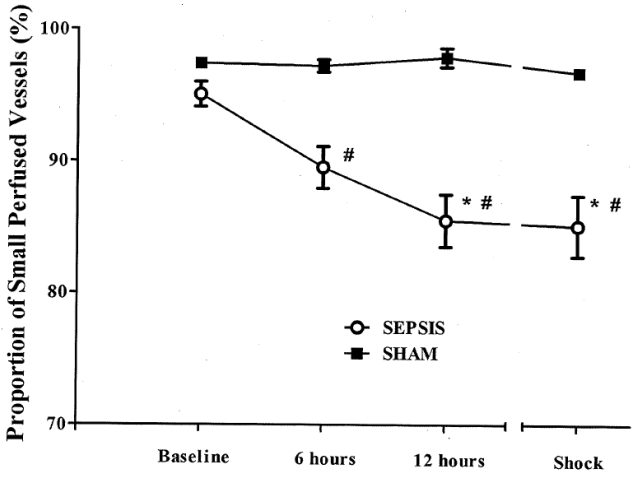
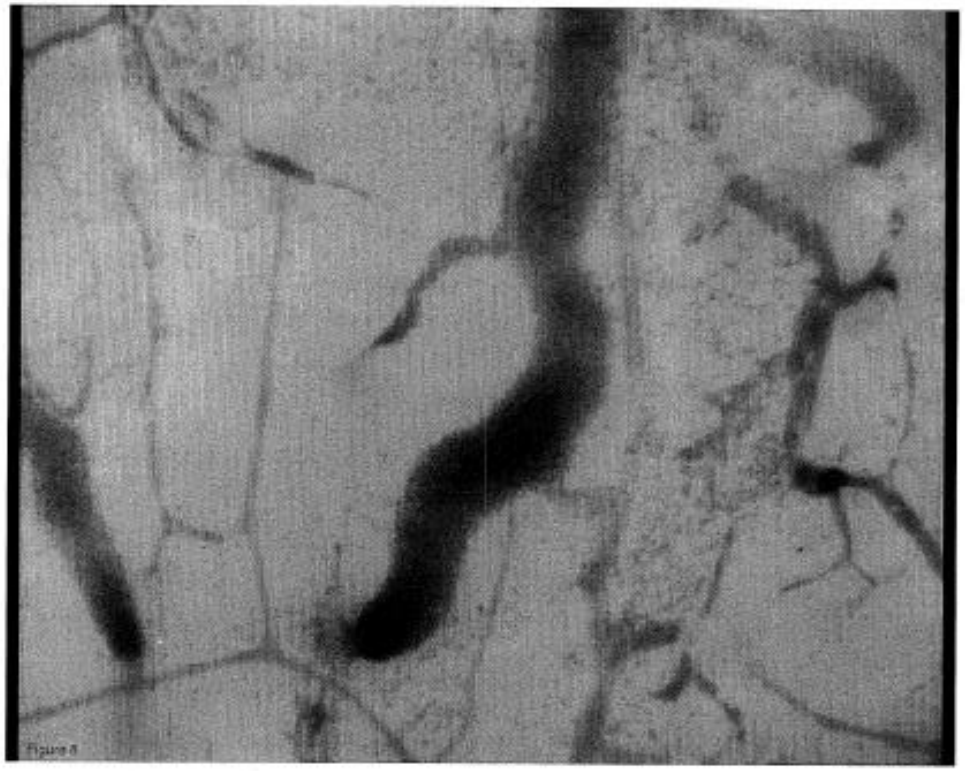
Sepsis und zerebrale Mikrozirkulation







Taccone FS et al. Critical Care 2010, 14:R140

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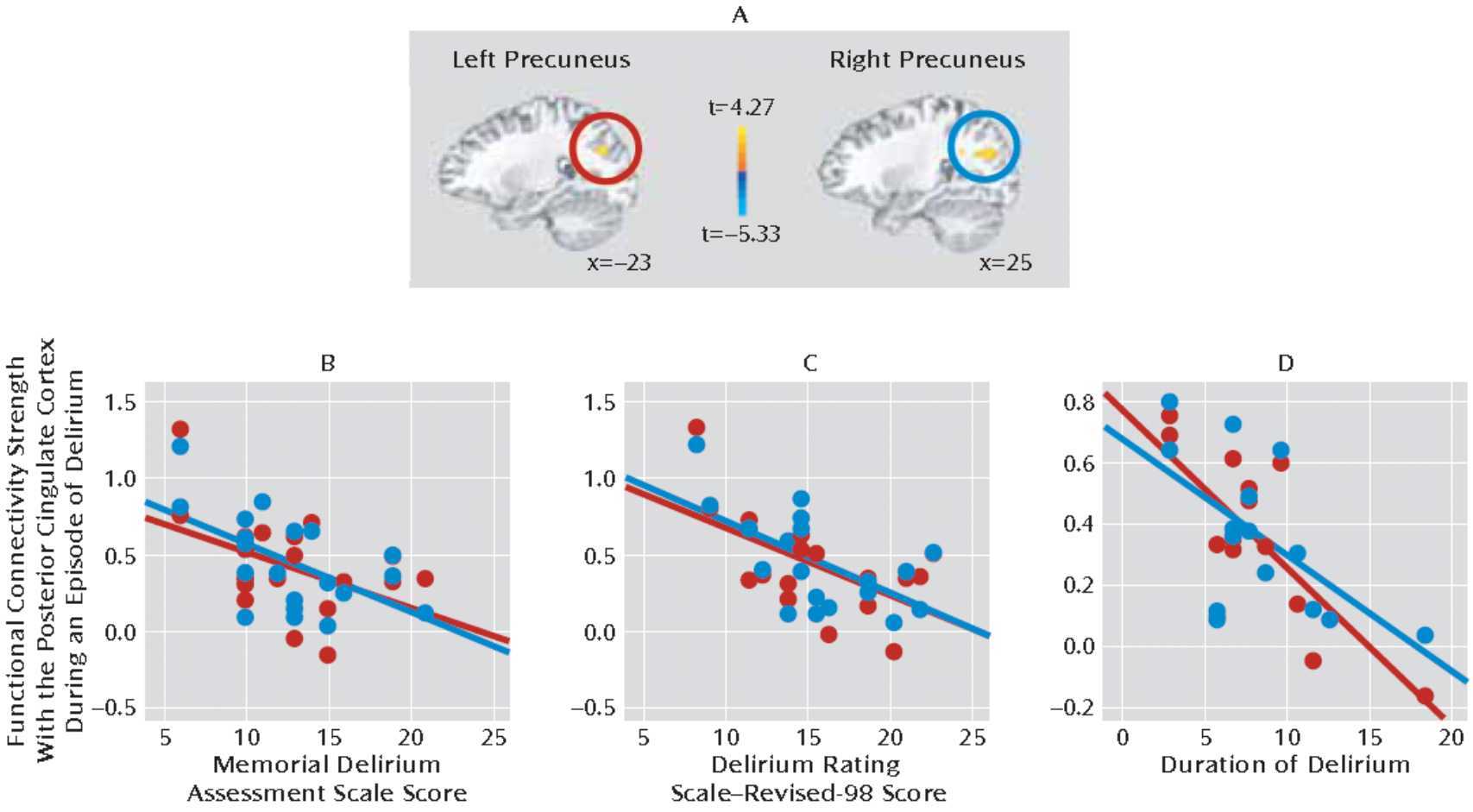
Hypothese der Netzwerkdyskonnektivität

FIGURE 2. Associations of Delirium Severity or Duration With Functional Connectivity Strengths of the Bilateral Precuneus With the Posterior Cingulate Cortex in During-Episode Patients[a]



Choi SH et al. Am J Psychiatry. 2012;169:498-507.

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Zusammenfassung

- Alles Hypothesen
- Delirium ≠ Delirium
- Fast immer Interaktion mehrerer Mechanismen

- Meine persönliche Meinung:
  - Jeder Patient «sucht sich» seine persönliche Pathophysiologie selbst aus
    - Heterogene Pathophysiologie
    - Kein «magic bullet»

Aktuelle Expertenmeinung

American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults.

American geriatrics society abstracted clinical practice guideline for postoperative delirium in older adults.

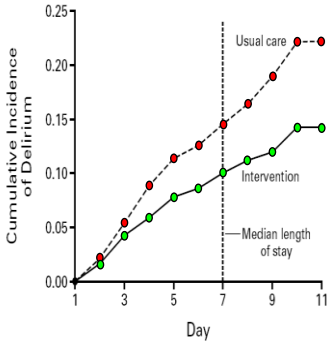
J Am Geriatr Soc. 2015 Jan;63(1):142-50.

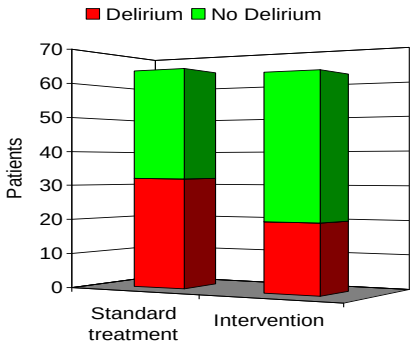
Strong recommendation

1. Multikomponentenintervention zur Prävention für Risikopatienten
2. Personalschulung
3. Ursachen suchen
4. Gute Analgesie (präferentiell opiatfrei)
5. Vermeiden von Medikamenten die Delirien auslösen können
6. Keine Neuverschreibung von Cholinesterasehemmern
7. Keine Benzodiazepine als first-line drugs für Agitation
8. Antipsychotika und Benzodiazepine beim hypoaktiven Delir vermeiden

Multikomponenten Strategien

- **Inouye SK et al. N Engl J Med 1999;340:669**
  - **Intervention:**
    - **Kognition, Schlafentzug, Mobilisation, Dehydratation**
  - **Signifikante Reduktion der Delirien**
  - **NNT: 19**
- **Marcantonio ER et al. J Am Geriatr Soc 2001;49:516**
  - **Intervention:**
    - **Tägliche Visite durch Geriater, 10 Zielparameter**
  - **Signifikante Reduktion der Delirien (32% *vs* 50%)**
  - **NNT: 6**
- **Milisen K et al. *J Am Geriatr Soc* 2001;49:523**
- **Bjorkelund KB et al. *Acta Anaesthesiol Scand* 2010;54:678**
- **Schweickert WD et al. Lancet 2009;373:1874**
- **ABCDE Approach: Vasilevskis EE et al. Chest 2010;138:1224**





Langfristige Effekte der Delirprävention

Table 3. Outcomes at 6-Month Follow-up

Outcome	Intervention Group No.	Intervention Group No. (%) or Adjusted Mean ± SD*	Control Group No.	Control Group No. (%) or Adjusted Mean ± SD*	*P* Value*
Self-rated health (1 to 5 scale)	257	2.2 ± 0.9	276	2.3 ± 0.9	0.16
Activities of daily living (0 to 14 scale)	345	12.6 ± 2.3	359	12.4 ± 2.3	0.47
Geriatric Depression Scale (0 to 15 scale)	295	4.0 ± 2.9	292	4.1 ± 2.9	0.66
Mini-Mental State Examination (0 to 23 scale)	288	19.4 ± 2.8	292	19.7 ± 2.8	0.15
Incontinence	344	103 (30)	354	132 (37)	0.02
Delirium	345	12 (3)	358	10 (3)	0.53
Home health visit in previous month	301	105 (35)	306	103 (34)	0.71
Homemaker visit in previous month	298	95 (32)	306	105 (34)	0.48
Rehospitalization	343	138 (40)	354	140 (40)	0.82
New nursing home placement	325	85 (26)	333	87 (26)	0.97

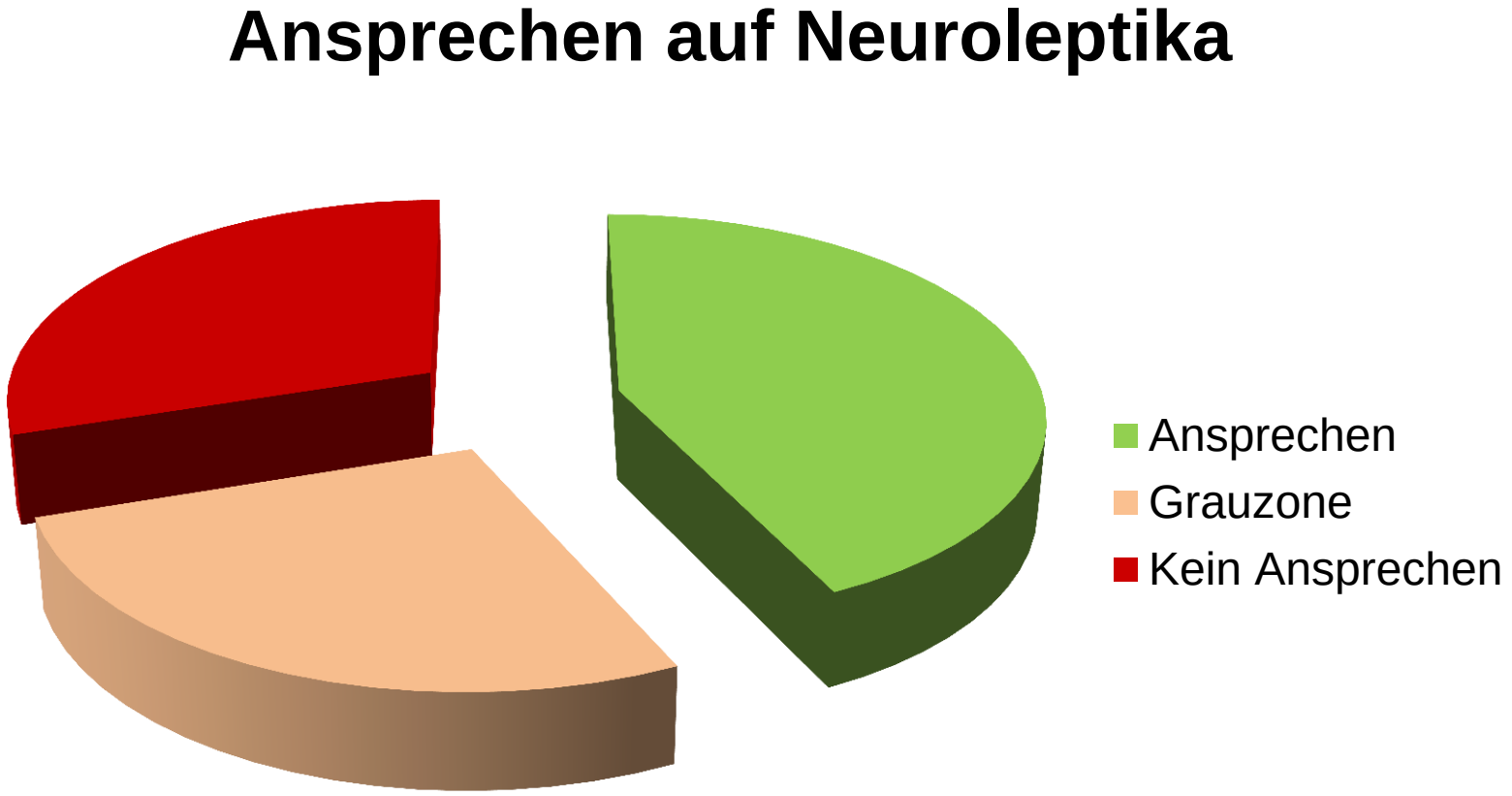
* Adjusted for age, sex, and delirium risk group (the original matching variables), as well as the baseline value of the variable of interest.

Bogardus ST et al. Am J Med 2003;114:383-390

Weak Recommendation

1. Multikomponentenintervention (nicht pharmakologisch) bei etabliertem Delir
2. Regionalanästhesie intra- und postoperativ
3. Antipsychotika für agitierte Patienten so wenig wie möglich so kurz wie möglich

Therapie: Neuroleptika



Mindestens 50% der Patienten zeigen eine Reduktion der Symptome > 50%

Seitz DP et al. J Clin Psychiatry 2007;68:11

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Neuroleptika

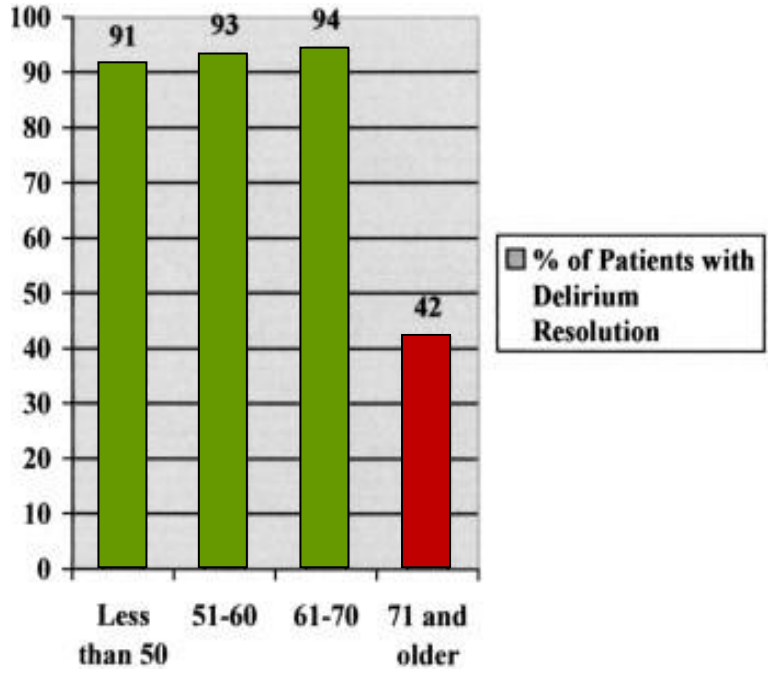
Medikament	Dosis	Verabreichung
Haloperidol	0.5–2 mg alle 2–12 h	po, iv, sc, im
Risperidone	0.25–2 mg alle 12–24 h	po, Effervetten
Quetiapine	12.5–200 mg alle 12–24 h	po
Olanzapine	2.5–10 mg alle 12–24 h	po, Effervetten

Olanzapine

TABLE 2. Logistic-regression analysis of predictors of response to olanzapine treatment

Variable	*P*	OR
Age	**0.001**	**171.5**
CNS spread	**0.005**	**74.9**
Subtype of delirium	**0.01**	**11.3**
Hypoxia	0.09	5.9
History of dementia	0.40	0.34
Delirium severity	0.1	5.03

Note. CNS = central nervous system; OR = odds ratio. Statistically significant results are given in boldface type.



Tumorpatienten: Alte Patienten und Patienten mit hypoaktivem Delir sprechen auf Olanzapine schlecht an

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Breitbart W et al. *Psychosomatics* 2002;43:175

Typisch oder atypisch?

THE COCHRANE COLLABORATION®

- Halodoperidol ***< 3 mg*** ist bezüglich Nebenwirkungen mit atypischen Neuroleptika vergleichbar
- Haloperidol ***> 4.5 mg*** scheint mit mehr Nebenwirkungen assoziert als atypische Neuroleptika

  Lonergan E et al. Antipsychotics for Delirium. Cochrane Database of Systematic Reviews. 2007

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

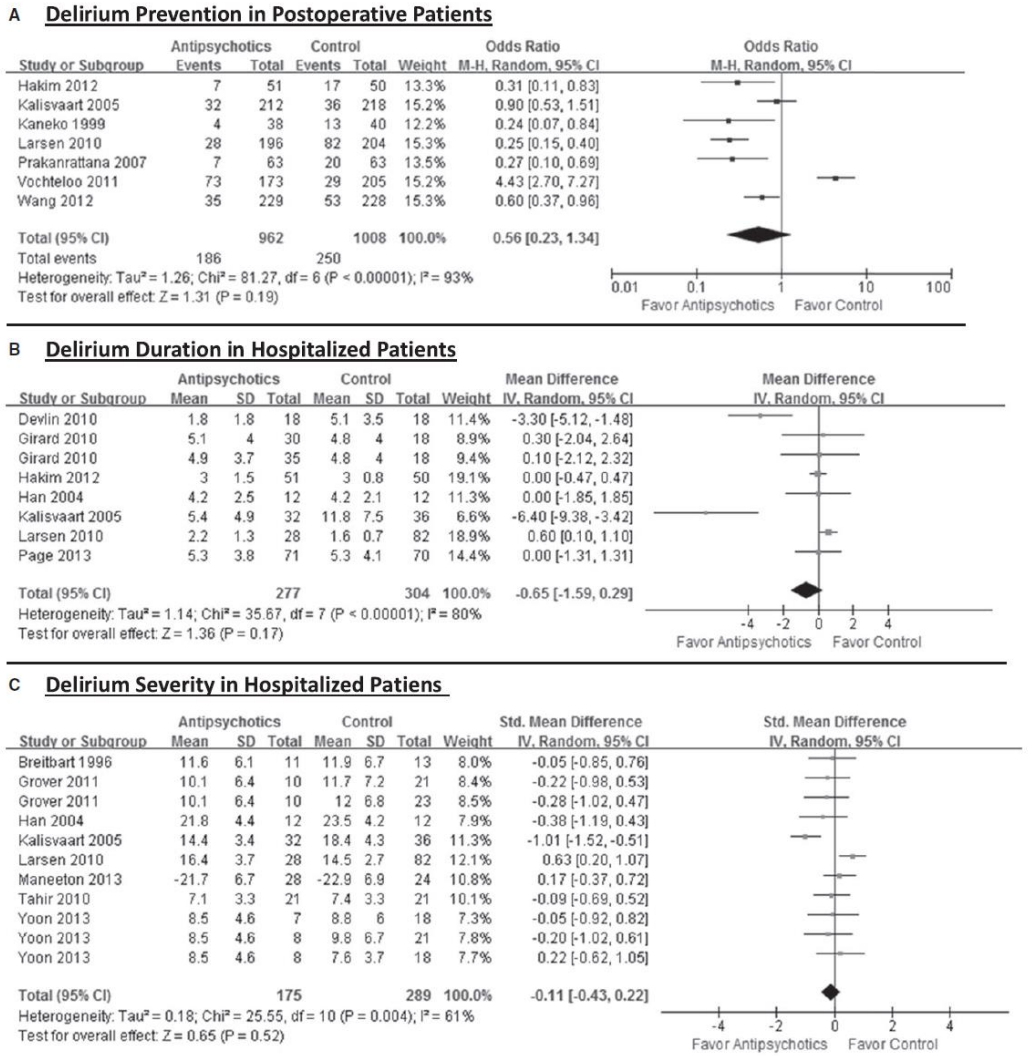
FDA Alert [9/17/2007]: Cases of sudden death, QT prolongation and Torsades de Pointes

2010: Zulassung für Haldol i.v. zurückgezogen

Atypische Neuroleptika?

- **FDA Alert [4/11/2005]**: Increased Mortality in Patients with **Dementia-Related Psychosis**
  - 17 plazebokontrollierte Studien, 5106 ältere Patienten mit demenz-assozierten Verhaltensstörungen
  - Sterberisiko in medikamentös behandelten Patienten 1.6 - 1.7 x höher als in der Plazebogruppe (2.6% vs 4.5% über ~10 Wochen).
  - Olanzapin, Aripiprazol, Risperidon, Quetiapin

Neuroleptika



Neufeld KJ et al. J Am Geriatr Soc 2016;64:705-14.

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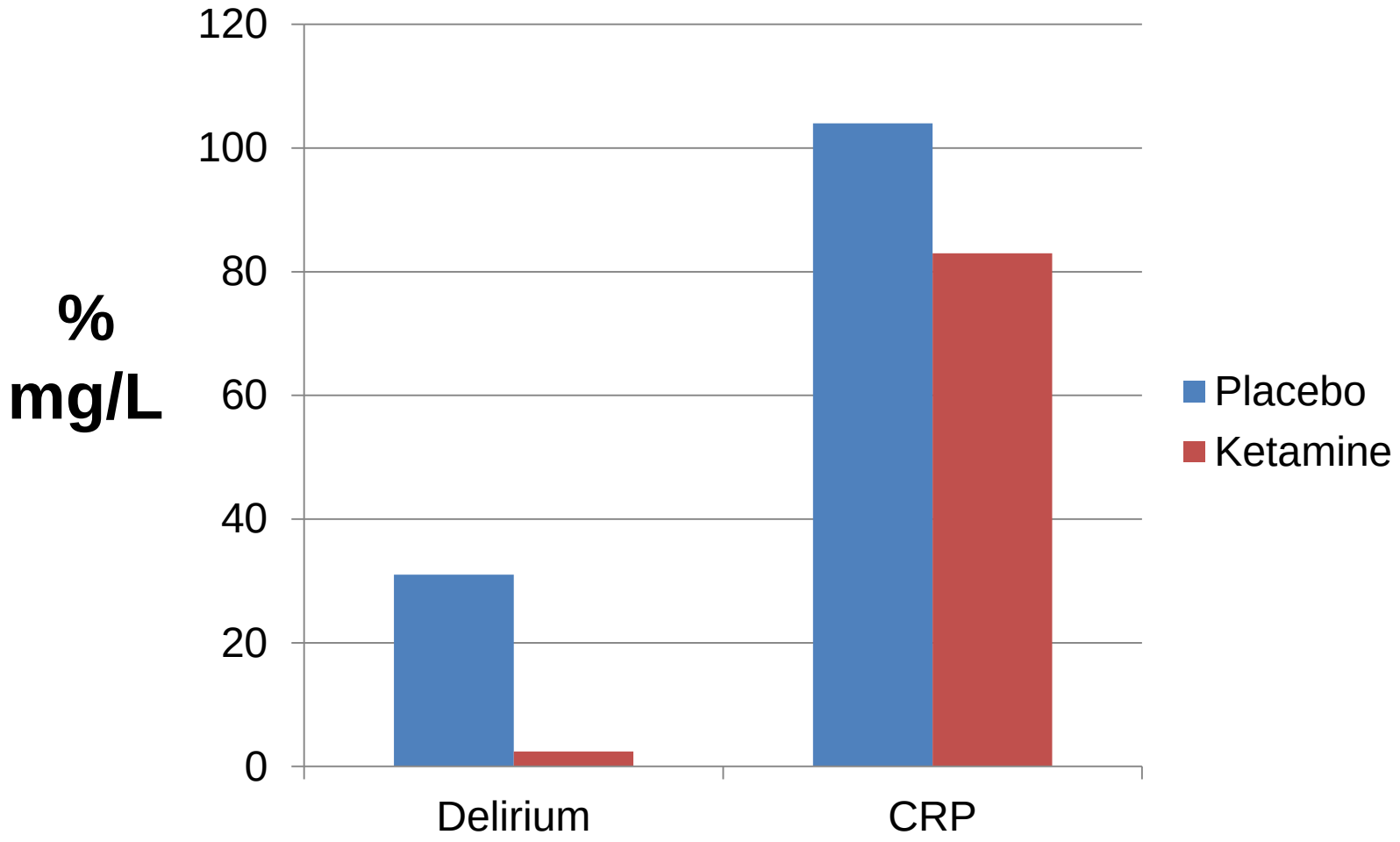
Insufficient Evidence

1. Prophylaktische Verschreibung von Neuroleptika
2. Spezialisierte «Delir-Einheiten»
3. Anästhesietiefenmonitoring

Neuroprotektion: Ketamin



Hudetz JA et al. J Cardiothorac Vasc Anesth 2009 Oct;23(5):651-7.

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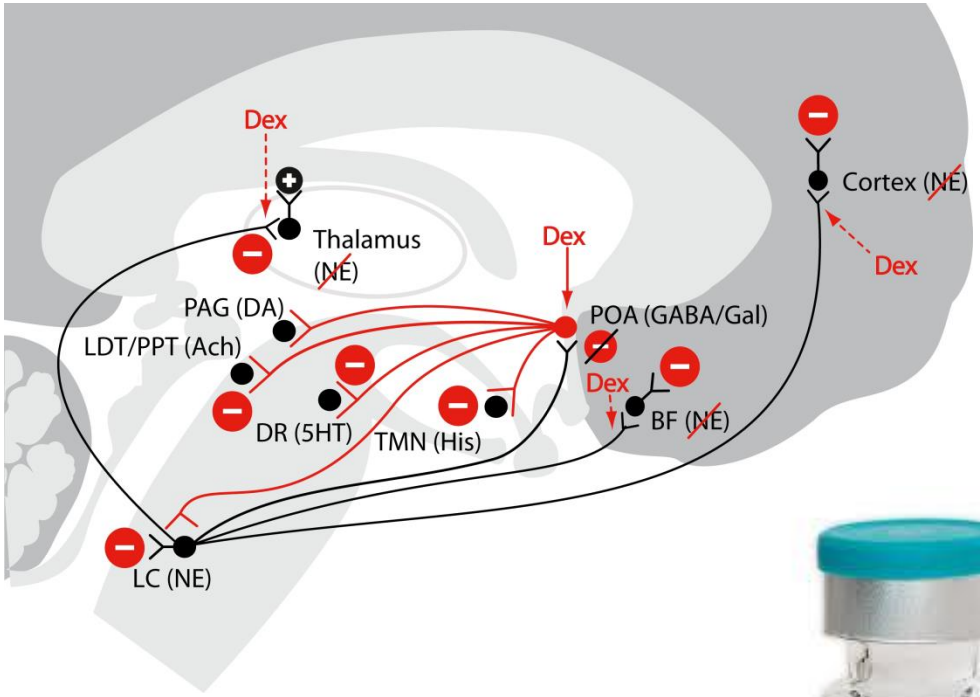
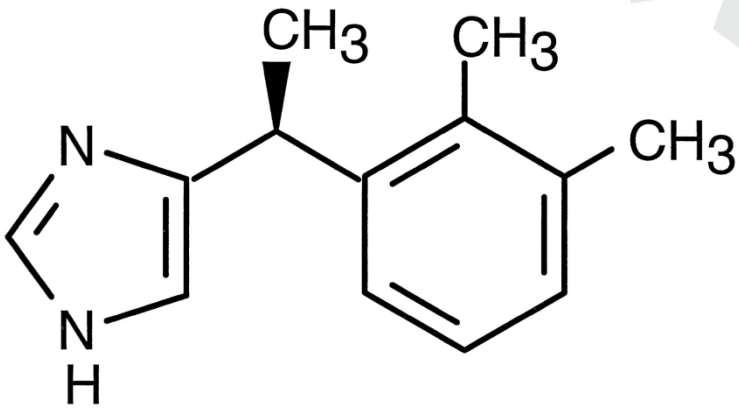
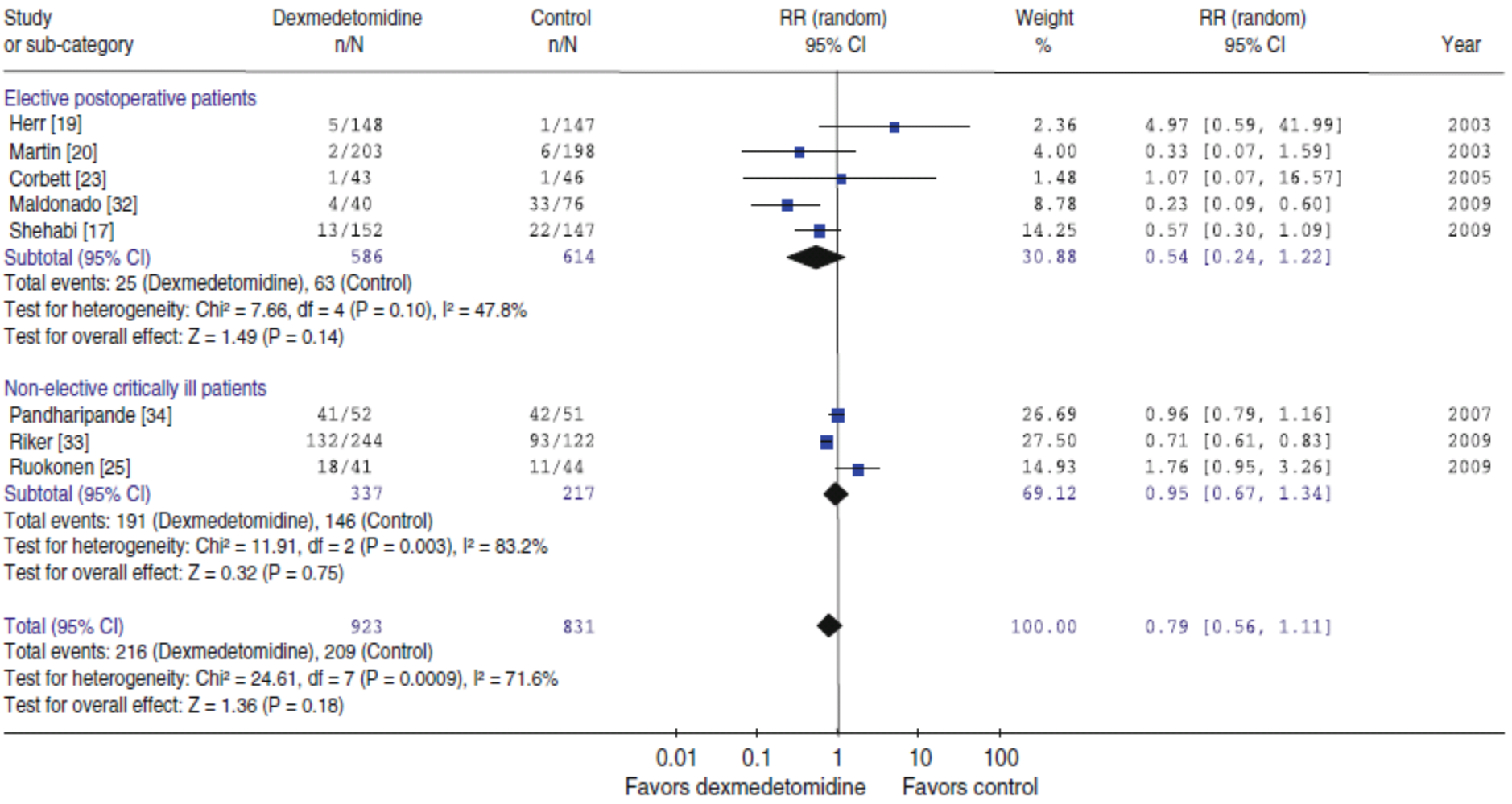
Dexmedetomidine (Dexdor®)





Dexmedetomidine



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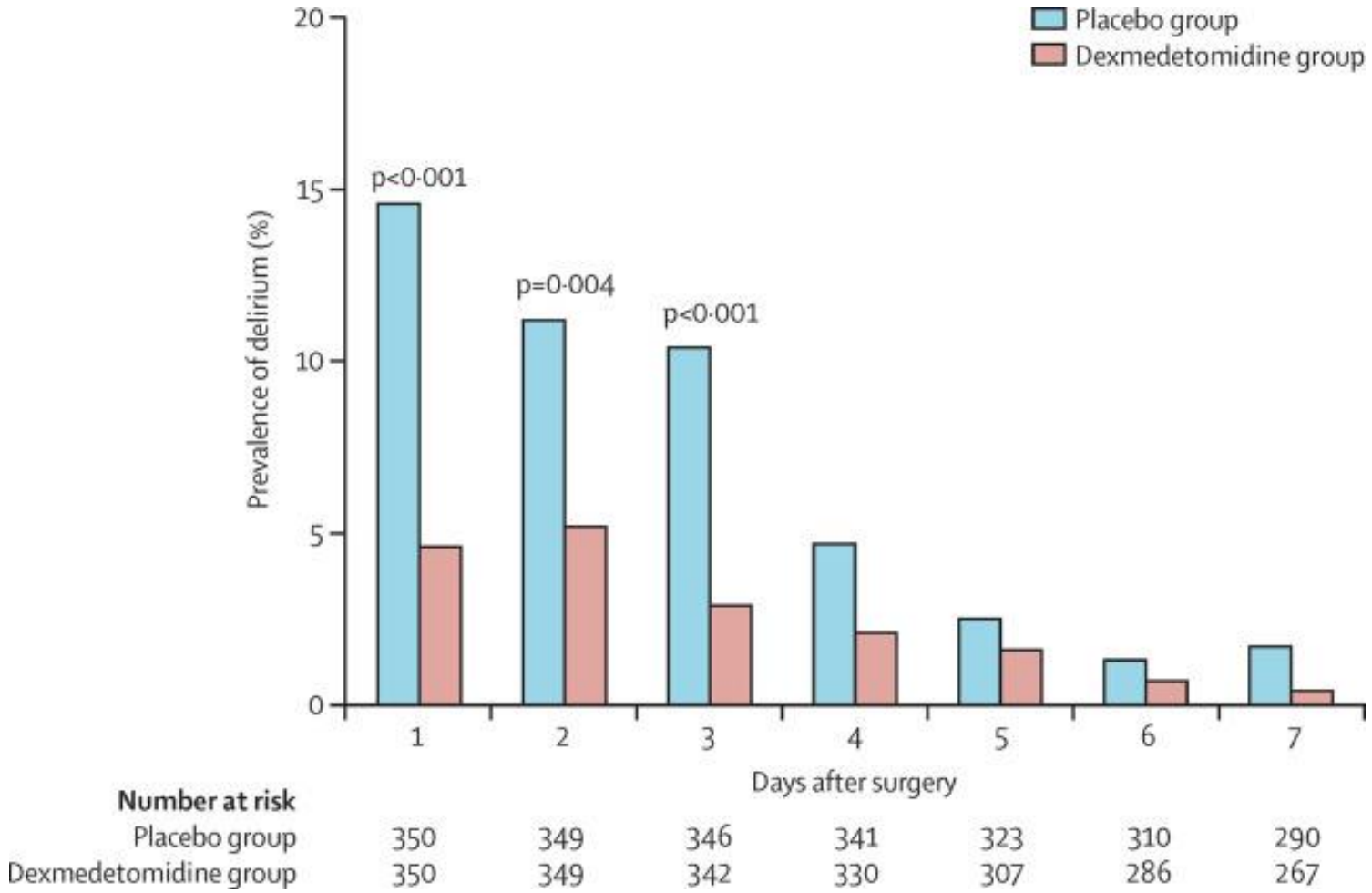
Dexmedetomidine



Su X et al. Lancet. 2016 Oct 15;388(10054):1893-1902.

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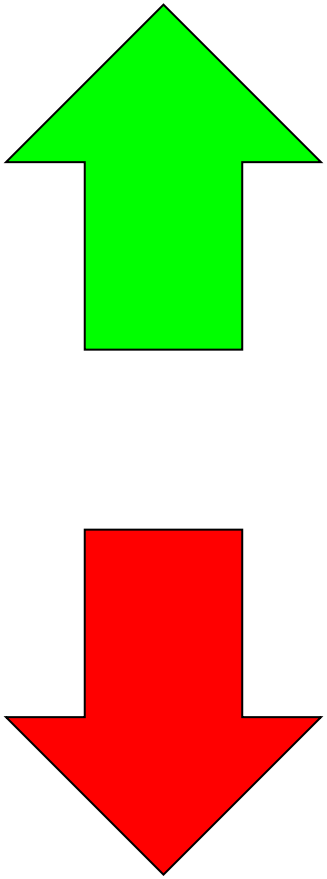
Benzodiazepine

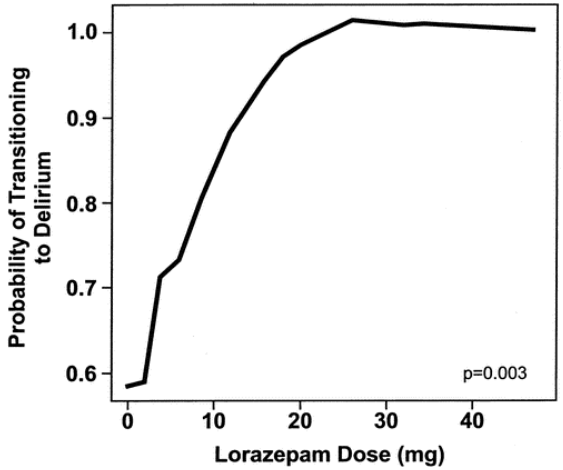


Management of Alcohol Withdrawal Delirium

An Evidence-Based Practice Guideline

Michael F. Mayo-Smith, MD, MPH; Lee H. Beecher, MD; Timothy L. Fischer, DO; David A. Gorelick, MD, PhD; Jeanette L. Guillaume, MA; Arnold Hill, MD; Gail Jara, BA; Chris Kasser, MD; John Melbourne, MD; for the Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine

ARCH INTERN MED/VOL 164, JULY 12, 2004



Pandharipande P et al. Anesthesiology 2006;104:21

Zusammenfassung

- Prävention: Nichts Neues
  - Nicht-pharmakologisch scheint zu funktionieren
  - Neuroleptika nicht empfohlen
  - Dexmedetomidine?

- Therapie?
  - *Rolle der Neuroleptika?*
  - *Dexmedetomidine?*

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