BRAIN DYSFUNCTION IN CRITICALLY ILL (SEPTIC) PATIENTS

Human hystopathology and animal models
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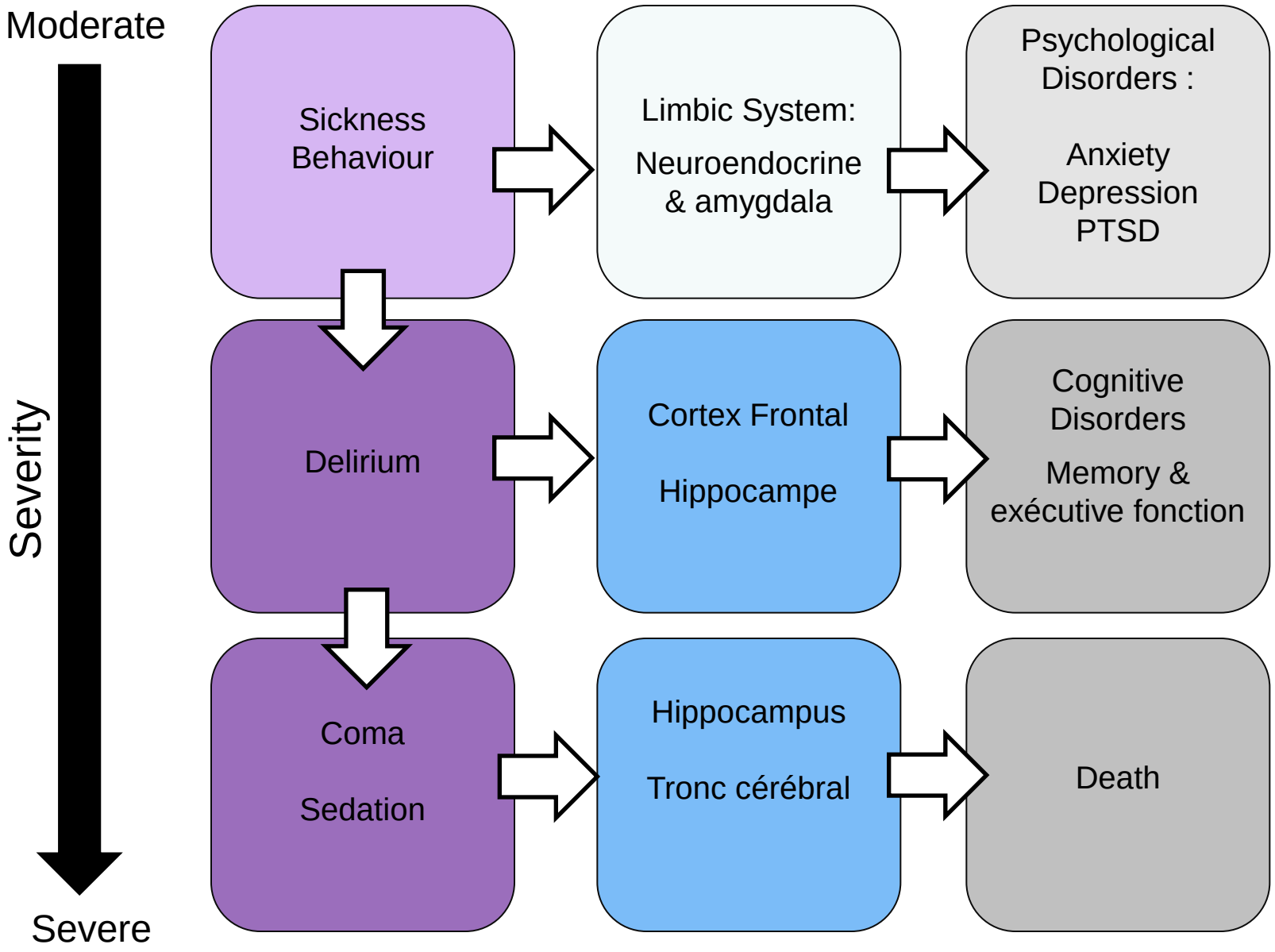
The Paradigm



DELIRIUM

DSM IV

A. **Troubles de la consciences: interaction avec environment, attention et concentration**

B. **Alteration d'au moins une fonction cognitive:**

- **Langage**
- **Mémoire**
- **Orientation temporo-spatiale**
- **Pensée et jugement**

C. **Début soudian ou rapidement progressif, fluctuation des symptomes**

D. **Secondaire à:**

- **Pathologie médicale**
- **Toxicité médicamenteurs**
- **Sevrage**

MORTALITE

Figure 3. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival

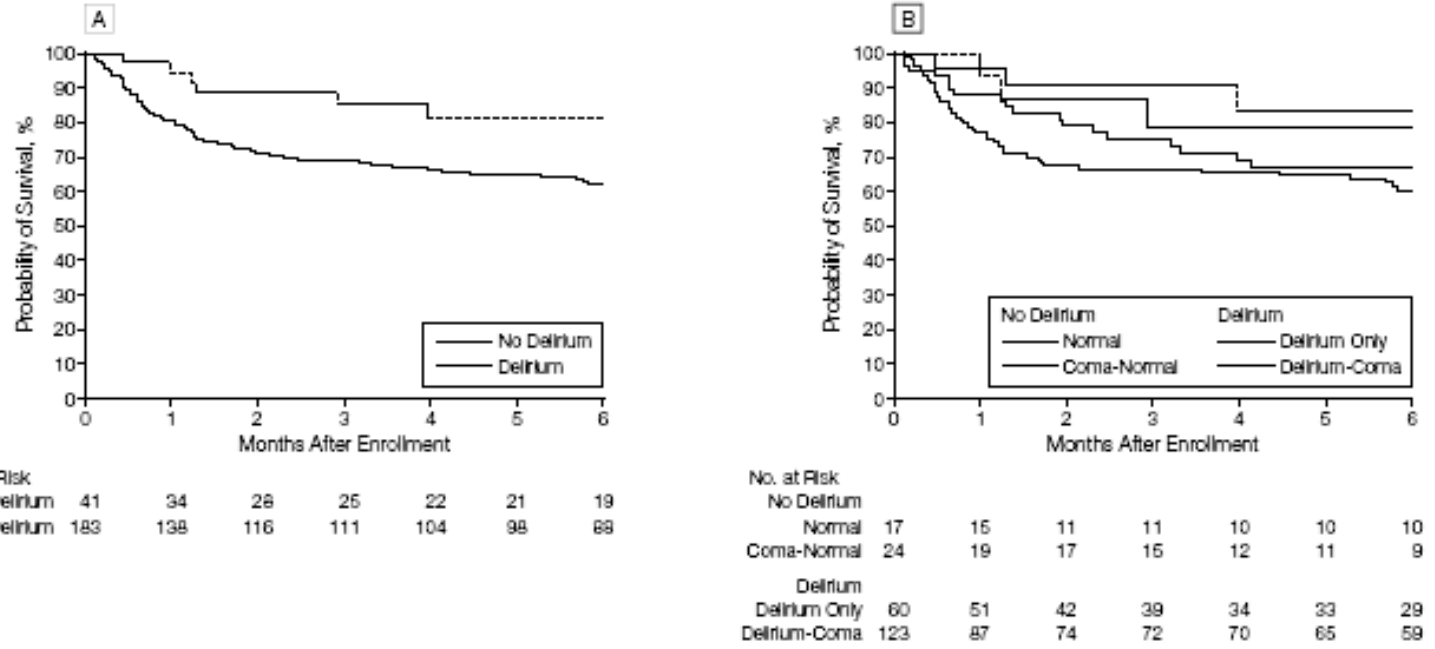
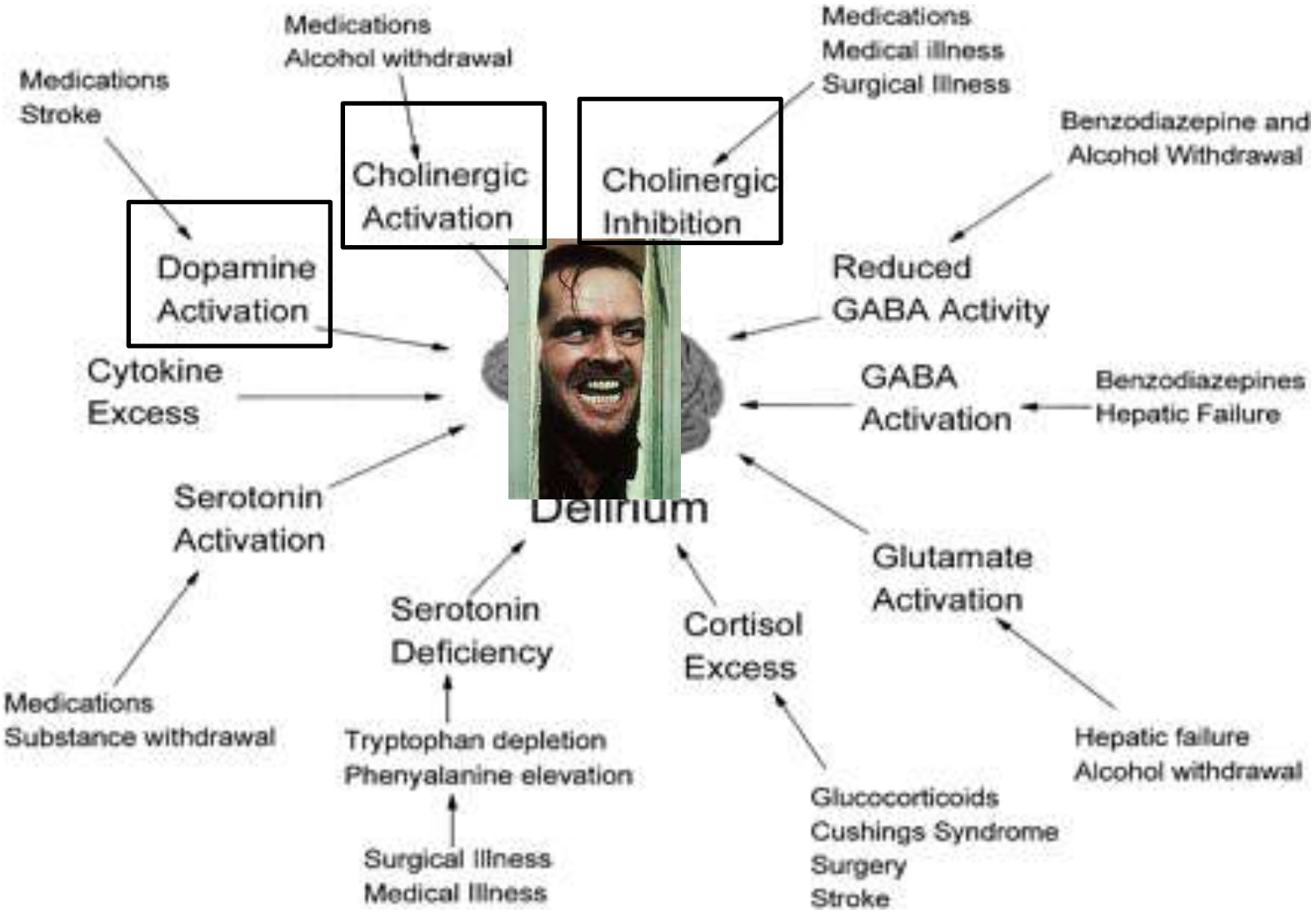


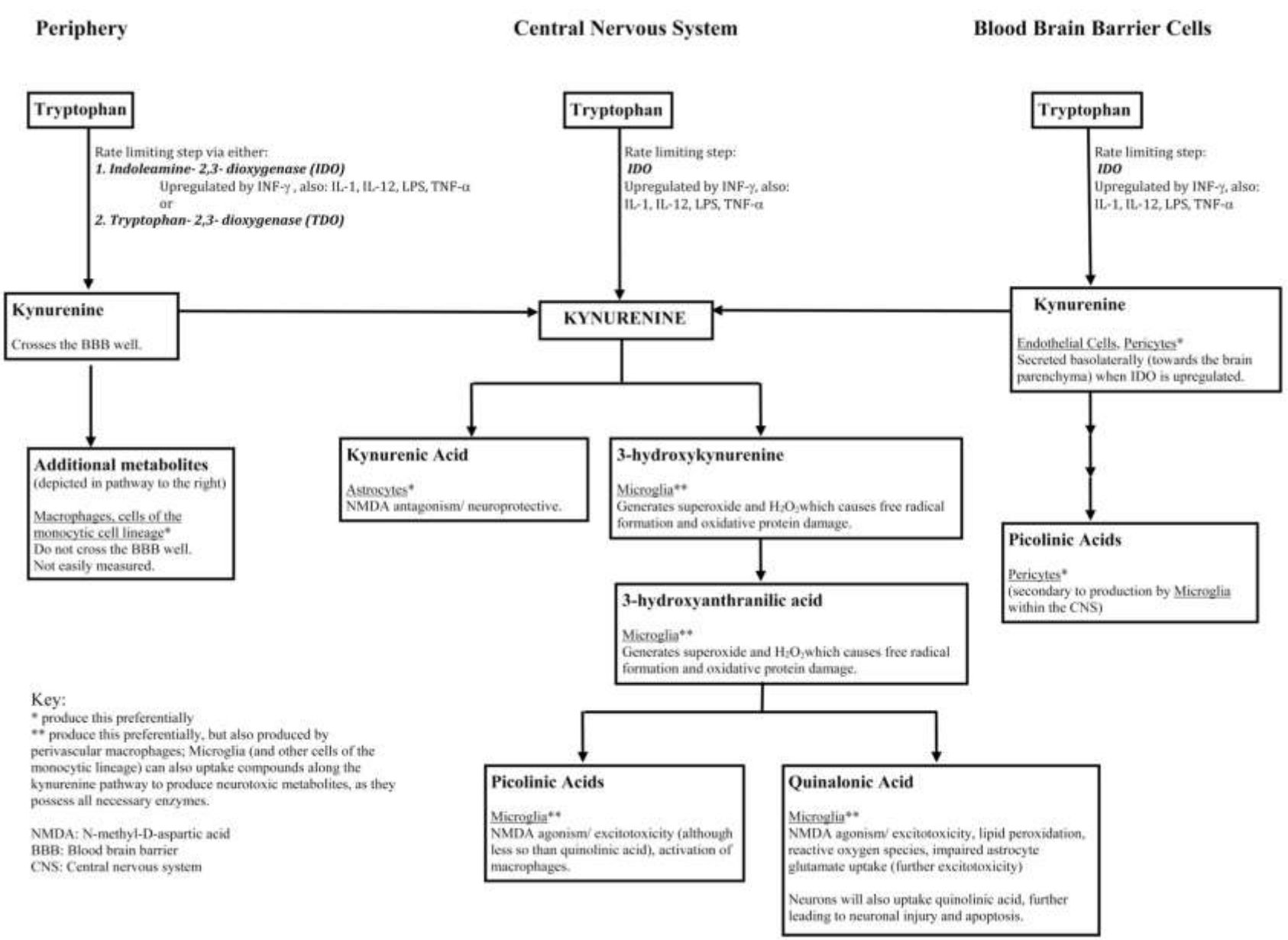
Table 3. Delirium Status and Clinical Outcomes Including 6-Month Mortality and Lengths of Stay

	No Delirium	Delirium	Adjusted *P* Value
	6-Month Mortality		
No.	41	183	
Rate, No. (%)	6 (15)	63 (34)	
Adjusted HR (95% CI)*	Reference	3.2 (1.4-7.7)	.008

Ely et al – JAMA - 2004

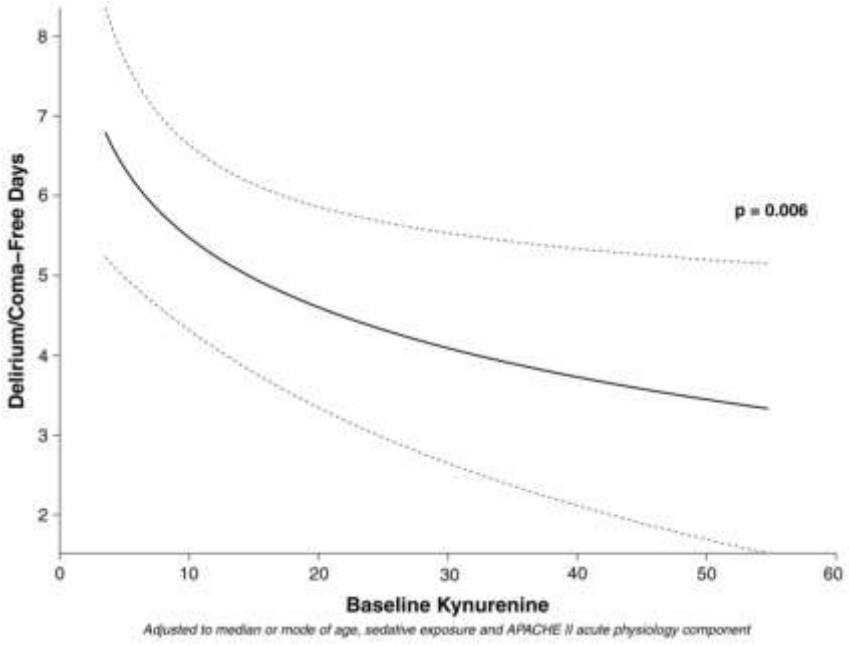
DELIRIUM: DESEQUILIBRE DE LA NEUROTRANSMISSION

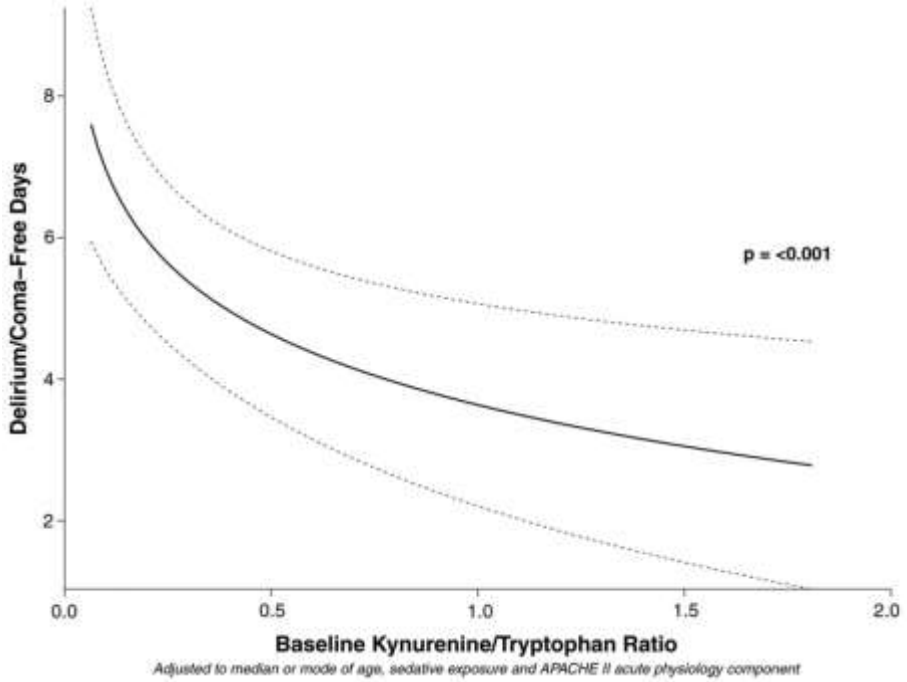




An imbalance favoring the production of neurotoxic metabolites leads to neuronal and glial cell injury, excitotoxicity, and apoptosis, which may be clinically manifested as delirium or coma.

KYNURENINE PATHWAY



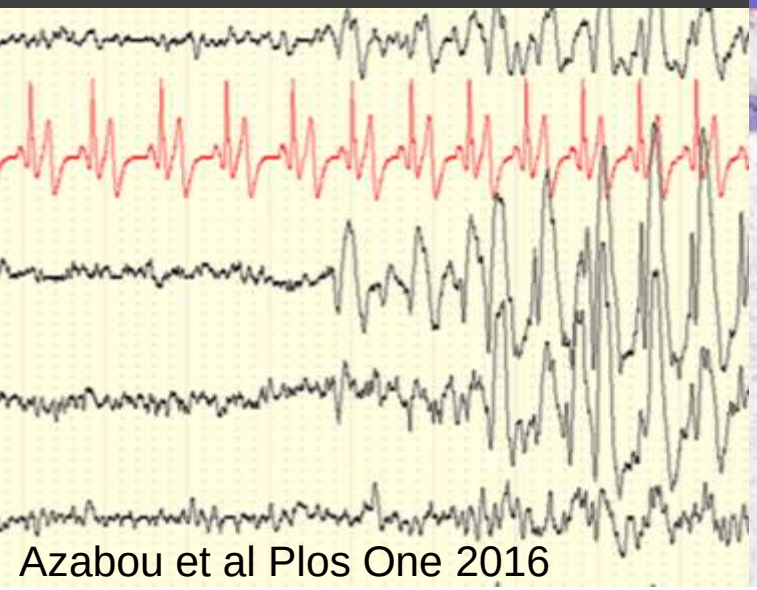


Adams Wilson et al - Crit Care Med - 2012

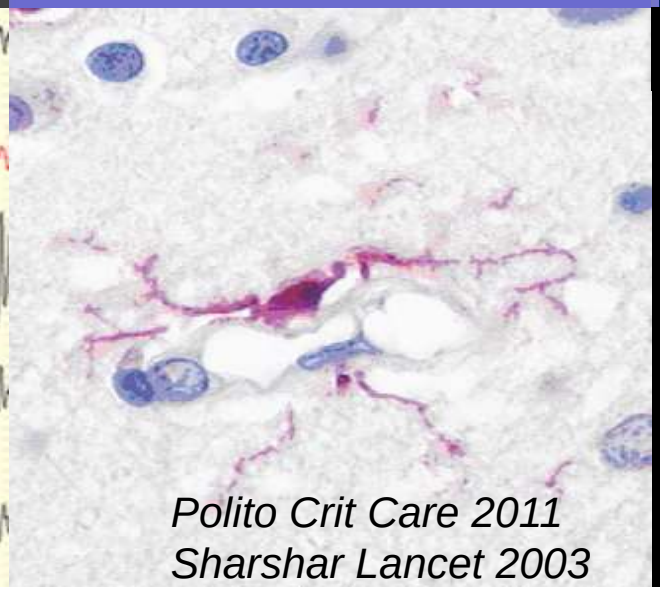
Sepsis Associated Encephalopathy - Pathophysiology

SYSTEMIC/LOCAL INFLAMMATORY RESPONSE

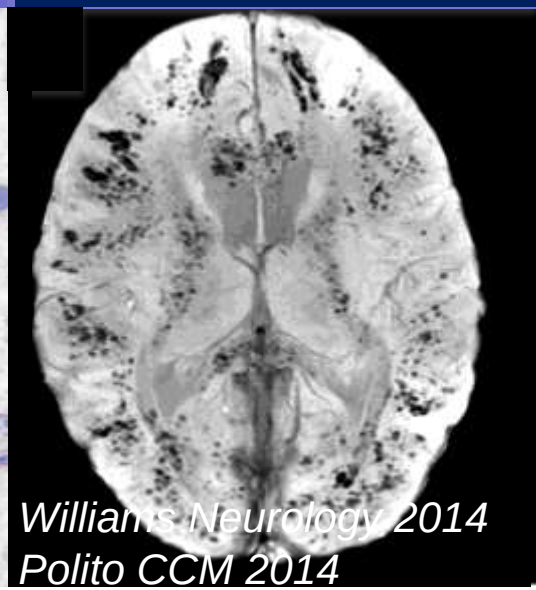
Excitotoxic	Neuroinflammatory	Ischemic



Azabou et al Plos One 2016



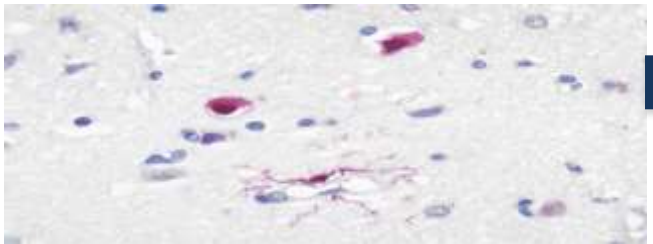
Polito Crit Care 2011
Sharshar Lancet 2003



Williams Neurology 2014
Polito CCM 2014

Neuronal apoptosis/dysfunction

Death ?



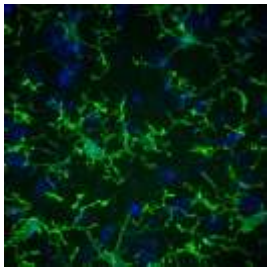
Post sepsis Psycho-Cognitive impairment ?

NEUROINFLAMMATORY PROCESS

EXPERIMENTAL OR CLINICAL DEMONSTRATION

1. Endothelial activation
2. Alteration of blood-brain barrier
   - Role of TNFa
   - Role of complement
3. Brain expression of cytokines and iNOS
4. Microglial activation
   - Amplification of neuro-inflammatory process
5. Brain cells oxidative stress
6. Brain cell apoptosis
7. Alteration of neurotransmission

STATINS?



GLUCOSE?

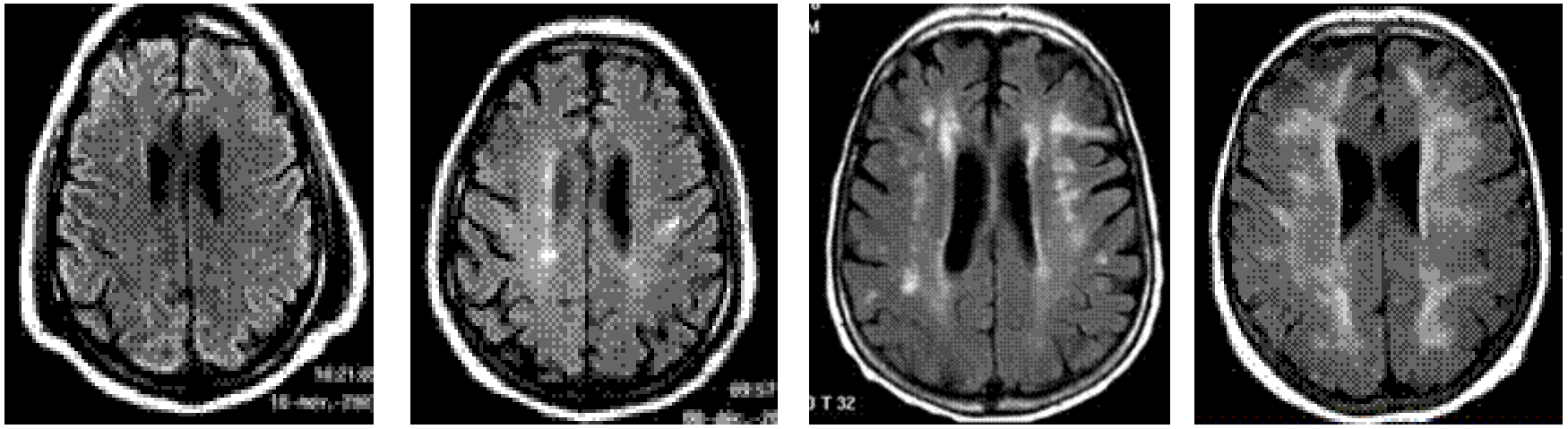
WHITE MATER HYPERDENSITIES

15/72 (21%) septic shock patients who developped an acute brain dysfunction

BBB increased permeability/axonal damage/Demyelination

Might be associated with long-term cognitive impairment (Morandi et al – Psychiatry - 2011)

BBB alteration



Before | After

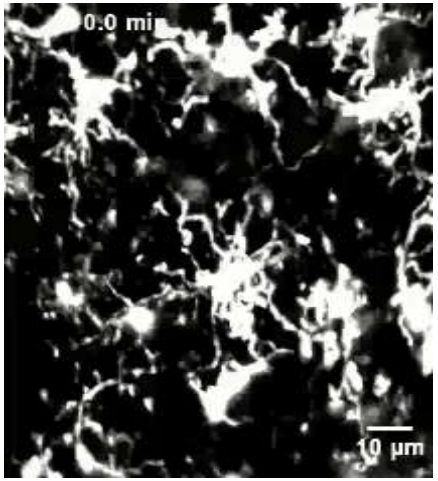
Acquired during sepsis

Grade II | Grade III

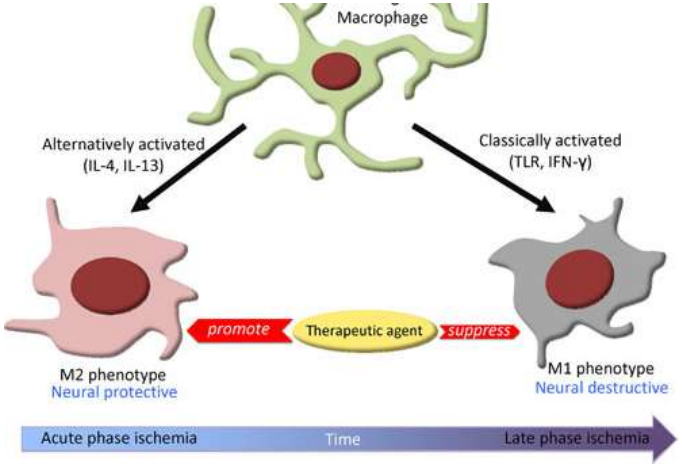
Sharshar et al - ICM – 2007;
Polito et al – Crit Care - 2013

MICROGLIAL CELLS

1. RAMIFICATION/DERAMIFICATION
2. MOBILITY
3. PHAGOCYTOSIS
4. SECRETION



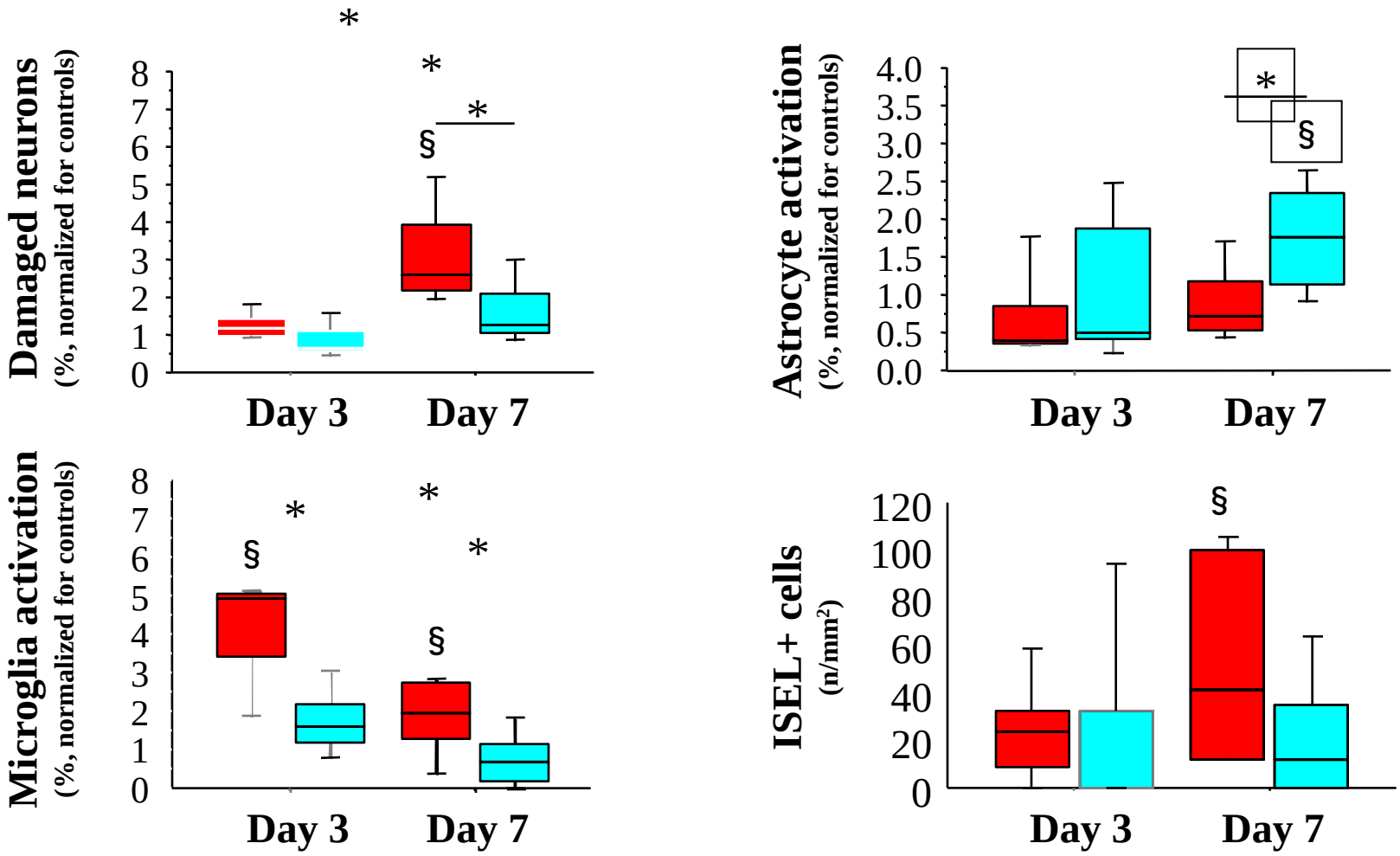
1. IMMUNE PHENOTYPE (M1, M2a and M2b)
2. MORPHOTYPE (Hyperramified to ameboid)
3. REGIONAL/TEMPORAL VARIATIONS



1. IMMUNE SURVEILLANCE
2. SYNAPTIC PRUNNING
3. CELLS INTERACTION

1. NEUROPROTECTION VS NEUROTOXIC

Blood glucose and cortex of critically ill rabbits



§: P<0.05 versus control

* : P<0.05 between HG and NG or between day 3 and 7

Hyperglycemia

Normoglycemia

Sonneville et al – JCEM - 2013

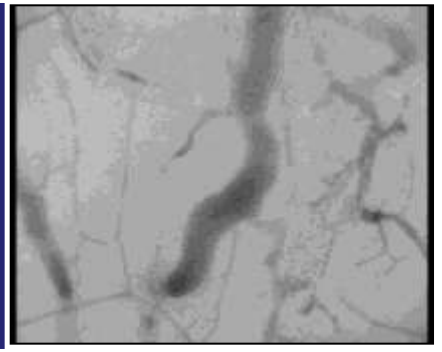
ISCHEMIC PROCESS

Macrocirculatory dysfunction

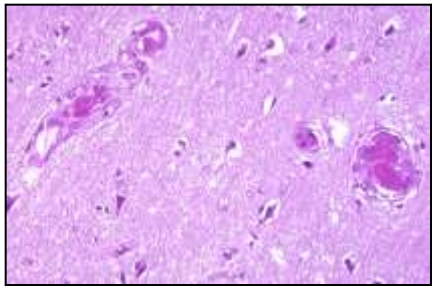
1. Systemic hypotension or decreased blood flow
2. Impaired autoregulation

Microcirculatory dysfunction

1. Role of TNFa
2. Role of complement



Clotting disorder



NEUROTOXIC PROCESS

- **SAE is characterized by EEG abnormalities**
- **Some EEG patterns are associated with outcome**
- **SAE results from neurotransmission impairment**
- **Sepsis impairs long-term potentiation**
- **Evidence of neuronal apoptosis**

Sharshar et al – Lancet – 2004
Oddo et al – Crit Care Med - 2009

BRAIN STRUCTURES

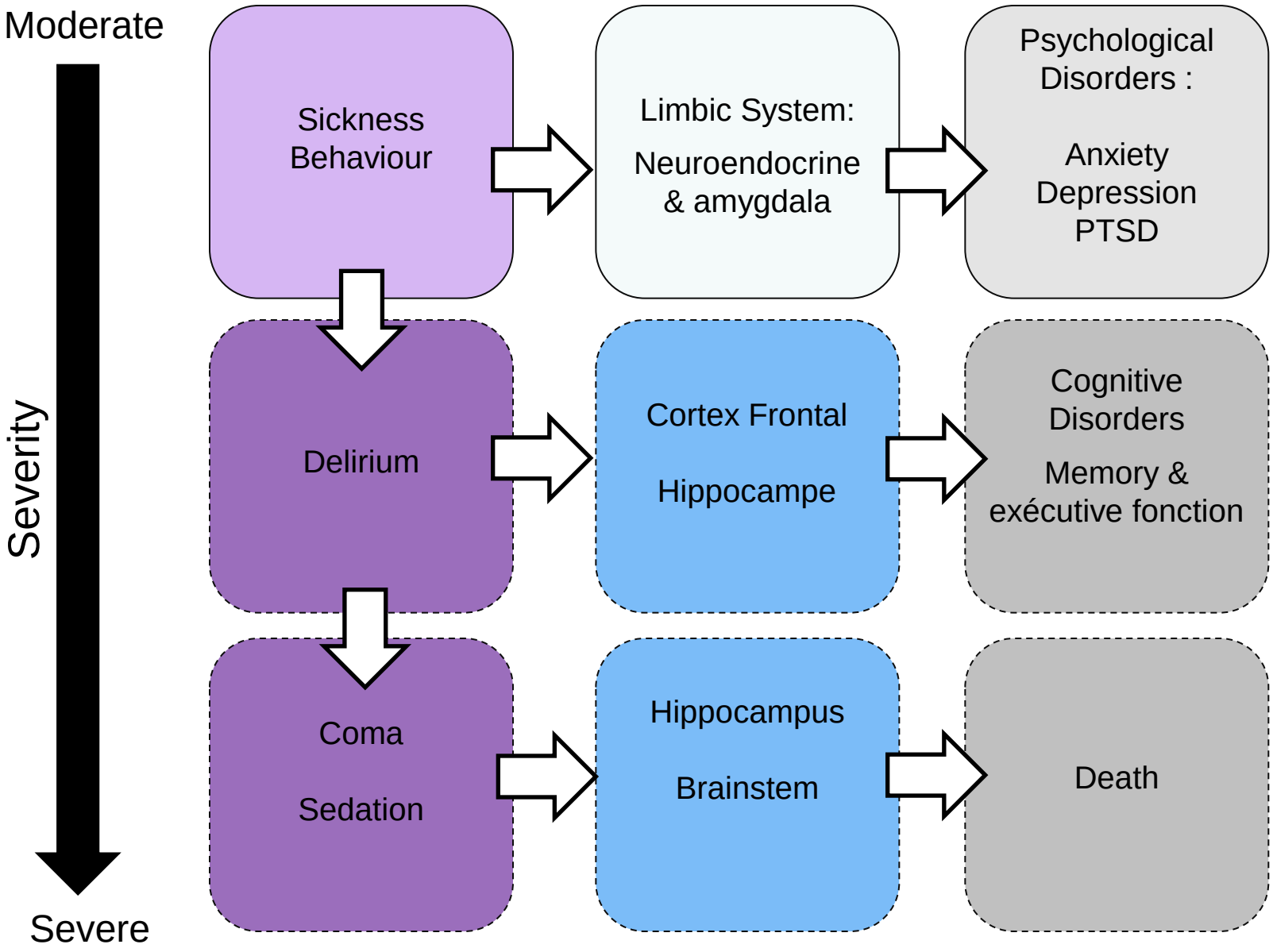
Hippocampus and frontal cortex

- **Acute brain dysfunction**
- **Long-term psycho-cognitive dysfunction**
- **But not mortality**

Concept of Brainstem Dysfunction

- **Mortality**
- **Impaired arousal**
- **Impaired immune response**

The Paradigm



POST-ICU SYNDROME

- NEUROMUSCULAR DYSFUNCTION (25 to 50%)
  - Weakness
  - Fatigue
  - Pain
- PSYCHOLOGICAL DISORDERS (10 to 30%)
  - Anxiety
  - Depression
  - PTSD
- COGNITIVE IMPAIRMENT (30 to 100%)
  - Memory
  - Executive function, attention
  - Verbal fluencey
- IMMUNOLOGICAL /NEUROENDOCRINE DYSFUNCTION

AGE
PREXISTING DISEASE
CRITICAL ILLNESS SEVERITY (SEPSIS, ARDS)
SEDATION/DELIRIUM

INTERDEPENDENCY

PSYCHOLOGICAL DISORDERS

NEUROMUSCULAR DYSFUNCTION

COGNITIVE IMPAIRME

NE/IMMUNE DYSFUNCTION

MULTDIMENSIONAL CARE

PSYCHOLOGISTS/PSYCHIATRISTS

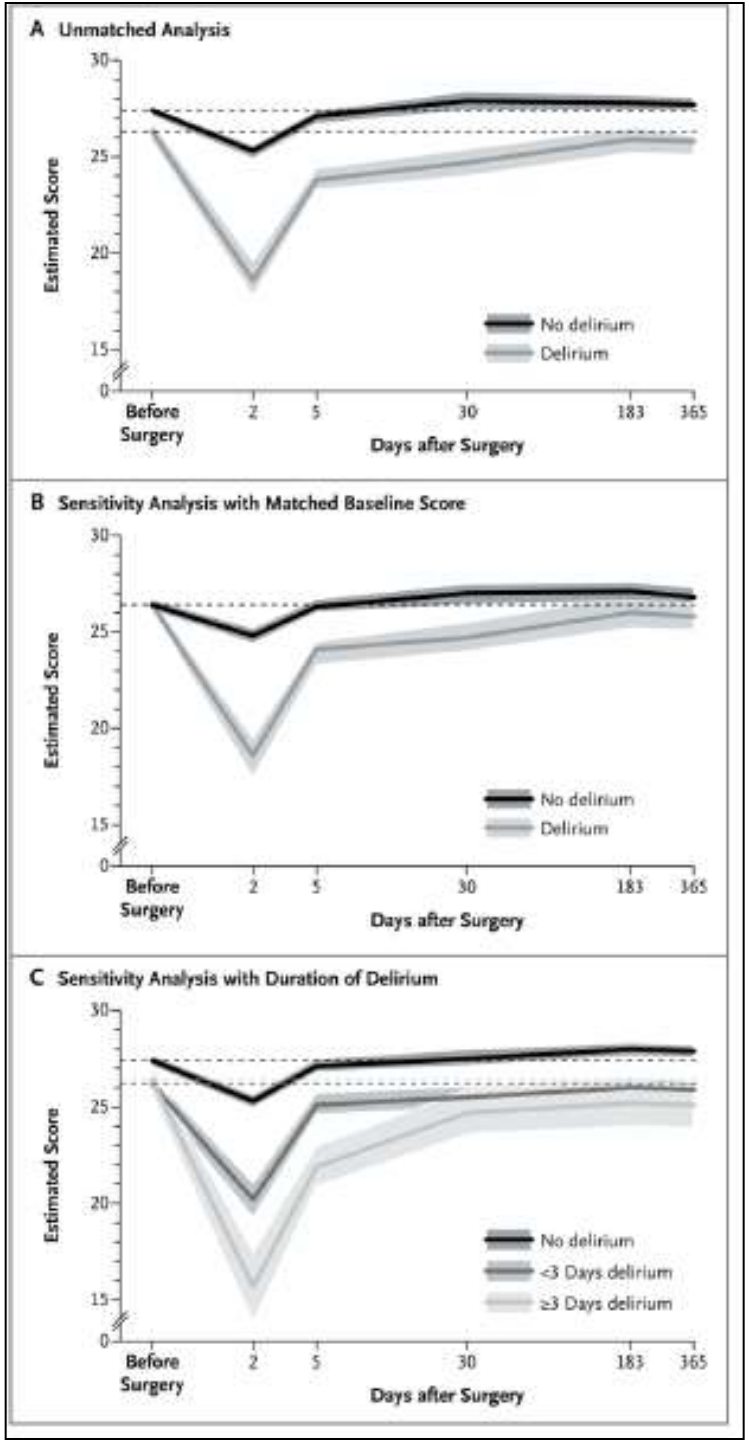
NEUROLOGISTS
PHYSIOTHERAPISTS
NEUROPHYSIOLOGISTS
PHYSIOLOGISTS

NEUROLOGISTS
PSYCHOLOGISTS

ENDOCRINOLOGISTS

HOW THE ICU PHYSICIAN CAN BE INTEGRATED? WHEN? FOR WH

DECLIN COGNITIF A MOYEN TERME



225 patients post-operatoire

Saczynski et al – NEMJ - 2012

DECLIN COGNITIF A MOYEN TERME

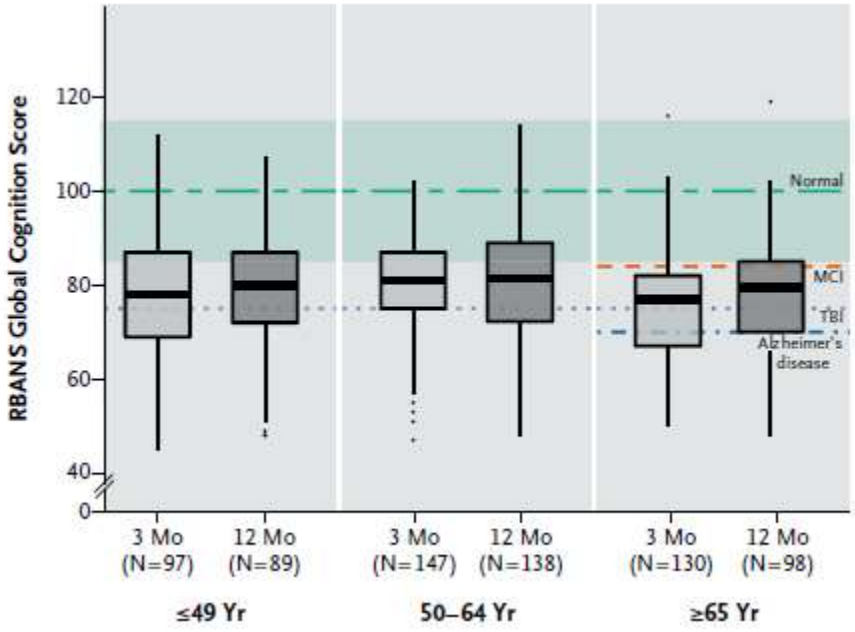
Cognitive outcomes during follow-up

Outcome, % (n/total)	Follow-up Assessment	
	3 months (n=76)*	12 months (n=52)*
No impairment	21% (16/76)	29% (15/52)
Mild/moderate impairment	17% (13/76)	35% (18/52)
Severe impairment	62% (47/76)	36% (19/52)

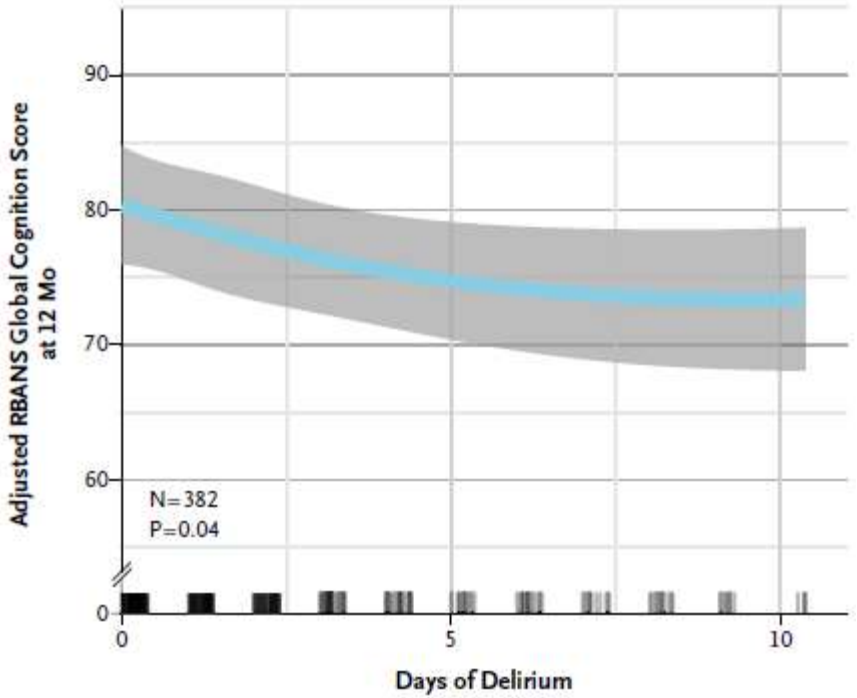
77 Medical ICU patients

Girard et al – Crit Care Med - 2010

Long-Term Cognitive Impairment after Critical Illness



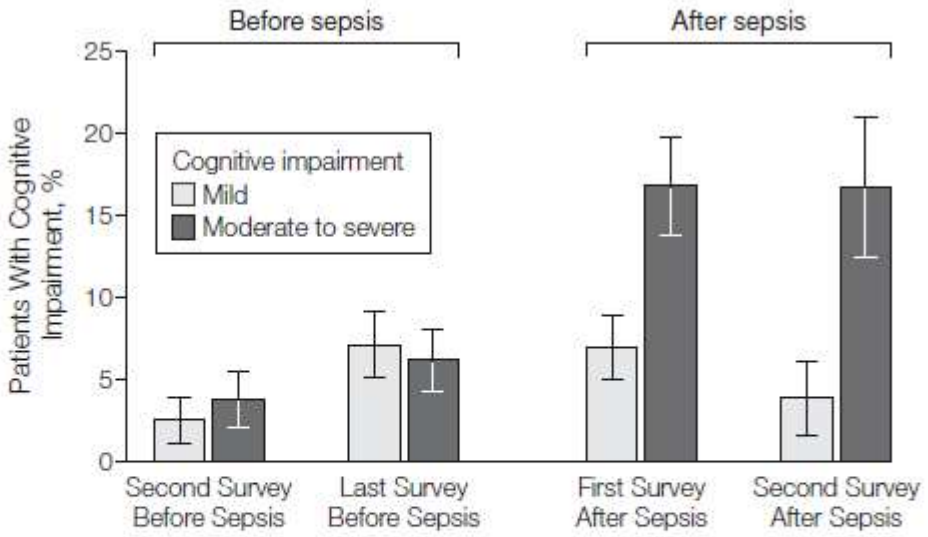
Global Cognition Scores in Survivors of Critical Illness.



Pandharipande et al – NEJM - 2013

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Figure 2. Cognitive Impairment Among Survivors of Severe Sepsis at Each Survey Time Point

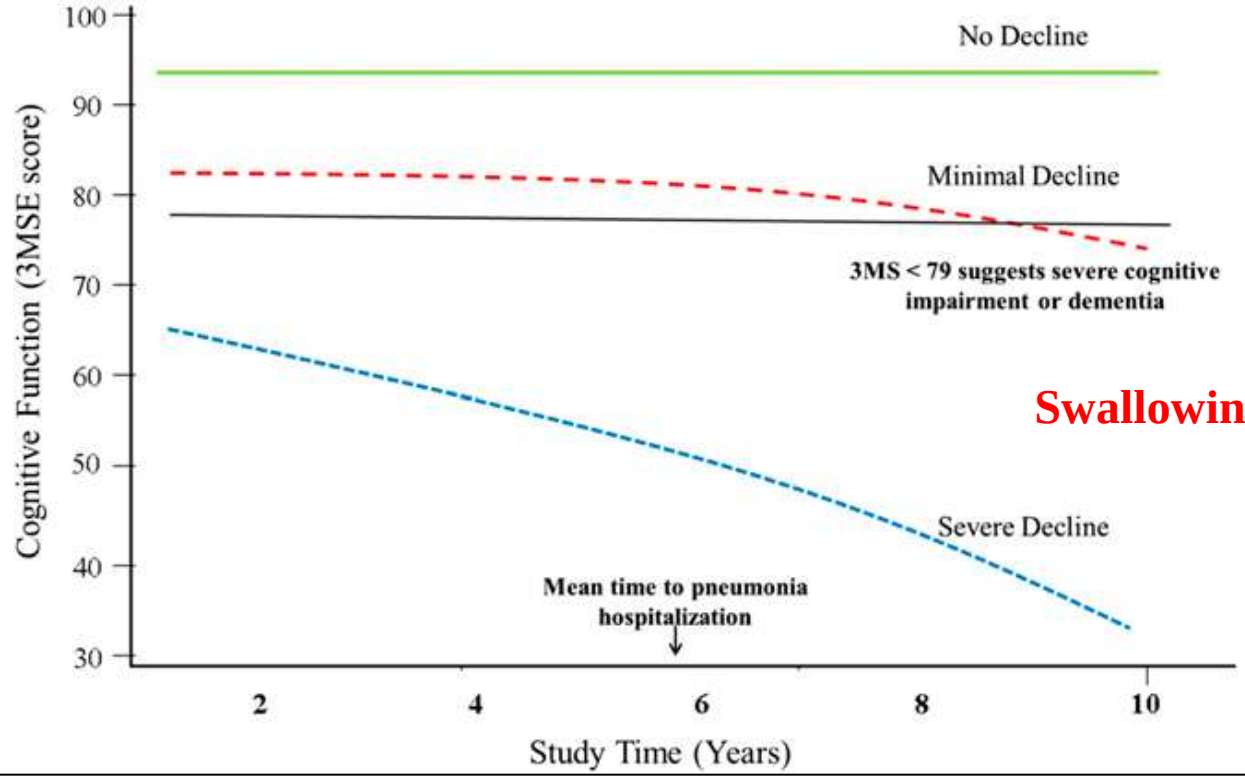


	Second Survey Before Sepsis	Last Survey Before Sepsis	First Survey After Sepsis	Second Survey After Sepsis
Time to sepsis admission, median (IQR), y	−3.1 (−3.7 to −2.7)	−1.1 (−1.7 to −0.7)	0.9 (0.4 to 1.4)	2.8 (2.3 to 3.4)
No. of patients	484	623	623	288

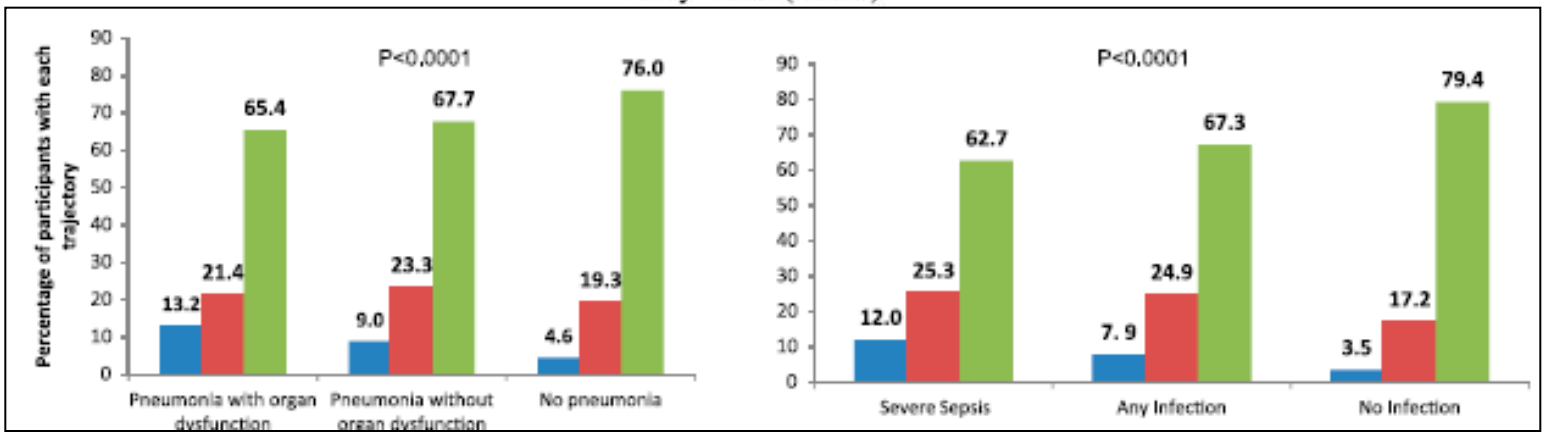
Error bars indicate 95% confidence intervals (CIs); IQR, interquartile range.
Interpretive Example: Compared with stable rates before severe sepsis, the prevalence of moderate to severe cognitive impairment increased from 6.1% (95% CI, 4.2%-8.0%) before severe sepsis to 16.7% (95% CI, 13.8%-19.7%) at the first survey after severe sepsis ($P < .001$ by χ^2 test; Table 2).

Iwashyna et at – JAMA - 2010

Bidirectional Relationship between Cognitive Function and Pneumonia

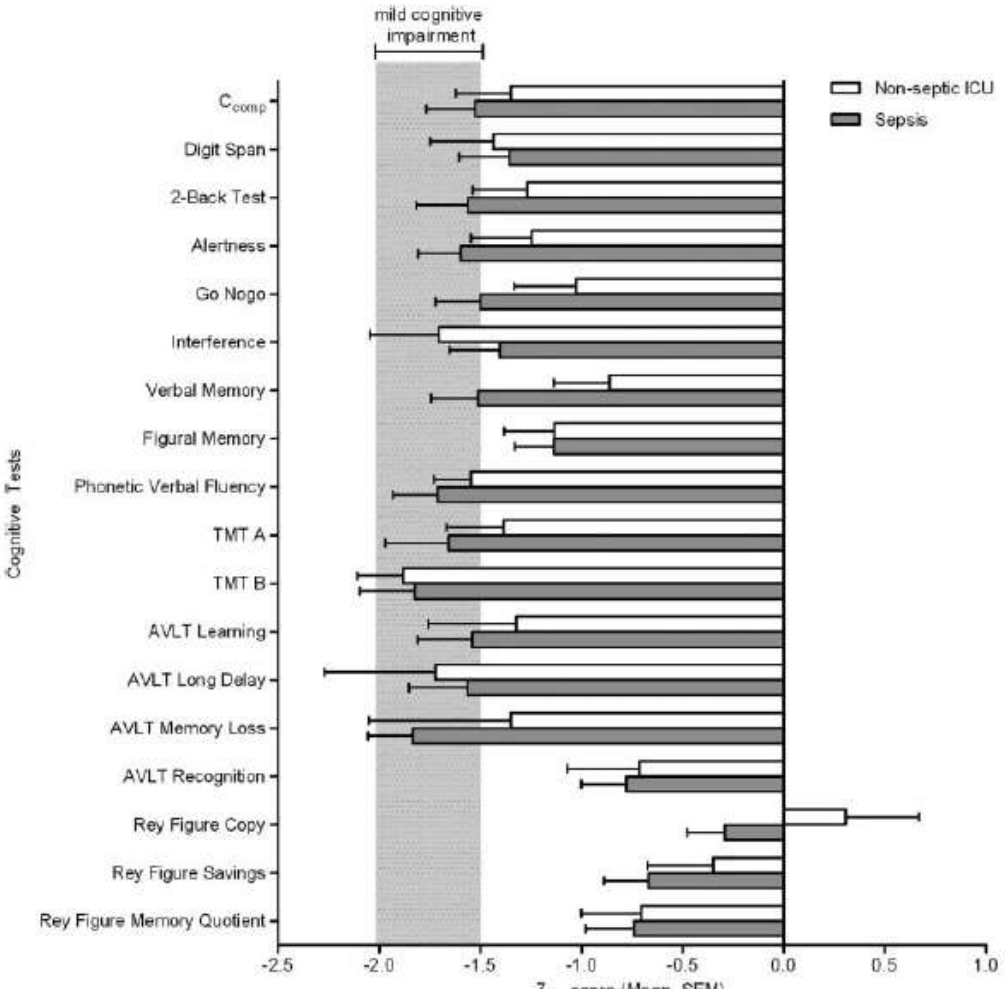


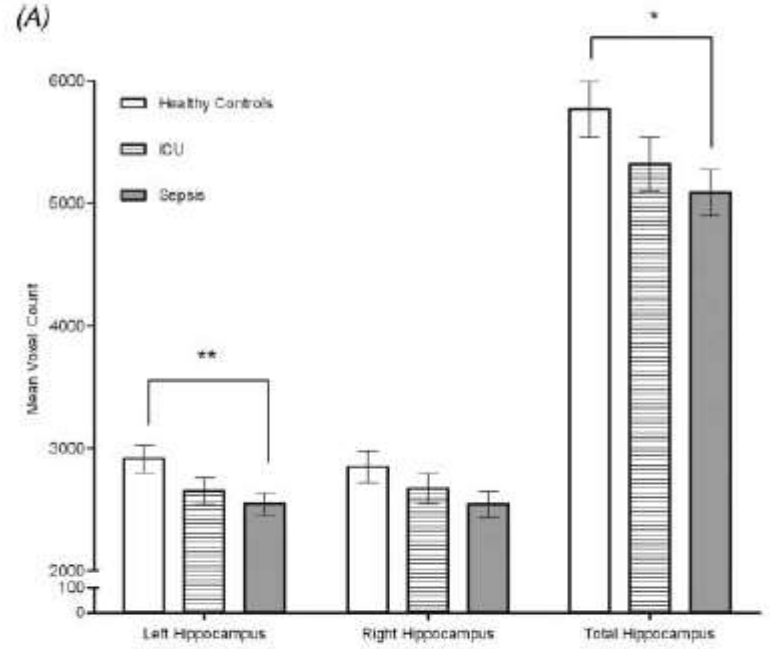
Swallowing dysfunction?

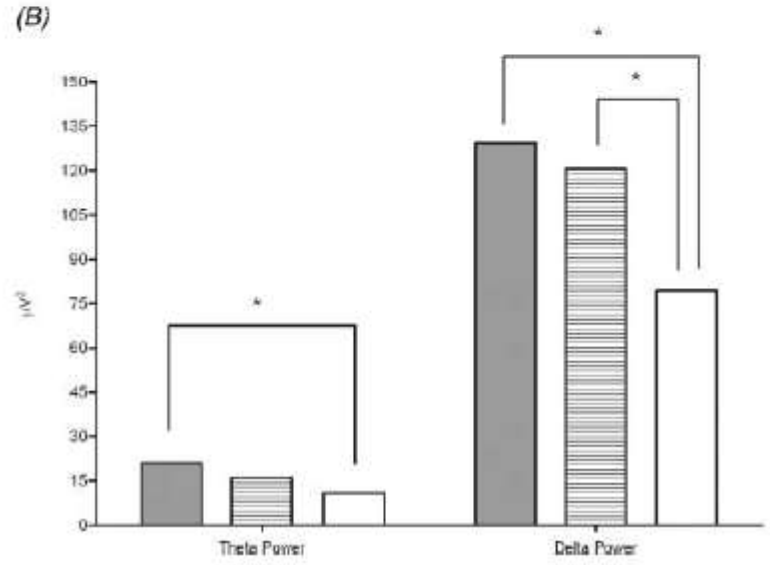


Shah et al- AJRCCM - 2013

Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors



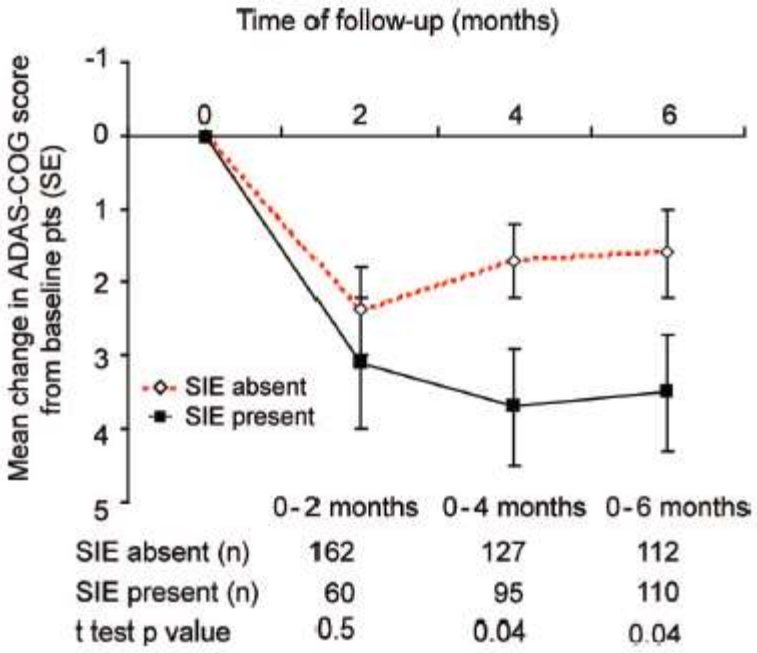




Semmler et al – JNNP - 2013

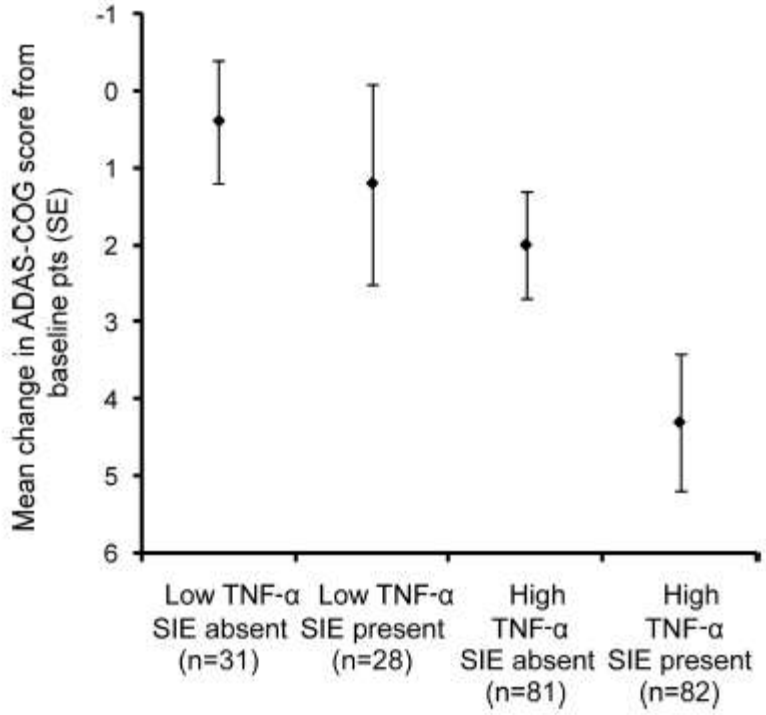
Systemic inflammation and disease progression in Alzheimer disease

Figure 1 Presence or absence of systemic inflammatory events and mean change in cognitive score from baseline



	0-2 months	0-4 months	0-6 months
SIE absent (n)	162	127	112
SIE present (n)	60	95	110
t test p value	0.5	0.04	0.04

Figure 2 Rate of cognitive decline at 6 months by presence of incident systemic inflammatory events and baseline serum TNF-α levels

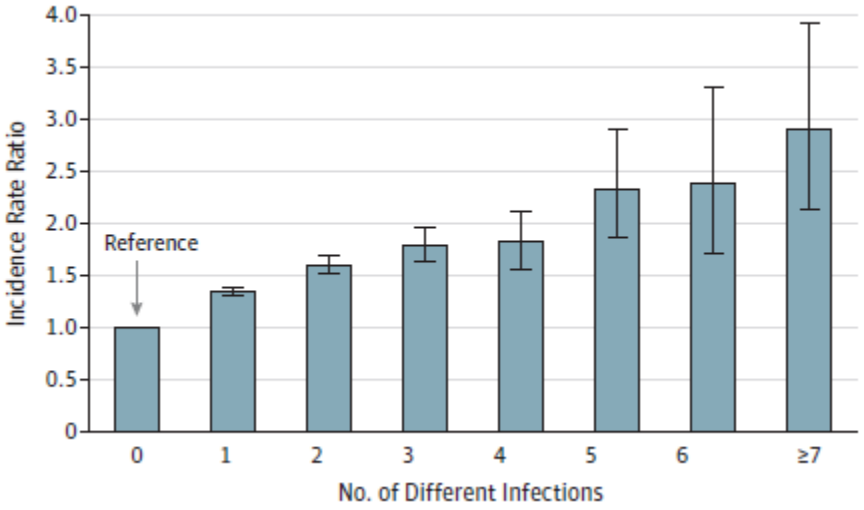


Holmes et al – Neurology - 2009

JAMA Psychiatry | Original Investigation

A Nationwide Cohort Study of the Association Between Hospitalization With Infection and Risk of Death by Suicide

A According to the number of hospitalizations with different infections



C According to the time since the last hospitalization with treatment for infection

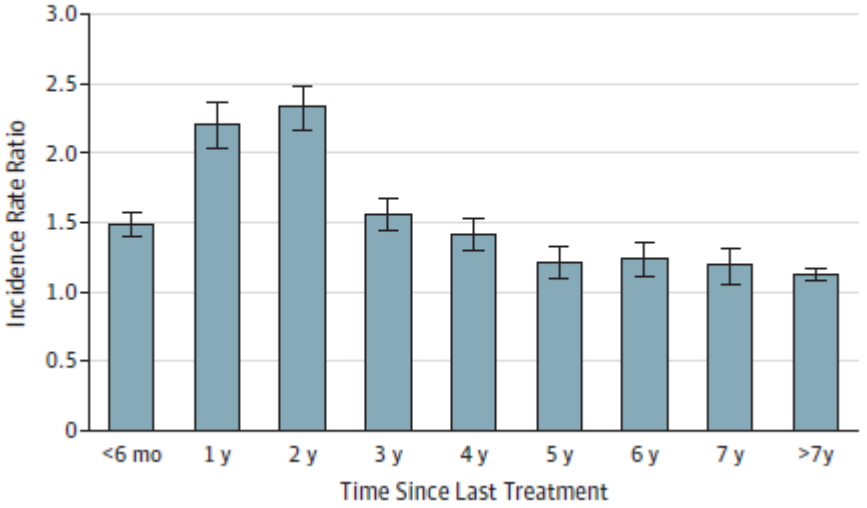


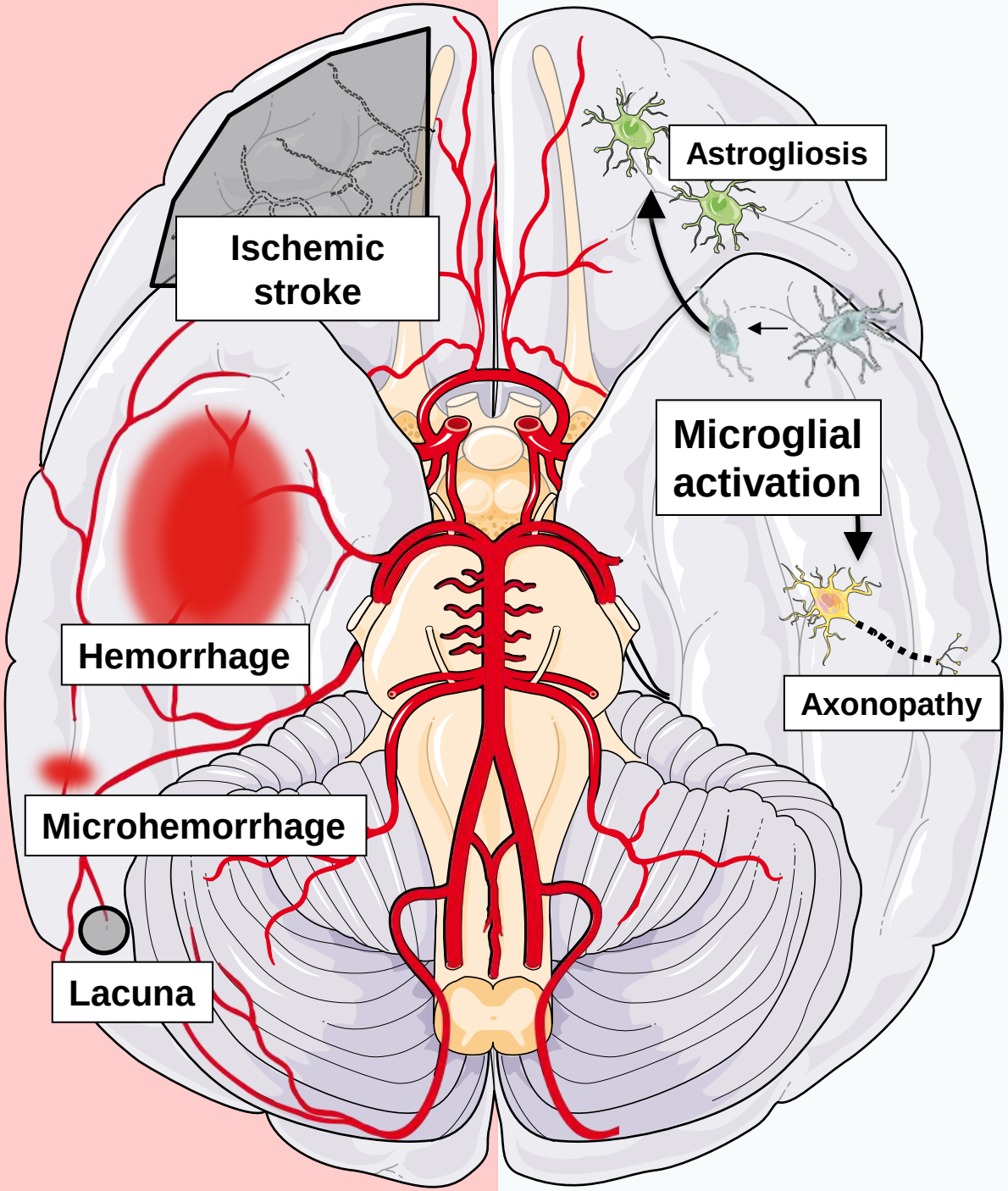
Table 2. Incidence Rate Ratios of Suicide in Denmark (1980-2011) Among Persons With Psychiatric Diagnoses According to the Time of Infection

Variable	No. of Suicides	Person-years	Incidence Rate Ratio (95% CI)	
			Basic Adjustment[a]	Fully Adjusted[b]
Psychiatric diagnosis with no history of infection	8164	5 556 835	1 [Reference]	1 [Reference]
Infection before a psychiatric diagnosis	1733	1 584 976	1.27 (1.21-1.34)	1.21 (1.15-1.28)
Infection after a psychiatric diagnosis	1875	1 409 183	1.04 (0.99-1.09)	0.93 (0.88-0.98)
Total	11 772	8 550 994	NA	NA

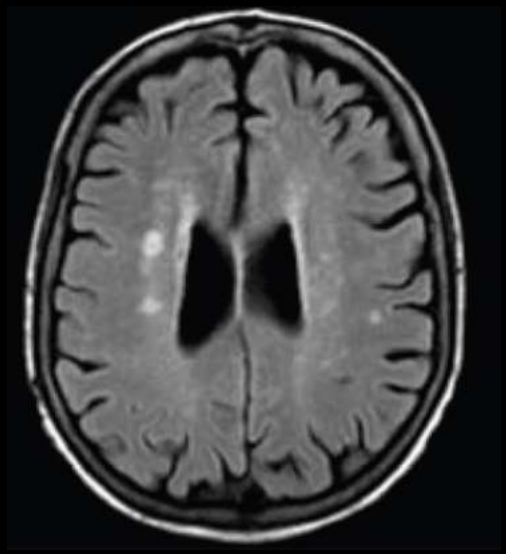
Lund-Sorensen et al – JAMA - 2016

MECHANISMS OF LONG-TERM COGNITIVE DECLINE IN SEPSIS

Vascular Hypothesis



Neuroinflammatory Hypothesis



MRI IN PATIENTS WITH DELIRIUM

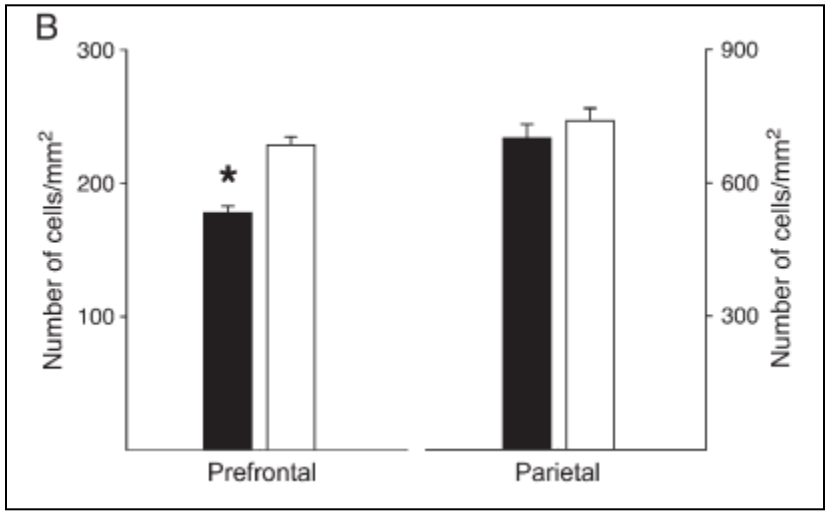
Increased risk of long-term cognitive dysfunction

1. **White matter hyperintensities**
2. **Brain atrophy**

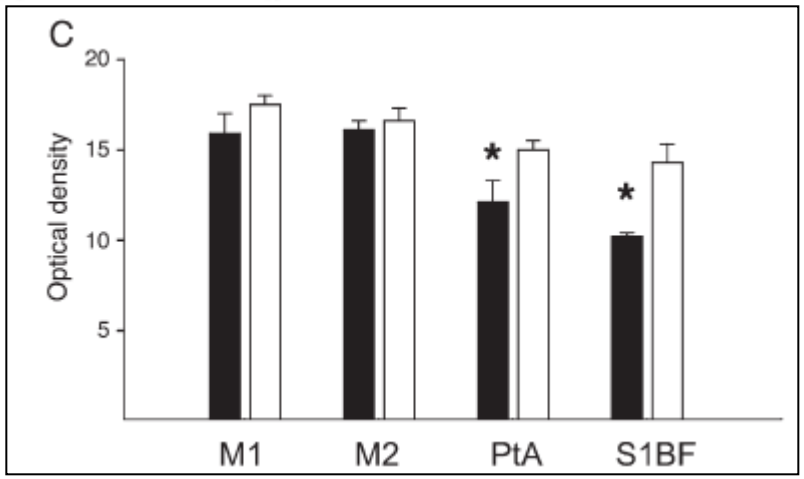
Morandi et al – Psychiatry- 2011

Long-term cognitive impairment, neuronal loss and reduced cortical cholinergic innervation after recovery from sepsis in a rodent model

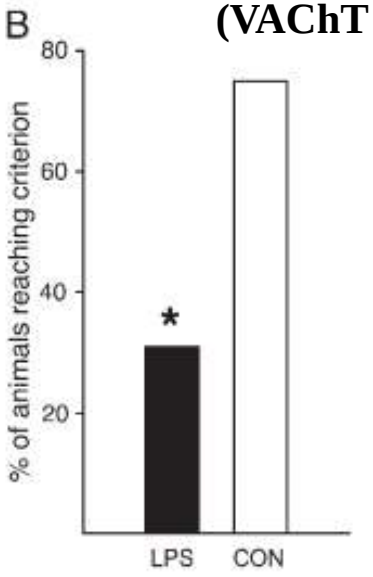
LPS – 3 months



Neuronal loss
(NeuN –immunoreactivity)



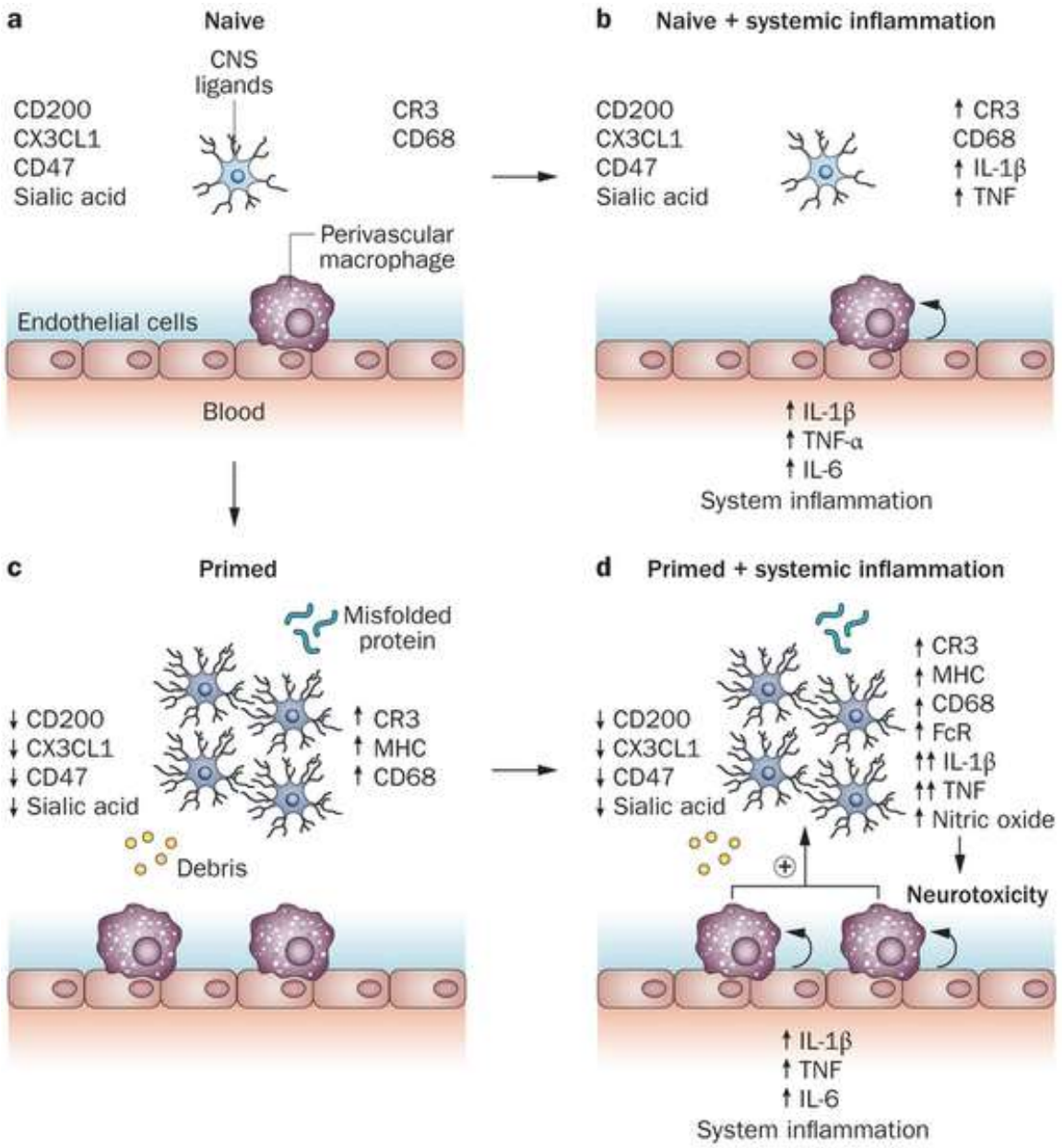
Reduced cholinergic innervation
(VAChT immunoradiography)



Impaired behavioral
(8-arms radial mace)

Semmler et al – Exp Neu - 2007

Microglial priming, a recent concept



Long-term cerebral consequences of sepsis

Catherine N Widmann, Michael T Heneka

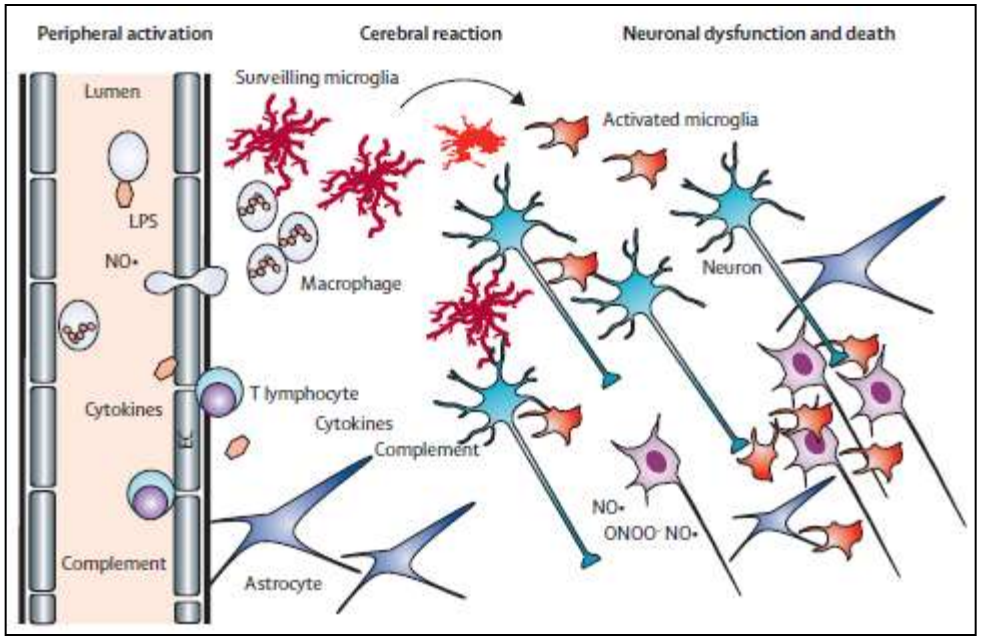
Initial acute-stage results of sepsis

- Sepsis-associated encephalopathy
- Acute systemic inflammation
- Cerebral damage (such as blood–brain barrier disruption, hyperfusion, cell apoptosis, neuronal loss, general slowing of EEG activity)
- (Micro)vascular damage in the CNS, vasogenic oedema, white matter hyperintensities
- Psychiatric burden (anxiety, depression, hallucinations, delusions)

Possible/permanent, long-term effects of sepsis

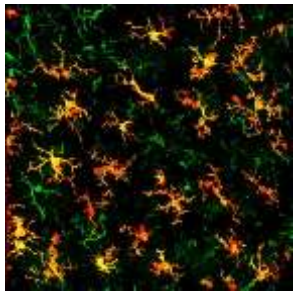
- Neurocognitive impairment (such as impaired attention, verbal fluency, verbal learning, and memory)
- Sustained brain inflammation?
- Cerebral damage (increased slow-wave activity in EEG, reduced volume of the hippocampus, chronic disruption of the blood–brain barrier)
- Increased risk of vascular brain disease (including a risk of vascular dementia)?
- Psychiatric burden (including raised levels of anxiety, depression, post-traumatic stress syndrome)
- Could other possible permanent effects of sepsis include the presence of Tau-pathology, an increase in amyloid β, and an increased risk of Alzheimer's disease?

Interventions for preventing or treating cognitive decline?



Lancet neurology - 2015

MICROGLIAL PRIMING



SEPSIS

EARLY MICROGLIAL ACTIVATION

MODULATION

PROTRACTED MICROGLIAL CHANGES
Morpho-Immuno-Metabolic phenotype

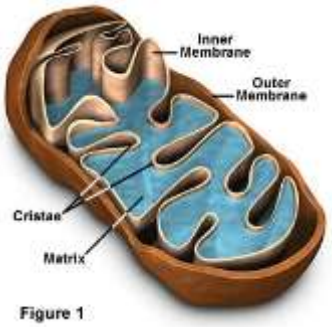
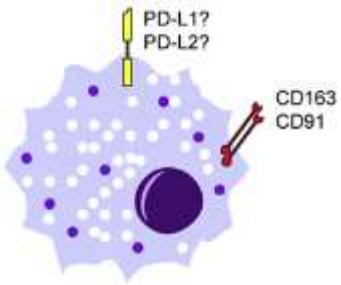


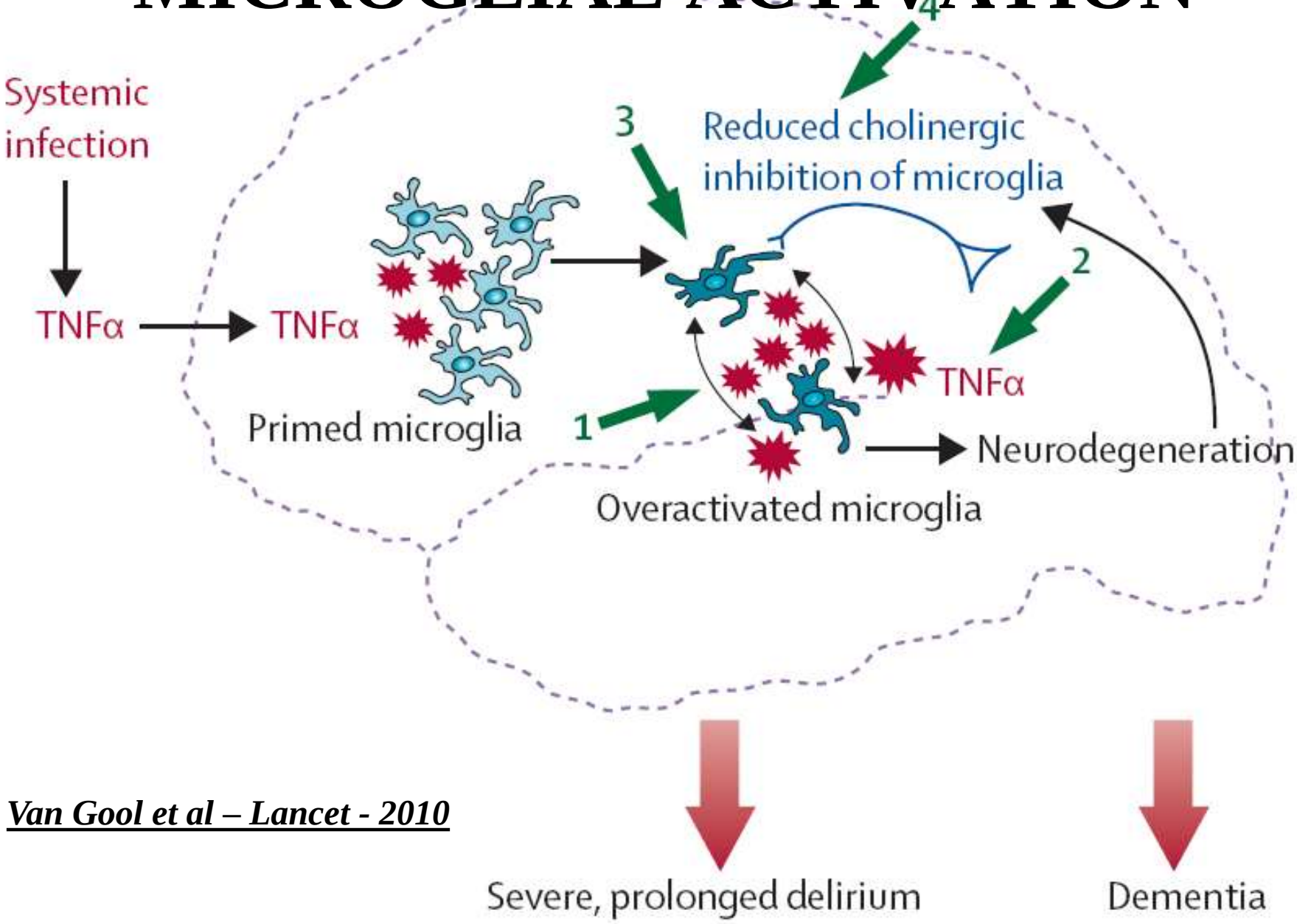
Figure 1



REACTIVITY TO A SECOND HIT

PSYCHO-COGNITIVE CONSEQUENCES

MICROGLIAL ACTIVATION



Van Gool et al – Lancet - 2010

PHENOTYPES

- PROCESSUS REVERSIBLE
  - Plus accessibles à un traitement?
- SEQUELLES FIXEES
- PROCESSUS IRREVERSIBLE
  - Neurodégénerescence

Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial

Although a sample size of 440 patients was planned, after inclusion of 104 patients with delirium, the trial was halted because

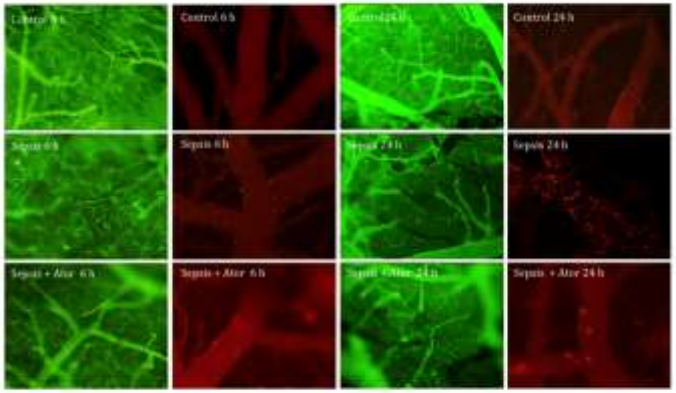
1.Mortality in the rivastigmine group (n=12, 22%) was higher than in the placebo group (n=4, 8%; p=0·07).

2.Median duration of delirium was longer in the rivastigmine group (5·0 days, IQR 2·7—14·2) than in the placebo group (3·0 days, IQR 1·0—9·3; p=0·06).

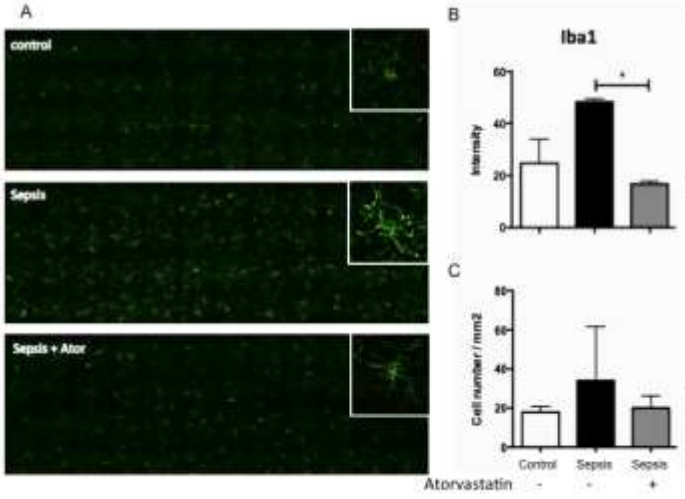
Van Eijk et al - Lancet - 2010

STATINS

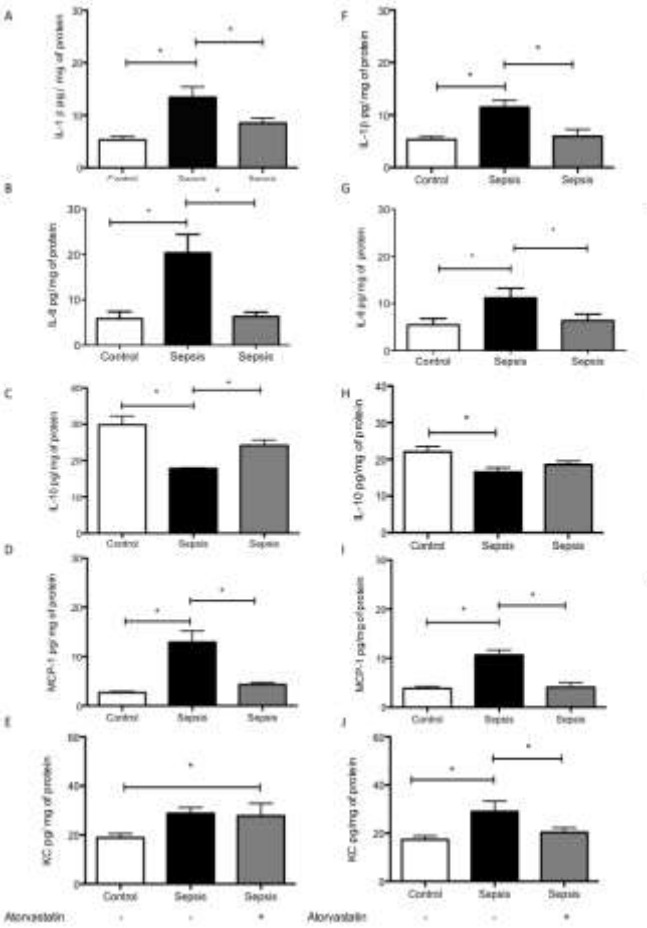
CLP mice + atrovastatine



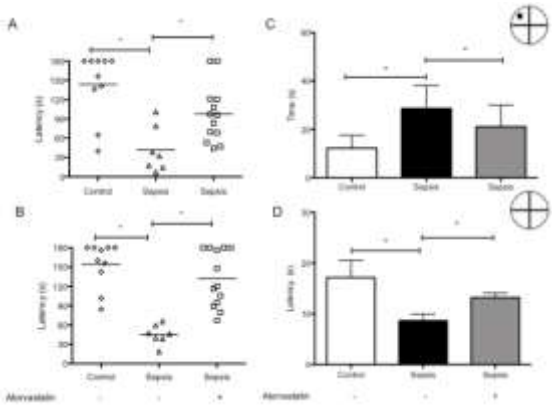
Reduced leukocytes adhesion



Reduced microglial activation



Reduced neuroinflammation

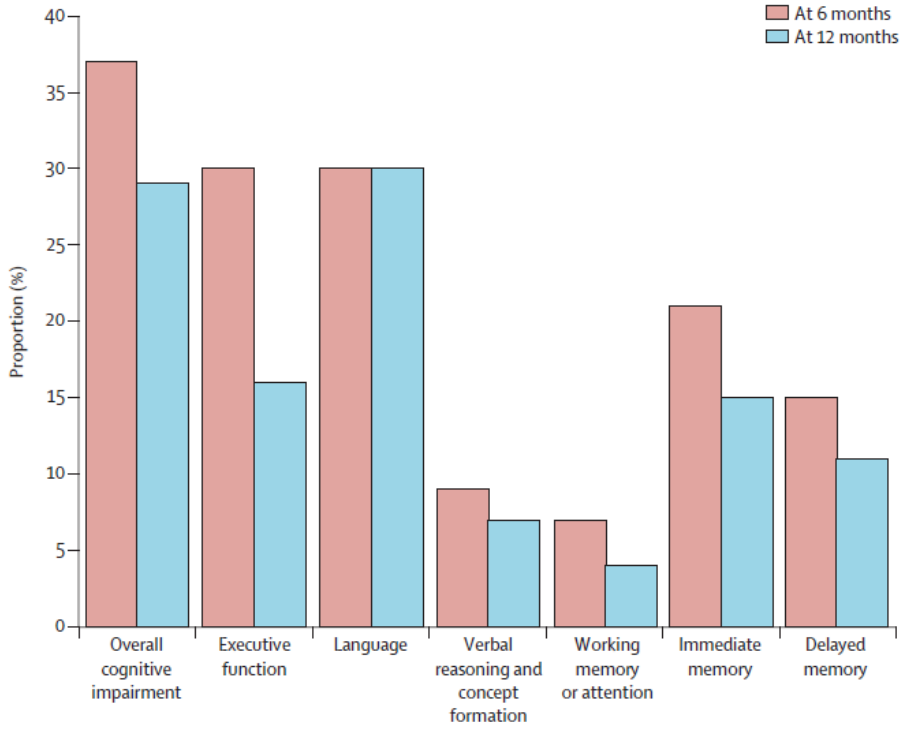


Improved cognition

Reis et al – Brain Behav & Immunity - 2016

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial

	Eligible for delirium or cognitive assessment		With data for delirium		Eligible for cognitive assessment	
	Rosuvastatin group (n=164)	Placebo group (n=165)	Rosuvastatin group (n=137)	Placebo group (n=135)	Rosuvastatin group (n= 83)	Placebo group (n=106)
Baseline characteristics						



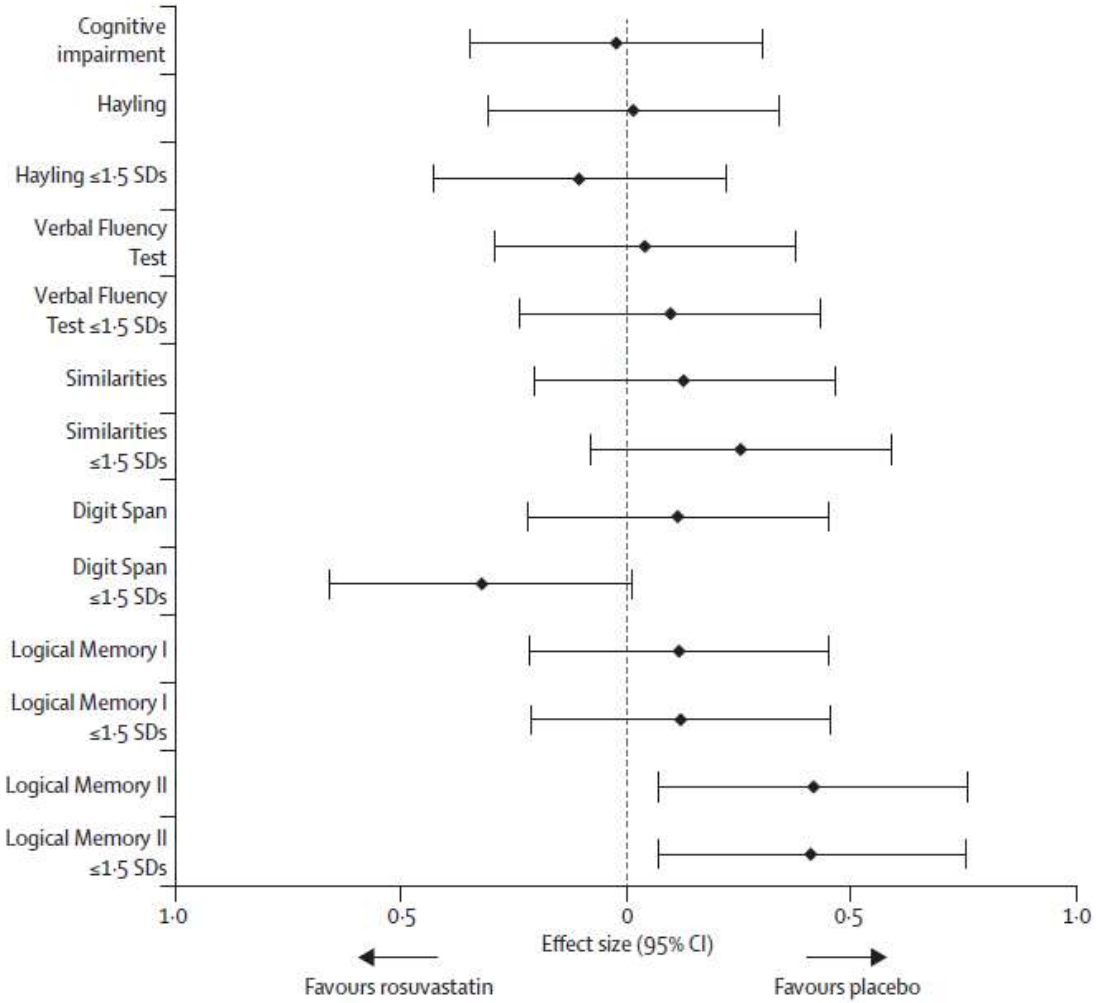
Needham et al – Lancet Resp Med - 2015

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial

	Rosuvastatin group (n=53)	Placebo group (n=77)	Treatment effect (95% CI)	p value
Cognitive impairment	19/53 (36%)	29/77 (38%)	0·93 (0·39 to 2·22)	0·87
Executive function (mean Hayling Sentence Completion score, SD)	4·5 (1·8)	4·4 (2·1)	0·0 (–0·6 to 0·6)	0·92
Patients with score ≤1·5 SD	14/53 (26%)	25/75 (33%)	0·74 (0·31 to 1·80)	0·51
Language (mean Verbal Fluency score, SD)	31 (13)	32 (11)	–1 (–4 to 3)	0·80
Patients with score ≤1·5 SD	18/52 (35%)	20/76 (26%)	1·44 (0·54 to 3·80)	0·46
Verbal reasoning and concept formation (mean Similarities score, SD)	9·7 (3·8)	9·9 (3·0)	–0·4 (–1·5 to 0·7)	0·44
Patients with score ≤1·5 SD	7/52 (13%)	5/76 (7%)	2·29 (0·60 to 8·77)	0·23
Working memory and attention (mean Digit Span score, SD)	9·2 (2·5)	9·5 (2·6)	–0·3 (–1·2 to 0·6)	0·49
Patients with score ≤1·5 SD	1/52 (2%)	8/76 (11%)	0·17 (0·02 to 1·52)	0·11
Immediate memory (mean Logical Memory I score, SD)	8·6 (3·4)	8·9 (3·3)	–0·4 (–1·5 to 0·7)	0·49
Patients with score ≤1·5 SD	12/50 (24%)	14/76 (18%)	1·37 (0·50 to 3·76)	0·54
Delayed memory (mean Logical Memory II score, SD)	7·9 (3·3)	8·8 (2·7)	–1·2 (–2·2 to –0·2)	0·017
Patients with score ≤1·5 SD	12/50 (24%)	7/73 (10%)	3·06 (1·00 to 9·37)	0·050

Needham et al – Lancet Resp Med - 2015

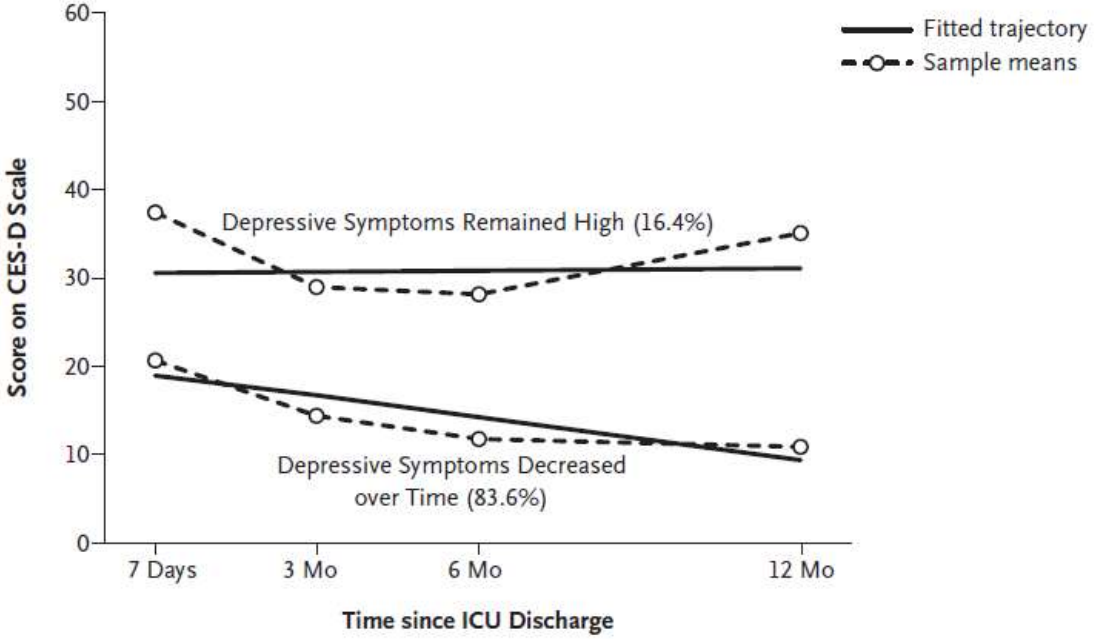
Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial



Needham et al – Lancet Resp Med - 2015

One-Year Outcomes in Caregivers of Critically Ill Patients

We prospectively enrolled 280 caregivers of patients who had received 7 or more days of mechanical ventilation in an ICU. Using hospital data and self-administered questionnaires, we collected information on caregiver and patient characteristics, including caregiver depressive symptoms, psychological well-being, health-related quality of life, sense of control over life, and effect of providing care on other activities. Assessments occurred 7 days and 3, 6, and 12 months after ICU discharge.



Cameron et al – NEJM - 2016

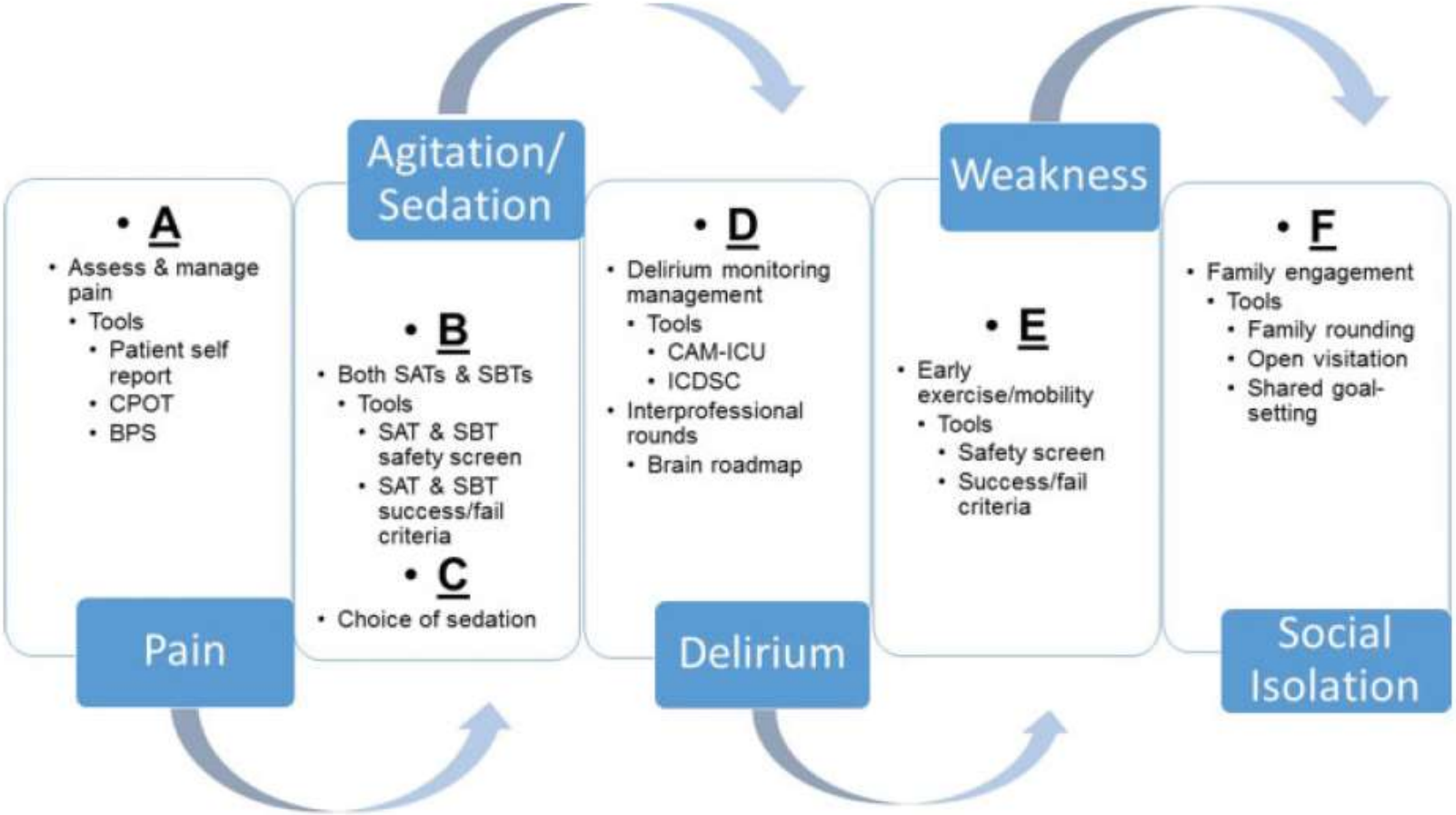
AUTRES APPROCHES

- PLASTICITE
  Rééducation cognitive
- NEUROGENESE
- NEUROINFLAMMATION
  réactivation microgliale
  prévention d'un nouveau sepsis
- NEUROTRANSMISSION

APPROCHE MULTIMODALE

CONTRÔLE DES FACTEURS DE RISQUE (DELIRIUM)

ABCDEF BUNDLE



Balas et al – Semin Resp Care Med - 2016

CONCLUSIONS

- Complications fréquentes ayant un impact sur la qualité de vie des patients et de leurs proches
- Physiopathologie complexe
- Détection systématique
- Approche multimodale

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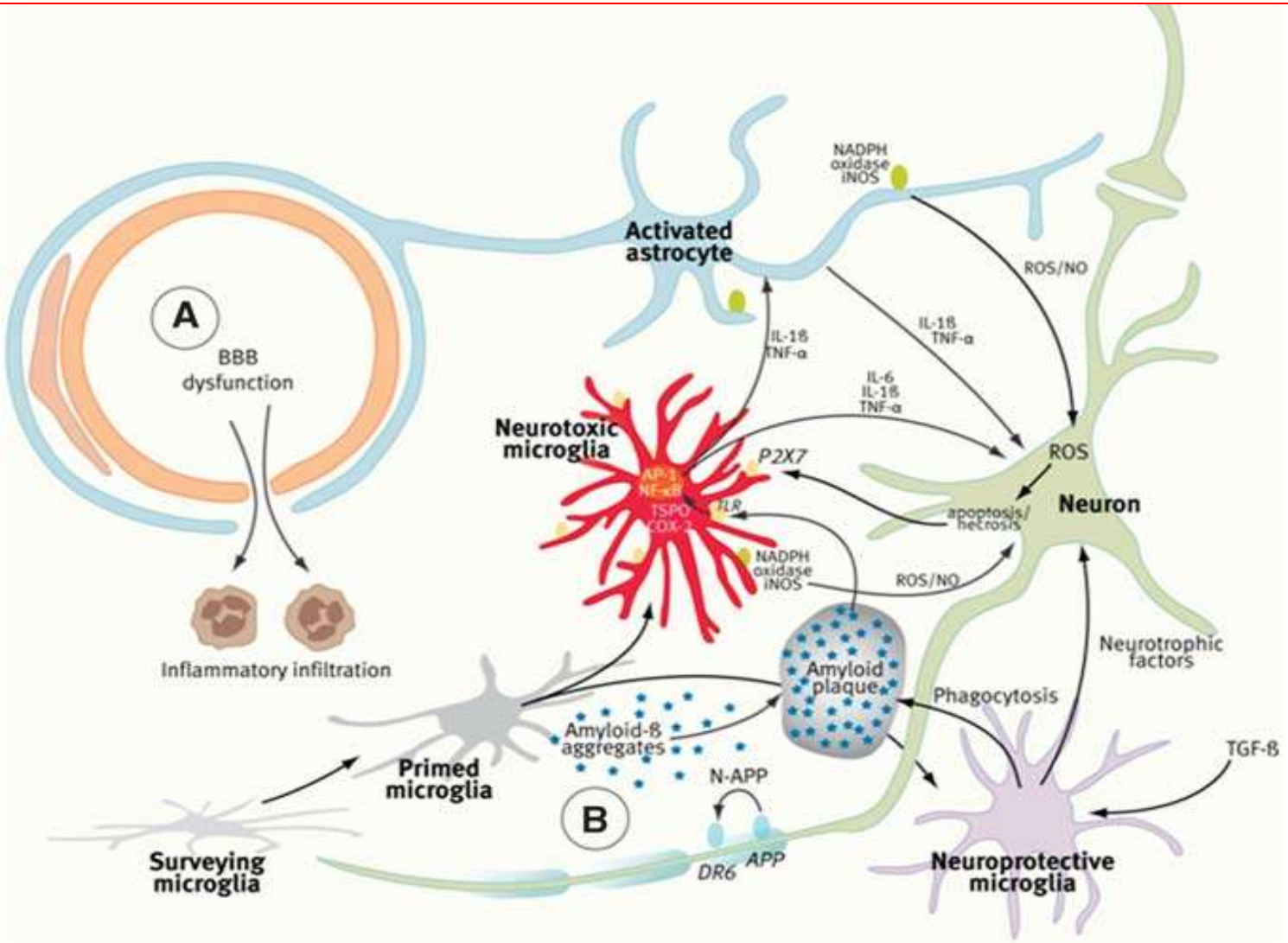
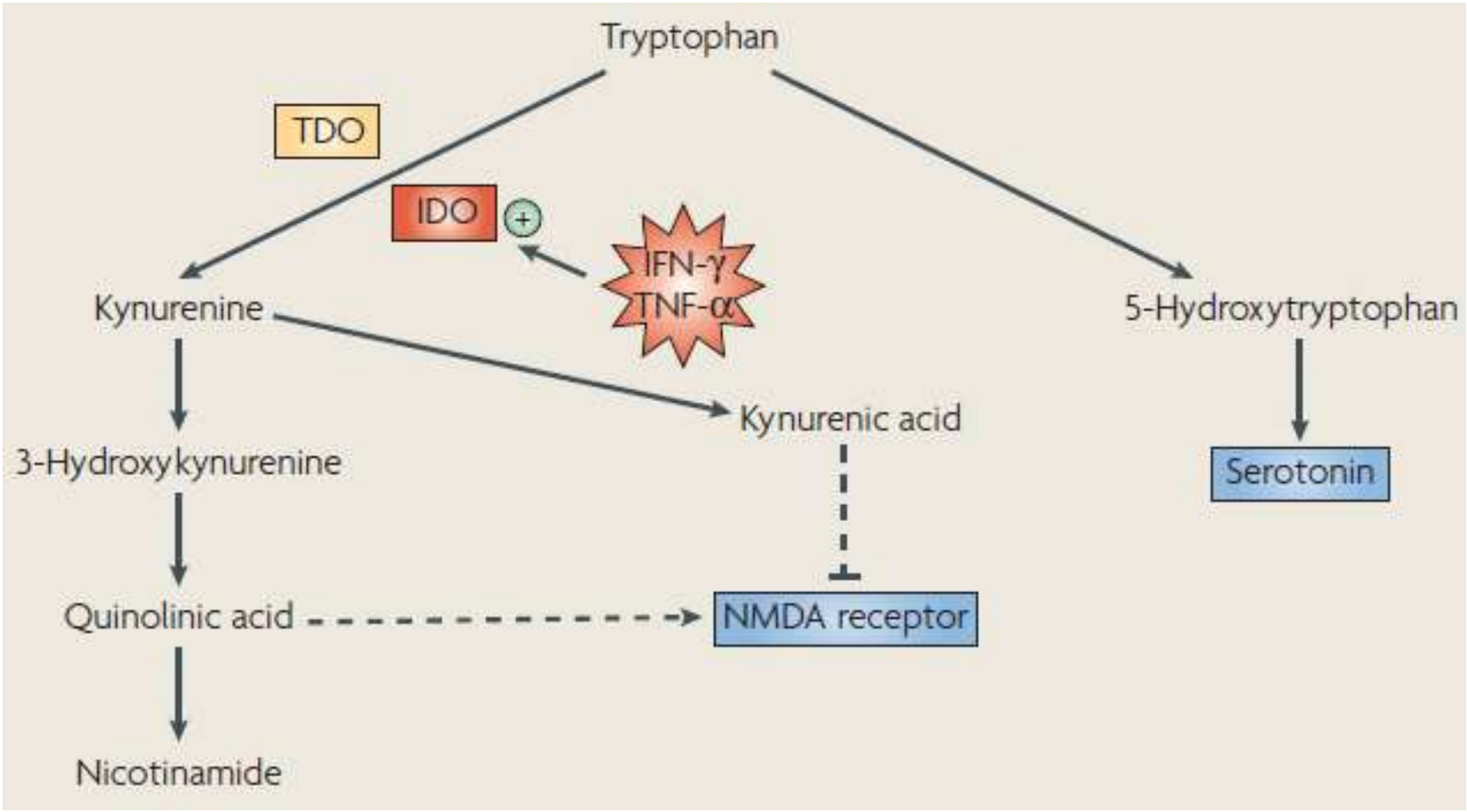
MERCI

NEUROINFLAMMATORY PROCESS

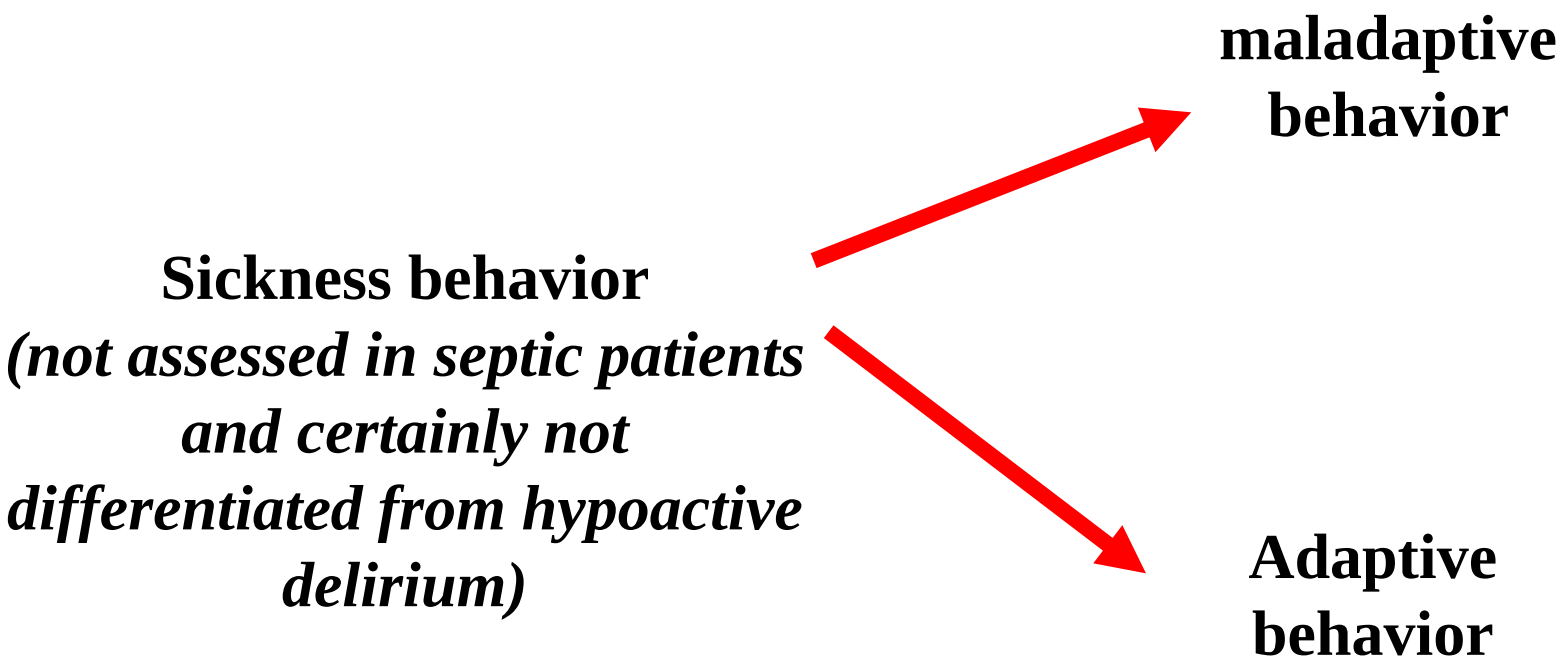


A TIME-DEPENDENT PHENOMENON

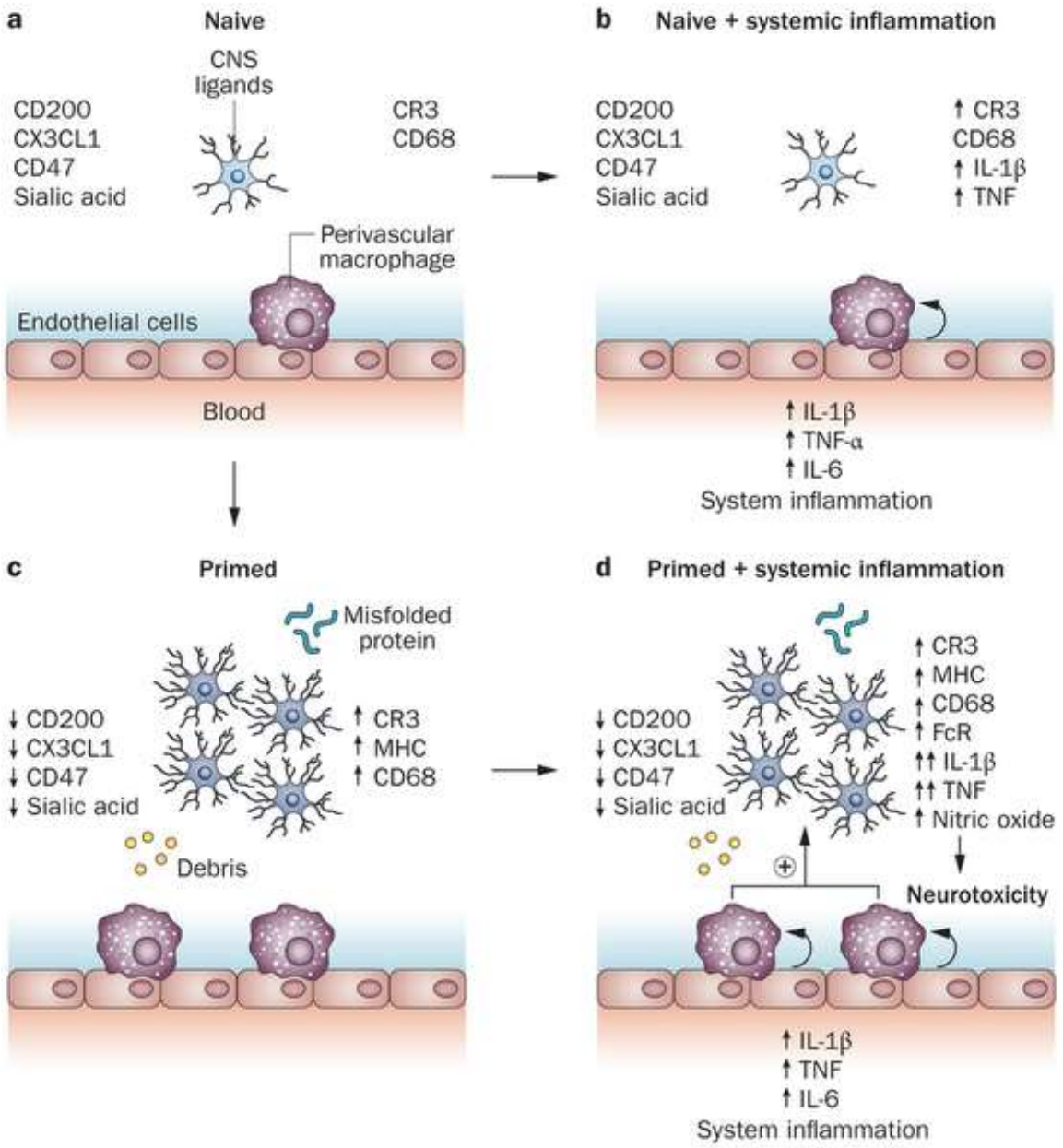
THE KYNURENINE PATHWAY



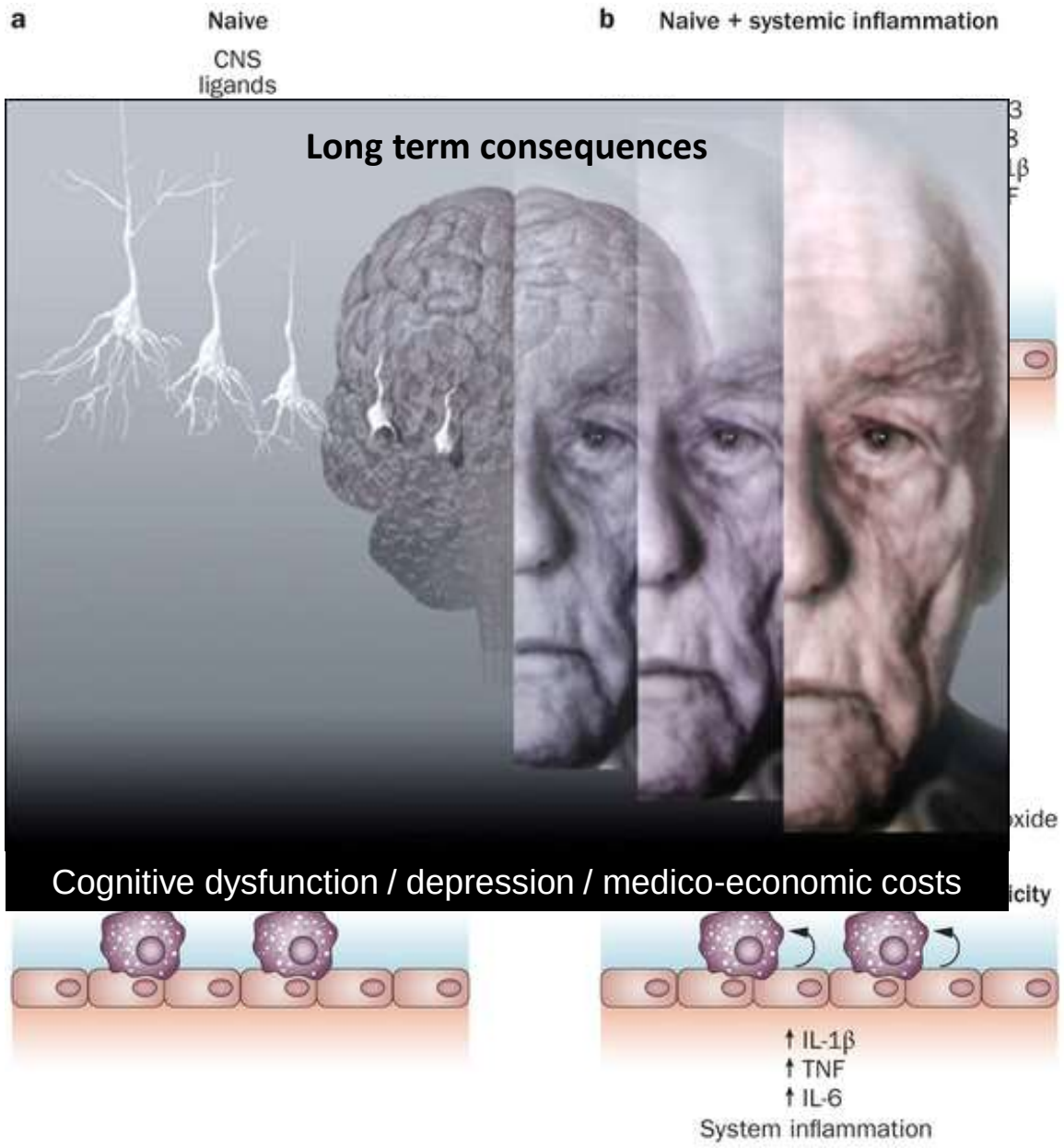
Dantzer et al – Nat Rev Sci - 2008


maladaptive behavior
Sickness behavior
(not assessed in septic patients and certainly not differentiated from hypoactive delirium)
Adaptive behavior

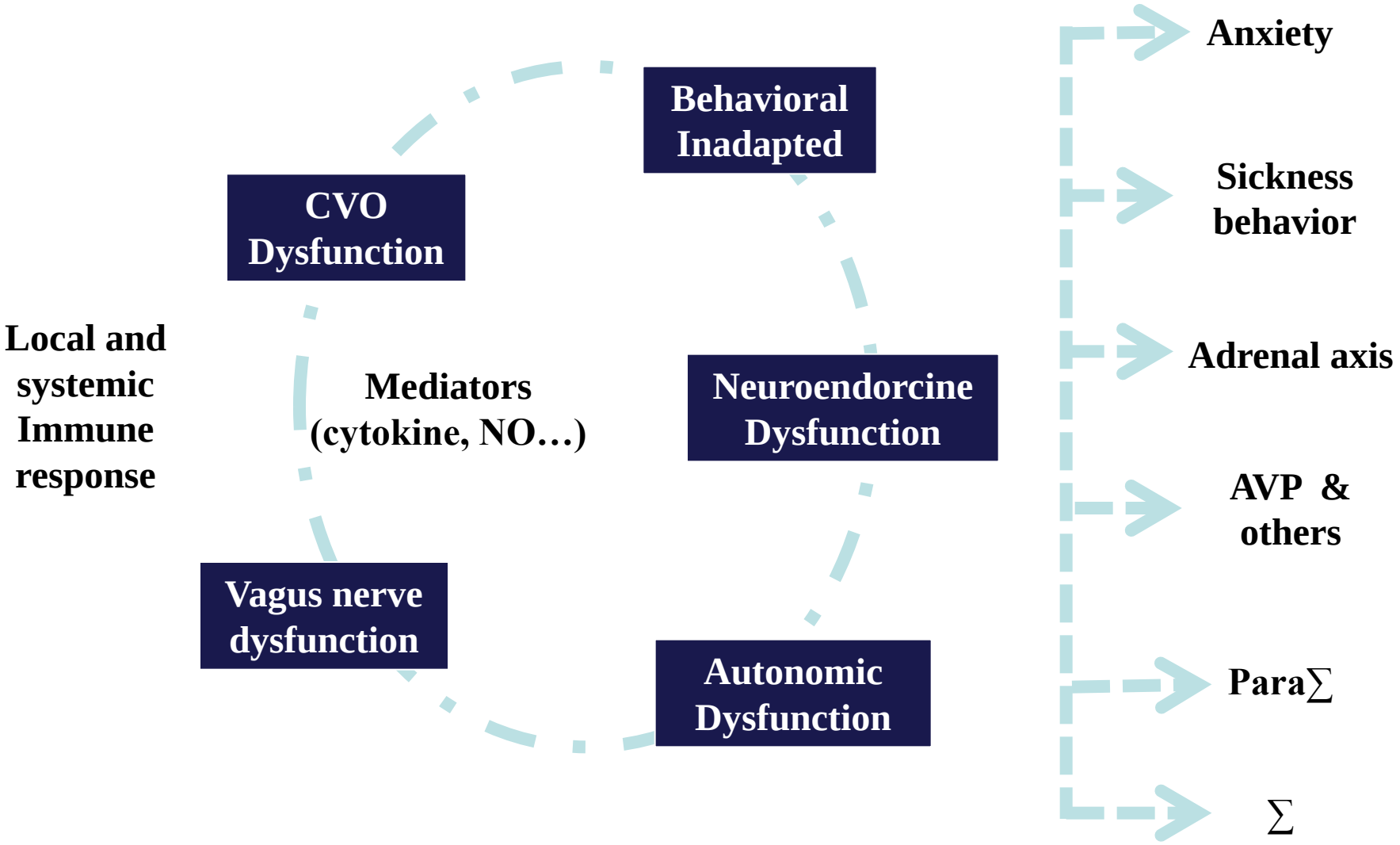
Microglial priming, a recent concept

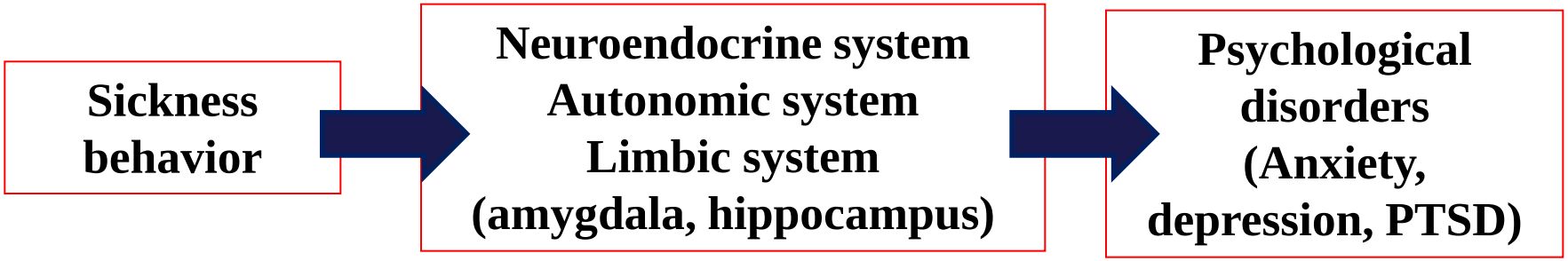


Microglial priming, a recent concept

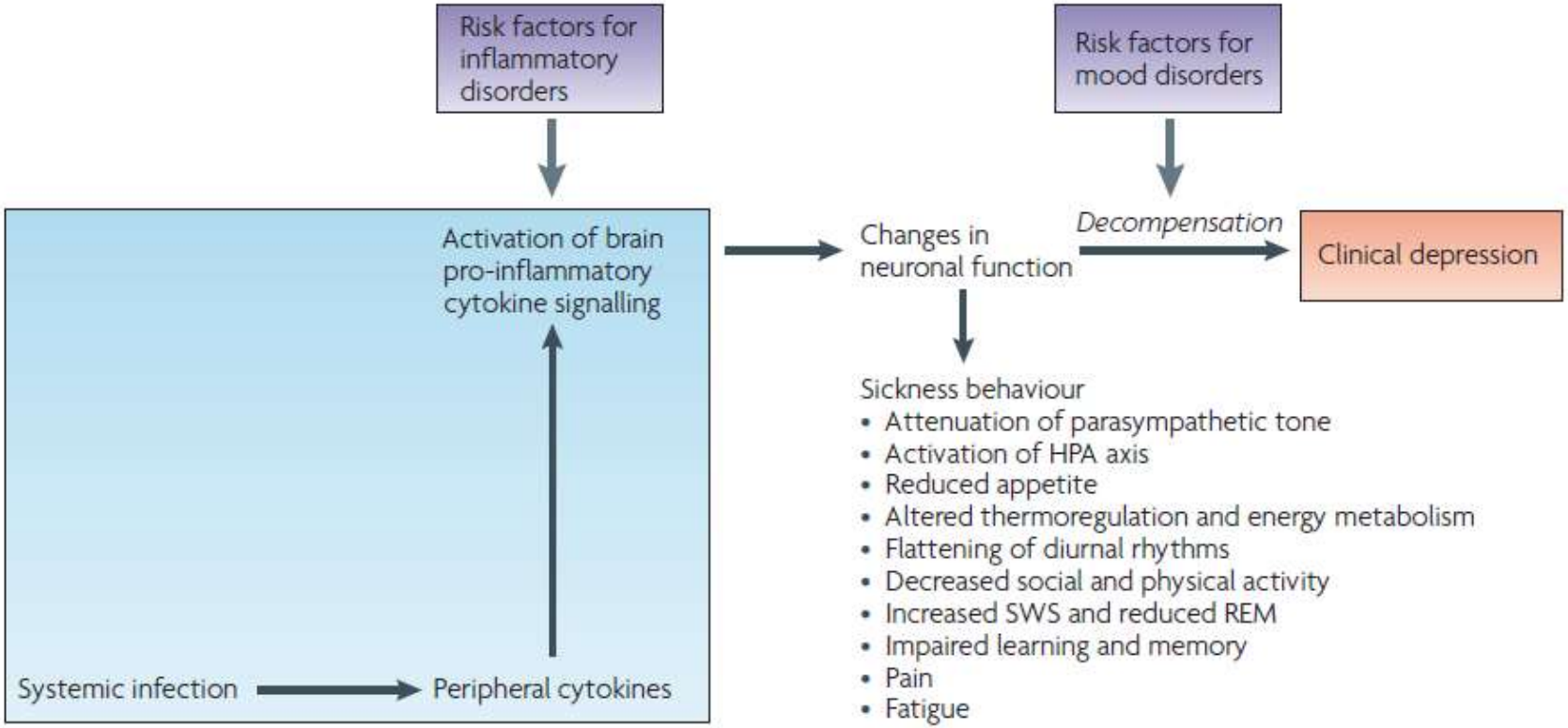


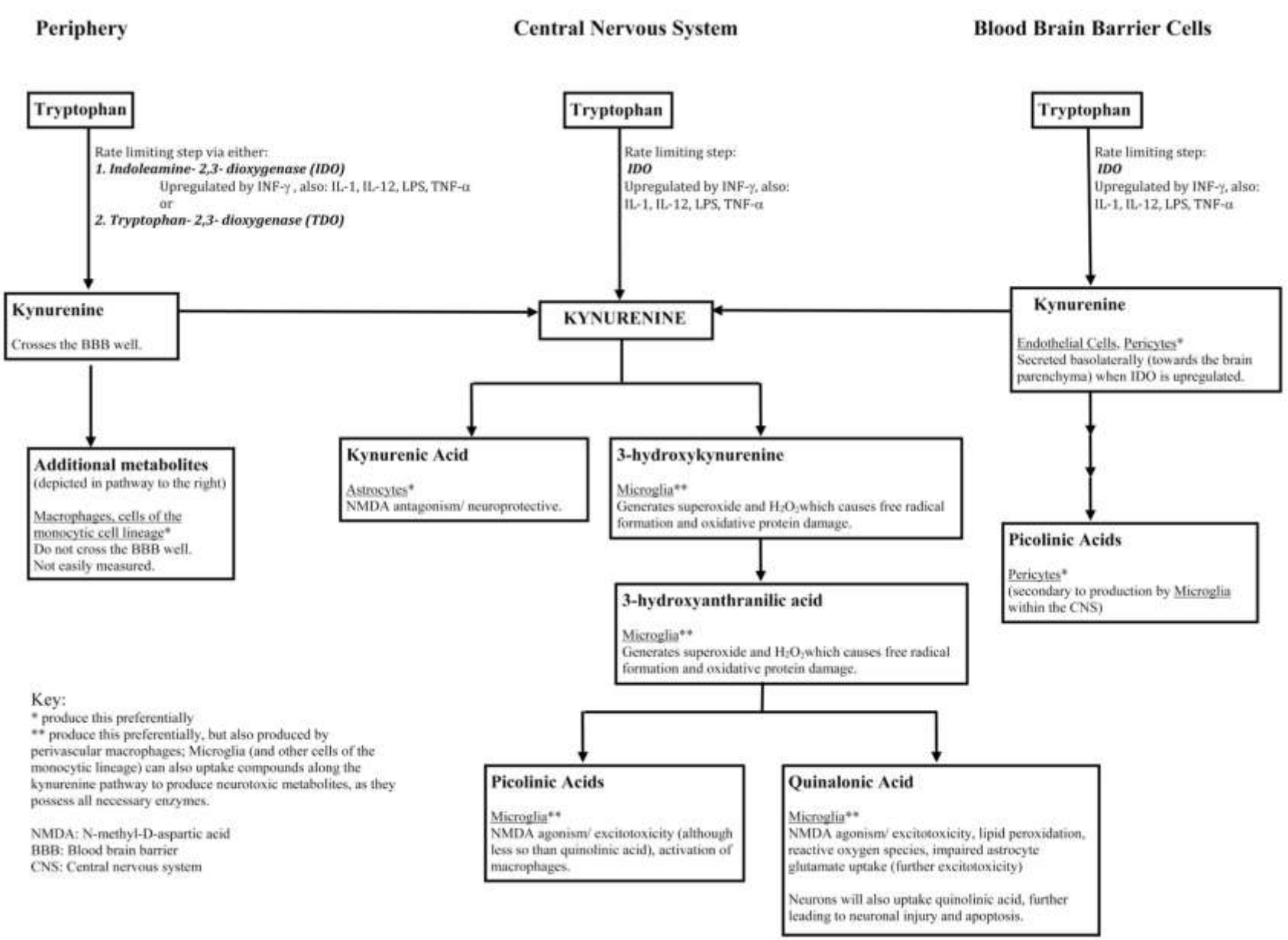
PATHOPHYSIOLOGICAL RESPONSE TO STRESS




Sickness behavior
Neuroendocrine system
Autonomic system
Limbic system
(amygdala, hippocampus)
Psychological disorders
(Anxiety, depression, PTSD)

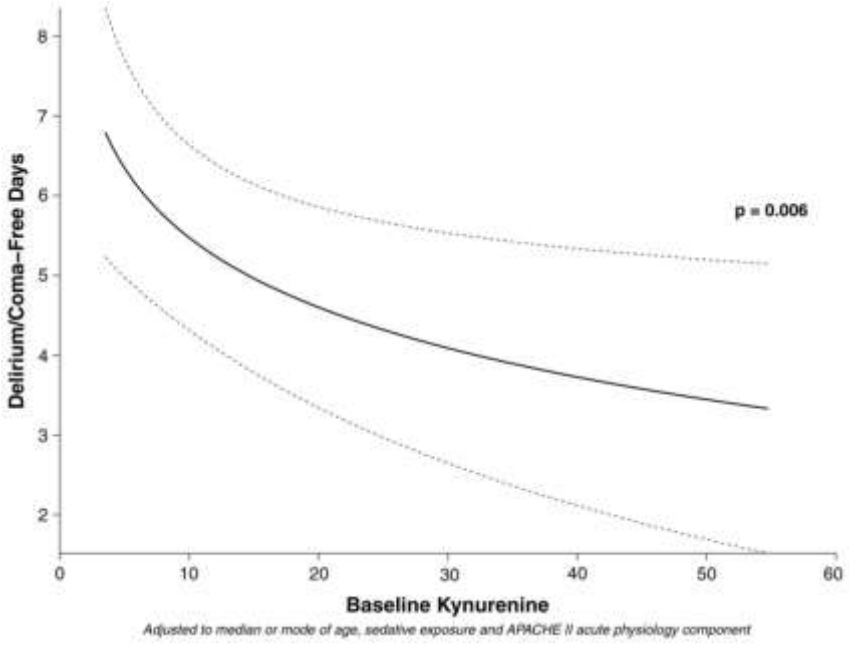
SICKNESS - DEPRESSION

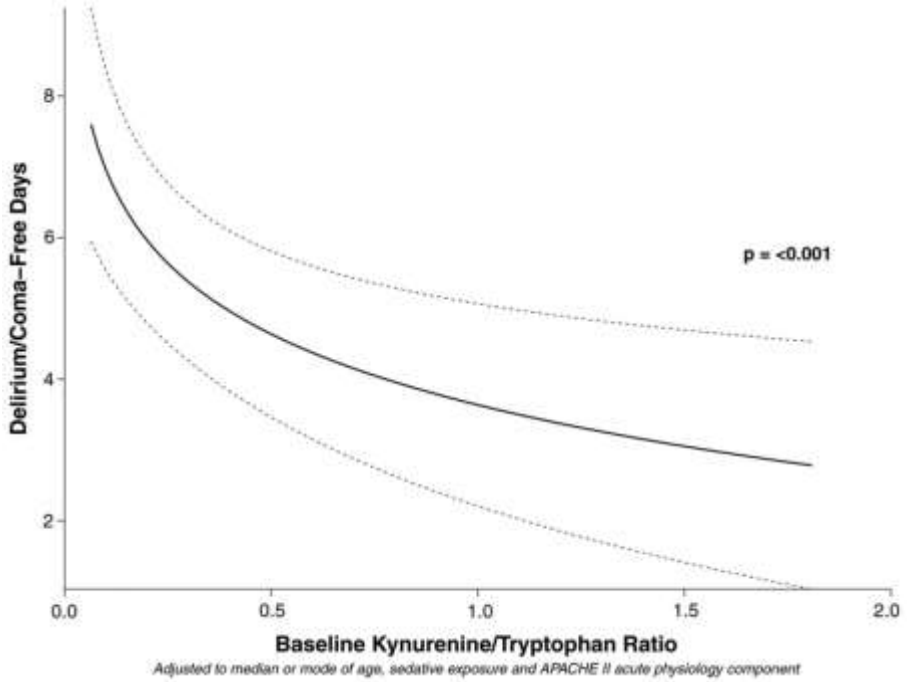




An imbalance favoring the production of neurotoxic metabolites leads to neuronal and glial cell injury, excitotoxicity, and apoptosis, which may be clinically manifested as delirium or coma.

KYNURENINE PATHWAY





Adams Wilson et al - Crit Care Med - 2012

CELLS

Table 1
Homeostatic cellular function in the brain and pathophysiology during sepsis-associated encephalopathy

	Cell Type	Homeostatic Function	Cellular Changes	Mechanisms	Consequences
Glial cells	Astrocytes	Synaptic plasticity,[105] neurovascular coupling,[75] microenvironment homeostasy,[105] BBB formation	Astrogliosis in mouse model[59] but not in patients	Unknown	↗ BBB permeability Neuroinflammation Mediator of tissue damage[105]
	Oligodendrocytes	Myelin sheath formation and maintain	Unknown	Unknown	Worse myelination development,[106] potently cognitive impairment
	Microglial cells	Innate immune system of the central nervous system[44] Inflammatory cell recruitment	Microgliosis,[54,58,63] modification of their activation state, M1 or M2 phenotype	Vagal nerve stimulation[52,107] IL-1β[49] and TNF-α[57] exposure Other activating factors	Excitotoxic compound release[106] iNOS expression[54] Neuroinflammation
Blood vessels	Endothelial cells	Blood vessel lining in their lumen Role in coagulation, vasoconstriction and vasodilation, inflammation,	Endothelial activation Inflammatory mediator leakage and production Cell recruitement[108]	TNF-α and other cytokine exposure[109]	↗ BBB permeability Microthrombi Infarct Ischemic lesions[5,58]
	Pericytes	Blood vessel stabilization, vasoconstriction, vasodilation[110]	Unknown	—	↗ BBB permeability Microthrombi, ischemic lesion, infarct Supply/demand oxygen inadequation[5]
Choroid plexus	Ependymal cell	Cerebrospinal fluid production, and resorption,	Unknown	—	—
	Neurons	Information processing	Dysfunction (long-term potentiation[95]) apoptosis[54,58]	Glutamate excitotoxicity Metabolic impairment	Cognitive impairment[7,9,64]

Mazeraud et al – Clin Chest Med - 2016

Summary

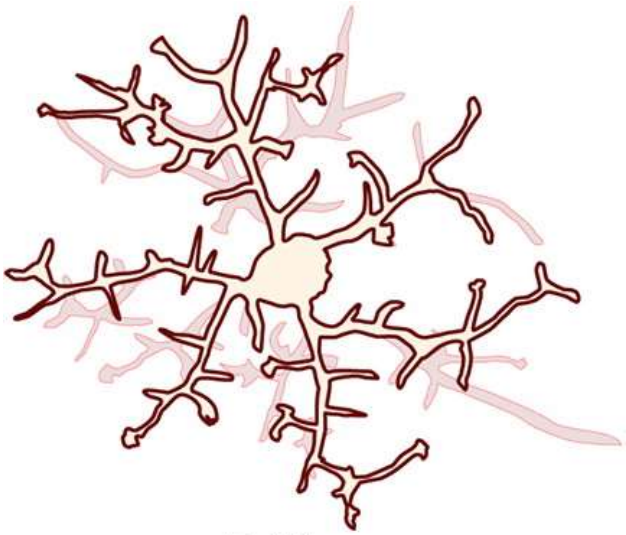
CLP

CEA	H6	H24	J15
Microglia Activation	++	+	0
Neurons excitation	+++	+	

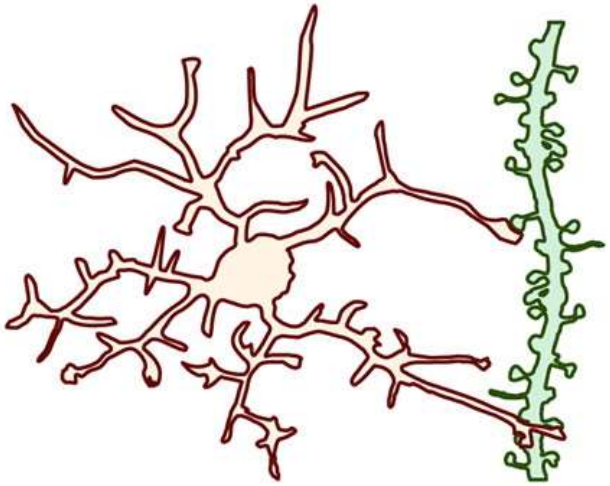
PTSD-like phenotype

Pharmacogenetic approach
DDREADS

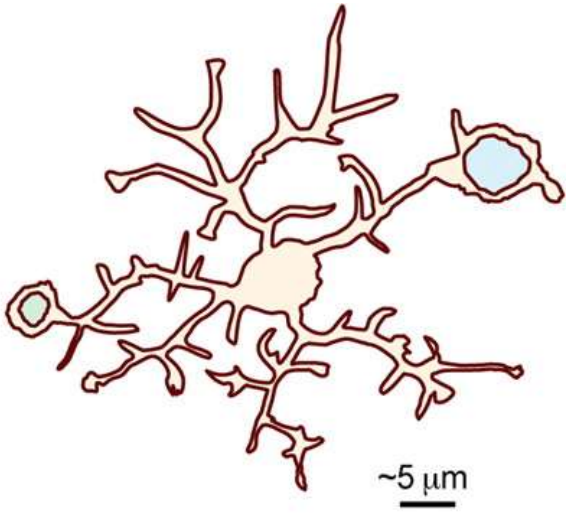
MICROGLIAL PRUNNING OF SYNAPSES



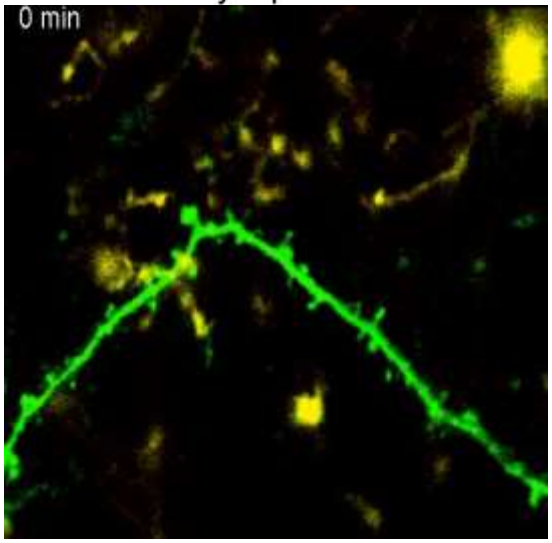
Motility



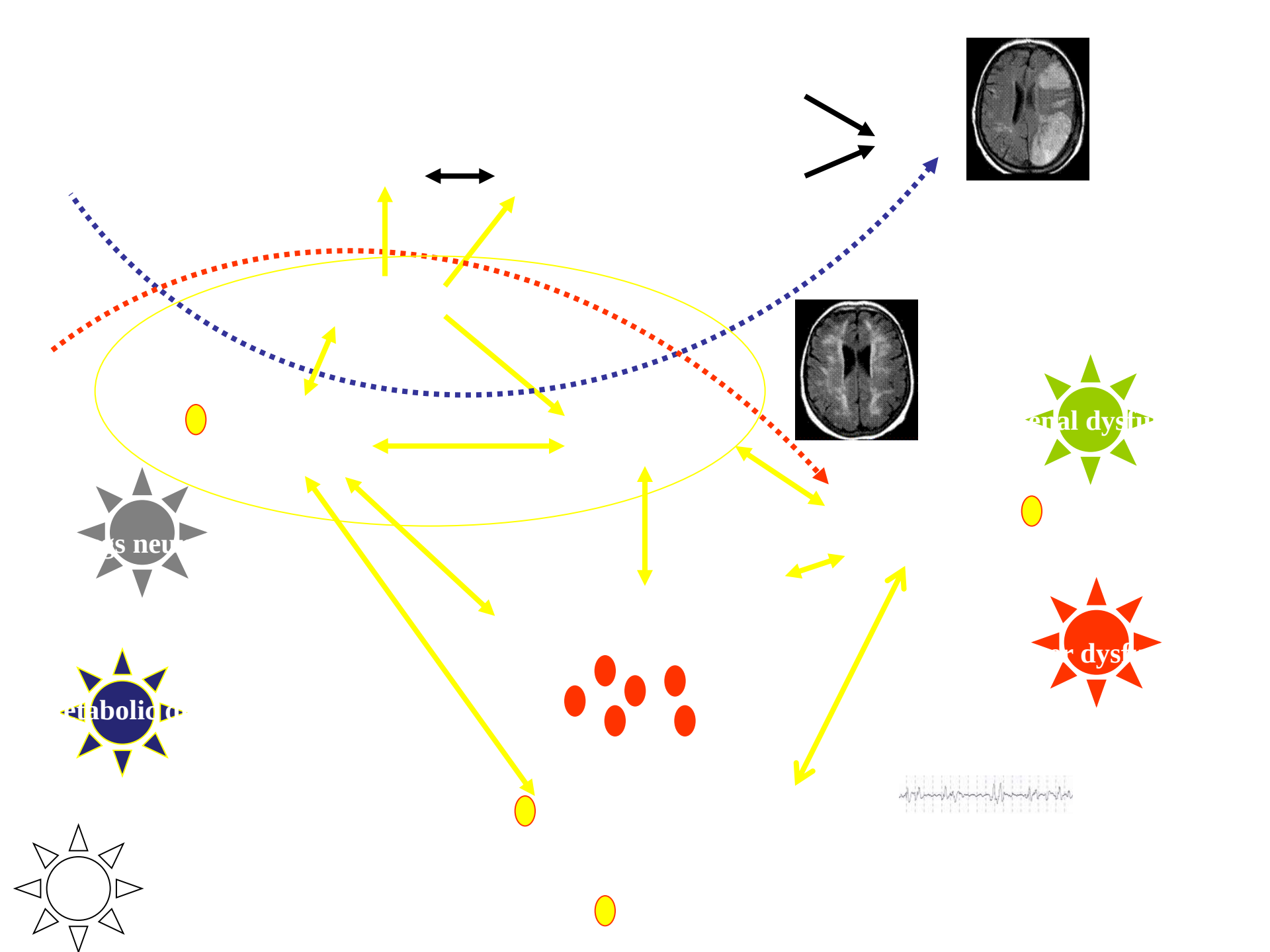
Synaptic interactions



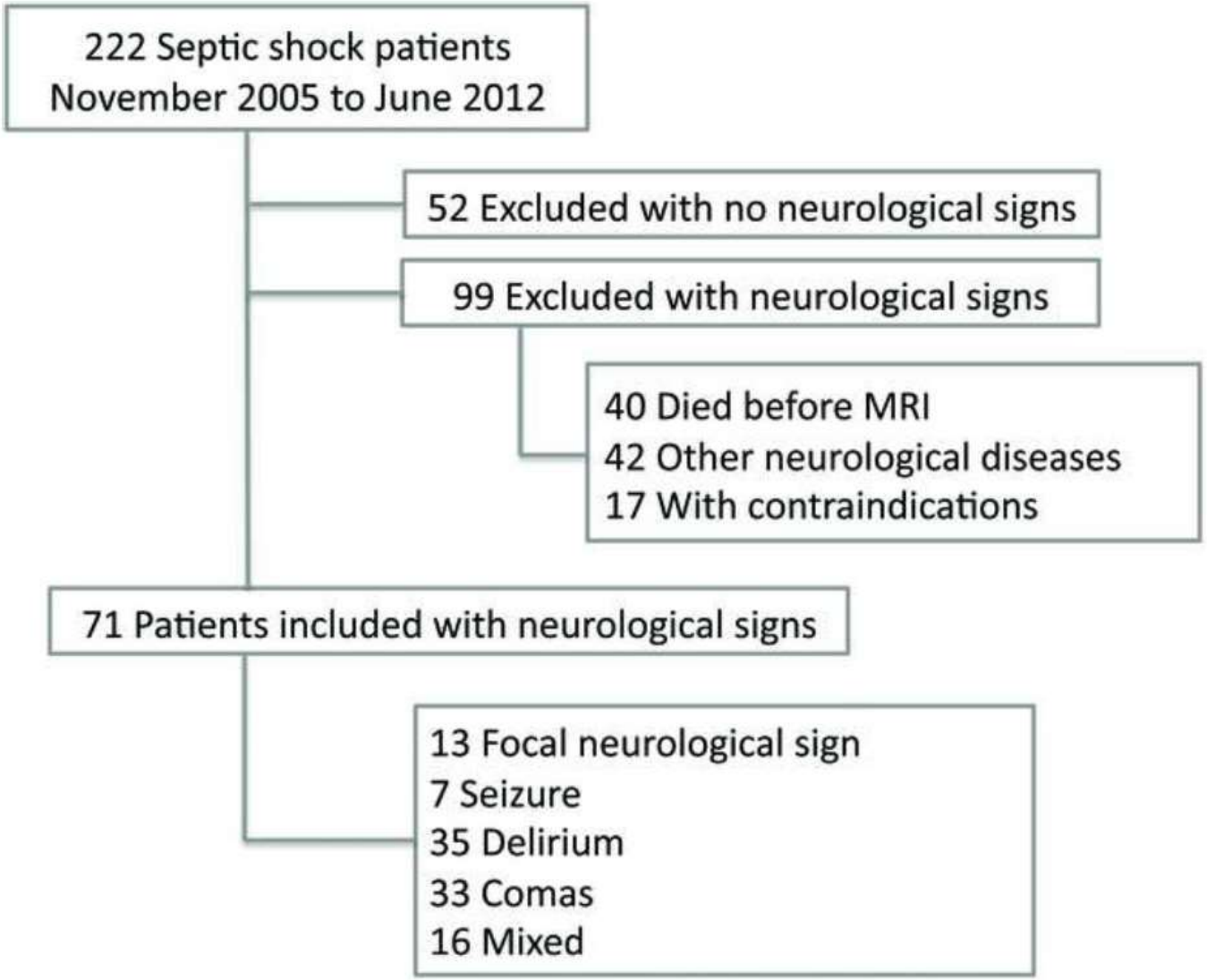
Phagocytosis



Tremblay M and al. *J. Neurosci.* (2011)

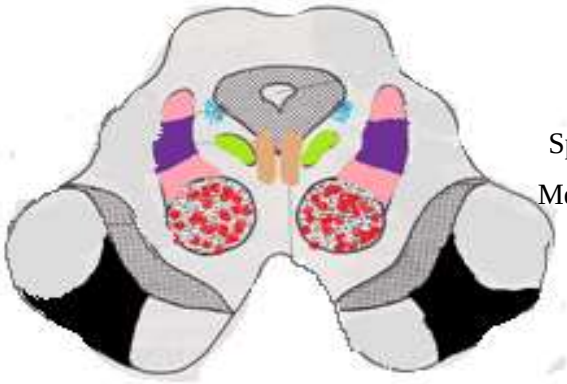


FLOW CHART



Polito et al – Crit Care - 2013

BRAINSTEM SYNDROMES



Spinothalamic tract

Medial lemniscus

Red nucleus

Cortico spinal tract

Midbrain

- Medial longitudinal fascilulus

- Nerve VIII

- Sympathetic fibers
- Facial nerve

- Trigeminal Nerve

Pons

- Medial Lemniscus

- Spinothalamic tract

- Cortico spinal tract
- Cerebellar connections

Vestibular n.

XII nerves

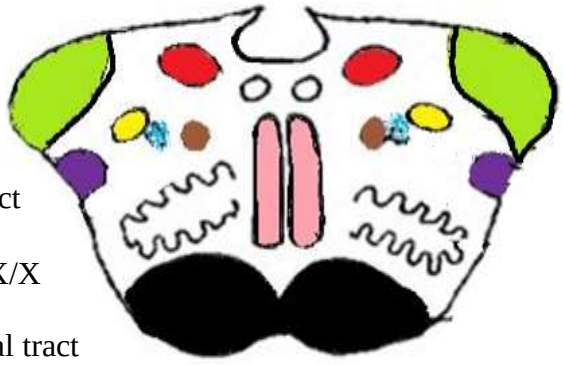
Inf cerebellar peduncle

Sympathetic fibers

Spinothalamic tract

Noyau ambiguus IX/X

Corticospinal tract

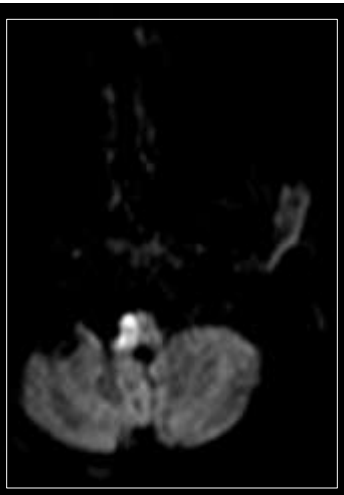


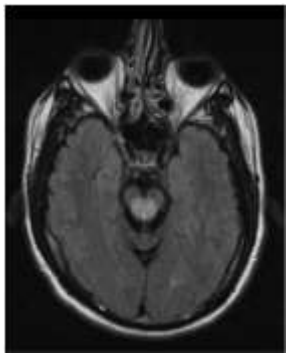
AV

Medulla

LTS

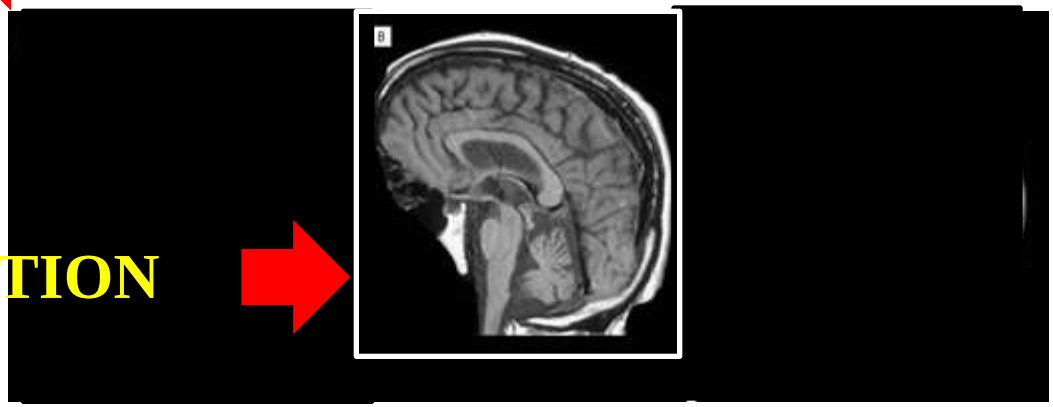
ISCHEMIC/HEMORRHAGIC

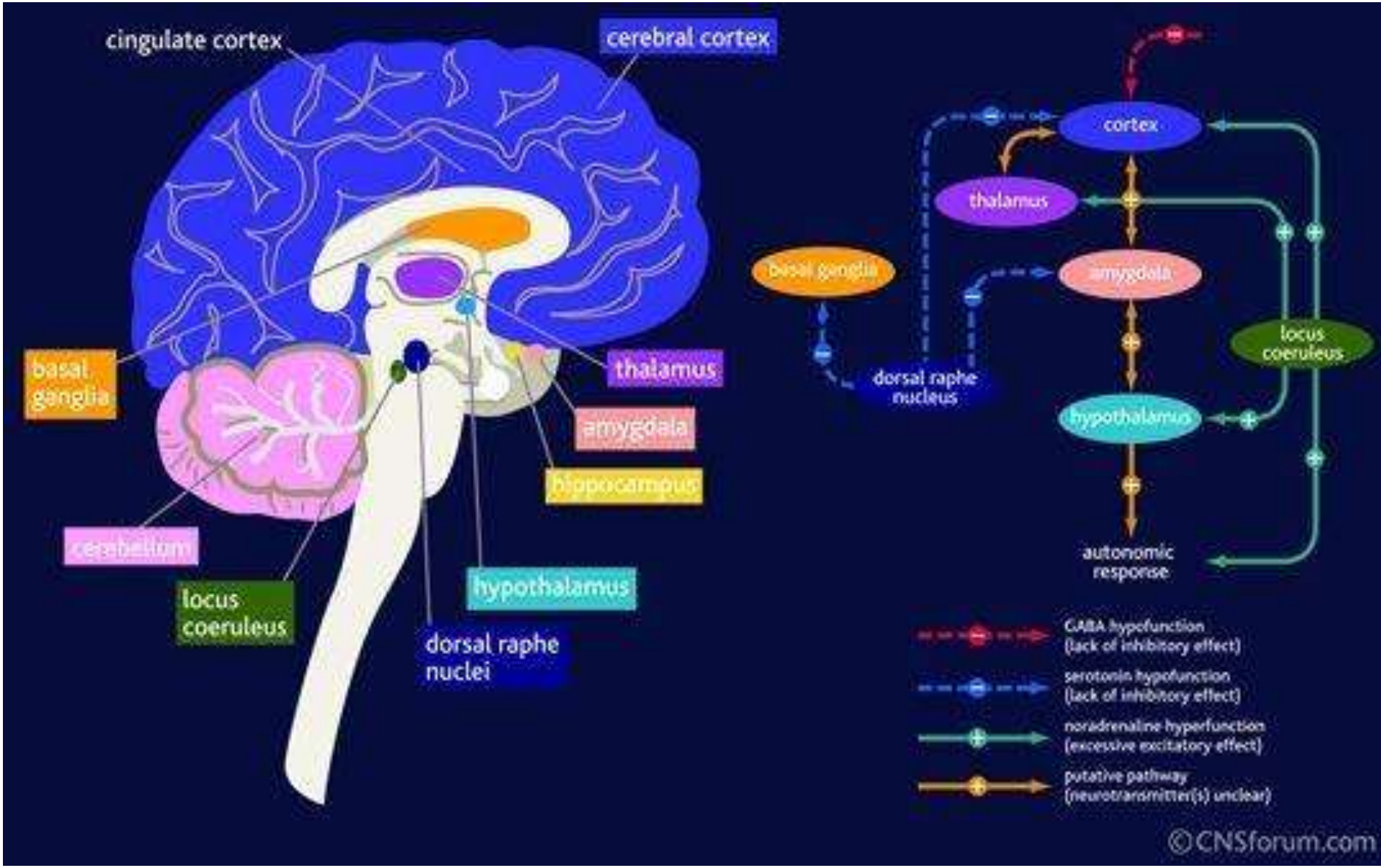




INFLAMMATION

NEURODEGENERATION




cingulate cortex
cerebral cortex
basal ganglia
thalamus
amygdala
hippocampus
cerebellum
locus coeruleus
hypothalamus
dorsal raphe nuclei
cortex
thalamus
basal ganglia
amygdala
locus coeruleus
dorsal raphe nucleus
hypothalamus
autonomic response
GABA hypofunction (lack of inhibitory effect)
serotonin hypofunction (lack of inhibitory effect)
noradrenaline hyperfunction (excessive excitatory effect)
putative pathway (neurotransmitter(s) unclear)
©CNSforum.com

FEAR TO DIE

Fear to Die/severe critical illness[$]	All N=356	Not Deteriorate N=192	Deteriorate N=164
NO/NO	122 (35)	75 (63)	47 (37)
YES/NO	98 (29)	65 (63)	36 (37)
NO/YES*	71 (19)	21 (30)	50 (70)
YES/YES**	62 (17)	31 (50)	31 (50)

Khi-2 P < 0.0001

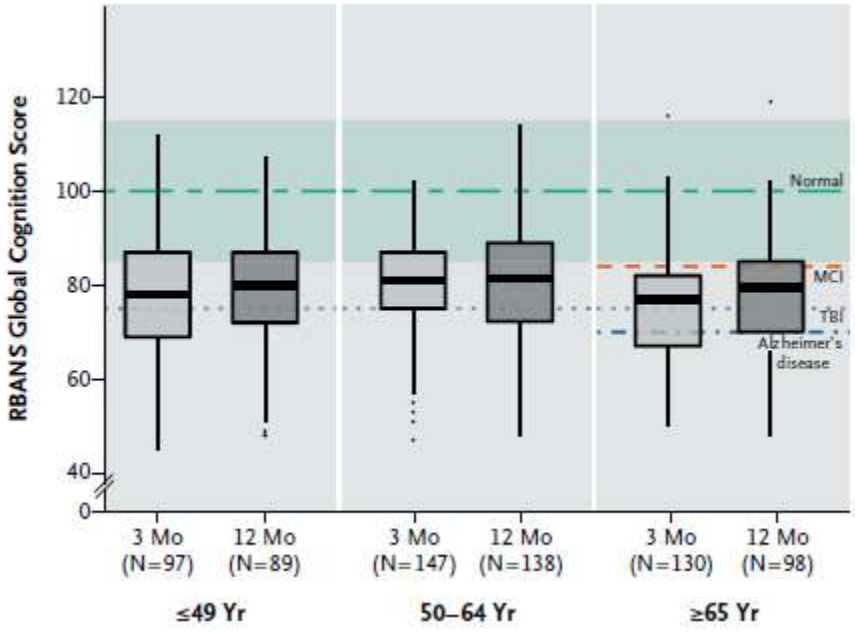
Khi-2 P = 0.016

[$] SAPS-II >30

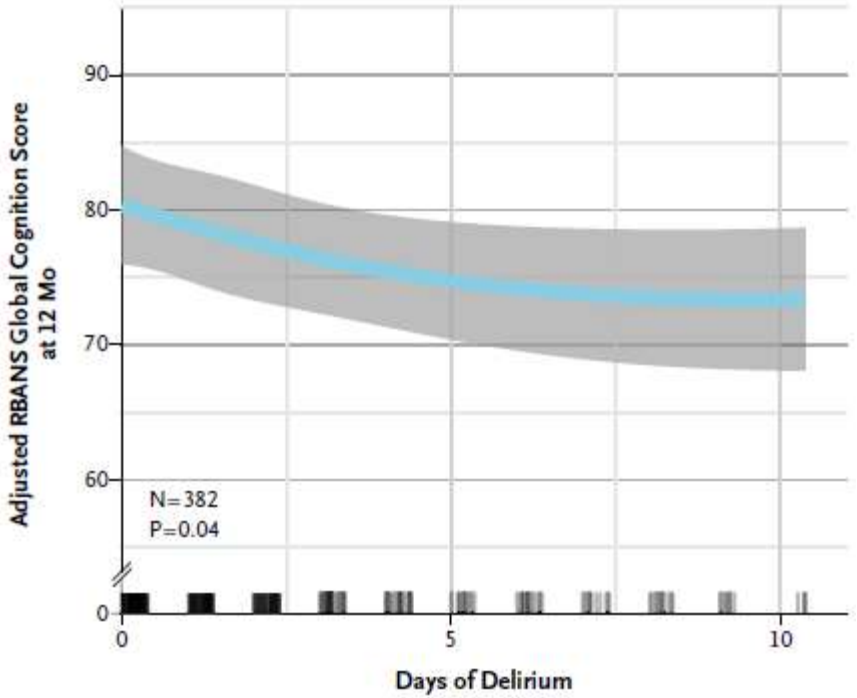
**Impairment of perception of severity?*

*** Aggravating effect of anxiety?*

Long-Term Cognitive Impairment after Critical Illness

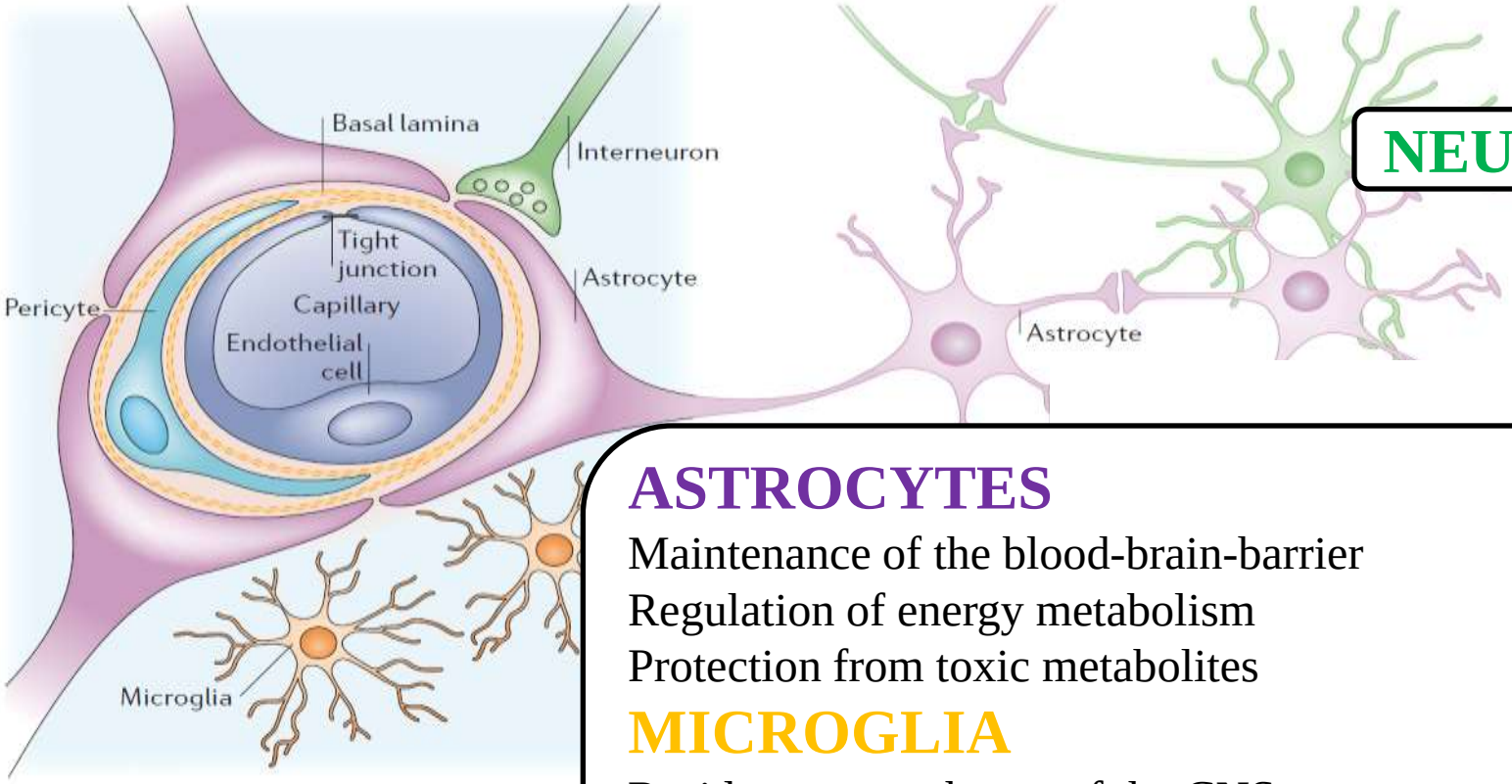


Global Cognition Scores in Survivors of Critical Illness.



Pandharipande et al – NEJM - 2013

PATHOPHYSIOLOGY



NEURONS

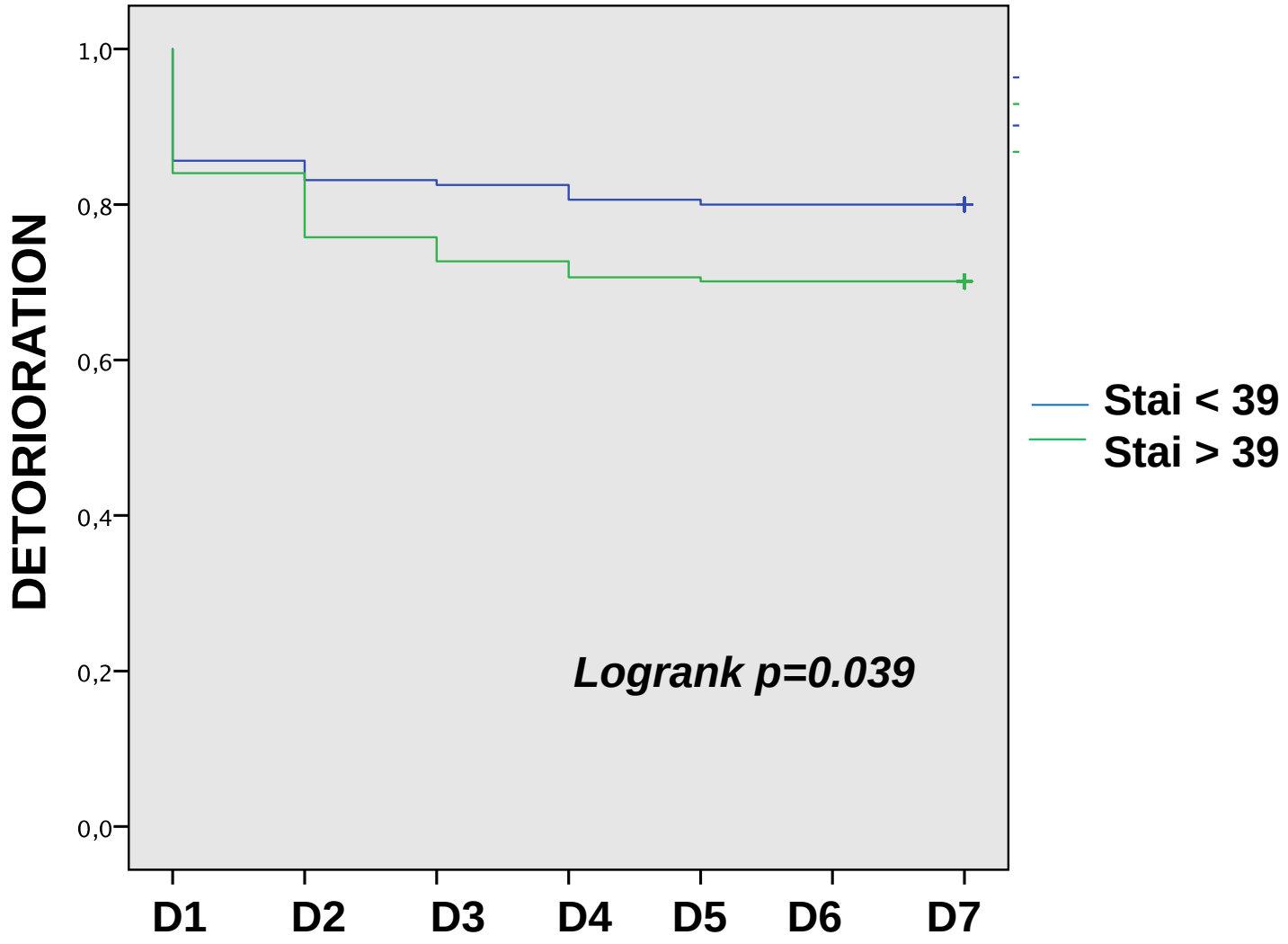
ASTROCYTES

Maintenance of the blood-brain-barrier
Regulation of energy metabolism
Protection from toxic metabolites

MICROGLIA

Resident macrophages of the CNS
Adopt an activated state in response to acute brain injury

Anxiety and deterioration



Anxious patients deteriorate more during the first 7 days in ICU

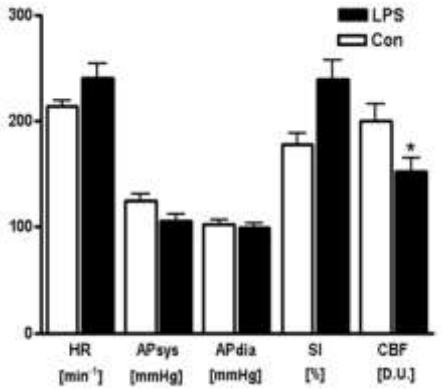
Multivariate Analysis

	OR [95%CI]	P
Knaus	**1.80 [1.09-2.99]**	**0.022**
SOFA Total	**1.44 [1.25-1.67]**	**< 0.0001**
NIV at admission	**4.47 [2.35-8.50]**	**< 0.0001**
STAI ≥ 40	**1.74 [1.01-2.89]**	**0.030**
IGS > 30 + No Fear to die	**2.23 [1.15-4.31]**	**0.017**

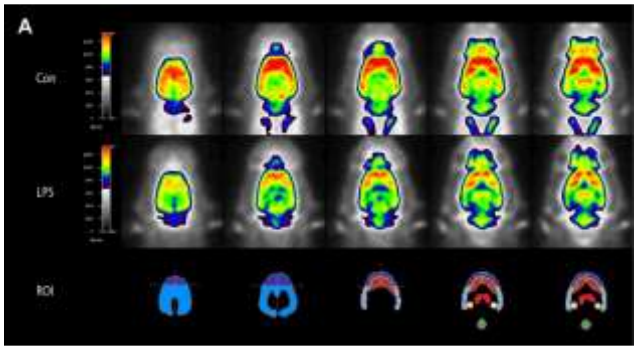
Anxiety is quantitatively and qualitatively associated with further deterioration

LPS

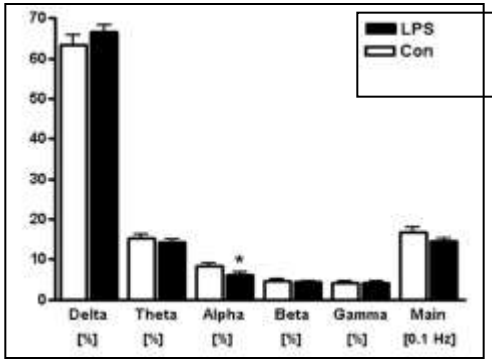
Impaired cerebral hemodynamics



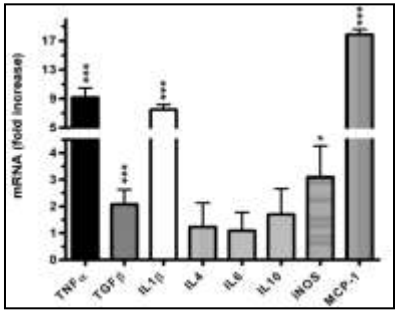
Impaired cerebral metabolism

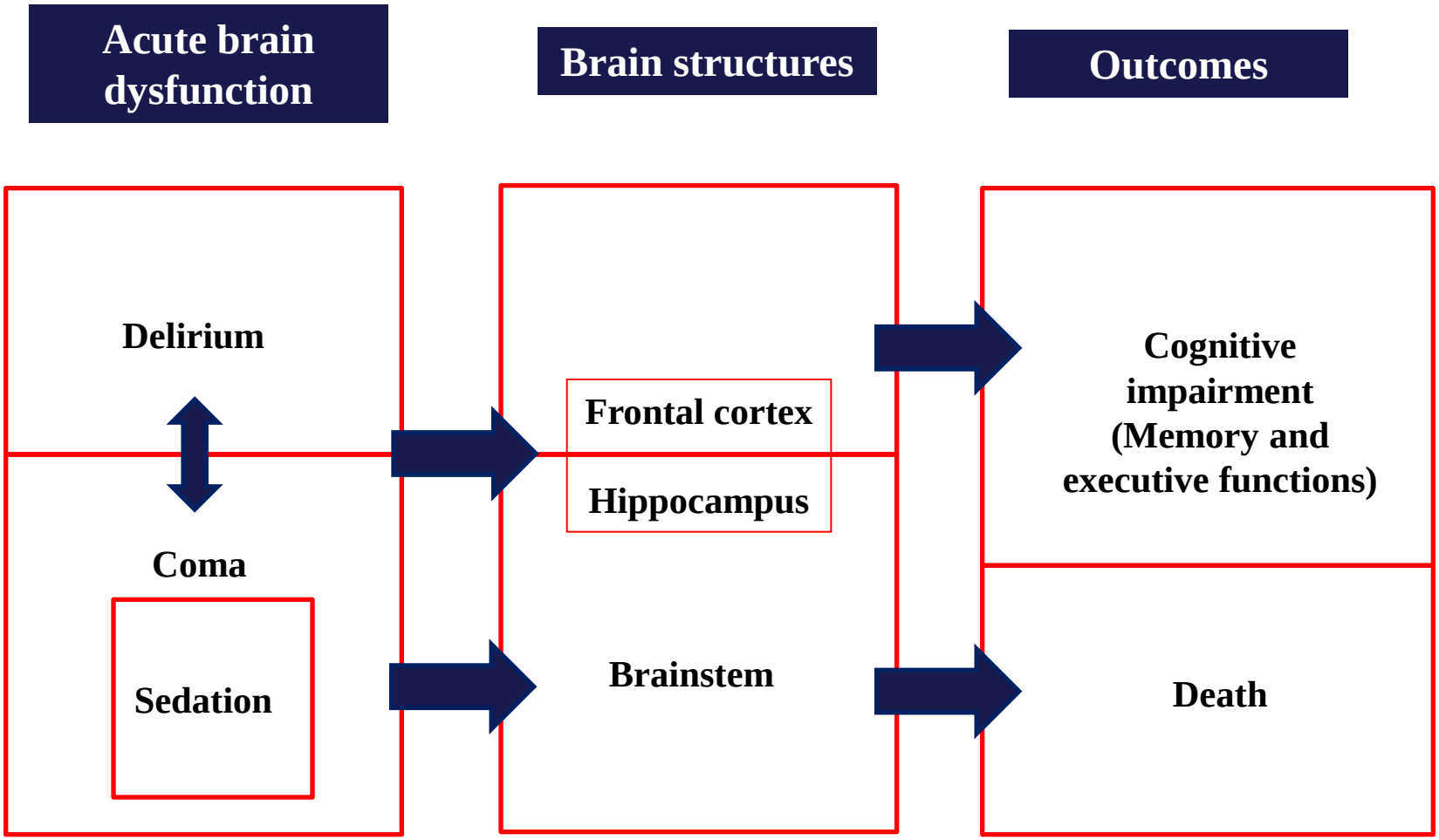


Neuro-inflammation



EEG



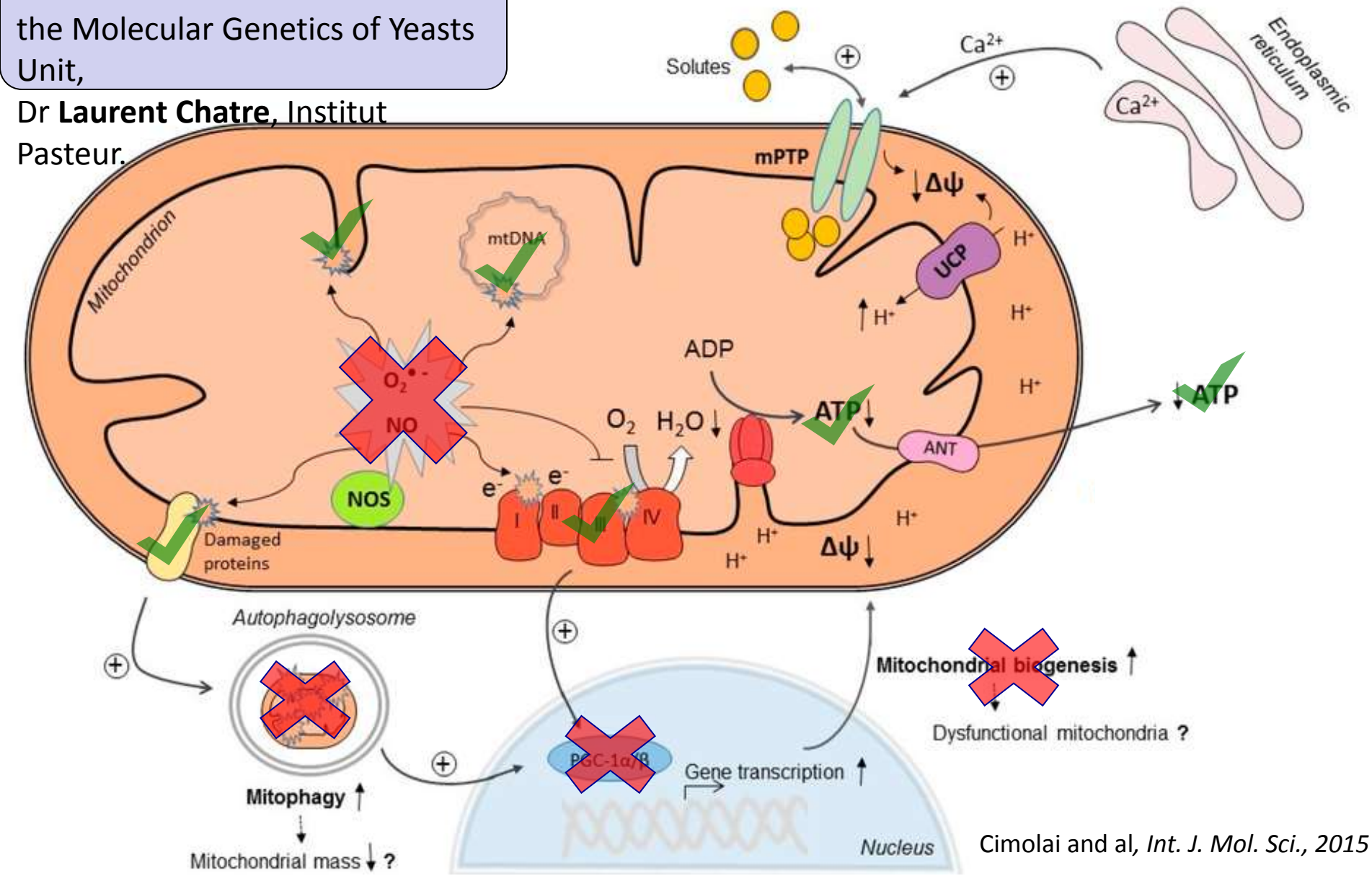


+ structures involved in arousal and consciousness

Annane et Sharshar – Lancet Resp Med - 2014

Microglial mitochondriopathy during sepsis

In collaboration with
the Molecular Genetics of Yeasts Unit,
Dr **Laurent Chatre**, Institut Pasteur.



Cimolai and al, *Int. J. Mol. Sci., 2015*

MRI IN SEPTIC SHOCK PATIENTS

Number (%)	n=71
Neurological findings	
Focal neurological signs	13 (18)
Coma	33 (46)
Seizure	7 (10)
Delirium	35 (49)
Mixed	16 (23)
Neuroradiological findings	
Leucoencephalopathy	15 (21)
Ischemia	21 (29)
Others	4 (6)
Mixed	6 (8)
Normal	37 (52)

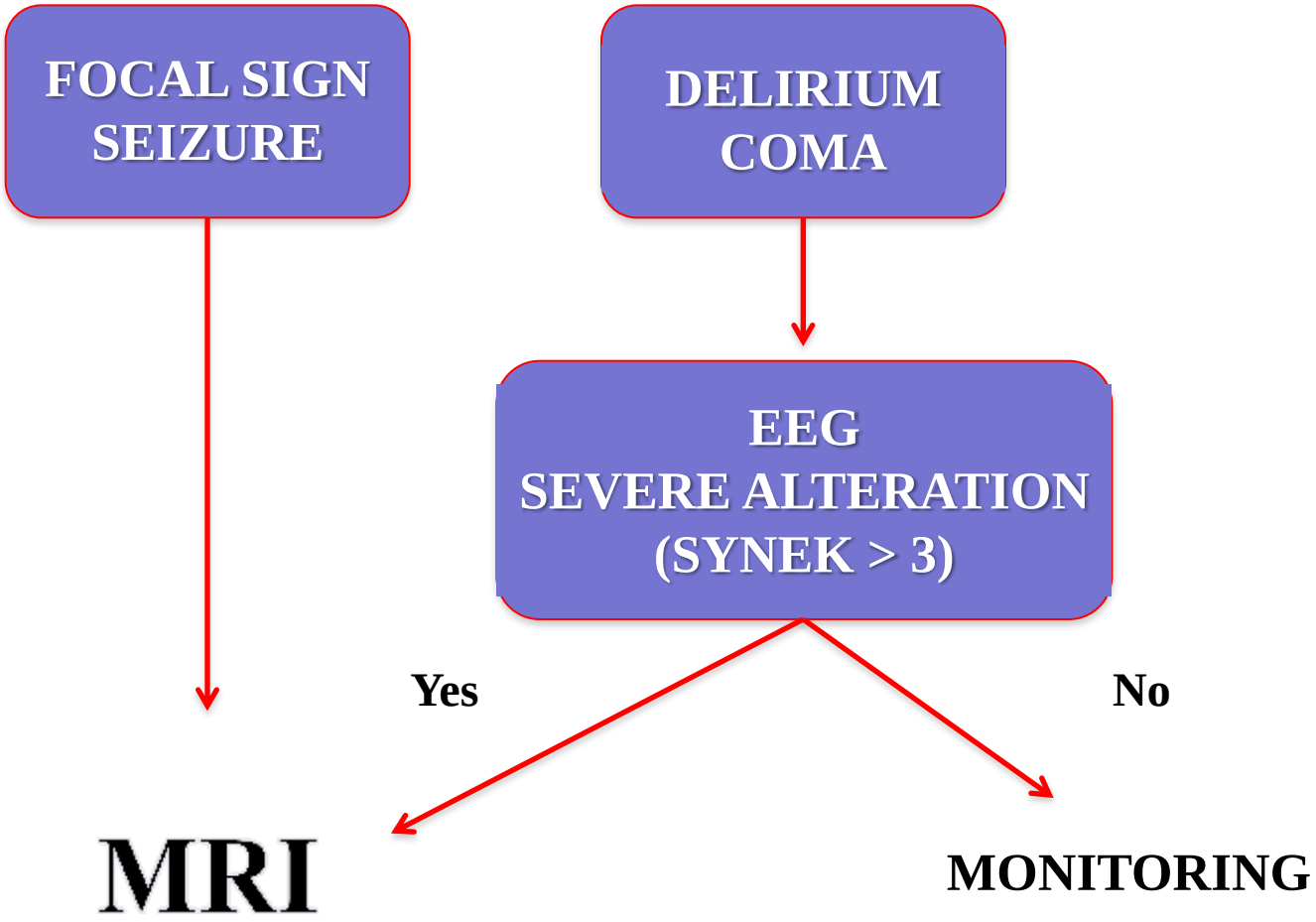
Polito et al – Crit Care - 2013

COMPARISON

	Total 63	Normal 37	Leucoencephalopathy 10	Ischemia 16	P
Demographics					
Age (years)	64 (55-75)	61 (48-78)	69 (67-75)	65 (63-74)	0·15
Women	25 (40)	12 (32)	4 (40)	9 (56)	0·30
Cardiovascular risk factors	37 (59)	19 (51)	8 (80)	10 (62)	0·25
SAPS II	49 (38-60)	52 (39-60)	49 (31-60)	48 (38-55)	0·79

Polito et al – Crit Care - 2013

PROBABILITY OF ABNORMAL MRI

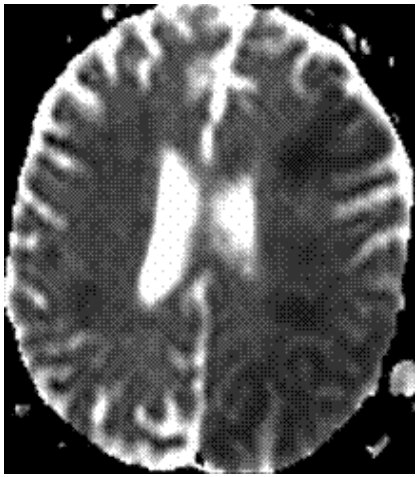


COMPARISON

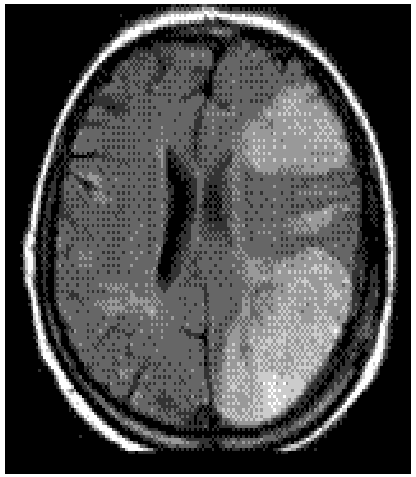
	Total 63	Normal 37	Leucoencephalopathy 10	Ischemia 16	P
DIC	28 (44)	17 (46)	2 (20)	11 (69)	0·04
Lowest plasma hemoglobin level (g/dl)	7·9 (7·0-10·1)	8·4 (7·1-10·0)	7·5 (6·9-11·1)	7·6 (6·9-9·9)	0·91
Neurological symptoms					
1. Focal neurological signs	11 (17)	2 (5)[b]	1 (10)[c]	8 (50)	0·004
2. Coma	31 (41)	17 (46)	2 (20)	10 (62)	0·11
3. Seizure	6 (10)	4 (11)	0 (0)	2 (12)	0·53
4. Delirium	31 (49)	19 (51)	7 (70)	5 (31)	0·15
Mortality	21 (33)	9 (24)[b]	2 (20)[c]	10 (62)	0·02
GOS 6 months ≤ 3	30 (48)	14 (38)[b]	3 (30)[c]	13 (81)	0·007

CEREBRAL INFARCTS

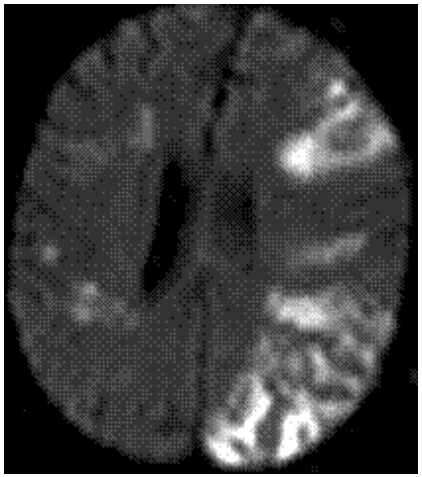
Septic shock complicated by severe DIC.
Patient died without recovering consciousnes



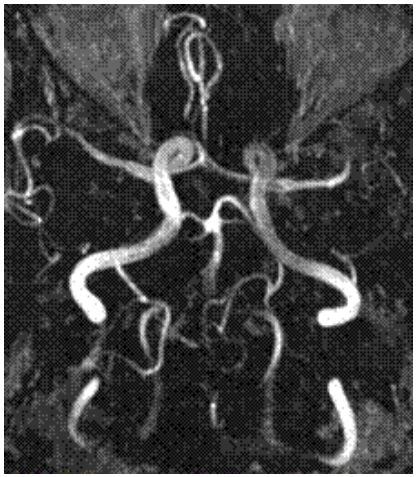
FLAIR



DWI



ADC

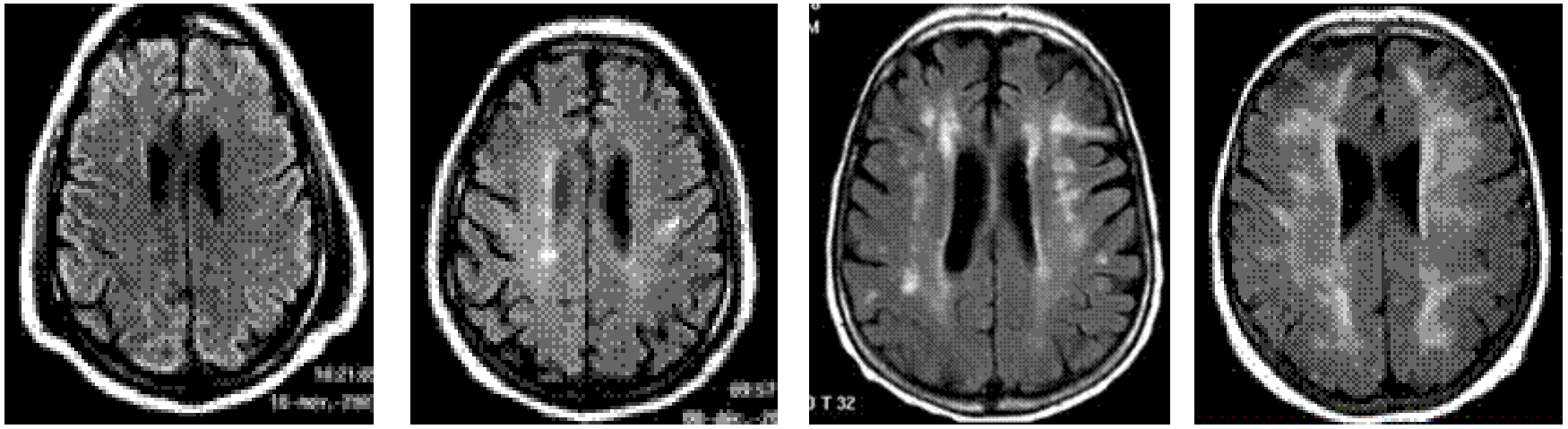


OCCLUSION

Polito et al – Crit Care - 2013

LEUCOENCEPHALOPATHY *(white matter hyperdensities)*

BBB alteration



Before — After

Acquired during sepsis

Grade II — Grade III

Sharshar et al - ICM – 2007;
Polito et al – Crit Care - 2013

Long-term cerebral consequences of sepsis

Catherine N Widmann, Michael T Heneka

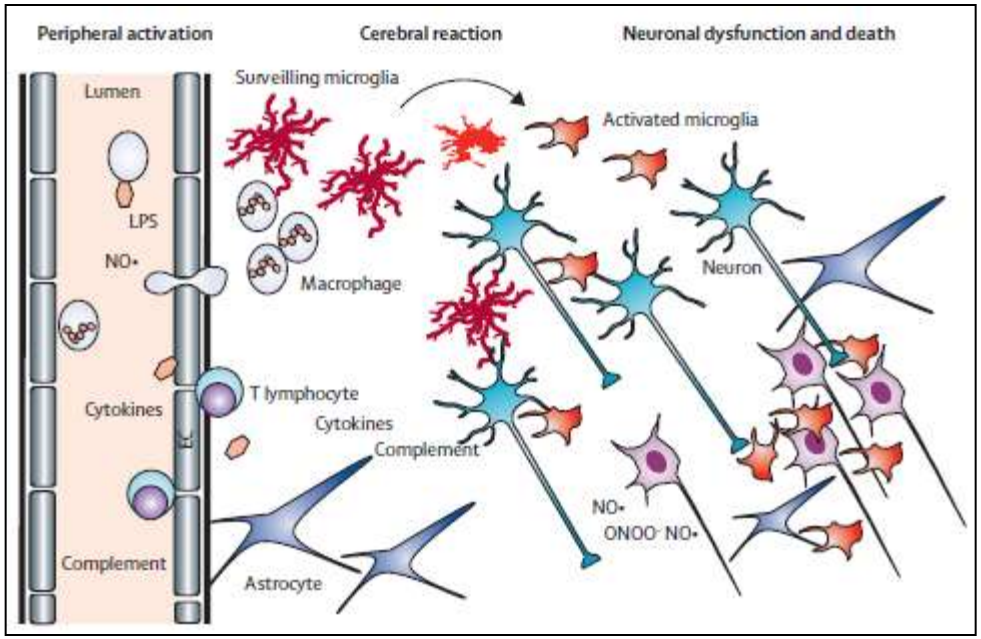
Initial acute-stage results of sepsis

- Sepsis-associated encephalopathy
- Acute systemic inflammation
- Cerebral damage (such as blood–brain barrier disruption, hyperfusion, cell apoptosis, neuronal loss, general slowing of EEG activity)
- (Micro)vascular damage in the CNS, vasogenic oedema, white matter hyperintensities
- Psychiatric burden (anxiety, depression, hallucinations, delusions)

Possible/permanent, long-term effects of sepsis

- Neurocognitive impairment (such as impaired attention, verbal fluency, verbal learning, and memory)
- Sustained brain inflammation?
- Cerebral damage (increased slow-wave activity in EEG, reduced volume of the hippocampus, chronic disruption of the blood–brain barrier)
- Increased risk of vascular brain disease (including a risk of vascular dementia)?
- Psychiatric burden (including raised levels of anxiety, depression, post-traumatic stress syndrome)
- Could other possible permanent effects of sepsis include the presence of Tau-pathology, an increase in amyloid β, and an increased risk of Alzheimer's disease?

Interventions for preventing or treating cognitive decline?



Lancet neurology - 2015

CEREBRAL BLOOD FLOW

CONTROVERSIAL

Should we monitor and “optimize” cerebral blood flow in patients with septic shock?

Table 1. Temporal and spatial expression of interleukin-1β, inducible nitric oxide synthase messenger RNA and Fos in circumventricular organs and adjacent structures after i.p. injection of 250 μg/kg lipopolysaccharide

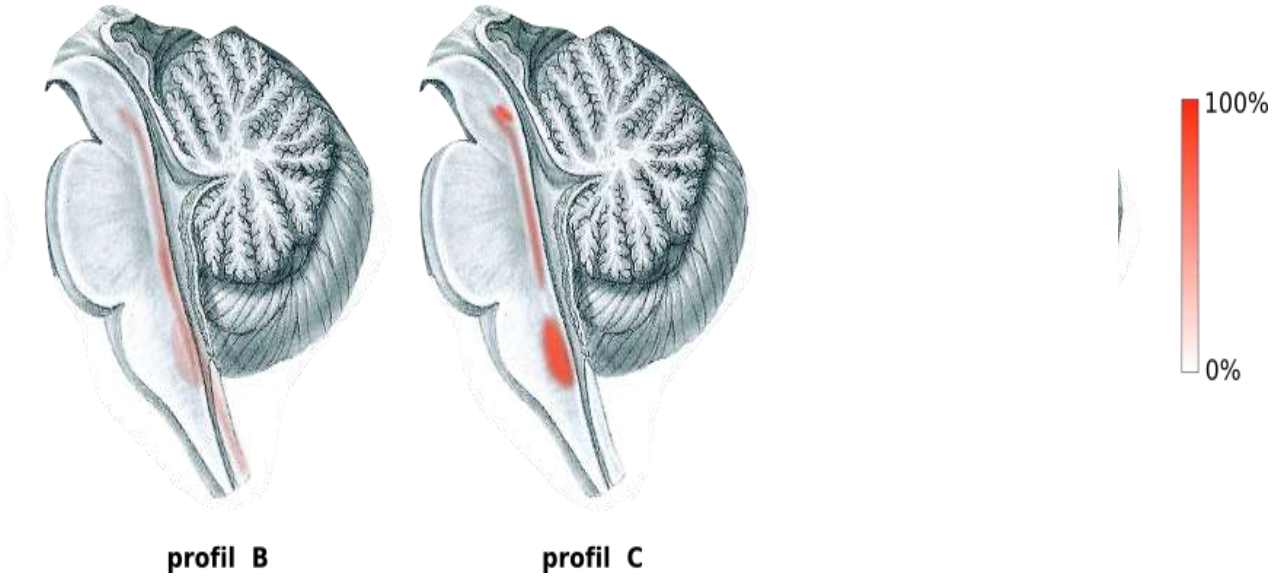
	2 h			4 h			8 h		
	IL-1β	iNOS	Fos	IL-1β	iNOS	Fos	IL-1β	iNOS	Fos
AP									
medial	+	–	–	+	–	–	++	–	+
ventrolateral border	+	–	–	+	–	–	+++	++	+
NTS	–	–	++	–	–	++	+	–	+
Median eminence									
ventral	+	–	–	+	–	–	++	–	–
dorsolateral border	–	–	–	–	–	–	++	+	–
Arcuate nucleus	–	–	–	–	–	–	+	–	–
OVLT									
medial	+	–	–	+	–	–	++	–	+
lateral borders	–	–	–	+	–	–	+++	++	+
Medial preoptic area	–	–	++		–	++	+	–	+
Subfornical organ									
ventromedial	+	–	–	+	–	–	++	–	+
dorsolateral border	+	–	–	+	–	–	+++	++	+
Hippocampal commissure	–	–	–		–	–	+	+	–
Choroid plexus	+	–	–	+	–	–	+	+	–

–, no or very few positive cells (n<5); +, few positive cells (5<n<25); ++, high number of positive cells (25<n<75); +++, very high number of positive cells (n>75); n, numbers of labelled cells in a representative section of a given structure.

Konsman et al - Neuroscience-1999

HYPOTHESIS

Continuum?
Reversibility?

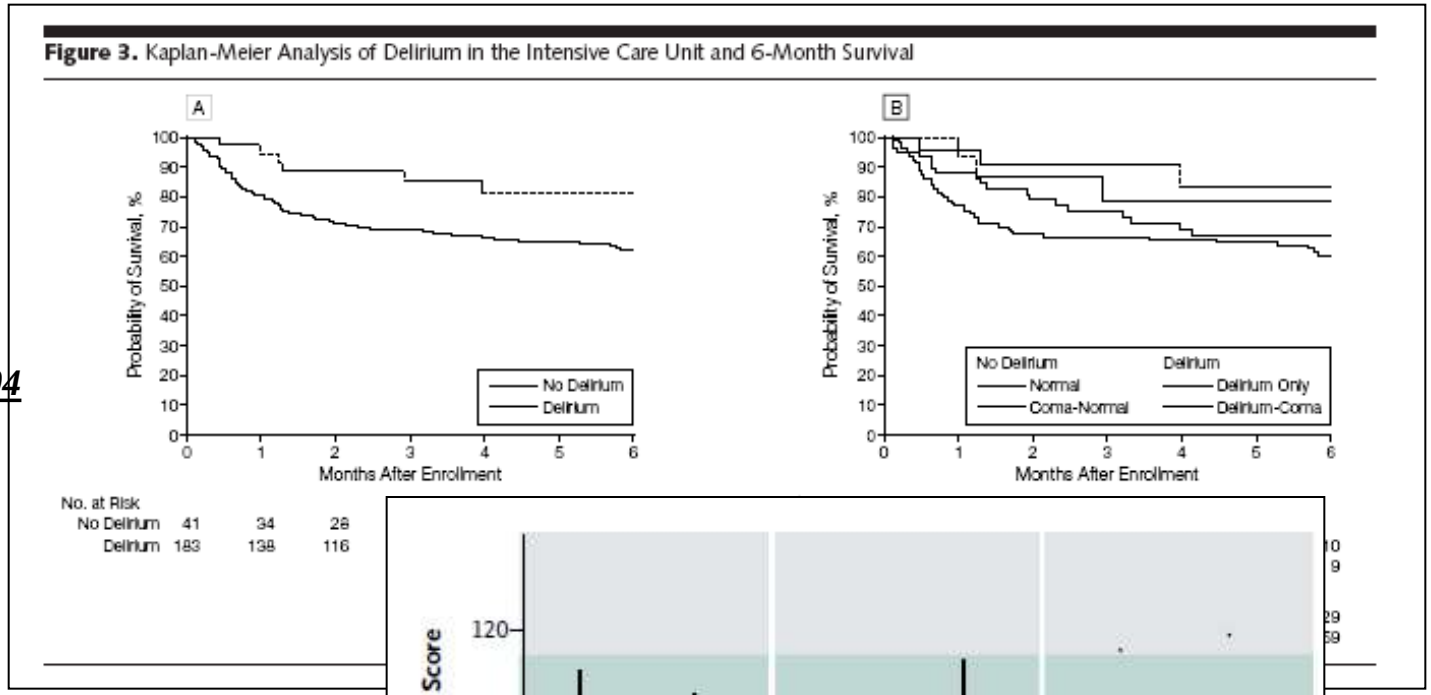


Continuum : process posteriorly spreading from the *area postrema*
(deprived from BBB, neuro-inflammatory signaling)

OUTCOMES

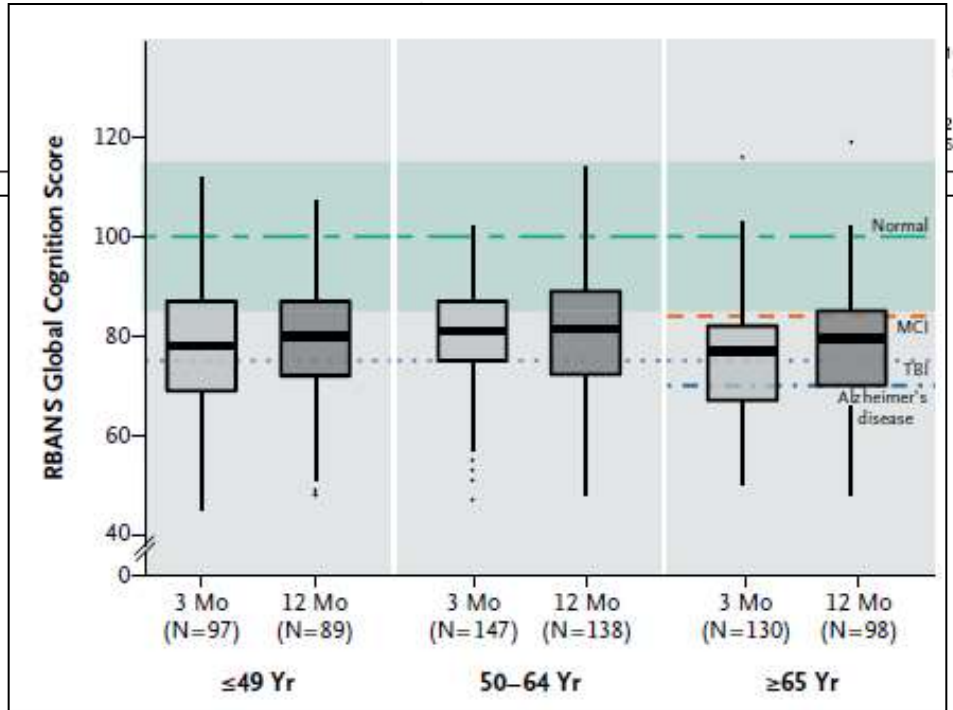
MORTALITY

Ely et al – JAMA - 2004



COGNITIVE IMPAIRMENT

Pandharipande et al – JAMA - 2013



BRAIN DYSFUNCTION

Incidence: 24 to 50% of septic patients ***(Keh et al 2016; Azabou et al 2016)***

Criteria for sepsis :

(*Singer et al 2016*)

Box 4. qSOFA (Quick SOFA) Criteria
Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≤100 mm Hg

Symptoms:

(*Polito et al 2013*)

Number (%)	n=71
Neurological findings	
Focal neurological signs	13 (18)
Coma	33 (46)
Seizure	7 (10)
Delirium	35 (49)
Mixed	16 (23)

Electroencephalogram:

(*Azabou et al 2015*)

Total number of EEG	110
Dominant frequency—n (%)	
alpha	21 (19)
delta	36 (33)
theta	53 (48)
Amplitude—n (%)	
low-voltage	71 (65)
normal	39 (35)
Absence of reactivity—n (%)	27 (25)
Electrographic seizure—n (%)	17 (15)
Periodic Discharges—n (%)	21 (19)
Triphasic waves—n (%)	7 (6)
Synek's scale (from 0 to 5)–median [IQR]	2 [1 to 3]
Synek's score ≥ 3 –n (%)	34 (31)

Outcomes

Increased mortality & morbidity **(*Edelman 1996, Polito 2013, Azabou 2015, Schmidt 2016*)**

EFFECTS OF SEDATION

- ***Most severe critically ill patients often require sedation***
- ***Sedation is a risk factor for brain dysfunction (delirium or delayed awakening) and can mask the occurrence of a brain dysfunction***
- ***How to detect acute brain dysfunction in sedated critically ill patients?***

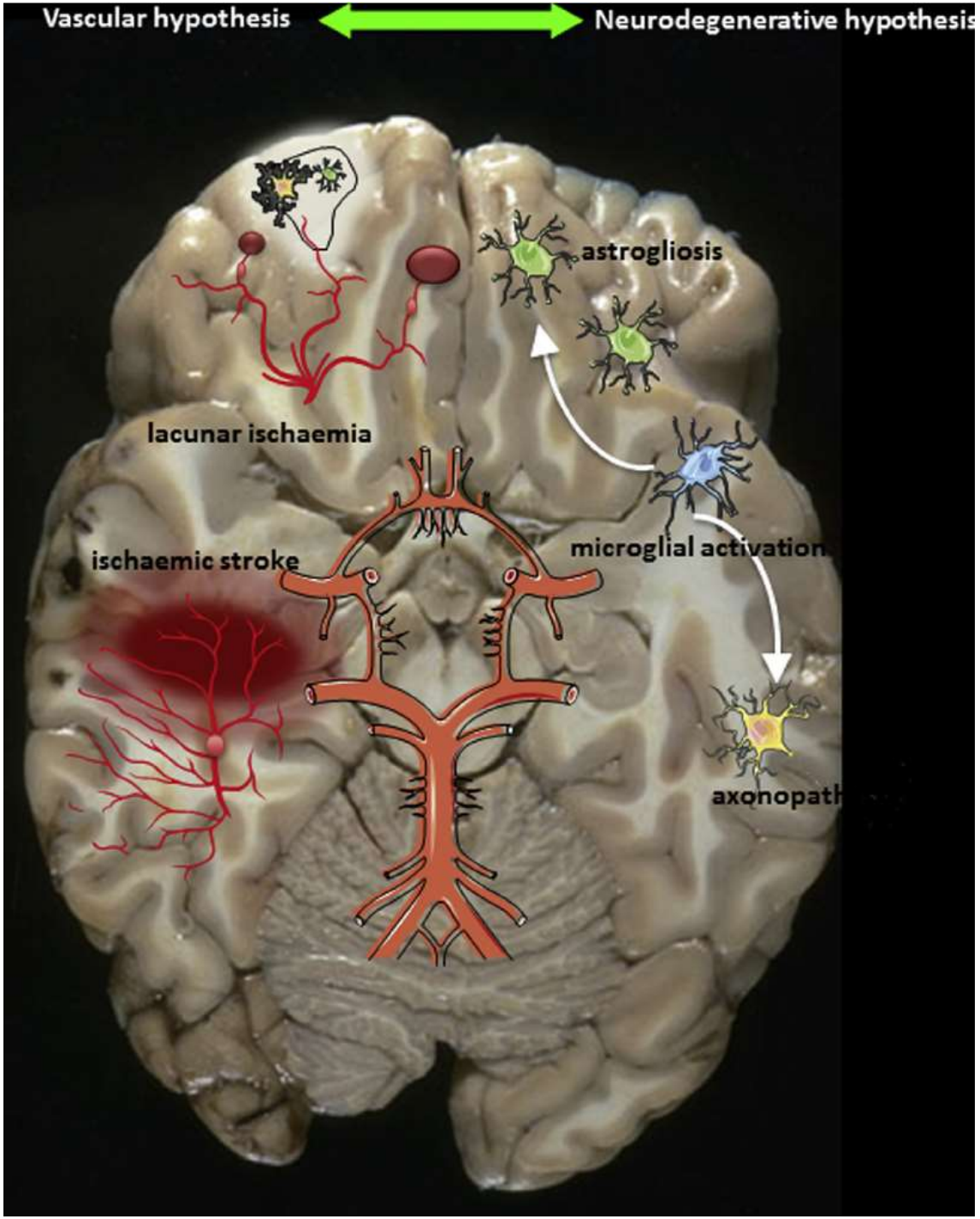
P14	14 (24)	22 (52)		
N20	19 (33)	29 (69)		
P14-N20	21 (36)	23 (55)		
N20-P25				
III	18 (31)	21 (50)		
V				
III-V			0 (0)	14 (23)
	17 (17)	18 (43)		
	21 (36)	26 (62)		

EEG IN SEDATED SEPTIC PATIENTS

N=110 septic patients

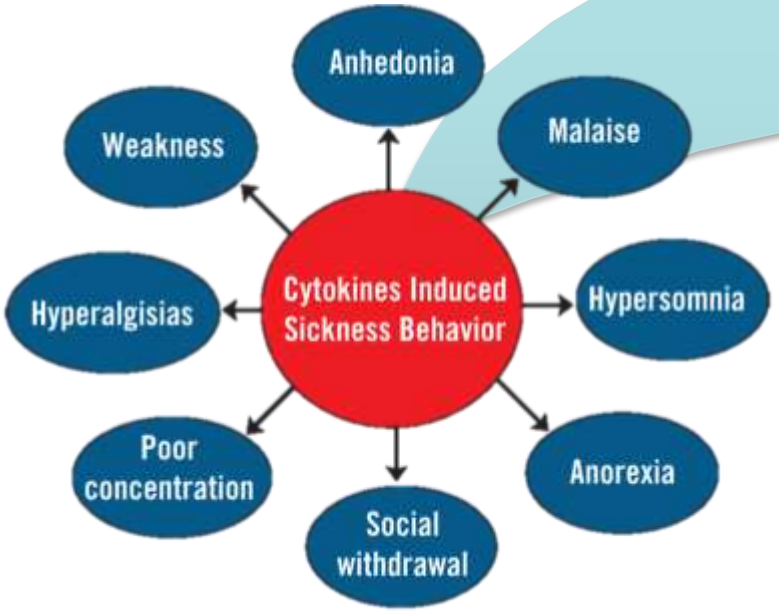
Variables		Sedated at time of EEG recording		Delirium at time of EEG recording (£)		Developed Delirium after EEG (¥)		In hospital Death	
		yes	no	yes	no	yes	no	yes	no
Number of patients	n (%)	46 (42)	64 (58)	22 (20)	42 (38)	32 (29)	48 (44)	23 (21)	87 (79)
Age (years)	mean (SD)	62.8 (16.0)	64.5 (19.6)	66.1 (19.8)	63.6 (19.6)	66.4 (16.9)	61.3 (18.9)	66.1 (15.9)	63.3 (18.5)
SAPS-II at admission	median [IQR]	54 ***	34	42 *	33[25 to 40]	45 **	34	44	37
		[37 to 66]	[27 to 45]	[30 to 53]	[25 to 40]	[36 to 63]	[27 to 47]	[36 to 65]	[28 to 54]
Septic shock	n (%)	30 (65) ***	15 (23)	8 (36)	7 (17)	20 (62)**	13 (27)	9 (39)	36 (41)
SOFA at inclusion	median [IQR]	9 ***	3	4 **	3	7 ***	4	10 **	5
		[7 to 12]	[2 to 5]	[3 to 7]	[2 to 4]	[5 to 11]	[2 to 7]	[6 to 15]	[3 to 7]
EEG findings									
Delta-predominant	n (%)	24 (52)***	12 (19)	7 (32)	5 (12)	16 (50)**	7 (15)	11 (48)*	25 (29)
Low voltage	n (%)	40 (87)***	31 (48)	11 (50)	20 (48)	25 (78)	28 (58)	14 (61)	57 (65)
Absence of reactivity	n (%)	19 (41)***	8 (12)	5 (23)	3 (7)	13 (41) **	5 (10)	10 (43)**	17 (20)
Electrographic seizure	n (%)	6 (13)	11 (17)	7 (32)*	4 (10)	5 (15)	5 (10)	4 (17)	13 (15)
Triphasic waves	n (%)	0 (0) *	7 (11)	4 (18)	3 (7)	1 (3)	2 (4)	2 (9)	5 (6)
Periodic Discharges	n (%)	10 (22)	11 (17)	5 (23)	6 (14)	8 (25) *	5 (10)	7 (30)*	14 (16)
Synek score ≥ 3	n (%)	23 (50)***	11 (17)	8 (36)**	3 (7)	14 (44)**	8 (17)	12 (52)***	22 (25)
Young score > 1	n (%)	26 (57)***	15 (23)	8 (36)	7 (17)	19 (59)***	8 (17)	12 (52)**	29 (33)

Azabou et al – Plosone - 2015


Vascular hypothesis
Neurodegenerative hypothesis
astrogliosis
lacunar ischaemia
microglial activation
ischaemic stroke
axonopath

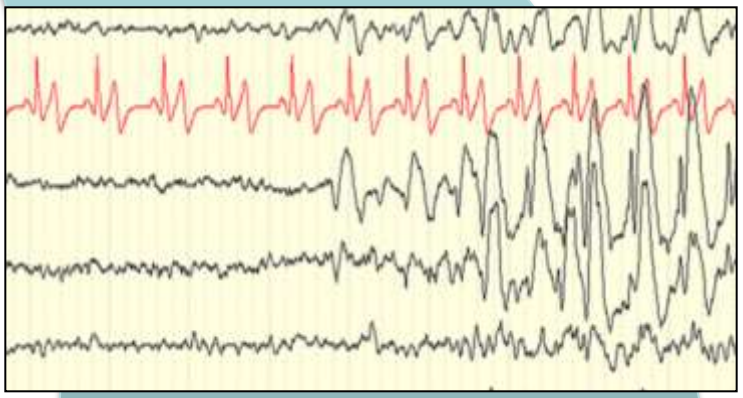
Acute CNS response to sepsis

Physiology: **Sickness Behaviour**



Brain dysfunction

- Confusion/*delirium*, sleepiness
- EEG abnormalities correlate with **mortality or delirium occurence**
- Coma requiring mechanical ventilation
- Epileptic crisis



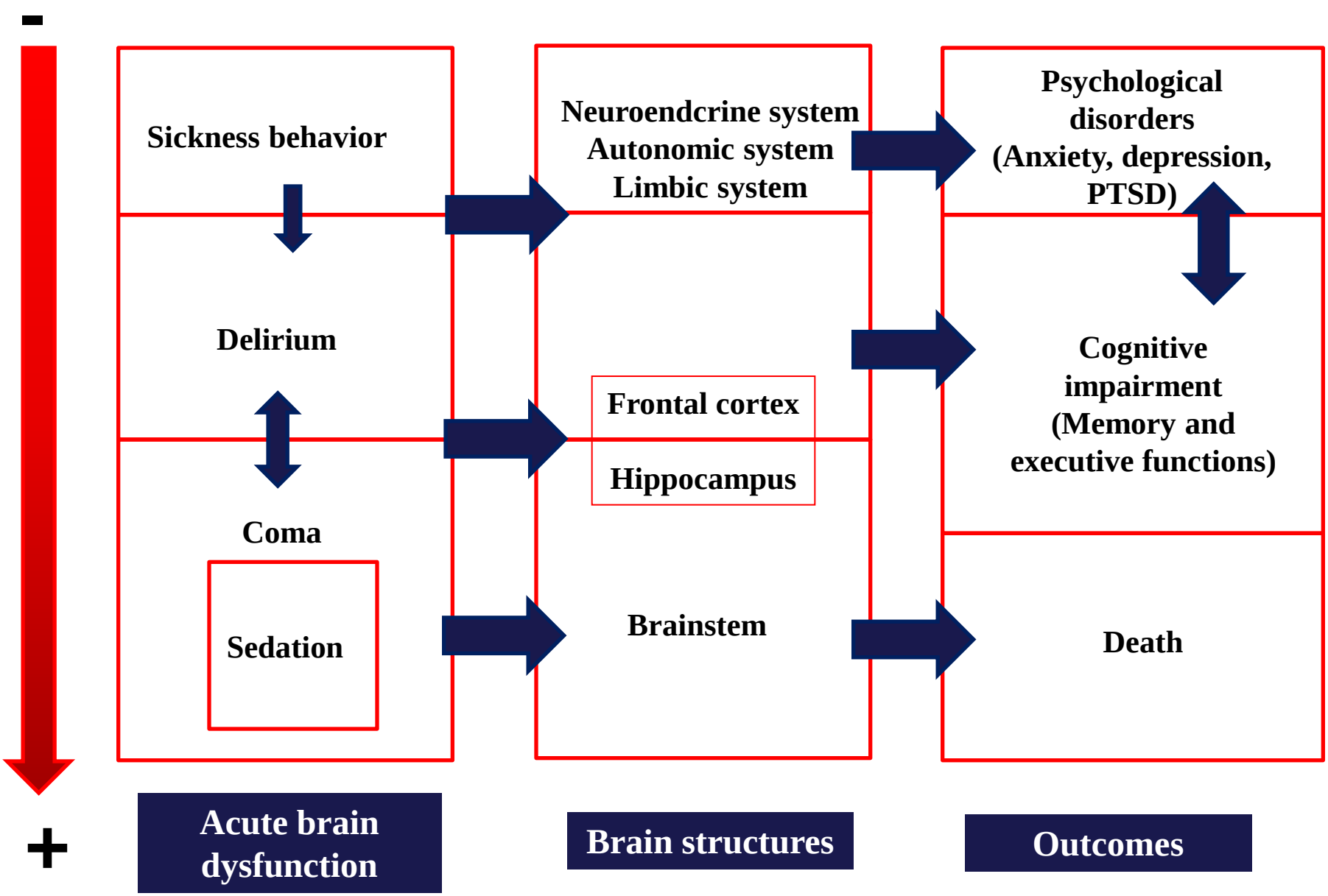
Anesth Anal. 1956 Mar-Apr;13(2):395-400; discussion, 400-2.

[Prolonged epileptic crisis provoked by streptococcal septicemia; hibernation recovery].

[Article in French]
DOUCHY E.

PMID: 15444936 [PubMed - indexed for MEDLINE]

Azabou et al Plos One 201

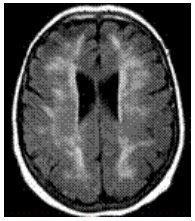


Annane et Sharshar – Lancet Resp Med - 2014

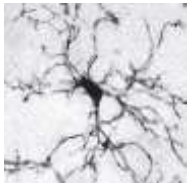
PATHOPHYSIOLOGY

SEPSIS-ASSOCIATED ENCEPHALOPATHY

Neuroinflammatory process
(Delirium => neurodegenerative)



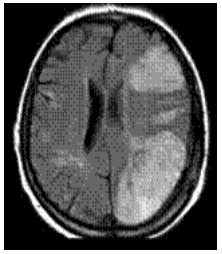
Cytokines
NO

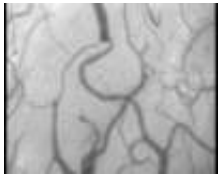


20% mortality

(Sharshar 2007, Polito 2011)

Ischemic process
(Delirium/focal => vascular dementia)



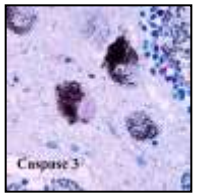


Macro/microcircu-latory dysfunction

60% mortality

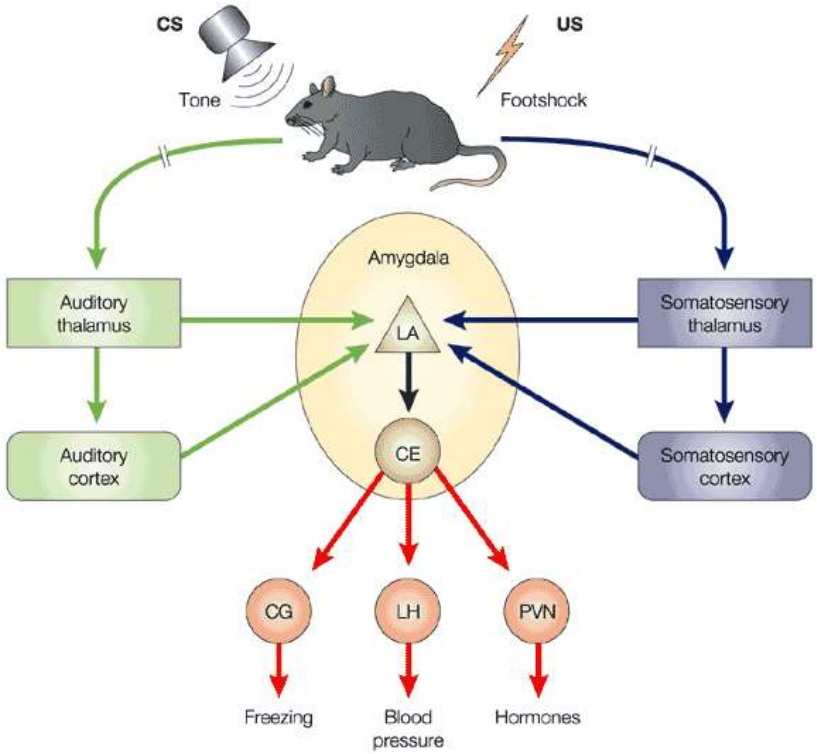
(Polito et al 2013, Sharshar 2007, Sharshar 2004)

Neurotoxic process (Delirium => neurodegenerative)



Amygdala – Fear conditionning

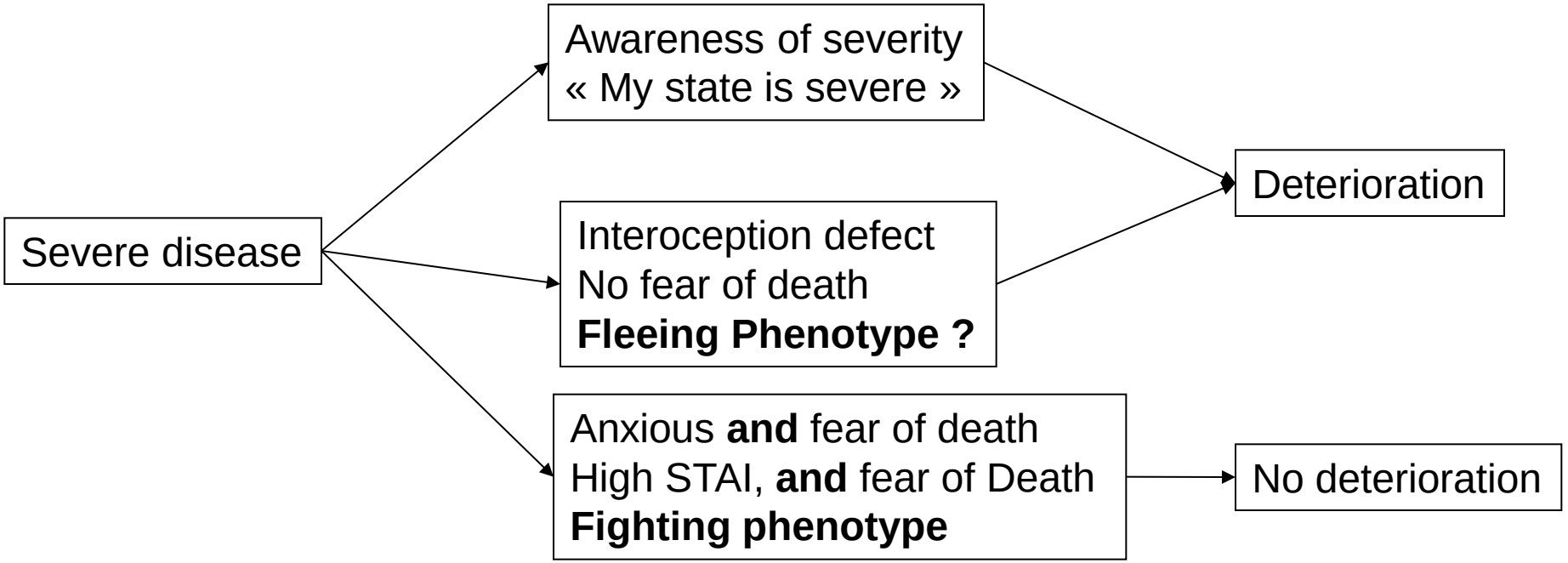
CS: conditionned stimulus
US: unconditionned stimuls



LA: lateral nucleus
CE: Central nucleus

During fear conditioning, the conditioned stimulus (CS) and unconditioned stimulus (US) are relayed to the lateral nucleus of the amygdala (LA) from thalamic and cortical regions of the auditory and somatosensory systems, respectively. The CS inputs enter the dorsal subregion of the LA, where interactions with the US induce plasticity in two functional cell types (so-called 'trigger' and 'storage' cells). CS information is then transmitted through further stations in the LA to the central nucleus of the amygdala (CE). Interactions between the lateral and central amygdala are more complex than illustrated, and involve local-circuit connections (see main text). The LA also communicates with the CE by way of connections with other amygdala regions (not shown), but the direct pathway seems to be sufficient to mediate fear conditioning. *Medina et al – Nature Rev Neuroscience - 2012*

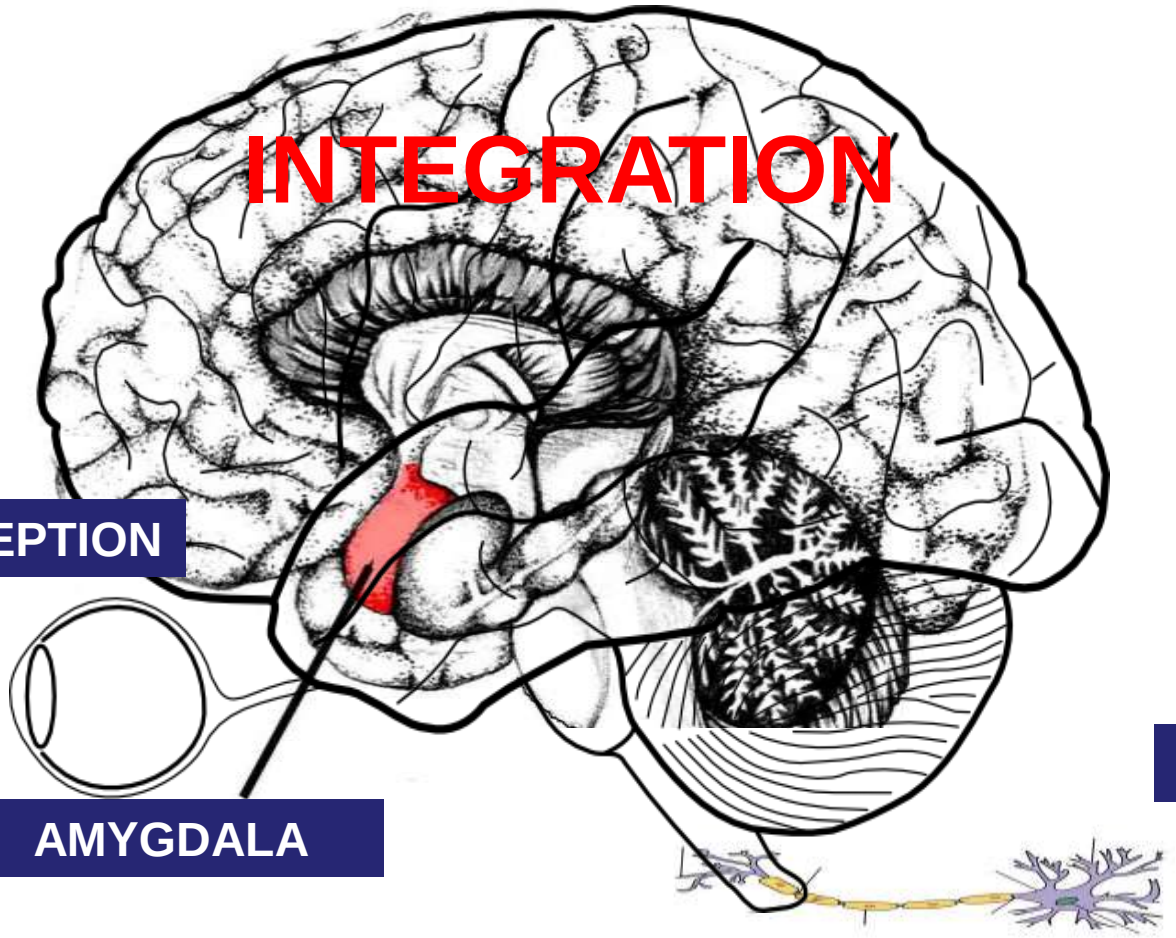
Conclusion



- Why? Are the neurobiological bases of Anxiety and fear to die different? Is there an impairment of perception or integration of danger?

CRITICAL ILLNESS → **IMPAIRED INTERO/EXTEROCEPTION** → **OUTCOMES**

Critical Illness: Impairment of perception or integration of danger ?



EXTEROCEPTION

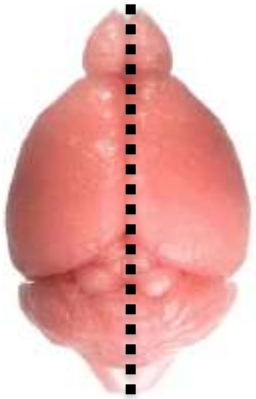
AMYGDALA

INTEROCEPTION

Perception of inner danger (ex. peritonistis)

Peritonitis as a model of sepsis

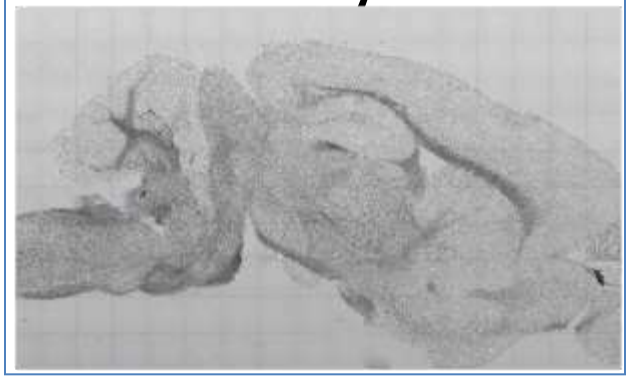
Caecal ligation and puncture



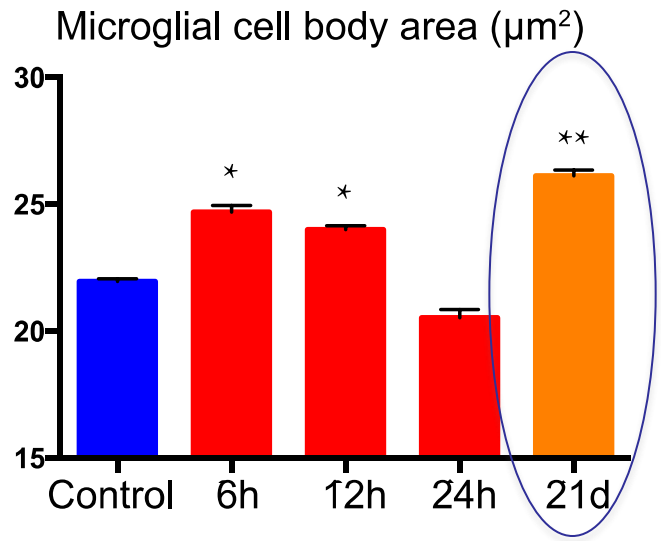
Microglial functional study

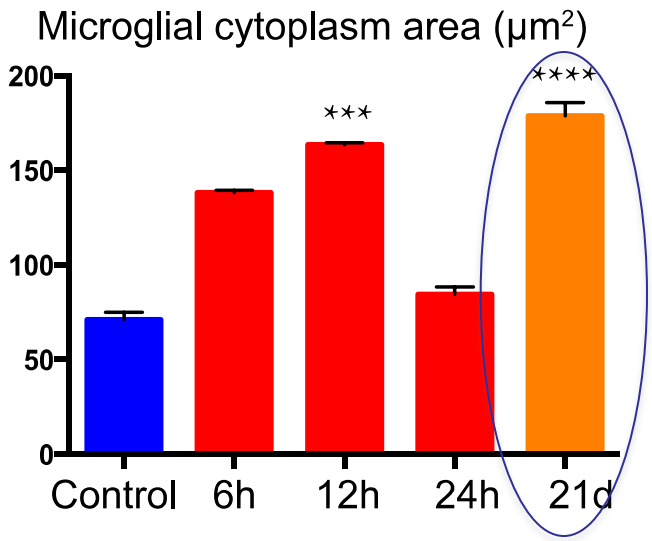
1. Proteomic approaches:
   - → In the tissue (Luminex®)
   - → In vitro (stimulation)
2. Cell sorting using FACS or magnetic beads (CD11b)
3. Transcriptomic approach: phenotype
4. Metabolic study using *In Situ* technics

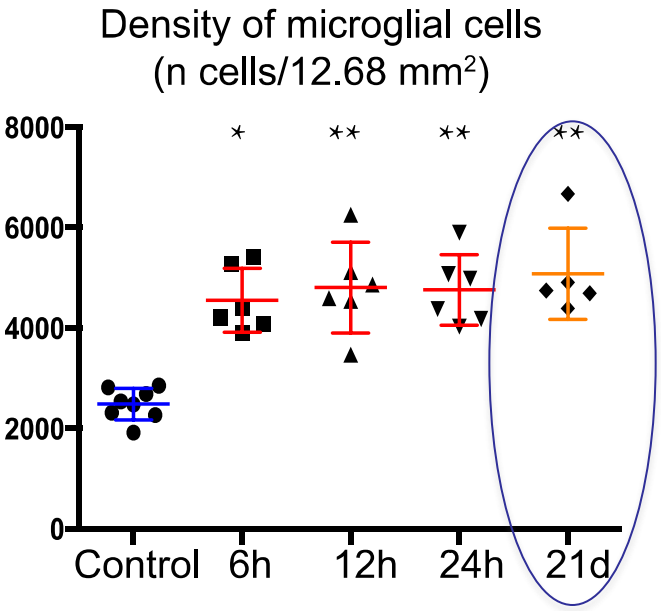
Microglial morphological study

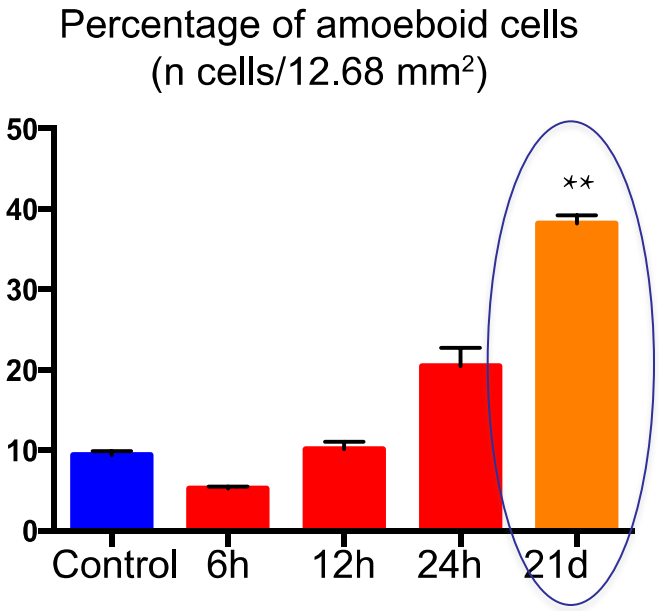


Sepsis results in early microglial reactivity

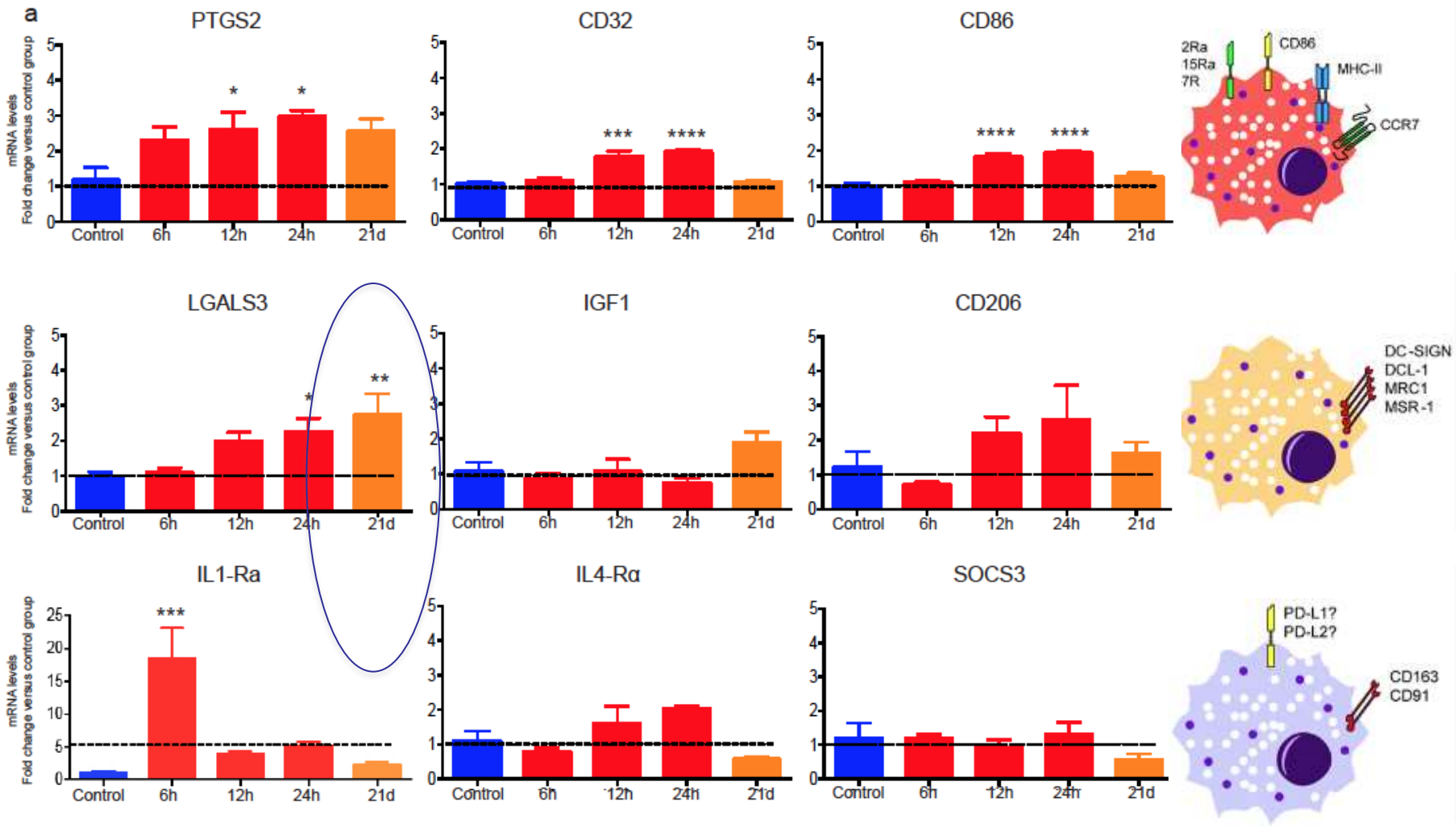








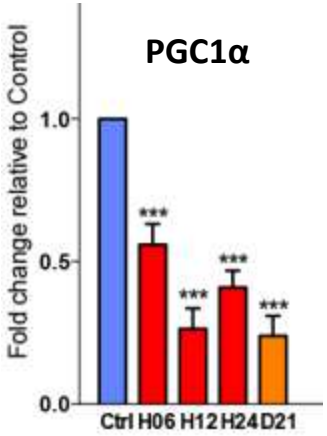
Microglia exhibits late anti-inflammatory profile



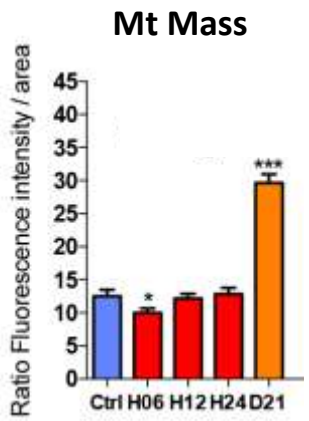
→ **Is this the microglial priming?**

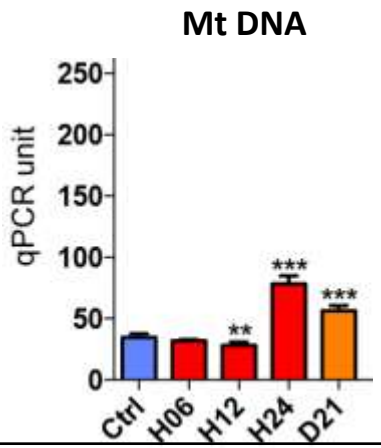
Mitochondrial energetic dysfunction

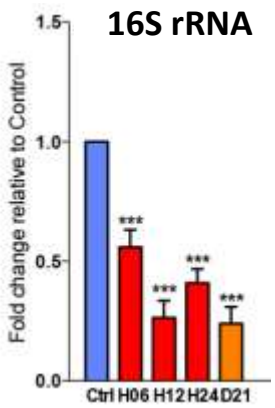
Mitochondrial biogenesis

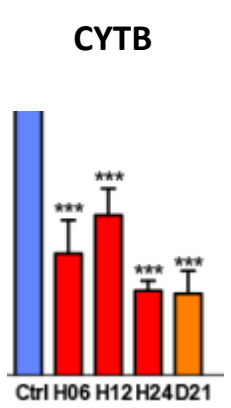


Mitochondrial mass and content

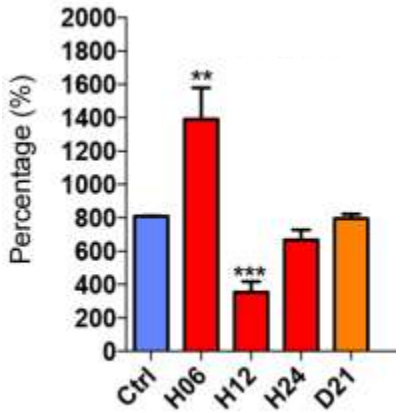




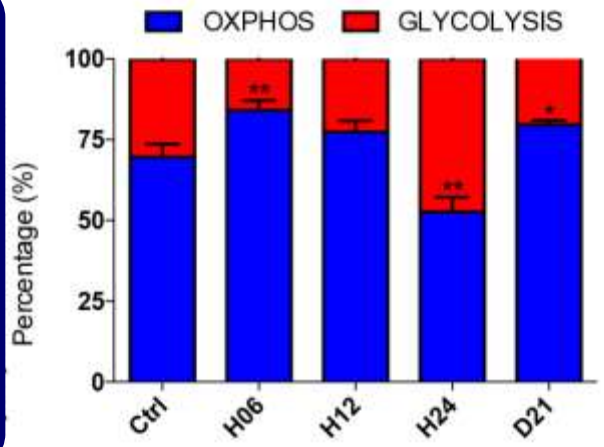




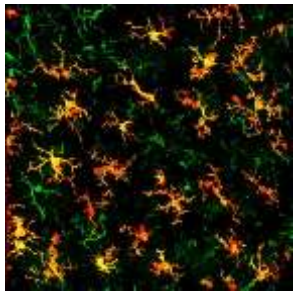
ATP production



OXPHOS/Glycolysis



MICROGLIAL PRIMING



SEPSIS

EARLY MICROGLIAL ACTIVATION

MODULATION

PROTRACTED MICROGLIAL CHANGES
Morpho-Immuno-Metabolic phenotype

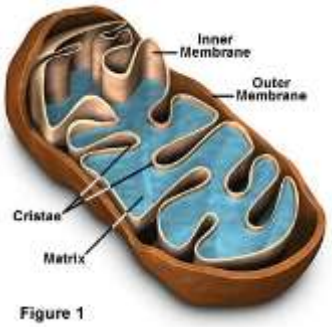
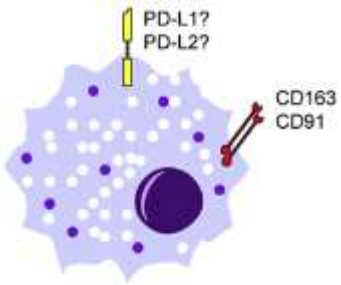


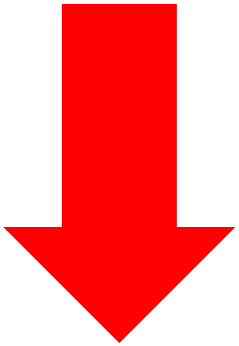
Figure 1



REACTIVITY TO A SECOND HIT

PSYCHO-COGNITIVE CONSEQUENCES

CLINICAL EVIDENCE OF BRAINSTEM DYSFUNCTION



EFFECT OF SEDATION ON BRAINSTEM REFLEXES

Brainstem responses can predict death and delirium in sedated patients in intensive care unit*

Non brain injured critical ill patients sedated by MDZ ± sufentanyl

Reproducibility of neurological examination was satisfactory 0.62 to 1)

Sharshar et al – Crit Care Med – 2011

NEUROLOGICAL ASSESSMENT

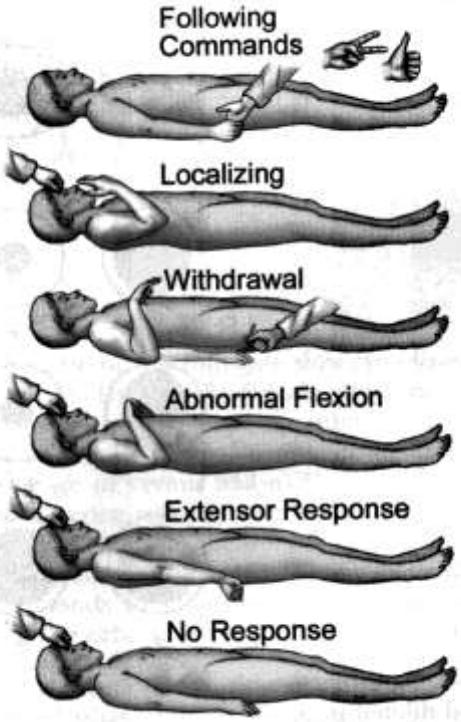
GLASGOW COMA SCALE

- **Eyes response**
- **Motor response**
- **Verbal response** (crossed out)

FOCAL SIGNS

Comparison between right and left body

1. Motor responses to order or painful stimulation
2. Limbs tone
3. Tendon reflexes
4. Plantar reflex



BRAINSTEM RESPONSES

1. Eyes spontaneous movement
2. Eyes position
3. Oculocephalogyre response
4. Pupillar size
5. Pupillar light reflex
6. Corneal reflex
7. Grimace
8. Cough reflex

Brainstem responses can predict death and delirium in sedated patients in intensive care unit*

12-24H OF SEDATION	Validation set
Number of patients	72/144
Midazolam (mg/kg)	1.3 (0.8 to 2.0)
Subfentanyl (µg/kg)	2.0 (0.7 to 4.6)
Sedation to inclusion (hours)	12 (12-24)
RASS	-4 (-4 to -2)
Blinking to strong light (%)	28 (39)
Absent eye movement (%)	67 (93)
Myosis (%)	38 (54)
Pupillary light response (%)	58 (82)
Corneal reflex (%)	66 (92)
Oculocephalic response (%)	33 (46)
Cough response (%)	60 (83)
Grimacing (%)	48 (69)

Sharshar et al – Crit Care Med – 2011

Brainstem responses can predict death and delirium in sedated patients in intensive care unit*

144 deeply sedated non brain-injured critically ill patients
Responses assessed between the 12th and 24th h of sedation

Mortality

	Development Set		Validation Set	
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)	*p*
Simplified Acute Physiologic Score II at inclusion	1.06 (1.02–1.09)	.003	1.03 (1.00–1.07)	.051
Absent cough response	7.80 (2.00–30.4)	.003	5.44 (1.35–22.0)	.017
C-index (SE)	0.836 (0.055)		0.743 (0.067)	

Data are presented as adjusted odds ratio (95% confidence interval). The model for 28-day mortality was maintained irrespective of the participating center ($p = .62$).

Sharshar et al – Crit Care Med – 2011

Brainstem responses can predict death and delirium in sedated patients in intensive care unit*

144 deeply sedated non brain-injured critically ill patients
Responses assessed between the 12th and 24th h of sedation

Post-sedation altered mental status (delayed awakening + delirium)

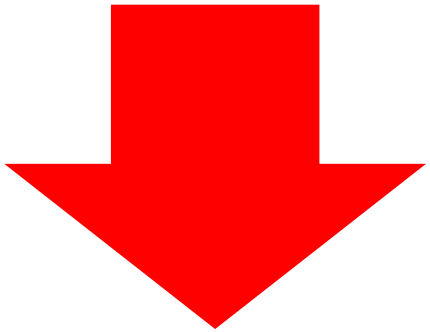
Criteria	Development Set Confusion or Coma		Validation Set Delirium or Coma	
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)	*p*
Simplified Acute Physiologic Score II at inclusion	1.04 (1.00–1.07)	.058	1.03 (0.99–1.08)	.10
Absent oculocephalic response	4.49 (1.34–15.1)	.015	5.64 (1.63–19.5)	.006
Simplified Acute Physiologic Score II at inclusion	1.04 (1.00–1.07)	.057	1.04 (0.99–1.09)	.088
Medical admission	0.92 (0.21–4.10)	.91	8.26 (1.94–35.2)	.004
Absent oculocephalic response	4.54 (1.34–15.4)	.015	6.10 (1.48–25.1)	.012

Data are presented as adjusted odds ratio (95% confidence interval). The model for altered mental status was maintained, irrespective of the participating center ($p = .47$).

Sharshar et al – Crit Care Med – 2011

NEUROLOGICAL EXAMINATION

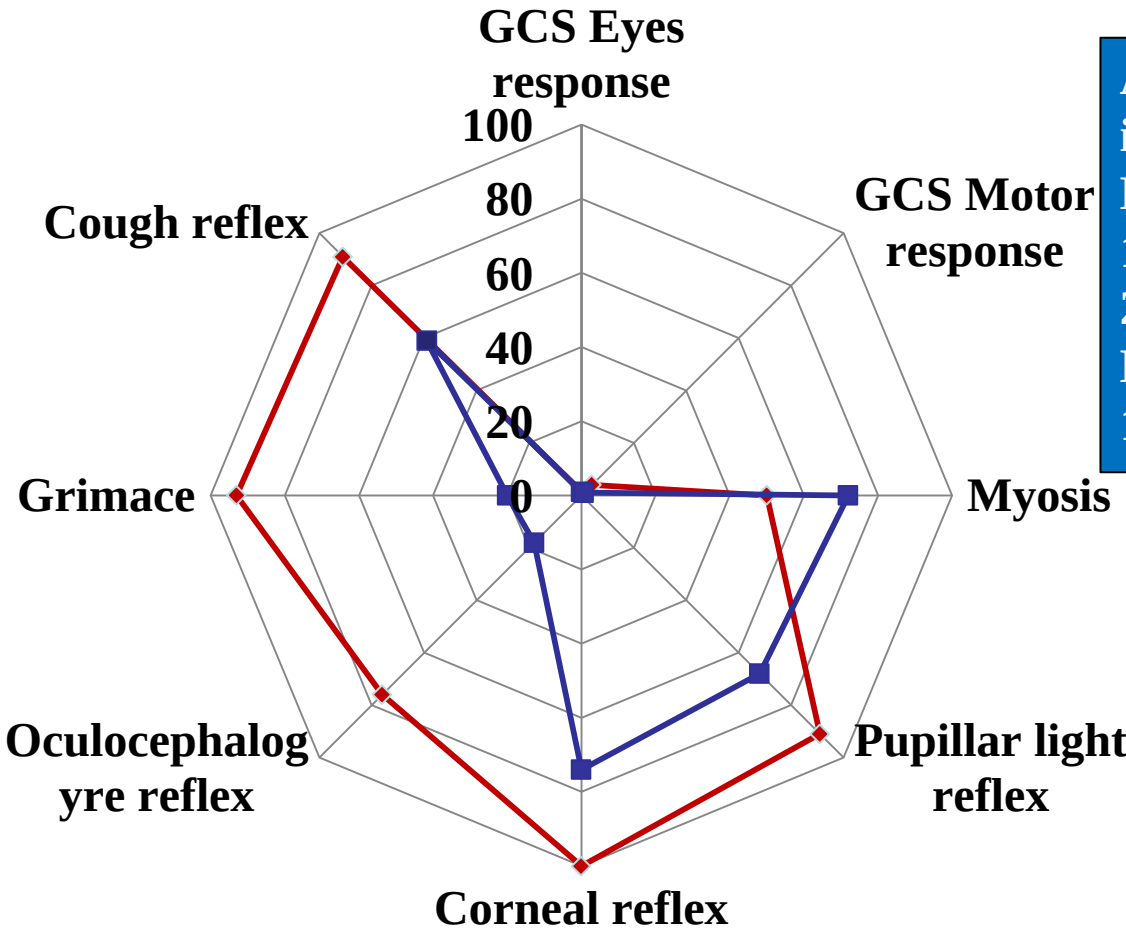
ONE BY ONE SIGN TO SYNDROMIC APPROACH



IS THERE A NEUROLOGICAL SYNDROME OF DEEPLY SEDATED PATIENTS?

SYNDROMIC APPROACH (Latent class analysis)

141 deeply sedated non-brain injured critically ill patients



Abolition of brainstem reflex is not at random
Do not correpond to:
1. **Particular lesion of the B**
2. **To a reported BS syndro**

Do not in agreement with
1. **Jacksonian paradigm**

Rohaut et al - Submitted

PROFILES

	Homogenous N=77 (55%)	Heterogenous N=64 (45%)	p
Midazolam cumulative dose	1.2 (0.8 to 2.0)	1.3 (0.7 to 1.9)	0.83
Sufentanyl cumulative dose	2.4 (1.3 to 4.4)	2.2 (1.5 to 4.4)	0.63
Age	65.1 (14.9)	69.3 (15.7)	0.14
Sexe (%)	34 (44)	23 (36)	0.39
SAPS-II	51 (36 to 65)	58 (47 to 77)	0.013
SOFA	10 (7 to 13)	14 (11 to 16)	< 0.0001
RASS -5	40 (52)	51 (80)	0.0007
Sepsis (%)	33 (41)	44 (41)	0.99
Coma (%)	14 (24)	26 (59)	< 0.05
Delirium (%)	34 (49)	25 (68)	< 0.05
Day 28 mortality	9 (12)	33 (52)	< 0.0001
ICU mortality (%)	15 (19)	38 (59)	< 0.0001

Rohaut et al - Submitted

MORTALITY

MULTIVARIATE ANALYSIS

	OR (95% CI)	*P*	OR (95% CI)	*P*
SAPS-II	1.04 (1.02 to 1.06)	0.0002	1.03 (1.01 to 1.06)	0.003
Latent class B	—	—	6.93 (2.88 to 16.7)	<0.0001
Likelihood ratio	15.60		37.08	<0.0001
c index (95% CI)	0.69 (0.60 to 0.79)		0.80 (0.73 to 0.88)	0.008
NRIc	—		0.945	<0.0001
IDI	—		0.138	<0.0001

Heterogeneous (Latent class B) remained associated with increased 28-days mortality, after adjustment on

1 - SAPS-II and RASS (OR [95%IC] = 6.44 [2.63-15.8], p <0.0001),

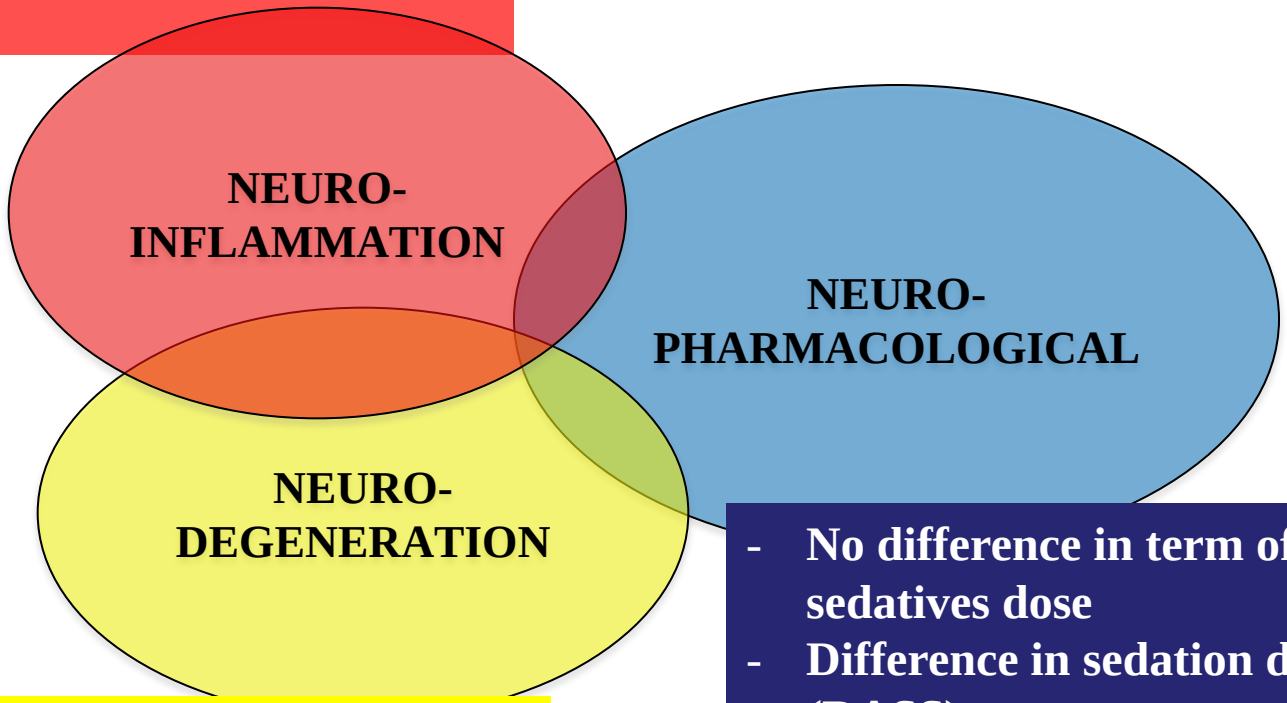
2 - SOFA (OR [95%IC]) 5.13 [2.08-12.6]; p = 0.0004)

3 - SOFA and RASS (OR [95%IC]) 5.02 [2.01-12.5]; p = 0.0005).

Rohaut et al - Submitted

POTENTIAL MECHANISMS

- Difference in SAPS-II and SOFA
--Experimental and neuropathological evidences



- No Difference in age
- Pre-existing neurodegenerative disease?

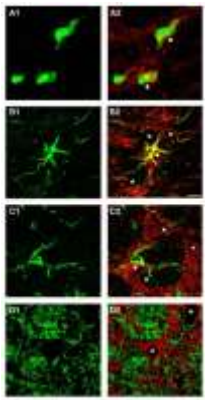
- No difference in term of sedatives dose
- Difference in sedation depth (RASS)
- Deeper satus of sedation
- effect of sedation reduction on profile heteregneous?

EXPERIMENTAL SEPSIS-RVLM

LPS IV

iNOS

T1



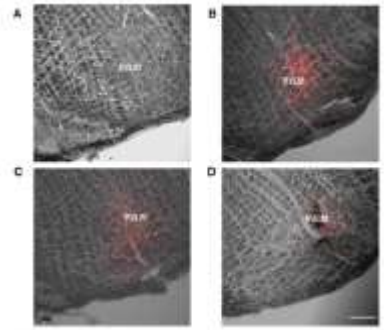
neurons

astrocytes

microglia

oligodendrocytes

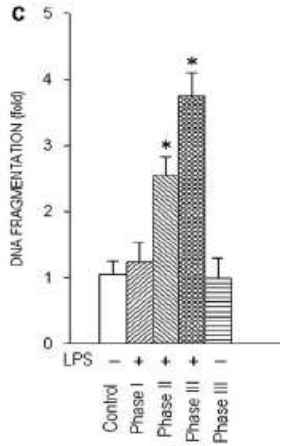
Superoxide (O_2-)



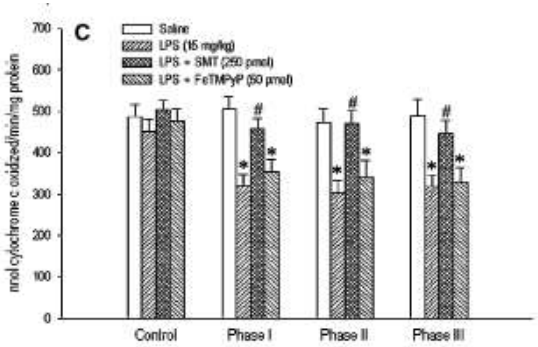
T2

T3

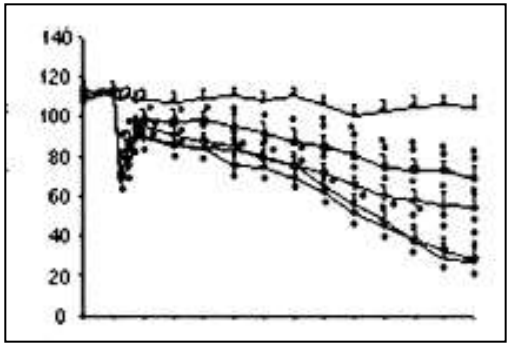
Apoptosis



Cytochrome C



Arterial hypotension



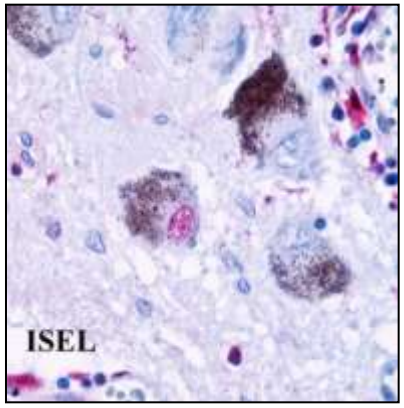
T4

Chan et al Free Rad 2005

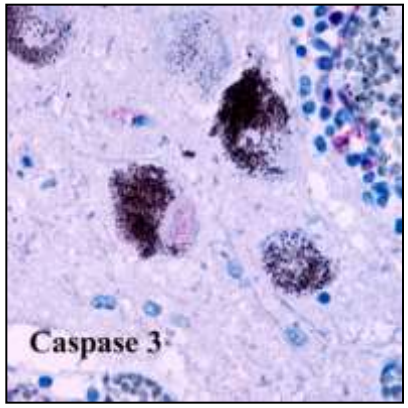
NEURONAL APOPTOSIS

Patients who had died from septic shock

(neuroendocrine and autonomic centers)



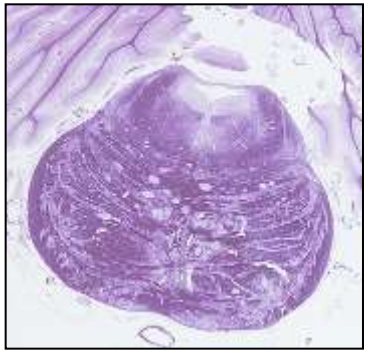
Locus coeruleus



MULTIFOCAL NECROTIZING LEUKOENCEPHALOPATHY

Sharshar et al - Lancet – 2003

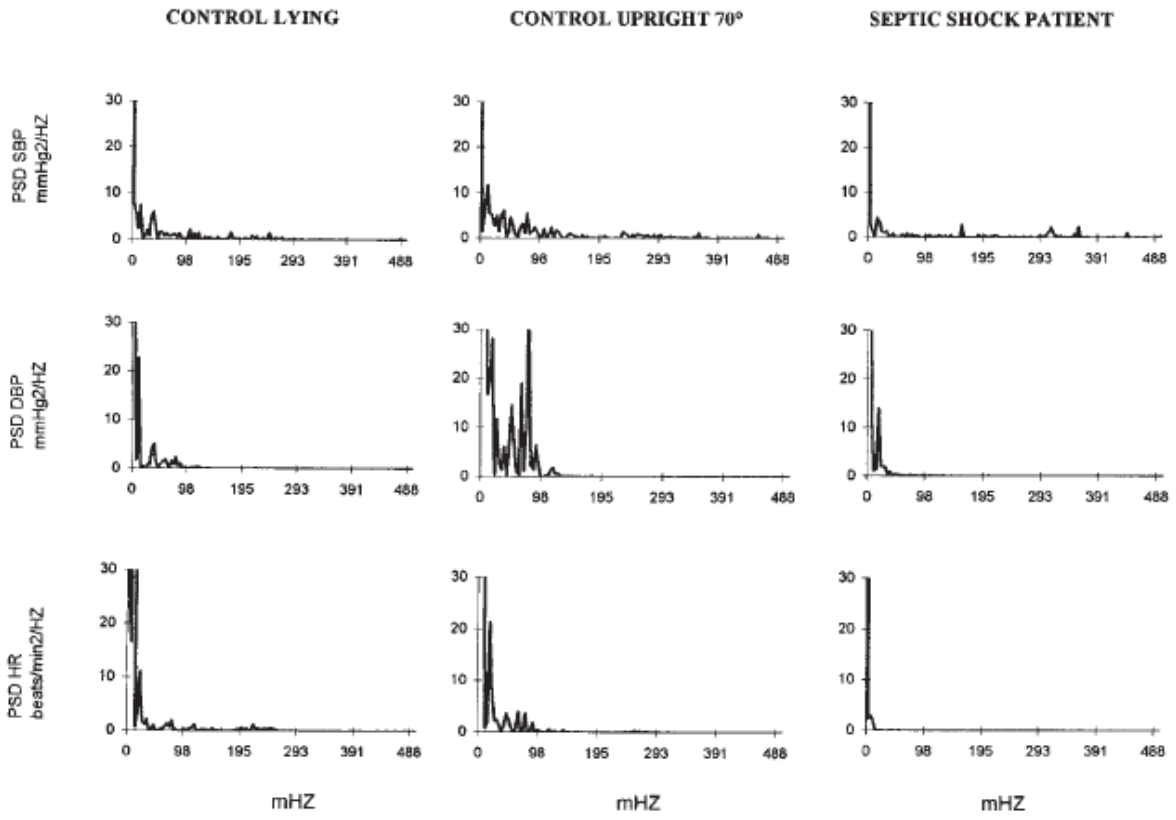
Sharshar et al – CCM- 2012



Inappropriate Sympathetic Activation at Onset of Septic Shock

A Spectral Analysis Approach

DJILLALI ANNANE, FABIEN TRABOLD, TAREK SHARSHAR, IRÈNE JARRIN, ANNE SOPHIE BLANC, JEAN CLAUDE RAPHAEL, and PHILIPPE GAJDOS



Annane et al – AJRCCM - 1999

BAROREFLEX SENSITIVITY

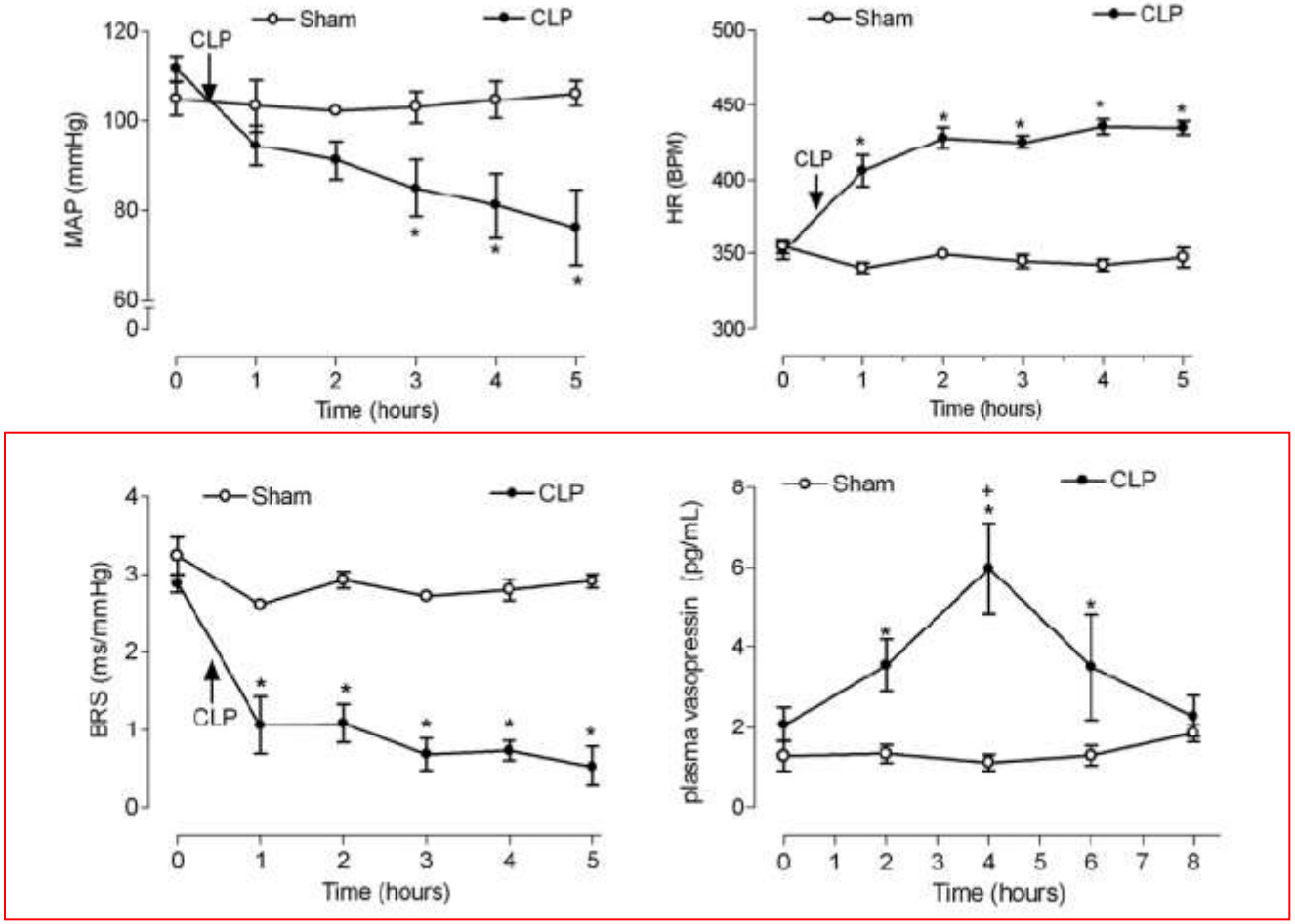
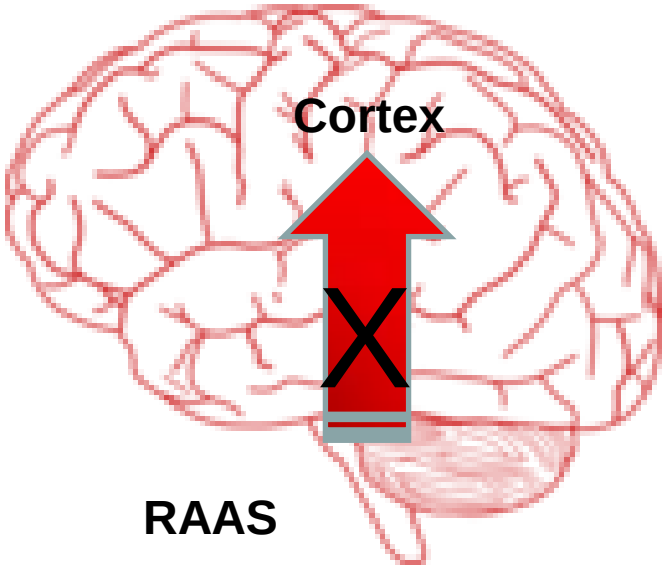


Fig. 2. Effect of cecal ligation and puncture (CLP) on mean arterial pressure (MAP), heart rate (HR), baroreflex sensitivity (BRS) and plasma vasopressi results are expressed as mean±SEM. Statistical analysis was performed using ANOVA followed by TUKEY test. *$P<0.05$ compared to sham. ^{+}P compared to other time points within CLP group. The number of animals was 5 for each group for cardiovascular measurements and 5–10 for each time-po plasma vasopressin measurements.

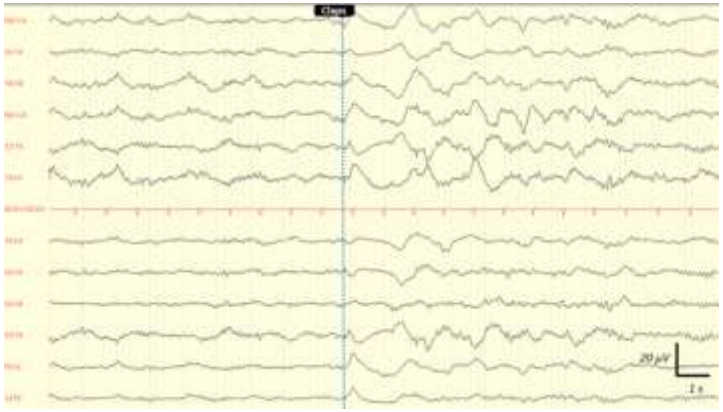
Pancoto et al - Auton Neurosci - 2007

Early Standard Electroencephalogram Abnormalities Predict Mortality in Septic Intensive Care Unit Patients

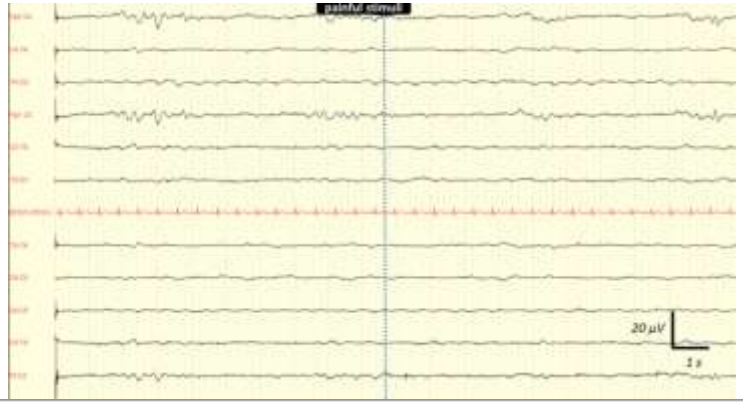
Azabou et al – Plosone - 2015



BRAINSTEM DYSFUNCTION

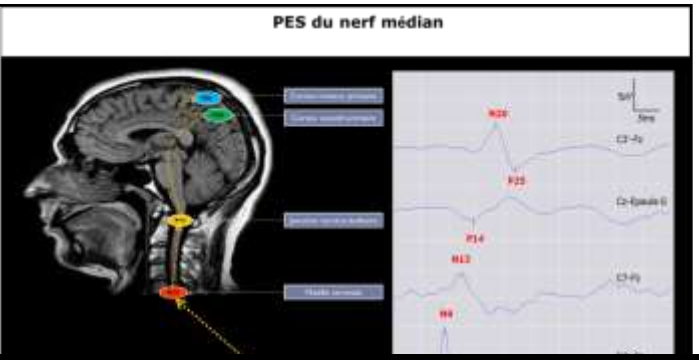


EEG reactivity



No EEG reactivity

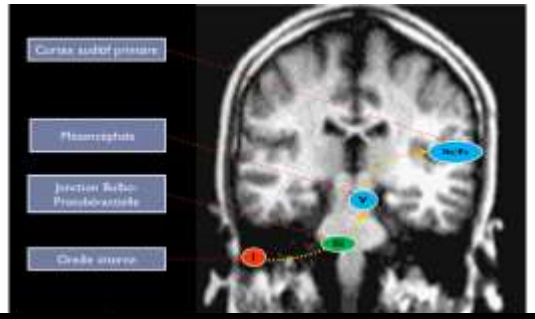
Variable	Adjusted on SAPS-II at admission and sedation			Adjusted on SOFA at EEG and sedation		
	OR	(95%CI)	P	OR	(95%CI)	P
Delta-dominant activity	3.36	(1.08 to 10.4)	0.036	3.08	(0.93 to 10.2)	0.066
Absence of reactivity	4.44	(1.37 to 14.3)	0.013	4.57	(1.36 to 15.4)	0.014



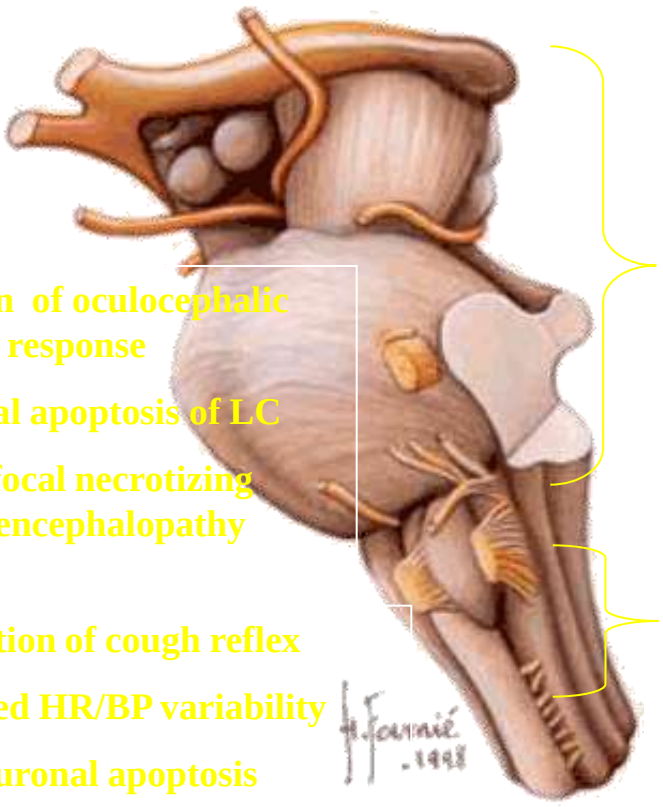
SSEP

n=86 critically ill deeply sedated patients

Sepsis: 56 (63%); Age: 61 ± 18; SAPS-II: 50 ± 18



AEP



Abolition of oculocephalic response

Neuronal apoptosis of LC

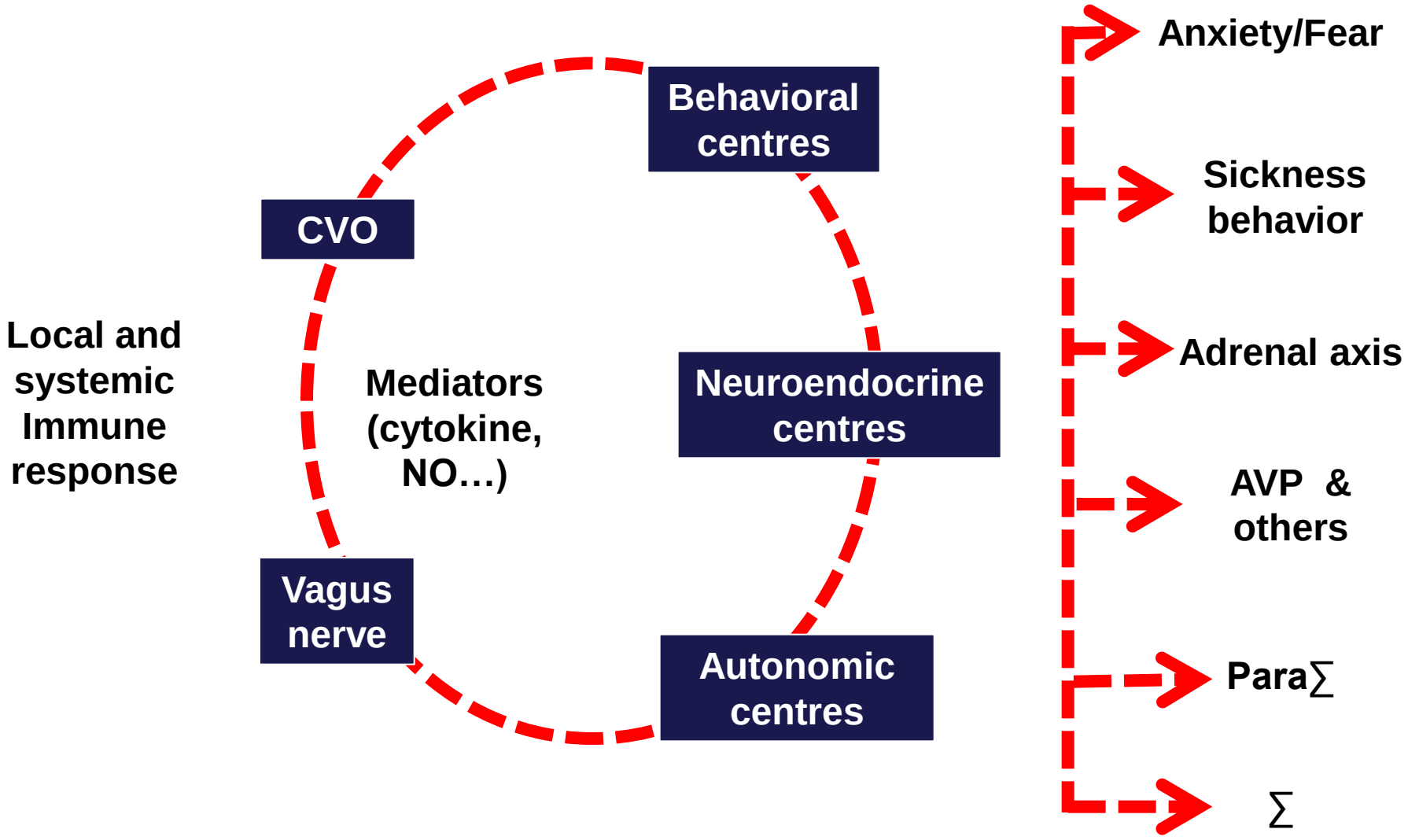
Multifocal necrotizing leukoencephalopathy

Abolition of cough reflex

Impaired HR/BP variability

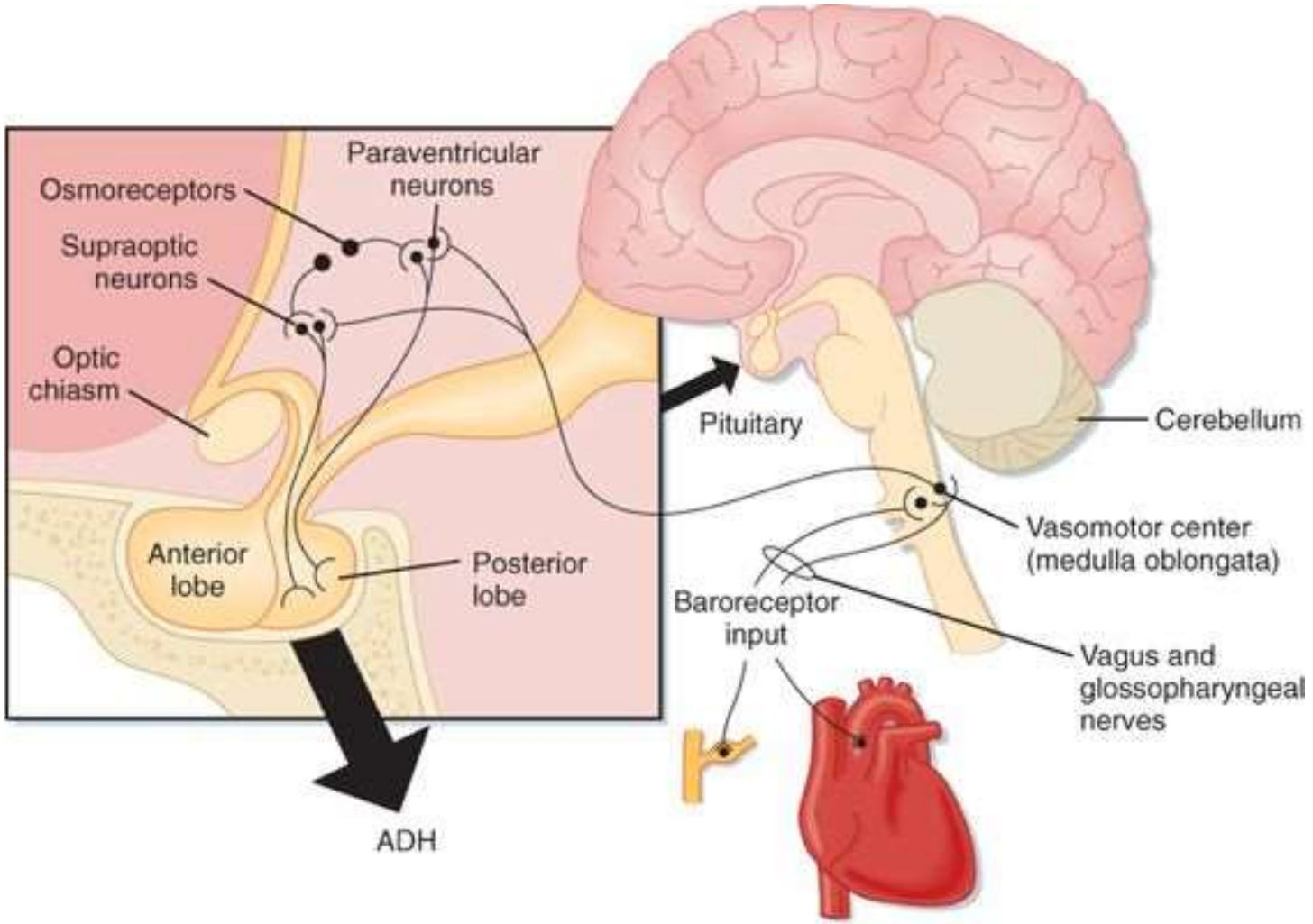
Neuronal apoptosis

Signaling dysfunction



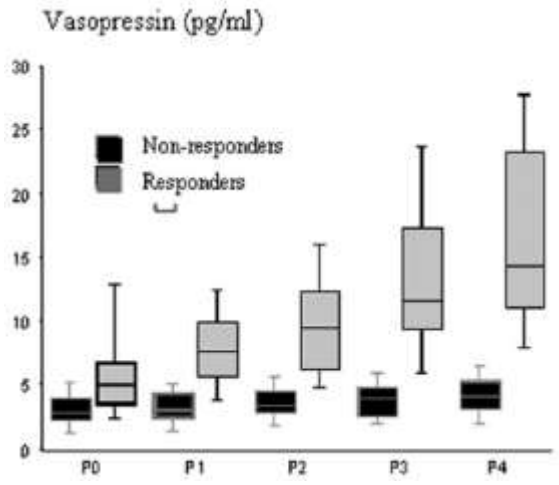
Osmoperception - Osmoregulation

Osmoreceptors are located in the OVLT (CVO deprived of BBB), sense changes in osmolality and modulate synthesis and release of AVP

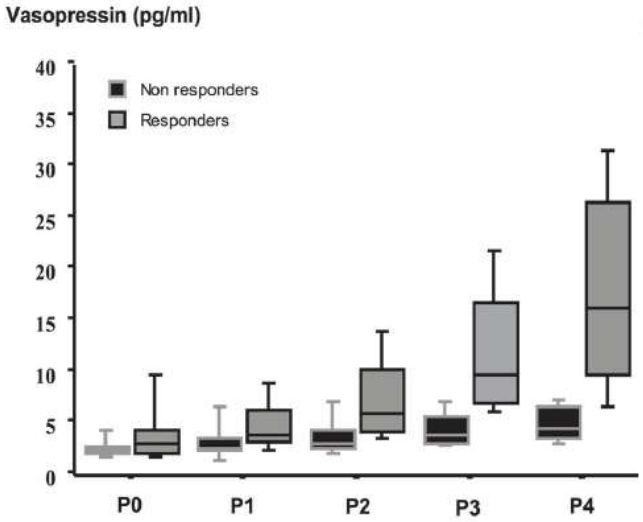


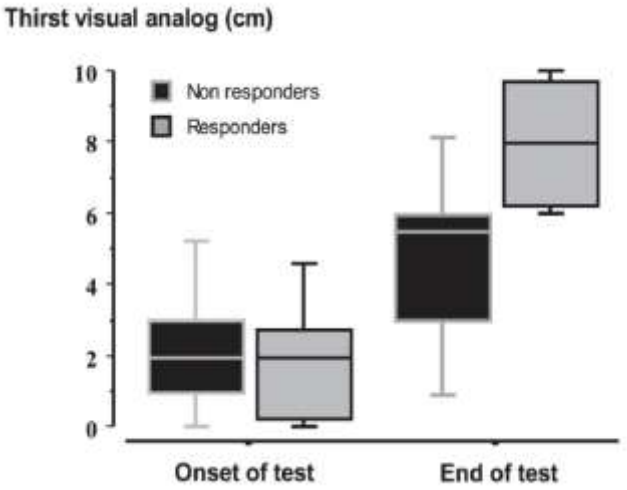
Osmoregulation of vasopressin secretion is altered in the postacute phase of septic shock*

Post-acute phase



Recovery phase



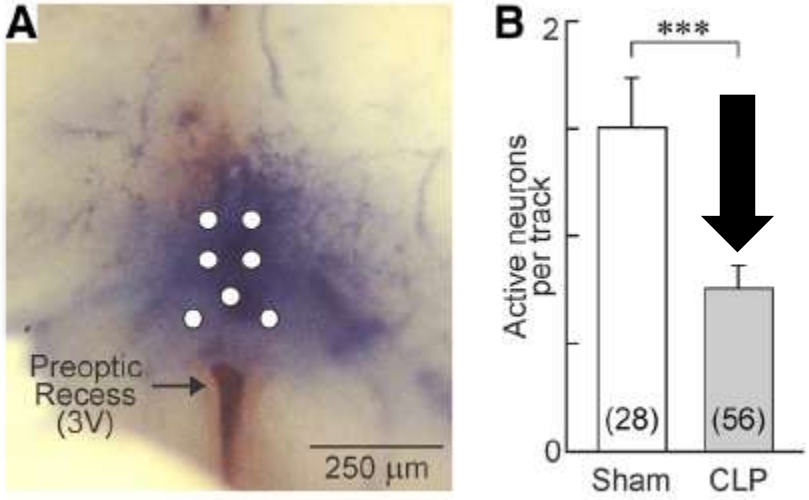


Osmoregulation and thirst perception alteration after Sepsis

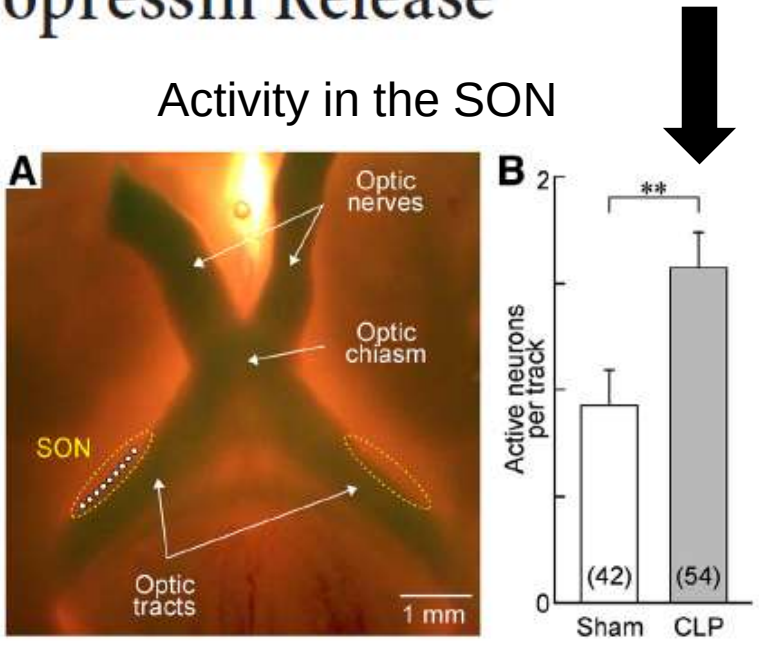
Siami et al – Crit Care Med – 2010; Siami et al – Plosone – 2013

Effects of Peritoneal Sepsis on Rat Central Osmoregulatory Neurons Mediating Thirst and Vasopressin Release

Activity in the OVLT

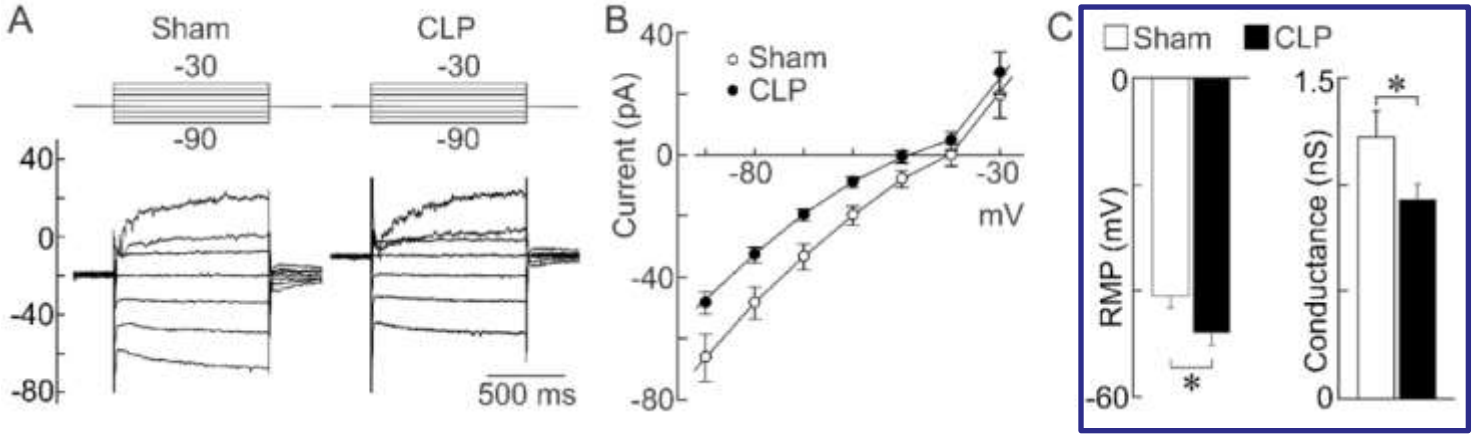


Activity in the SON



Reduced activity

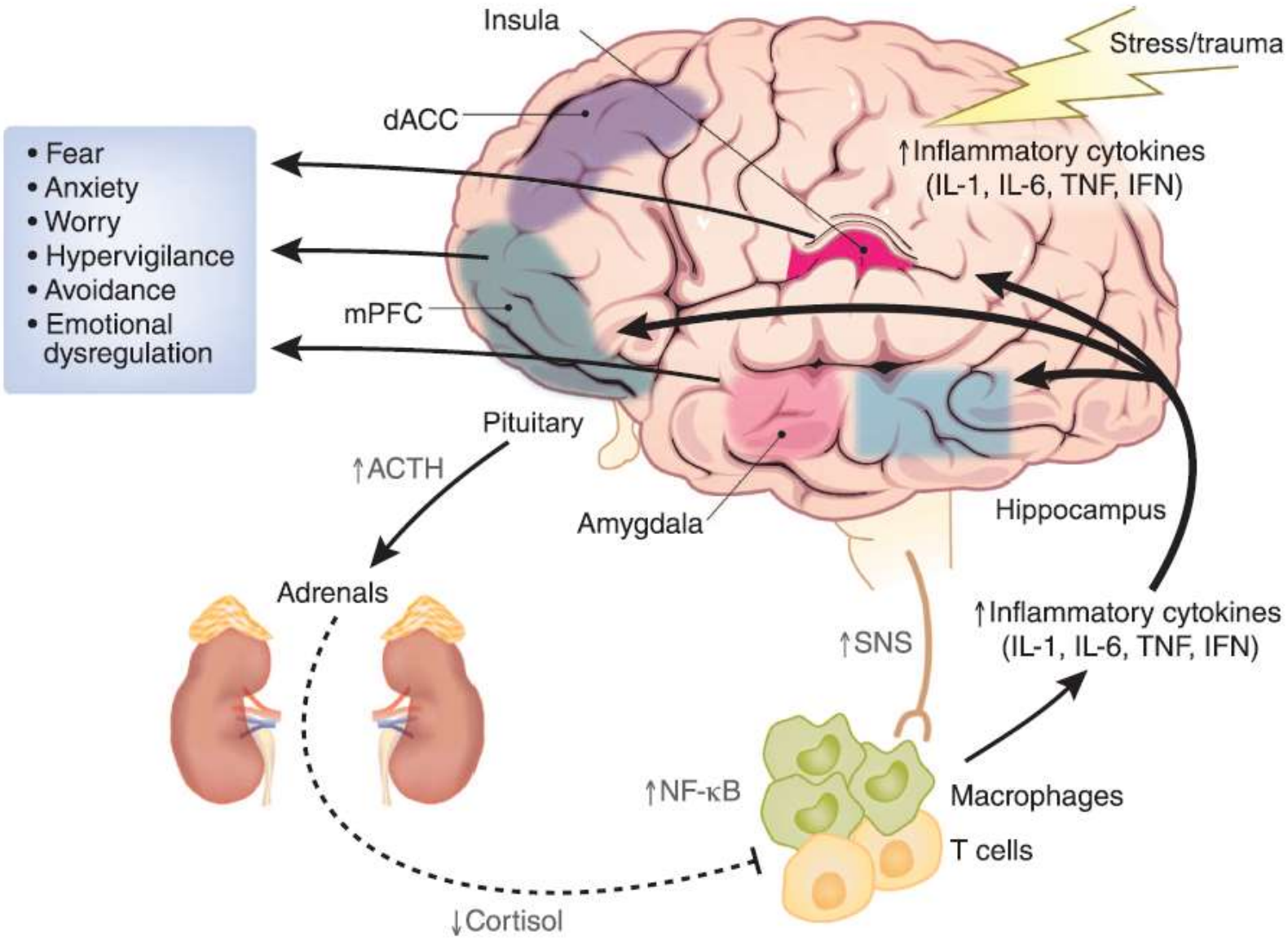
Increased activity



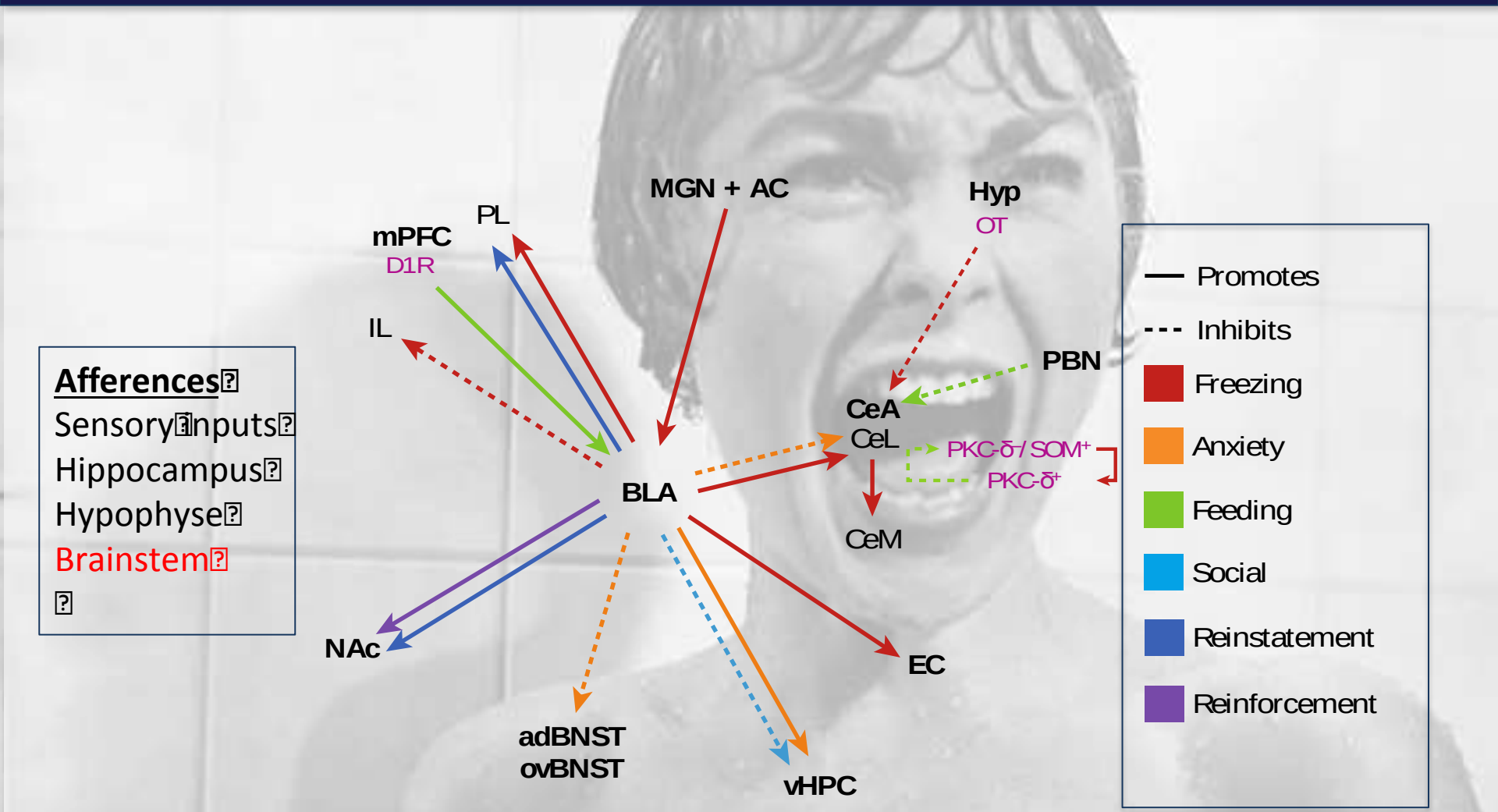
Patch-Clamp: Hyperpolarisation of OVLT neurons in CLP mice

Stare et al – J Neurosci - 2015

Behavioural response to stress

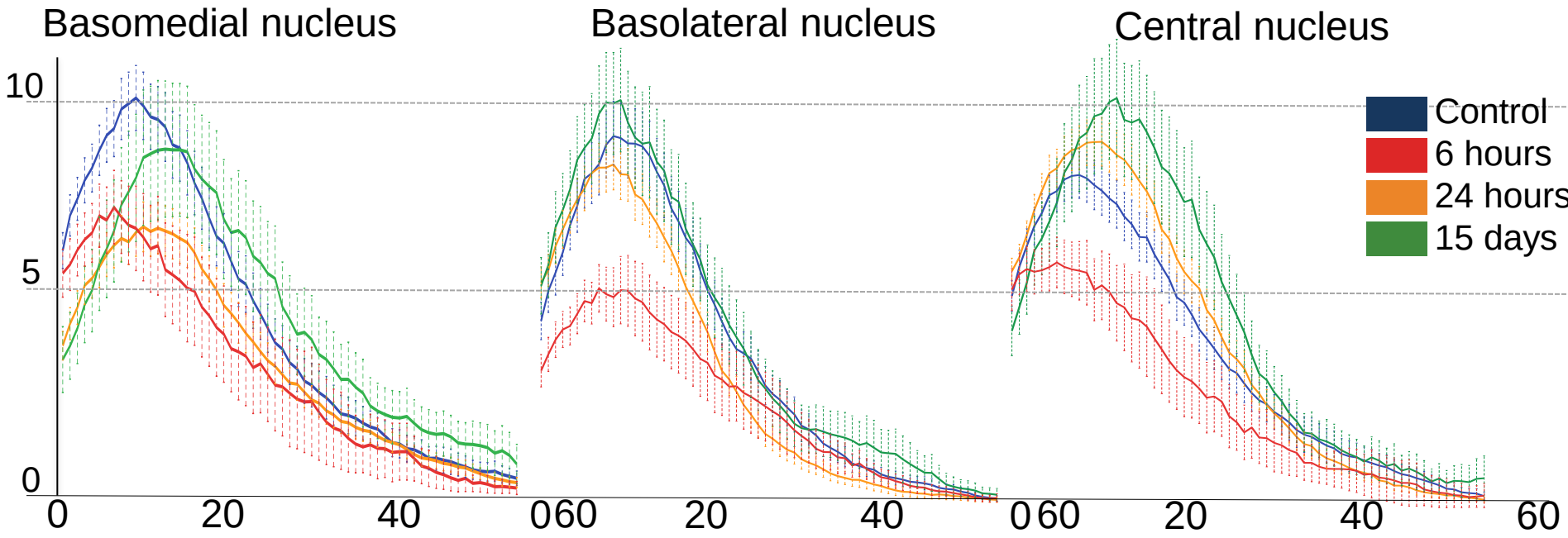


Role of amygdala



The role of amygdala is to adapt behaviour or emotions to stimuli

CeA Microglial activation at H6



The microglia in the central nuclei of the amygdala is intensely activated during sepsis and comes back to normal after 15 days

THE AMYGDALA TUNING

BRAIN DYSFUNCTION IN CRITICALLY ILL (SEPTIC) PATIENTS

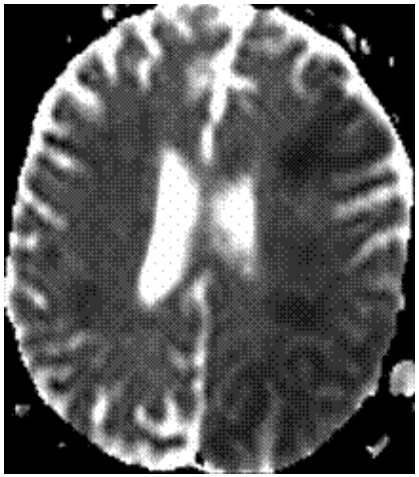
- **Frequent**
  - Clinical marker of sepsis (*onset, uncontrolled or relapsing*)
  - Up to 50% of septic patients
  - Impairment of consciousness
- **Detectable**
  - Neurological examination (*validated scales*)
  - Neurophysiological tests (*EEG, EP*)
- **Severe**
  - Increased mortality (up to 60%)
  - Long-term cognitive impairment
  - Long-term psychological disorders

Box 4. qSOFA (Quick SOFA) Criteria
Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≤100 mm Hg

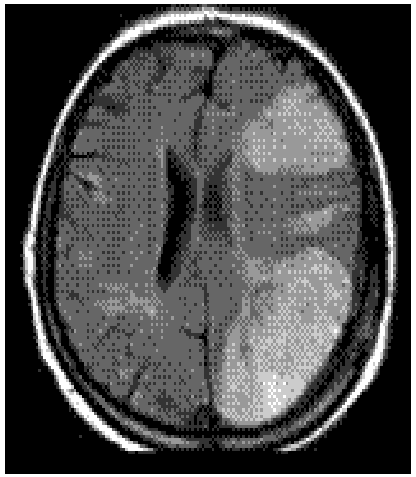
Singer et al – JAMA - 2016

CEREBRAL INFARCTS

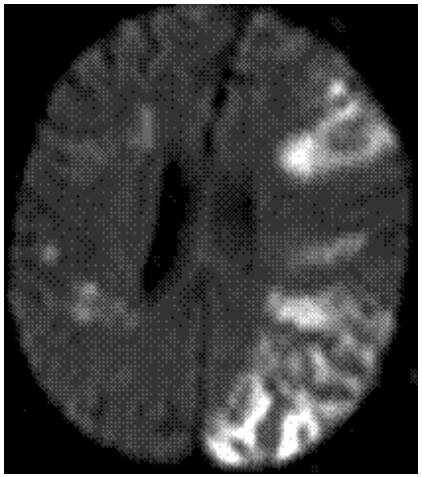
21/72 (29%) of septic shock patients who developped an acute brain dysfunction
Associated with low platelets count and DIC
Associated with increased mortality up to 60%



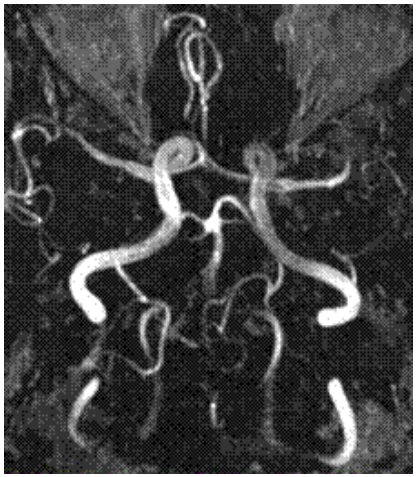
FLAIR



DWI



ADC

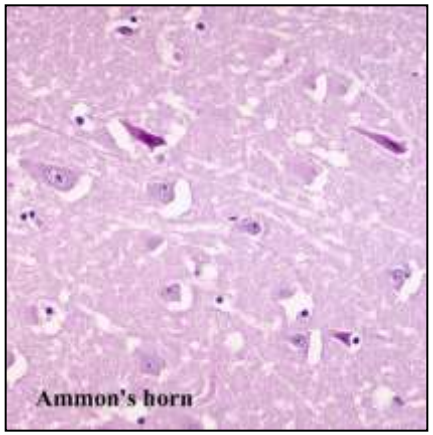


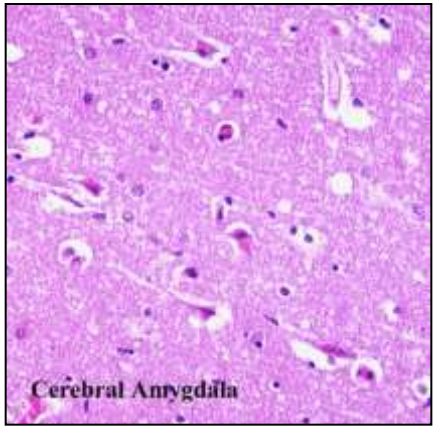
OCCLUSION

Polito et al – Crit Care - 2013

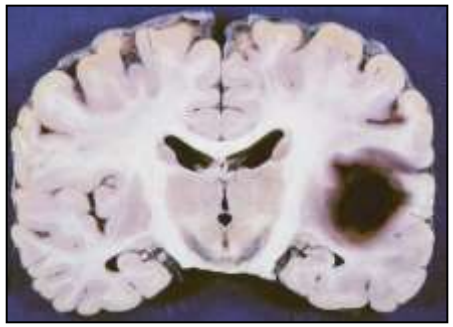
NEUROPATHOLOGY

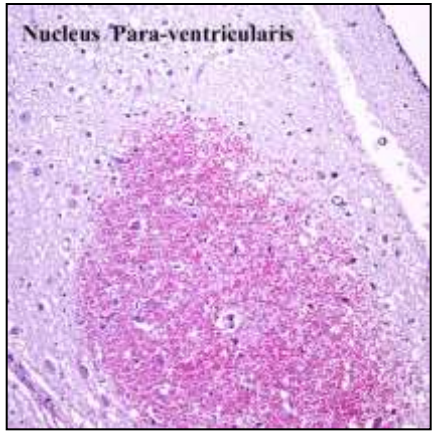
ISCHEMIA (100%)



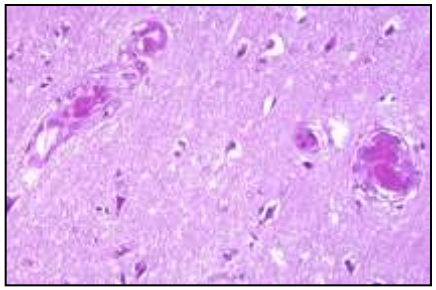


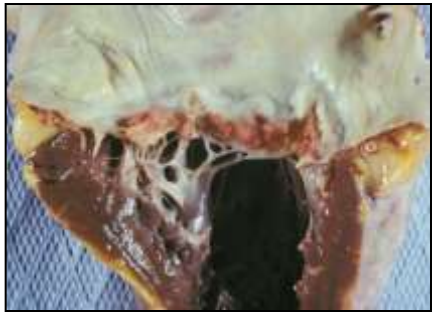
HEMORRHAGE (30%)



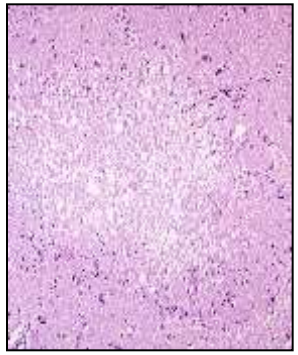


IDC (30%)



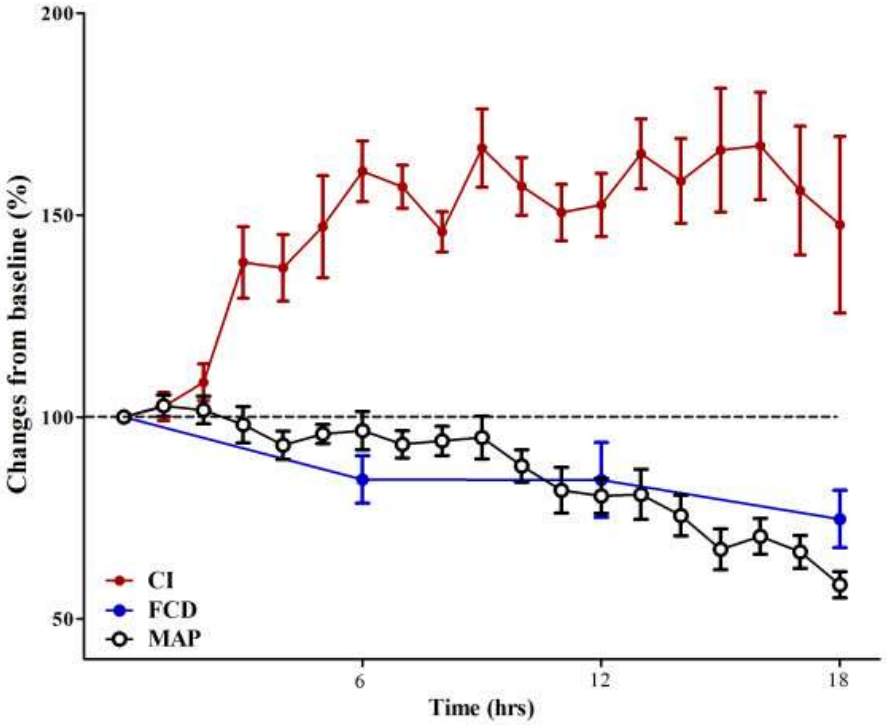


MICRO ABSCESSES (10%)



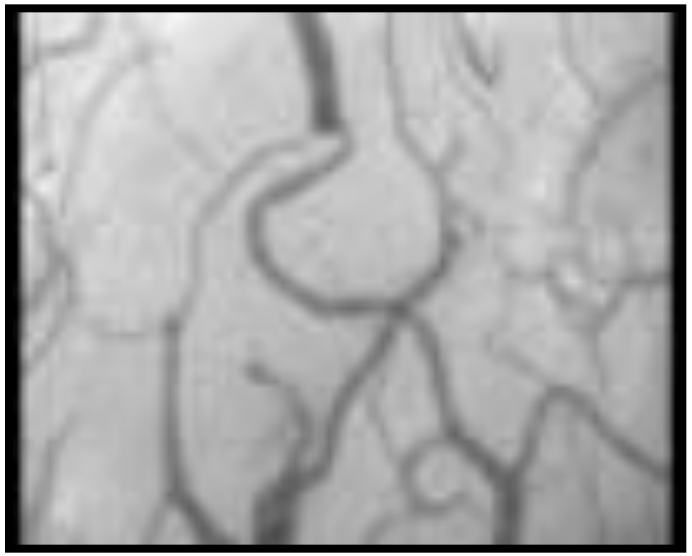
Sharshar et al - Brain Pathology - 2004

MICROCIRCULATION

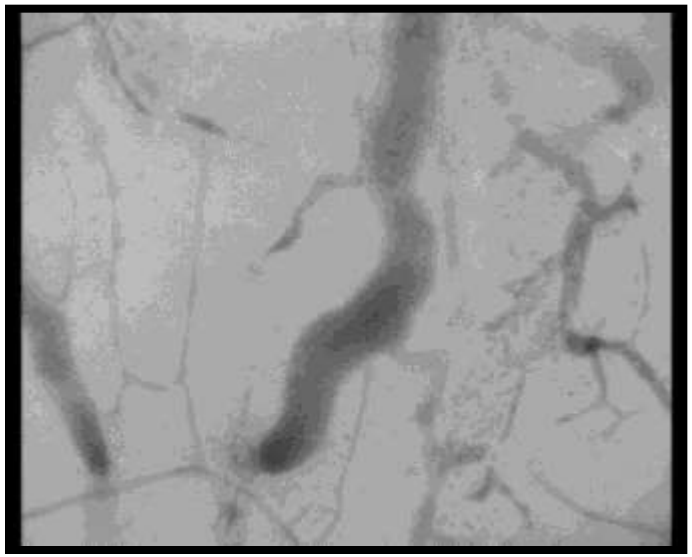


CI: cardiac index
FCD: functional capillary density

Control



Septic



Taccone et al – Crit Care - 2010