63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

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Microbiota e delirium

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ASSOCIAZIONE ITALIANA PSICOGERIATRIA

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

CONFLICT OF INTEREST DISCLOSURE

No potential conflict of interest to report

PubMed (((delirium[Title]) AND confusion*[Title]) AND microbiot*[Title]) AND

Search results

Items: 0

No documents match your search terms

Delirium

- Il delirium è una sindrome neuropsichiatrica caratterizzata da un cambiamento acuto delle performances cognitive (con particolare riferimento alle capacità attentive e alla consapevolezza di se nell'ambiente), un'alterata «vigilanza» e una tendenza alla fluttuazione dei sintomi
  - Acute Brain Dysfunction
- è una diretta conseguenza di un problema clinico, intossicazione o sospensione di farmaci, esposizione a tossine, o è dovuto a molteplici eziologie.

DSM-5, Am Psychiatr Assoc, May 2013

Transient Cognitive Disorders (Delirium, Acute Confusional States) in the Elderly

- "Acute confusion is a far more common herald of the onset of physical illness in an old person than are, for example, fever, pain or tachycardia"
- "Failure to diagnose delirium and to identify and treat its underlying causes may have lethal consequences for the patient, since it may constitute the most prominent presenting feature of myocardial infarction, pneumonia, or some other life-threatening physical illness".

Lipowski ZJ, Am J Psychiatry 1983
Lipowski ZJ, NEJM 1989

Table 4 Clinical signs and symptoms in patients with UTI and without UTI

Symptoms	UTI $n=45$ N (%)	No UTI $n=241$ N (%)	P value[a]
Bacteria in urinary sample	23 (51.1)	30 (14.9)	< 0.001
Pyuria[b]	28 (62.2)	55 (27.4)	< 0.001
Hematuria[c]	10 (22.2)	32 (15.9)	0.31
Fever[d]	5 (11.1)	9 (4.5)	0.09
Abdominal pain	11 (24.4)	7 (3.5)	< 0.001
Urgency	14 (31.1)	3 (1.5)	< 0.001
Frequency	28 (62.2)	39 (19.6)	< 0.001
Pain when urinating	20 (44.4)	8 (4.0)	< 0.001
Flank pain/renal angle tenderness	9 (20.0)	7 (3.5)	< 0.001
Delirium[e]	13 (28.9)	36 (18.0)	0.1
Tachycardia	5 (11.1)	3 (1.5)	0.006
Hypotension	9 (20.0)	24 (12.1)	0.16
Loss of appetite	4 (8.9)	12 (6.0)	0.48
Faints/falls, n (%)	134 (28.9)	59 (29.5)	0.94

Wojszel Z, Eur Ger Med 2018

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Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. XX, No. XX, 1–7
doi:10.1093/gerona/gly154
Advance Access publication July 04, 2018

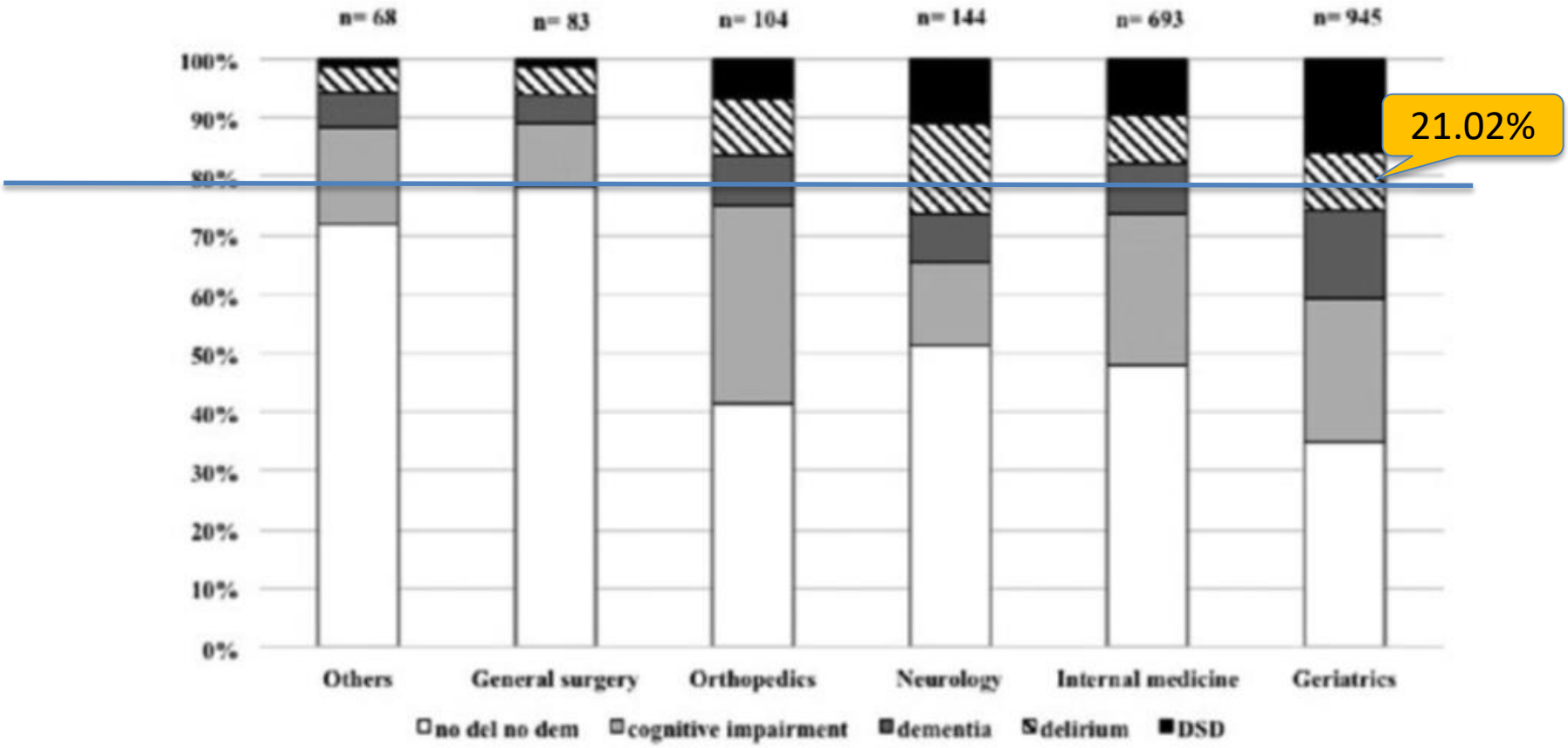
OXFORD

Research Article

Delirium, Dementia, and In-Hospital Mortality: The Results From the Italian Delirium Day 2016, A National Multicenter Study

Alessandro Morandi, MD, MPH,[1] Simona G. Di Santo, MS,[2] Antonella Zambon, PhD,[3] Andrea Mazzone, MD,[4] Antonio Cherubini, MD, PhD,[5] Enrico Mossello, MD, PhD,[6] Mario Bo, MD, PhD,[7] Alessandra Marengoni, MD, PhD,[8] Angelo Bianchetti, MD,[9] Stefano Cappa, MD,[10] Filippo Fimognari,[11] Raffaele Antonelli Incalzi, MD,[12,13] Pietro Gareri, MD,[14,15] Francesco Perticone, MD,[16] Mauro Campanini, MD,[17] Italo Penco, MD,[18] Marco Montorsi, MD,[19,20] Mauro Di Bari, MD, PhD,[6] Marco Trabucchi, MD,[21] and Giuseppe Bellelli, MD[3,22] on behalf of the Italian Study Group on Delirium (ISGoD)

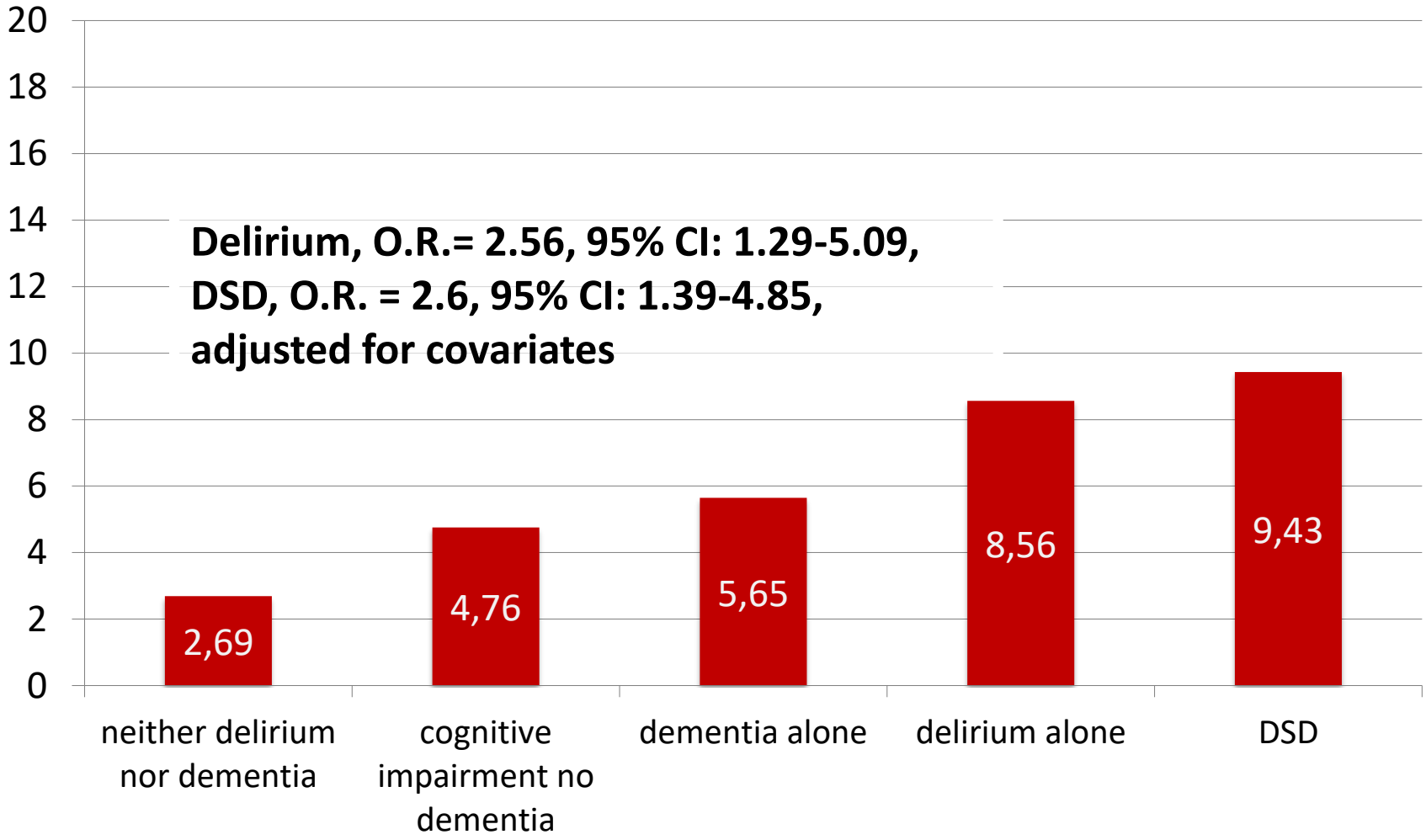
Prevalence (%) of delirium alone, DSD, cognitive impairment/dementia alone or neither in hospital wards (2037 pts Delirium day 2016)



DSD = Delirium Superimposed on Dementia
The group "Others" include patients from Cardiologic, Neurosurgical and Infectious Disease hospital wards

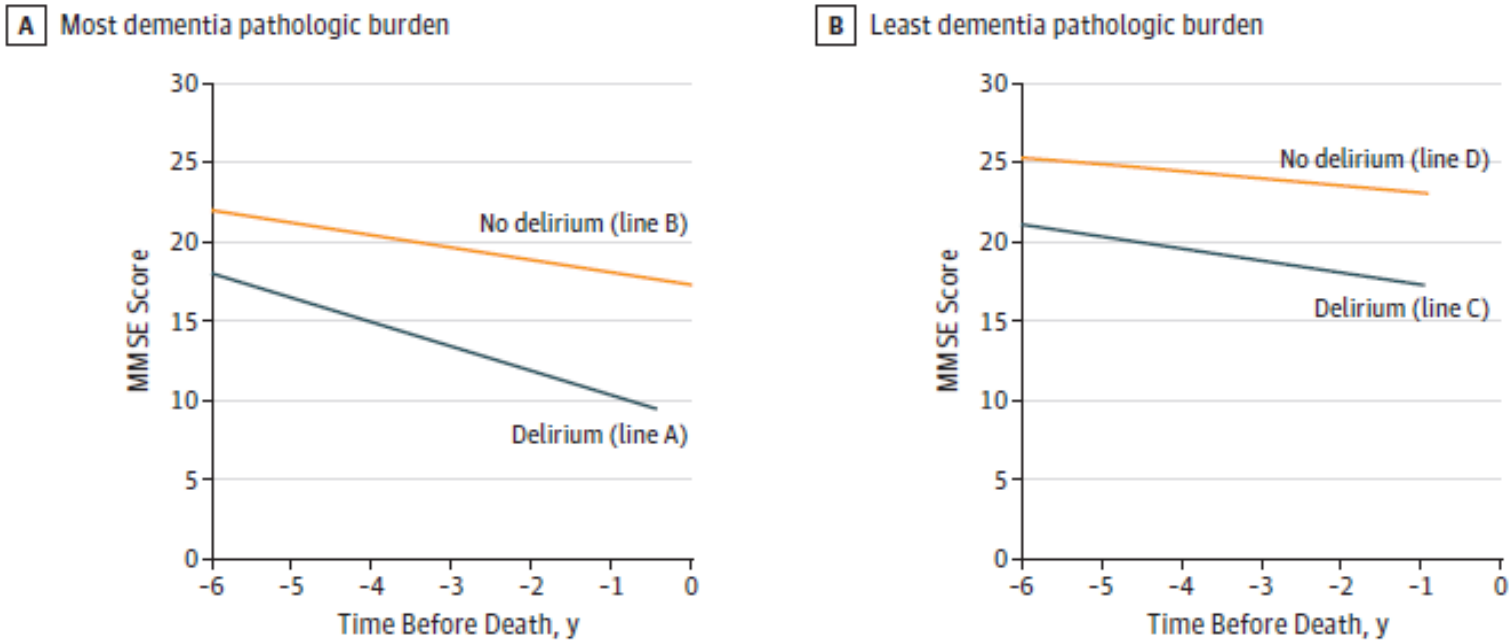
Morandi A et al, J Gerontol Med Sci, Jul 4. doi: 10.1093/gerona/gly154.

In-hospital mortality rate (%) in 2037 patients with data on vital status at discharge according to the presence of delirium, dementia or neither



Morandi A et al, J Gerontol Med Sci, Jul 4. doi: 10.1093/gerona/gly154.

Delirium accelerate Cognitive Decline in patients with pre-existing Dementia



No. of patients alive

No delirium	261	336	385	439	500	553
Delirium	141	165	193	215	227	236

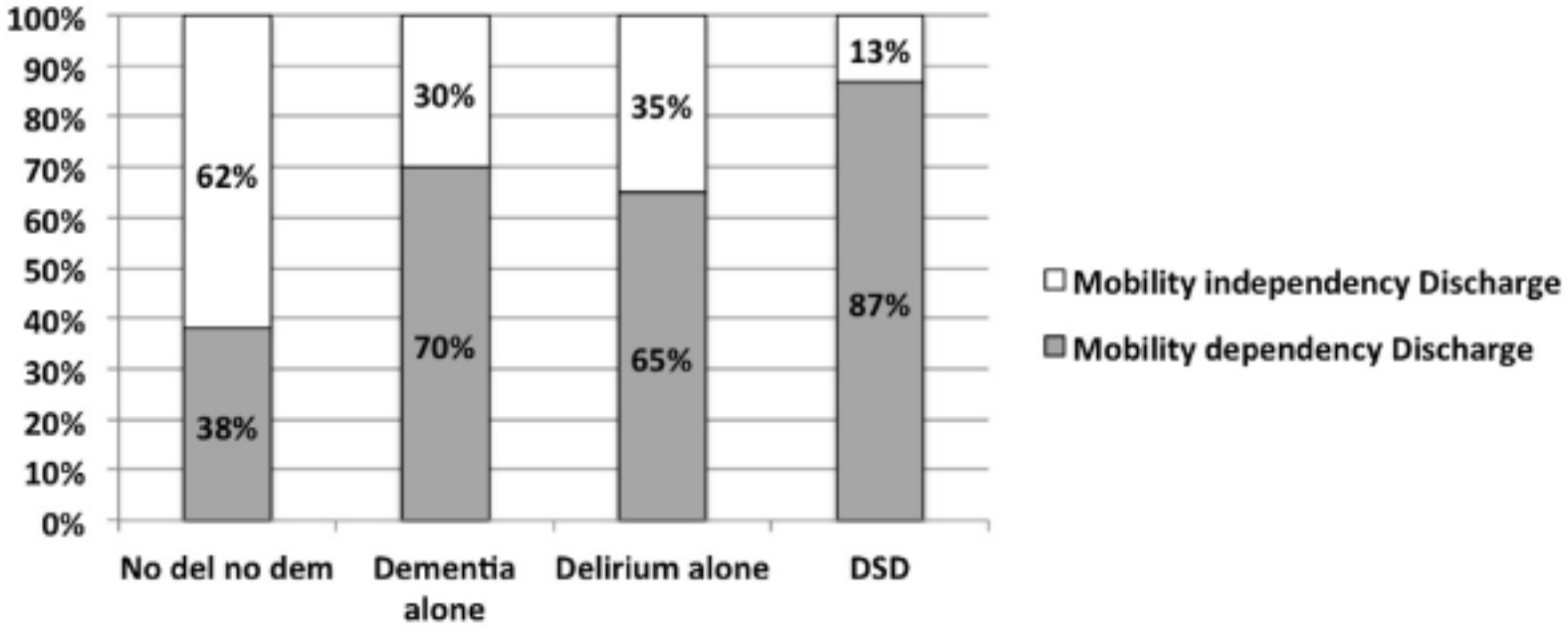
No. of patients alive

No delirium	77	90	104	110	117	120
Delirium	34	37	37	39	40	40

Davis D et al, JAMA Psychiatry 2017

Delirium Superimposed on Dementia Strongly Predicts Worse Outcomes in Older Rehabilitation Inpatients

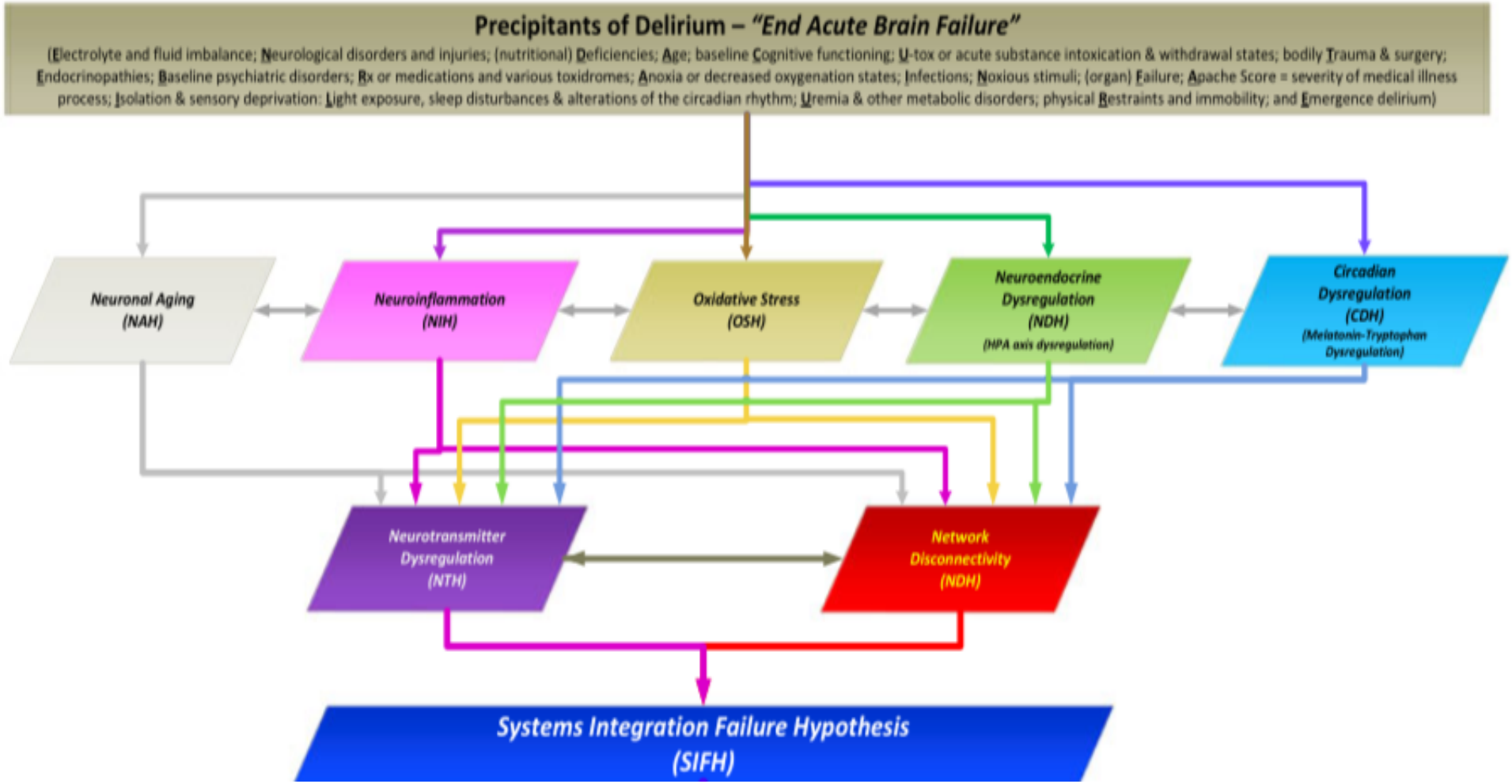
Alessandro Morandi MD, MPH [a,b,*], Daniel Davis MB, ChB, MRCP [c], Donna M. Fick PhD [d], Renato Turco MD [a,b], Malaz Boustani MD, MPH [e], Elena Lucchi PsyD [a,b], Fabio Guerini MD [a,b], Sara Morghen PsyD [a,b], Tiziana Torpilliesi MD [a,b], Simona Gentile MD [a,b], Alasdair M. MacLullich MRCP (UK), PhD [f], Marco Trabucchi MD [b,g], Giuseppe Bellelli MD [b,h]



JAMDA 15 (2014) 349–354

Gut brain axis e delirium: quali possibili nessi fisiopatogenetici?

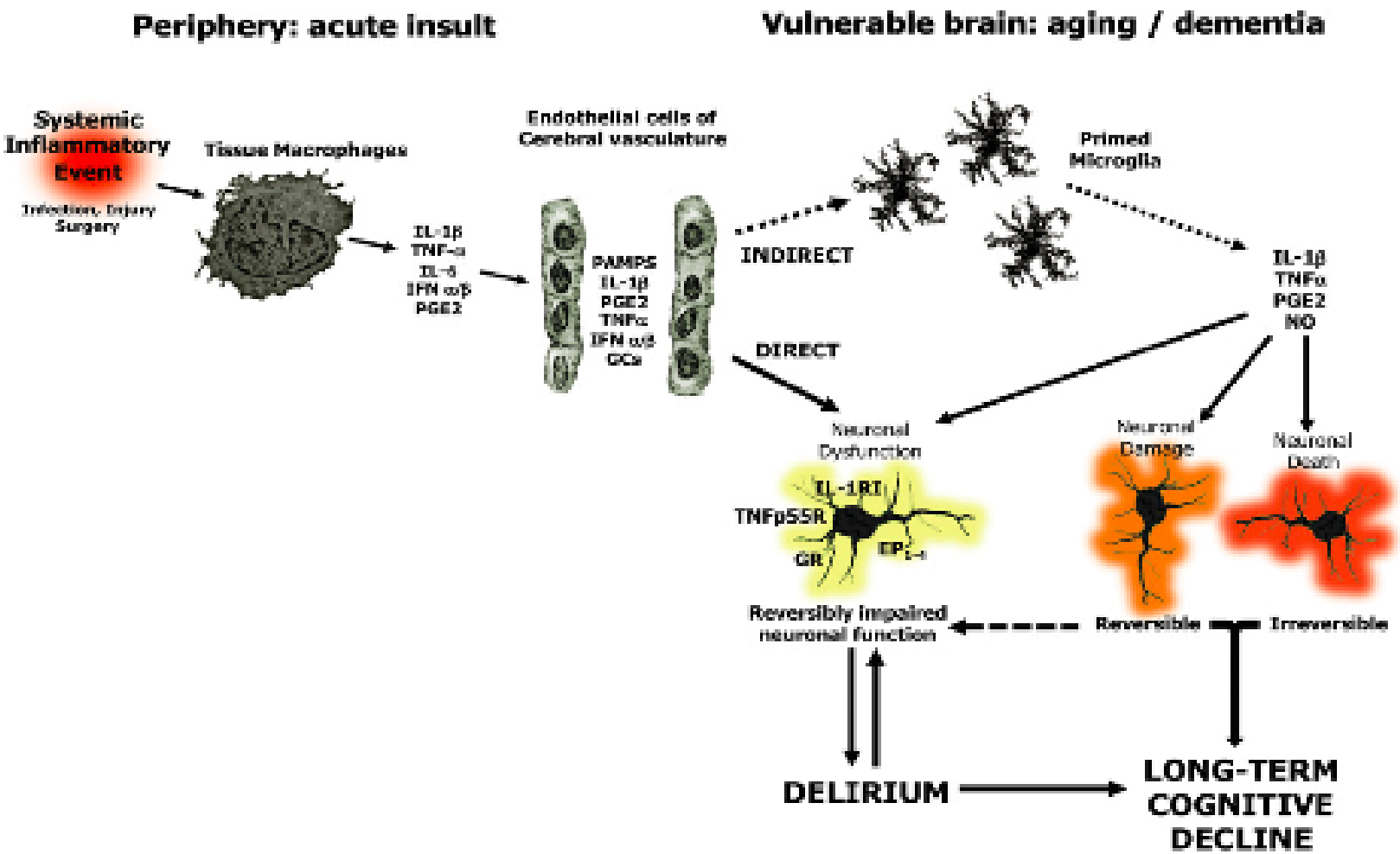
Neurotransmitter's imbalance as the common pathway of multiple pathophysiological mechanisms in provoking delirium



Maldonado J, Int J Ger Psych 2017

Systemic inflammation and delirium: important co-factors in the progression of dementia

Colm Cunningham[1]
School of Biochemistry and Immunology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Republic of Ireland



Biochem. Soc. Trans. (2011) 39, 945–953; doi:10.1042/BST0390945

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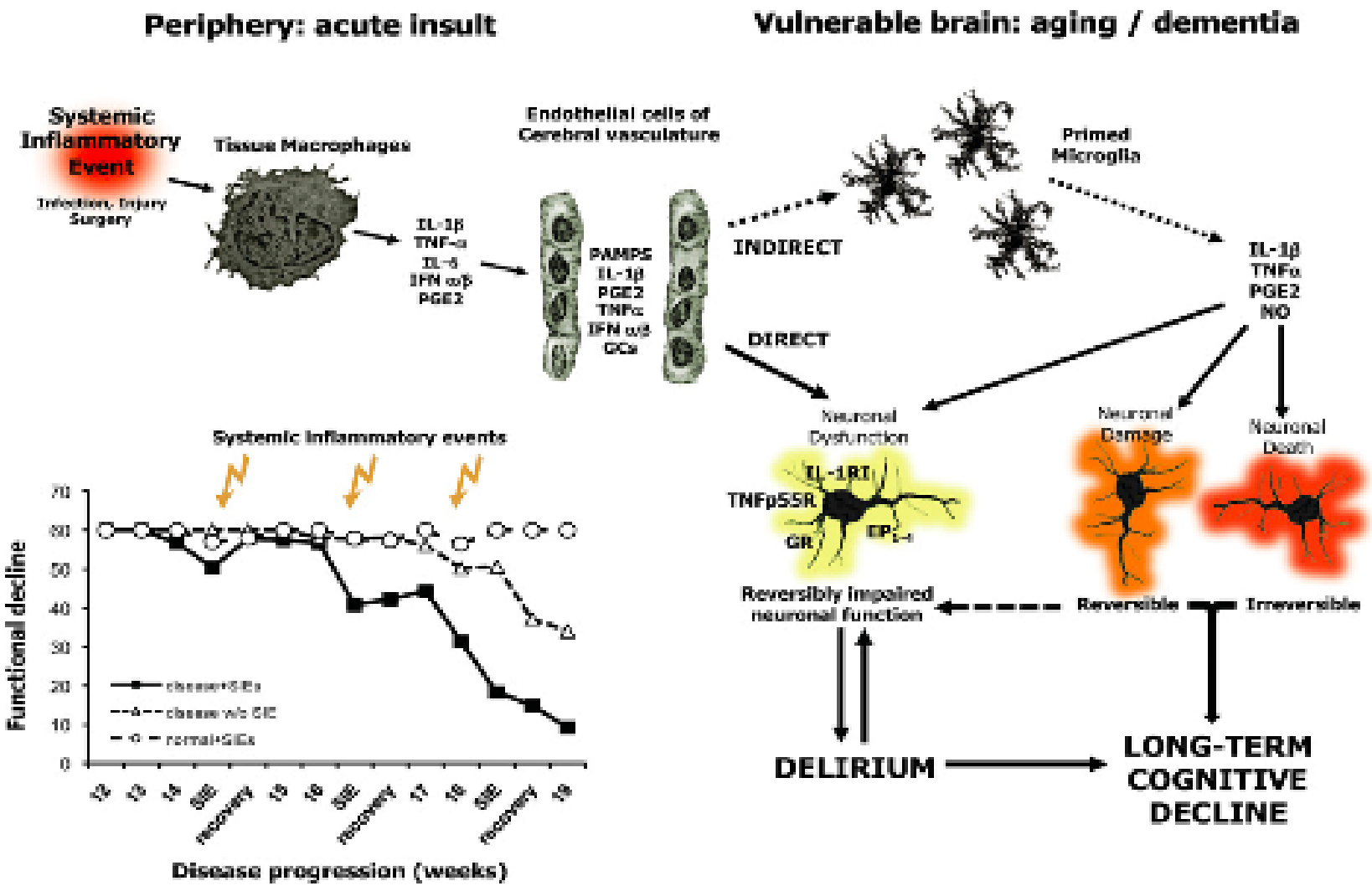
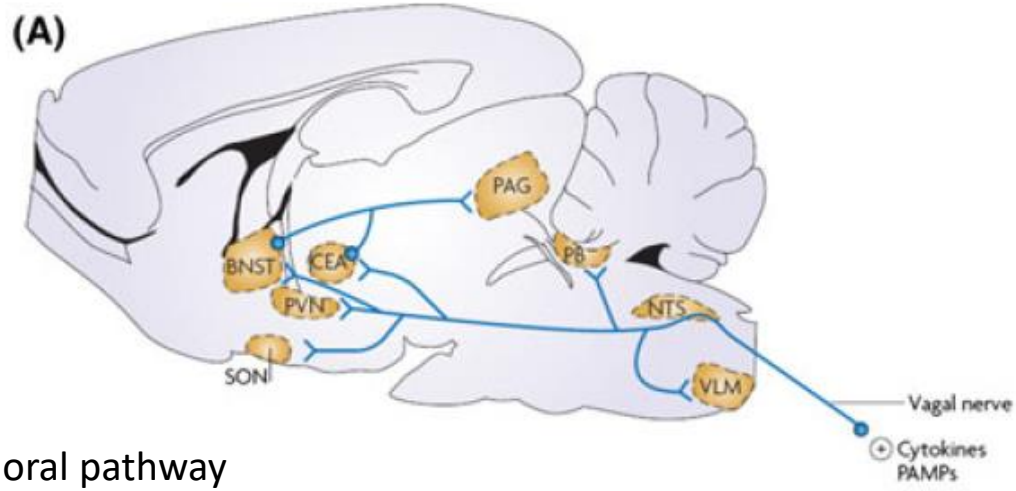


Biochem. Soc. Trans. (2011) 39, 945–953; doi:10.1042/BST0390945

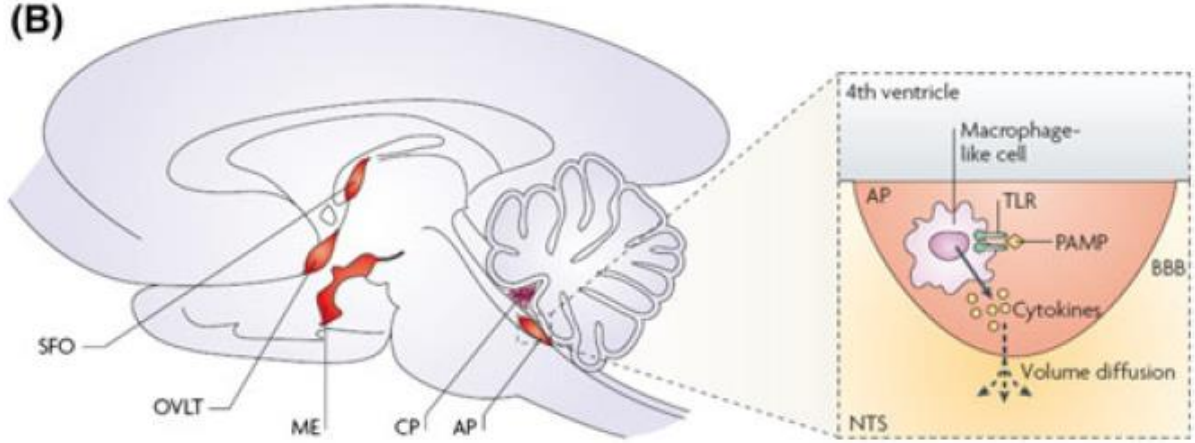
Pathways that transduce immune signals from the periphery to the brain

Maldonado J, Int J Ger Psych 2017

Neural pathway

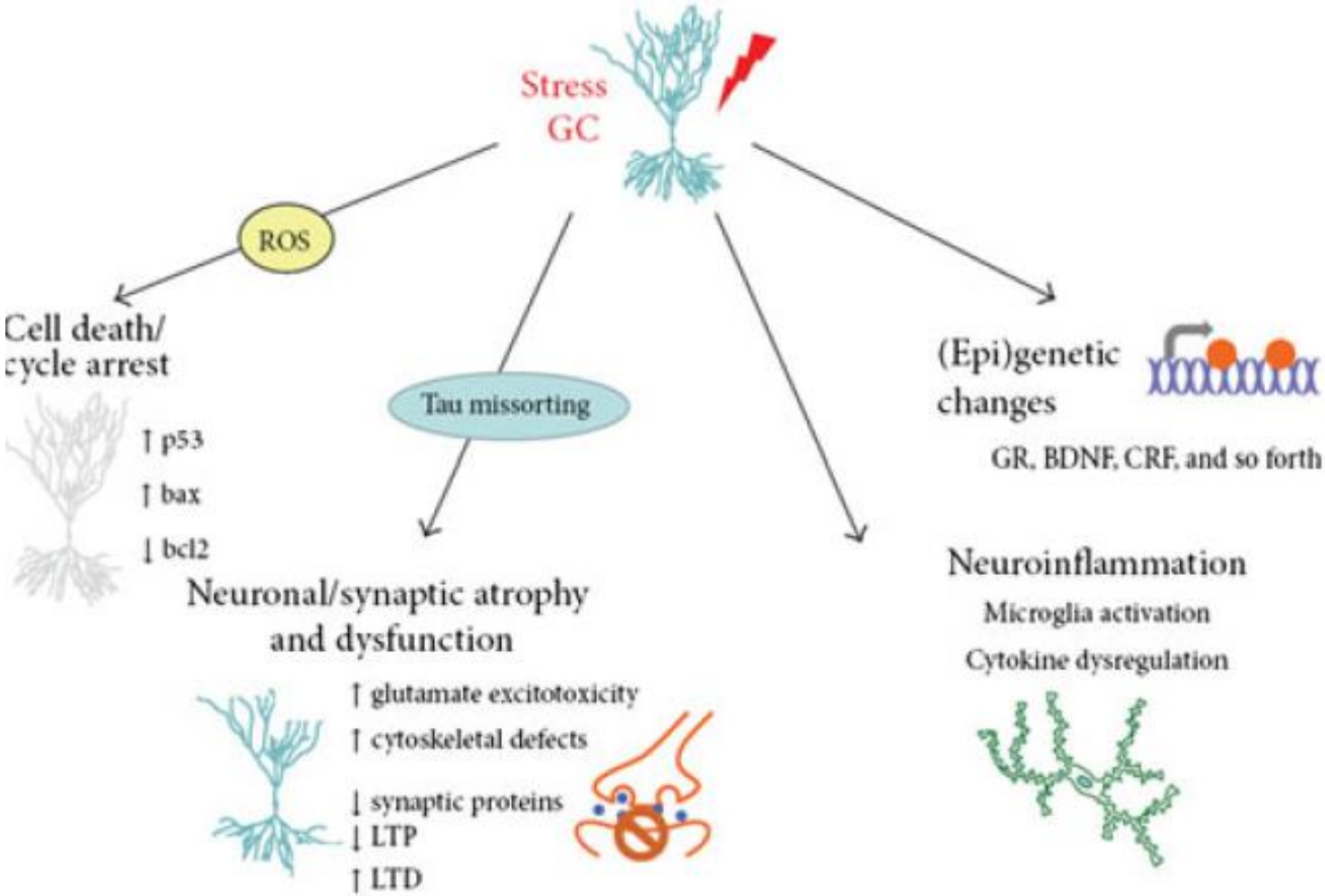


Humoral pathway



Neuroendocrine circuits in delirium

Maldonado J, Int J Ger Psych 2017

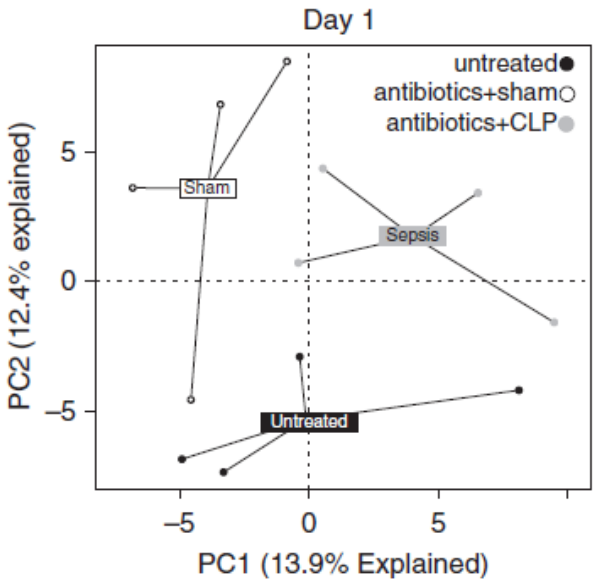


Bacterial Dissemination to the Brain in Sepsis

Benjamin H. Singer[1,2], Robert P. Dickson[1,2], Scott J. Denstaedt[1], Michael W. Newstead[1], Kwi Kim[3], Nicole R. Falkowski[1], John R. Erb-Downward[1], Thomas M. Schmidt[3], Gary B. Huffnagle[1,3], and Theodore J. Standiford[1]

Abdominal sepsis induced in mice by cecal ligation and puncture, and bacterial DNA detected in homogenized brain tissue was studied after 24 hours.

A



B

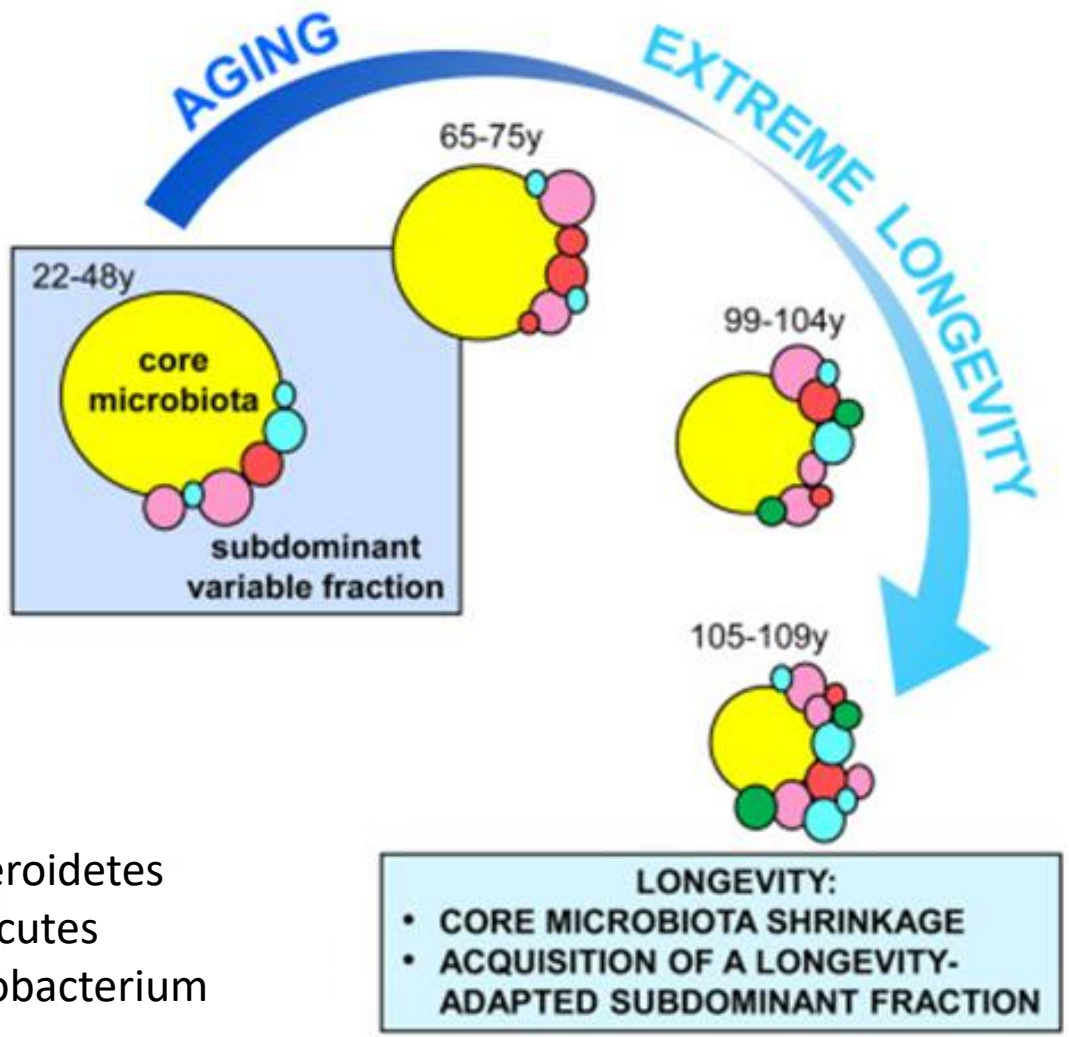
Am J Resp Crit Care Med Volume 197; 6: 2(

Considerazioni

- Vari meccanismi fisiopatogenetici (neuroinfiammazione, stress ossidativo e disregolazione neuroendocrina) oltre che una traslocazione diretta di batteri a livello del SNC spiegherebbero perché il delirium potrebbe insorgere a seguito di alterazioni della flora microbica intestinale

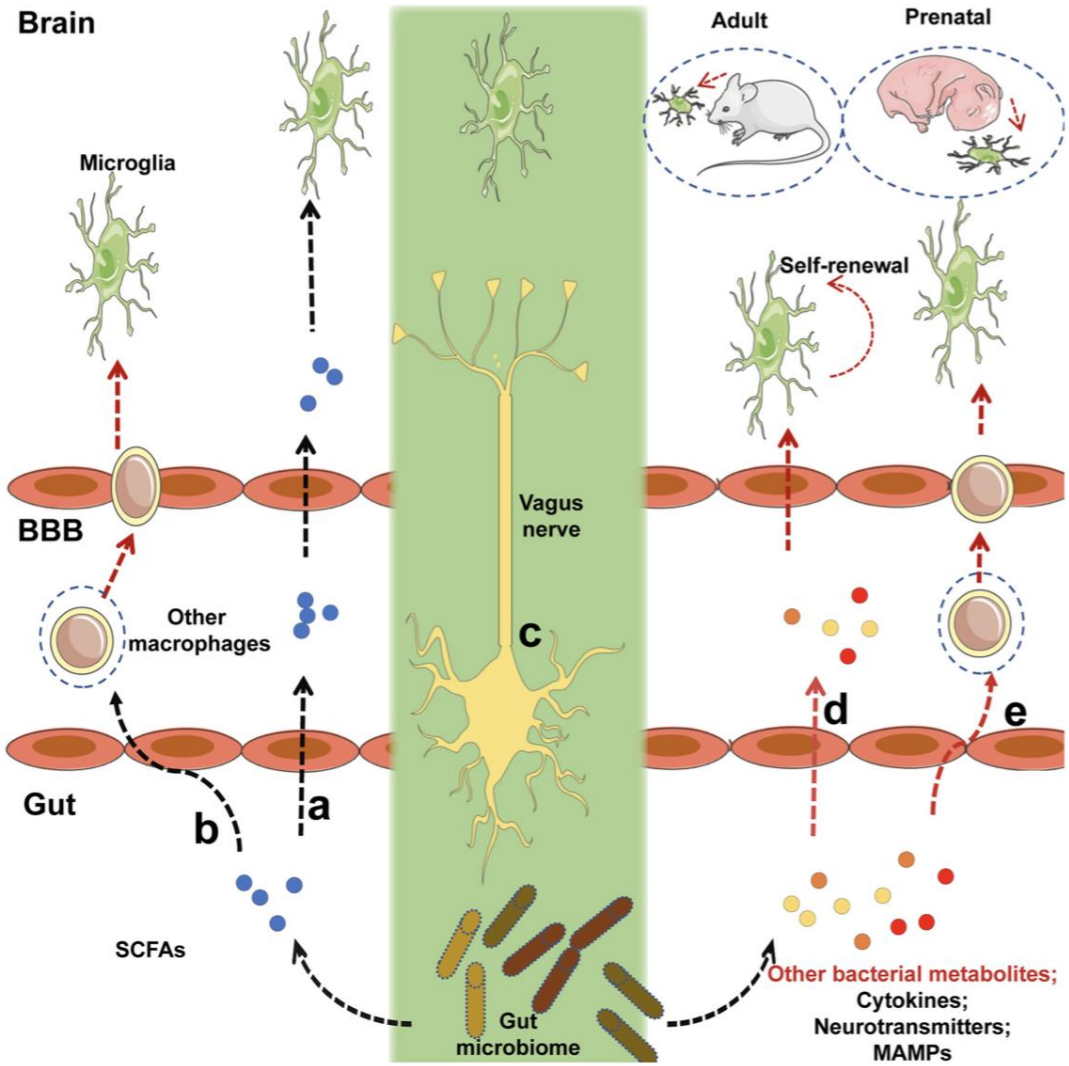
Gut brain axis e delirium: quali implicazioni possibili per le strategie di cura?

Changes in microbial system occurring with ageing



↑Bacteroidetes
↓Firmicutes
↓Bifidobacterium

Il microbiota intestinale regola la funzione della microglia



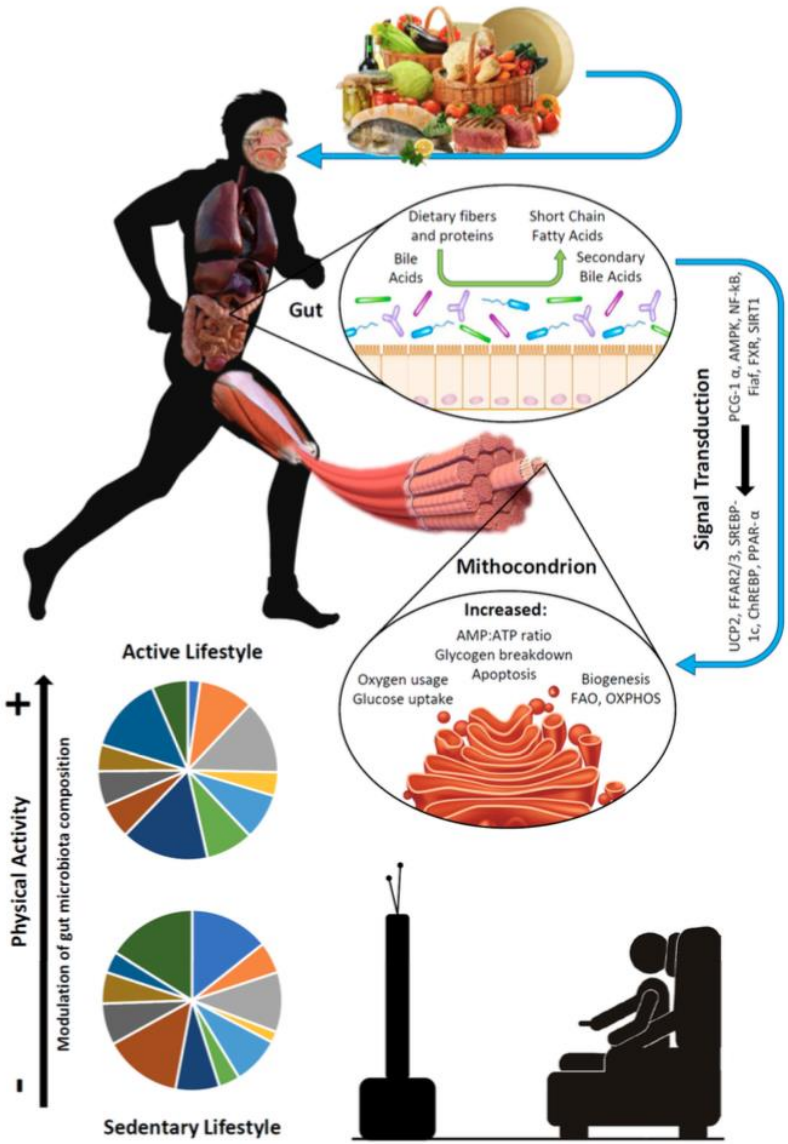
..e attiva la risposta immunitaria

Microglia-associated factors	Function of indicated factor (References)	GF	ABX
Spi1 (encodes PU.1)	Central microglial transcription and survival factor (68)	↑	-
Ddit4	Activation of cell proliferation (74)	↑	→
Csf1r	Central microglial transcription and survival factor (8)	↑	-
CSF1R	Surface factors of microglia downregulated during maturation (22)	↑	-
F4/80	As above (22)	↑	↑
CD31	As above (22)	↑	→

Ddit4, DNA damage-inducible transcript 4; Spi1, Spleen focus forming virus (SFFV) proviral integration oncogene; Csf1r, Colony stimulating factor 1 receptor; F4/80, adhesion G protein-coupled receptor E1 (Aliases); CD31, Platelet/endothelial cell adhesion molecule 1 (Aliases); GF, germ-free; ABX, antibiotics; ↑ means upregulation, → means unaltered, and – means uncertain.

 Wang Y et al, Front Immunol 2018

Aging Gut Microbiota at the Cross-Road between Nutrition, Physical Frailty, and Sarcopenia: Is There a Gut–Muscle Axis?

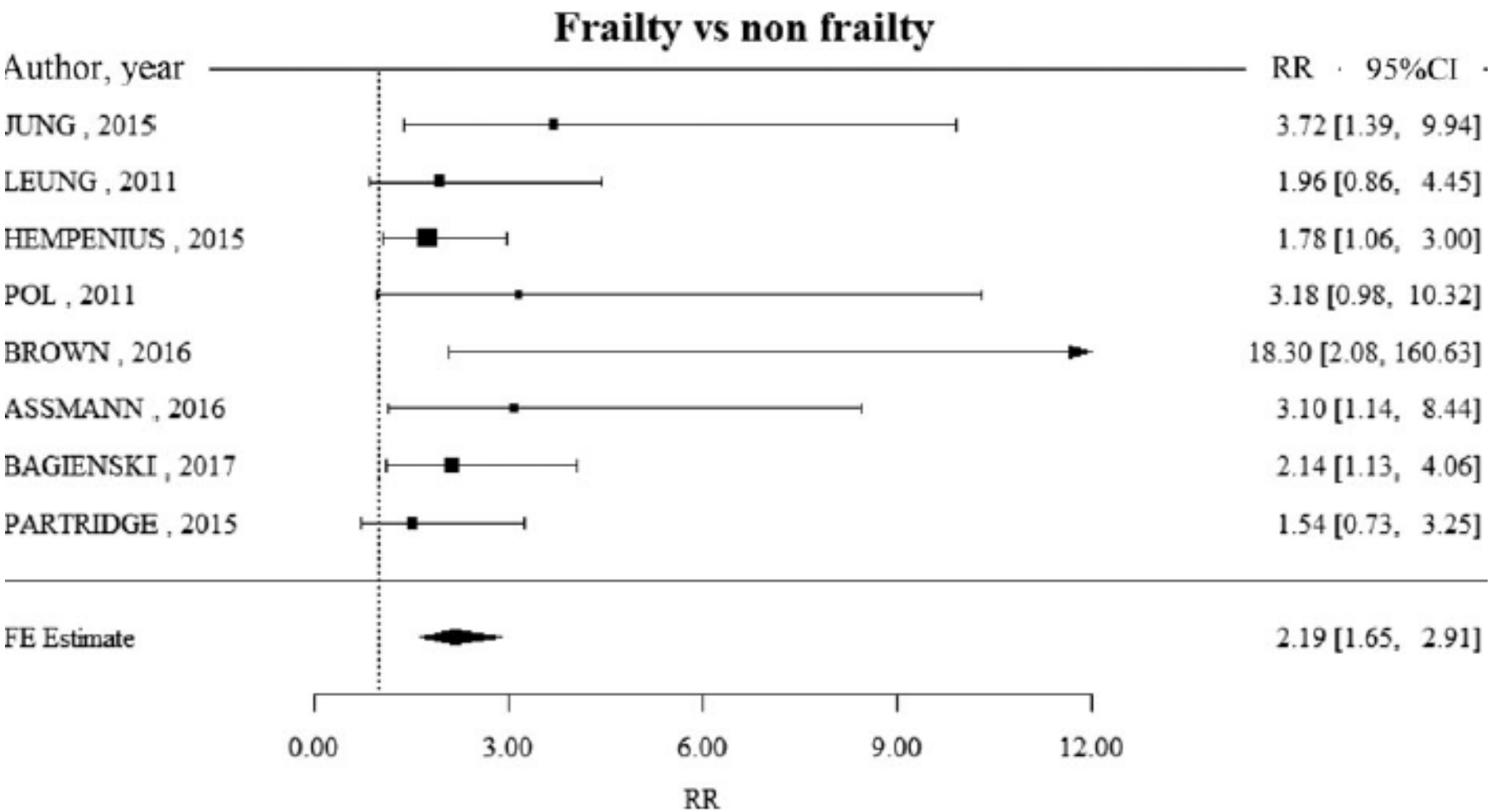


Ticinesi A et al, Nutrients 2017

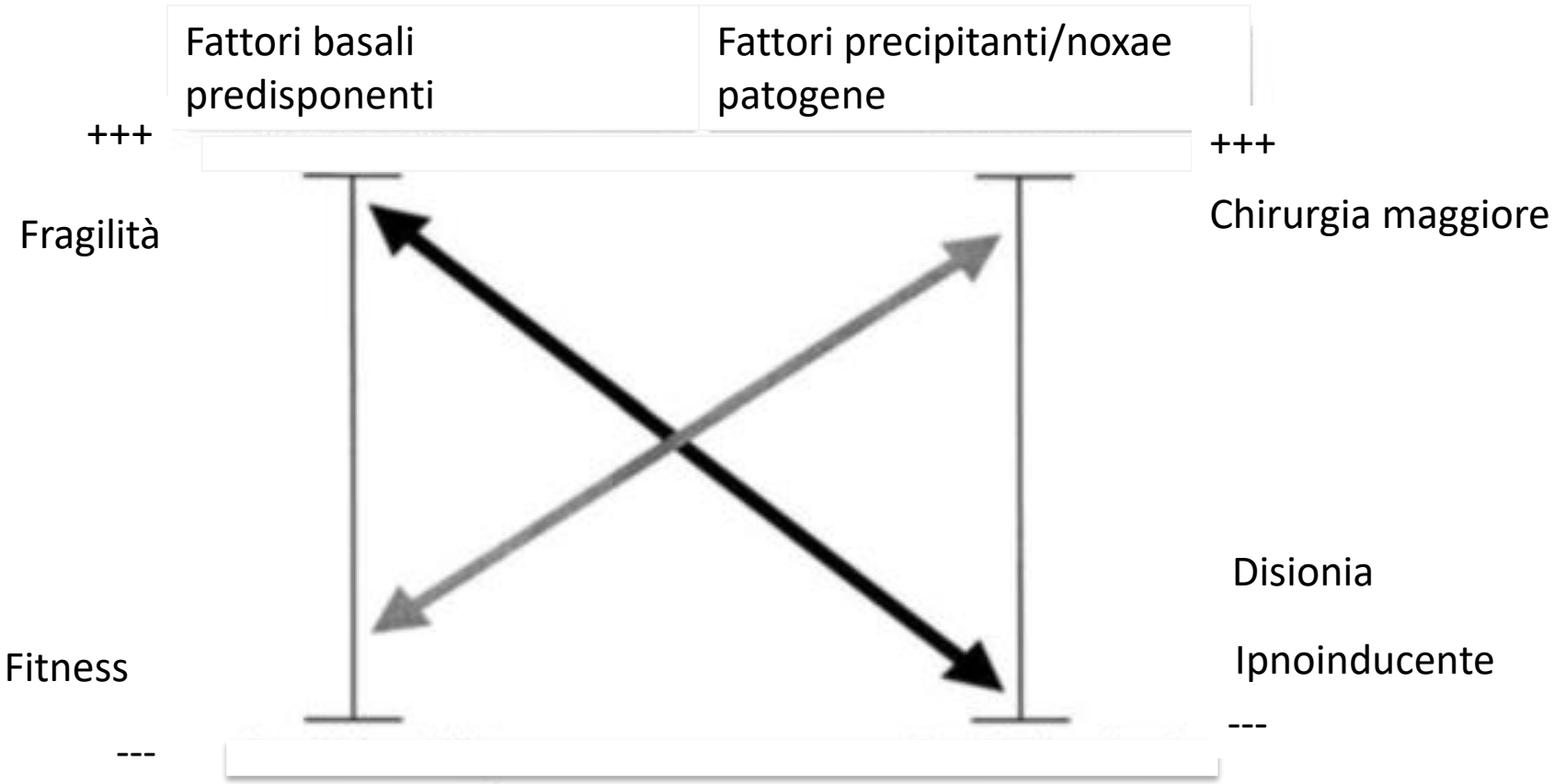
Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature

Ilaria Persico, MD, Matteo Cesari, MD, PhD,†‡ Alessandro Morandi, MD, MPH,§ Justin Haas,¶ Paolo Mazzola, MD,* Antonella Zambon, PhD,‖ Giorgio Annoni, MD,*** and Giuseppe Bellelli, MD****

J Am Geriatr Soc 2018; 1–9

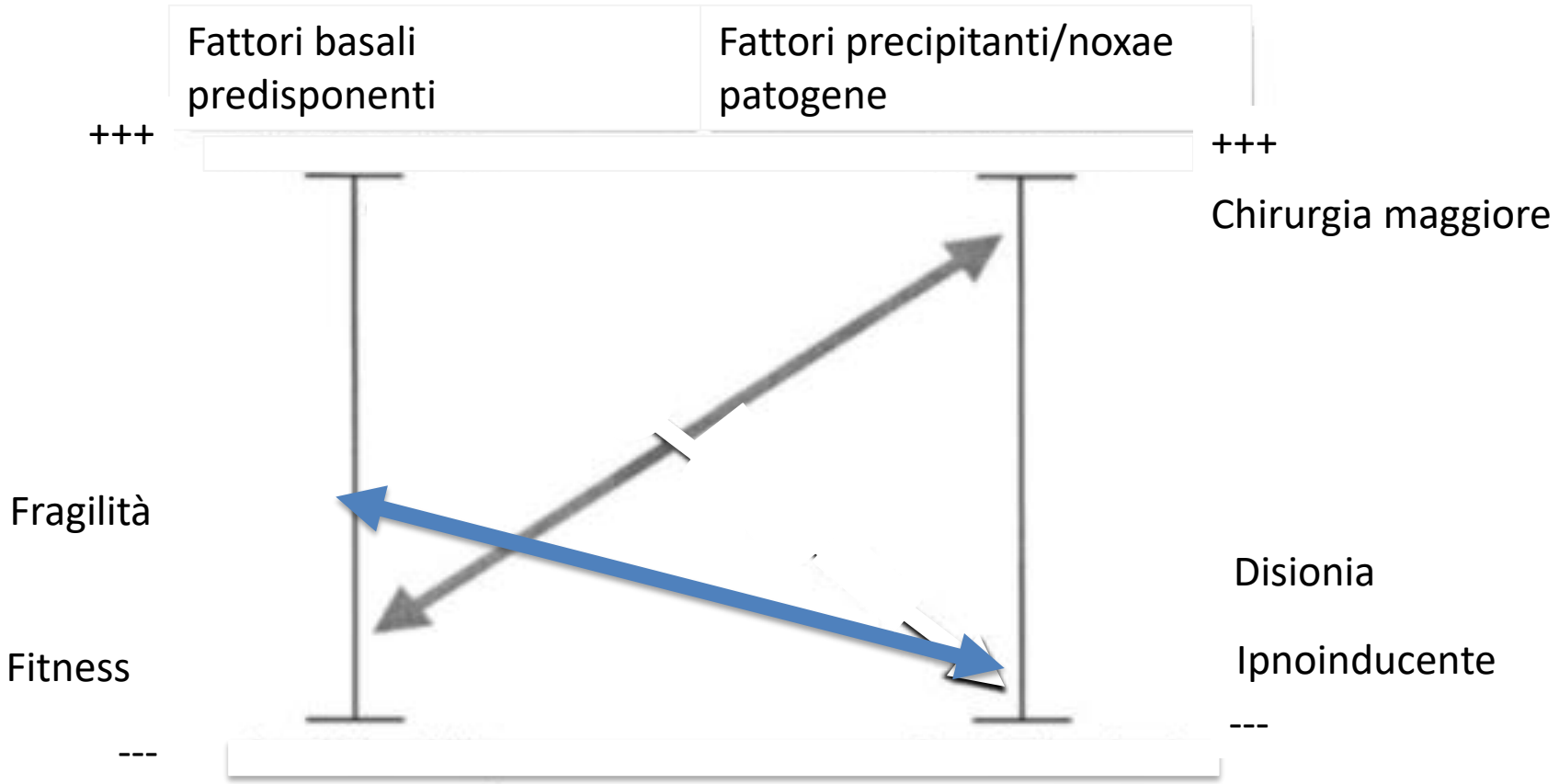


Modello multifattoriale del delirium: interazione tra fattori predisponenti e noxae precipitanti nello sviluppo di delirium.



Mod da Inouye SK, J Am Geriatr Soc 2018

Modello multifattoriale del delirium: interazione tra fattori predisponenti e noxae precipitanti nello sviluppo di delirium.



Mod da Inouye SK, J Am Geriatr Soc 2018

Article

Effect of a Prebiotic Formulation on Frailty Syndrome: A Randomized, Double-Blind Clinical Trial

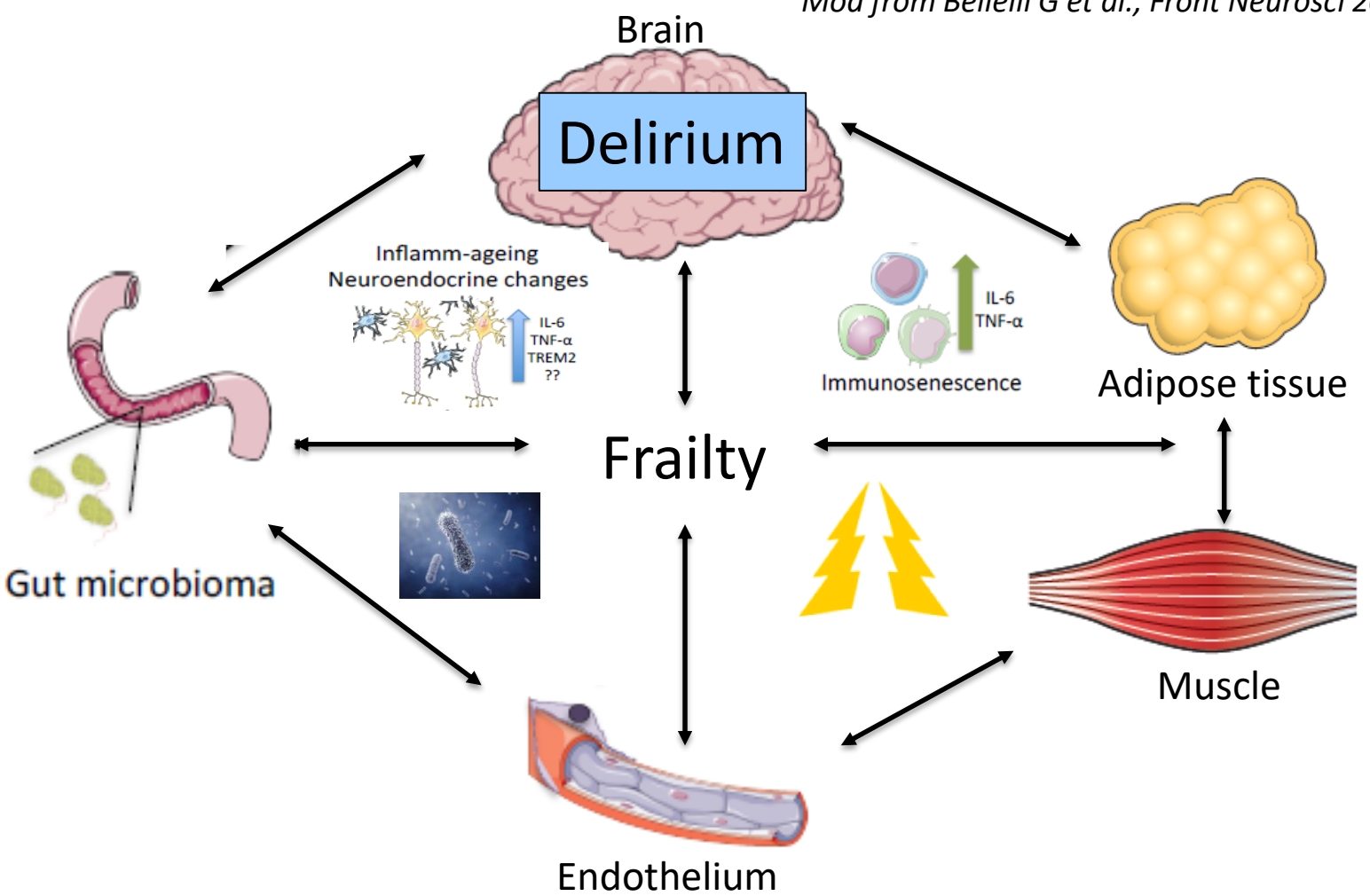
Cristina Buigues [1,†], Julio Fernández-Garrido [1,†], Leo Pruimboom [2,3], Aldert J. Hoogland [4], Rut Navarro-Martínez [1], Mary Martínez-Martínez [5], Yolanda Verdejo [5], Mari Carmen Mascarós [5], Carlos Peris [5] and Omar Cauli [1,*]

Variable	Baseline		Significance	Post-Treatment		Significance
	Placebo Group (n = 22)	Dermocare Pre® (n = 28)	p Value	Placebo Group (n = 22)	Dermocare Pre® (n = 28)	p Value
Exhaustion (score 0–3: 0 "never"; 1 "A few times" (1–2 days per week); 2 "Often" (3–4 days per week); or 3 "Most of the time" (almost each day))	1.1 ± 1.7	1.4 ± 1.7	0.74	1.7 ± 1.2	0.8 ± 1.4 **	0.002
Slow walk (s) (time needed to walk 4.6 m)	8.6 ± 9.0	8.4 ± 6.0	0.91	8.7 ± 4.2	7.9 ± 4.5	0.48
Grip strength (right hand, kg)	11.5 ± 5.7	10.6 ± 8.2	0.61	10.2 ± 4.1	12.4 ± 3.2 *	0.04
Grip strength (left hand, kg)	10.2 ± 5.8	10.1 ± 7.6	0.92	9.1 ± 3.7	9.8 ± 3.5	0.50
Self health-perception (score 0–10, being 0 the worst and 10 the best)	7.1 ± 2.3	7.1 ± 2.1	0.96	6.8 ± 2.4	6.8 ± 2.0	0.96
Body mass index	26.1 ± 4.1	25.8 ± 4.2	0.97	26.0 ± 3.8	25.9 ± 4.1	0.96
Athens insomnia scale	3.4 ± 3.0	4.1 ± 4.7	0.77	4.5 ± 5.3	4.0 ± 4.3	0.68
Barthel index	76.2 ± 13.0	74.6 ± 17.7	0.69	78.3 ± 13.9	77.1 ± 29.9	0.87
Mini–Mental state examination	26.1 ± 2.2	26.5 ± 3.1	0.89	25.9 ± 2.1	26.4 ± 2.2	0.85

Int. J. Mol. Sci. **2016**, *17*, 932

Proposed mechanisms to correlate delirium, frailty and gut microbioma

Mod from Bellelli G et al., Front Neurosci 2018



Conclusioni

- I meccanismi fisiopatogenetici del delirium (neuroinfiammazione, alterazioni neuroendocrine, stress ossidativo) sono condizionati dall'attività della dalla microglia e della flora microbica intestinale (gut brain axis) oltre che da una possibile traslocazione battericaa livello cerebrale
- Vi sono iniziali evidenze che la variazione della flora batterica intestinale può revertire la fragilità, che a sua volta è un fattore predisponente il delirium
- Vi è spazio per la prevenzione del delirium?