# Systemic inflammation triggers acute delirium and brain injury and contributes to accelerated neurodegeneration


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wellcome trust

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# Delirium

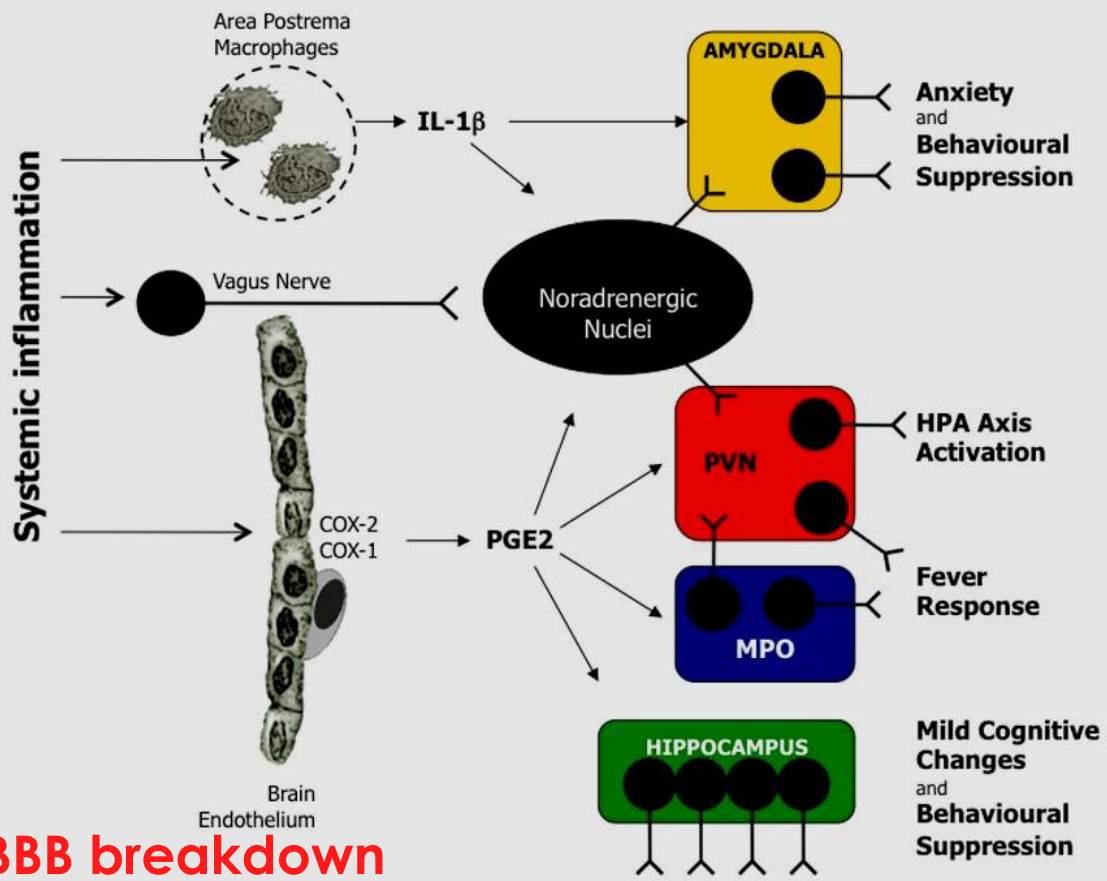
**Delirium is an acute and transient impairment of consciousness, thinking, memory, psychomotor behaviour, perception and emotion**

- Up to 20% in 500-bed general hospital (underdiagnosed)
- Extremely distressing acute episodes
- Costs billions in extended hospital stays
- Acceleration of dementia, new institutionalisation
- Risk factors & triggers: dementia and systemic inflammation
- Fundamental neuroscience level: hardly studied

2)

1)

3)

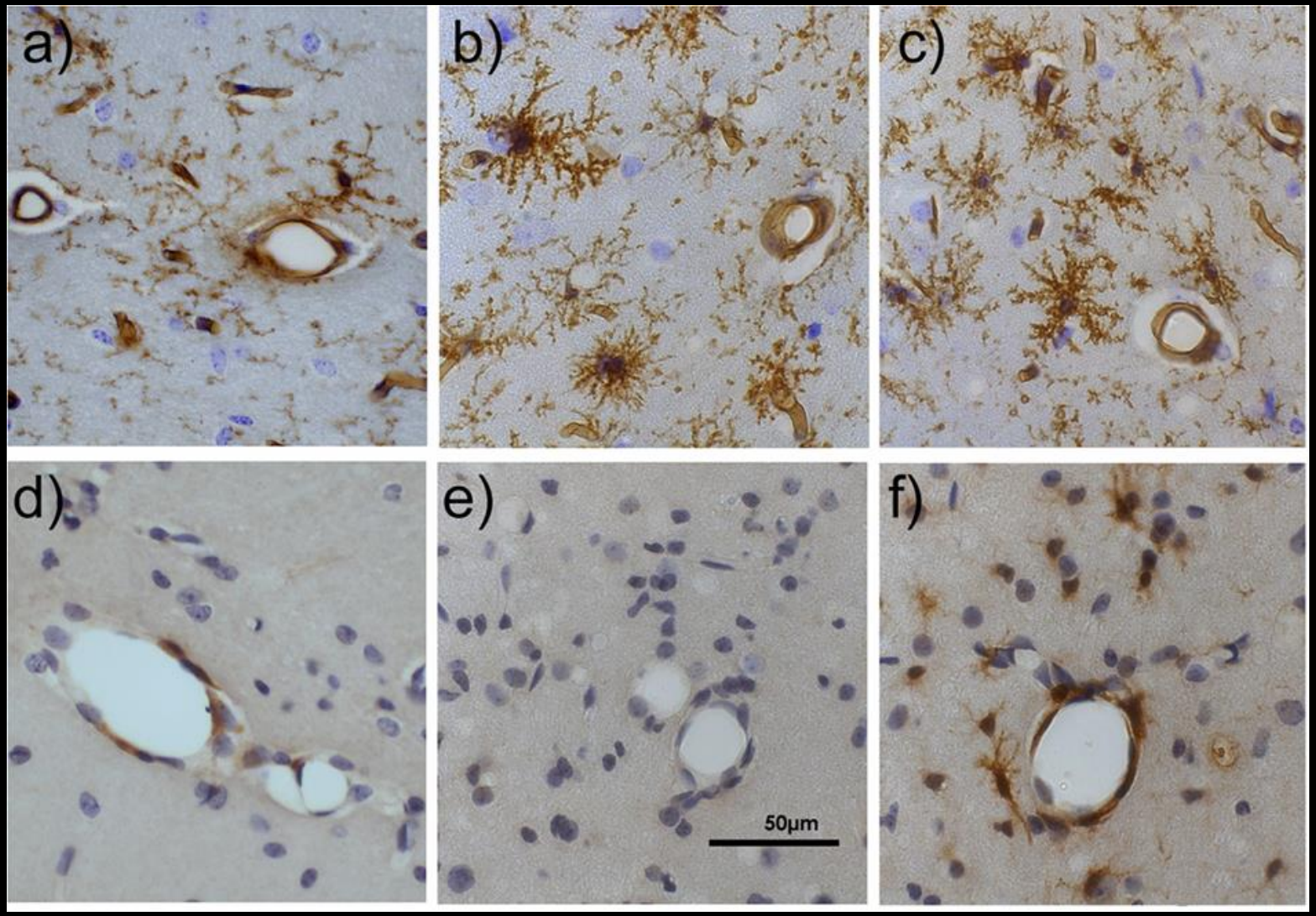



Dantzer et al., Nature Rev. Neurosci, 2008
Saper et al., Nature Neuroscience, 2012

Cunningham & MacLullich, BBI, 2013

# Microglial Priming

Cunningham et al., J. Neurosci. 2005

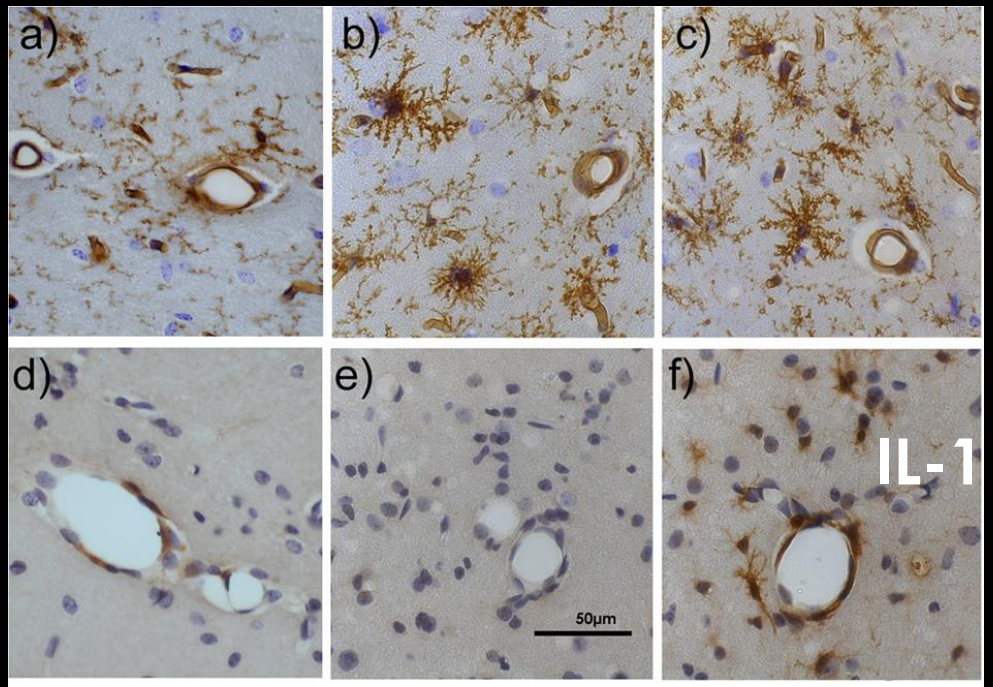



µglia

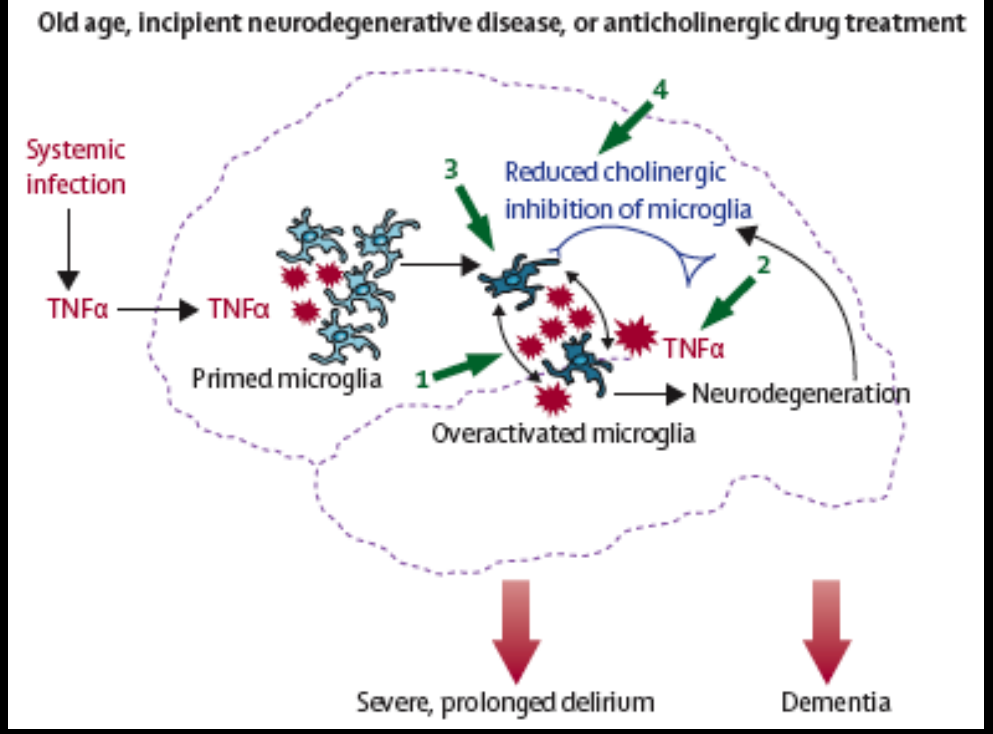
IL-1

# Microglial Priming

Cunningham et al.,
J Neuroscience, 2005

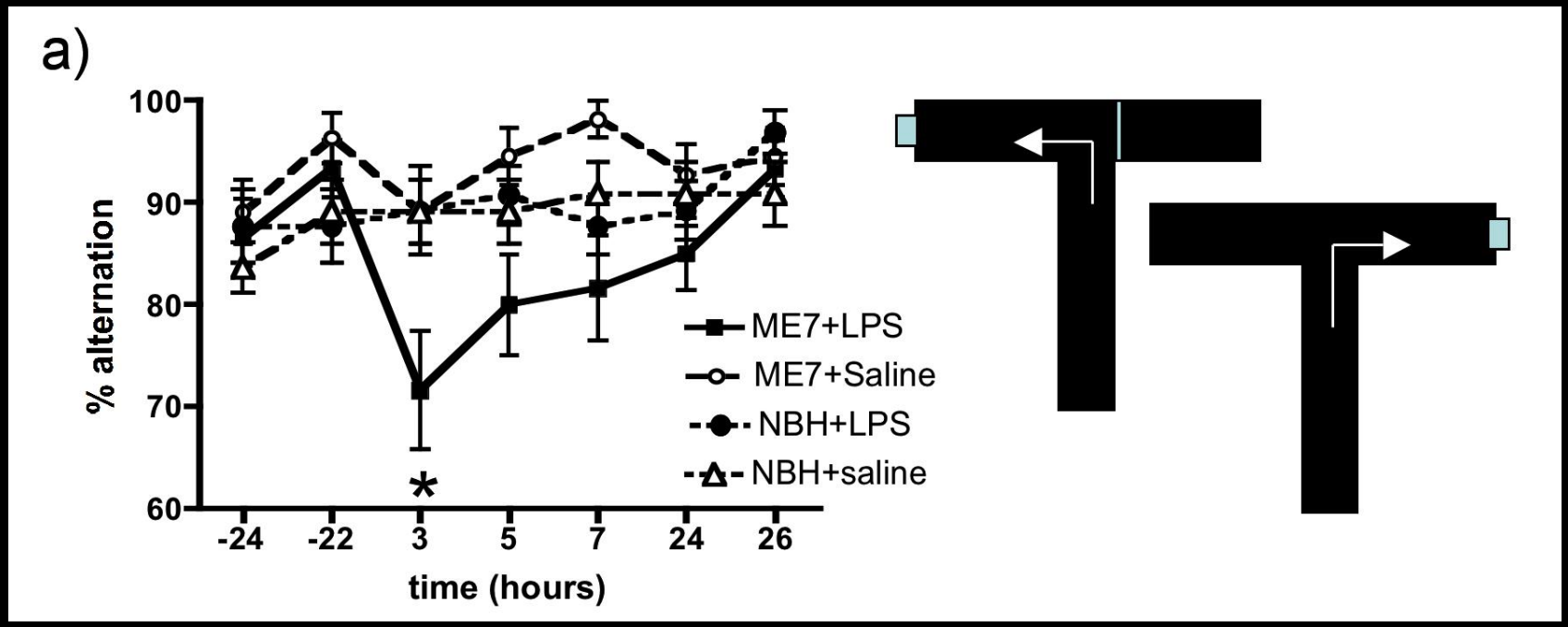



Van Gool et al.,
Lancet, February 2010



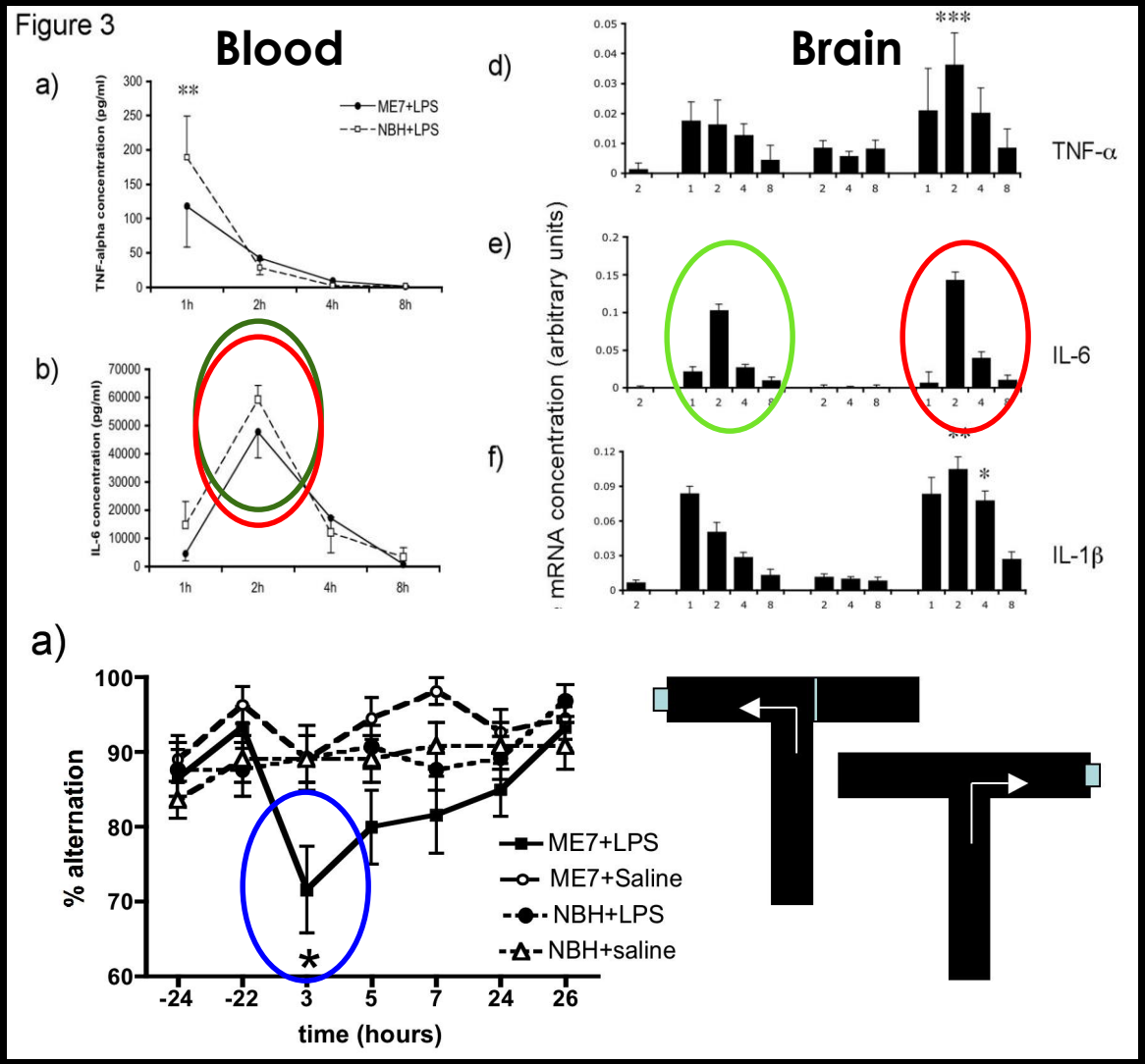
# Model system 1: ME7 (chronic neurodegeneration) +LPS

## Acute, transient working memory deficit induced by systemic LPS (100µg/kg)




Murray et al., Neurobiology of Aging, 2012

# Model system 1: mild LPS superimposed on neurodegenerative disease




LPS induces IL-6 equally in **normal** animals and in those With **neurodegenerative Disease**

Only those with prior degeneration show **acute cognitive deficits** upon LPS.

Murray et al., Neurobiology of Aging, 2012

**Equivalent IL-6 responses, differential cognitive deficits**

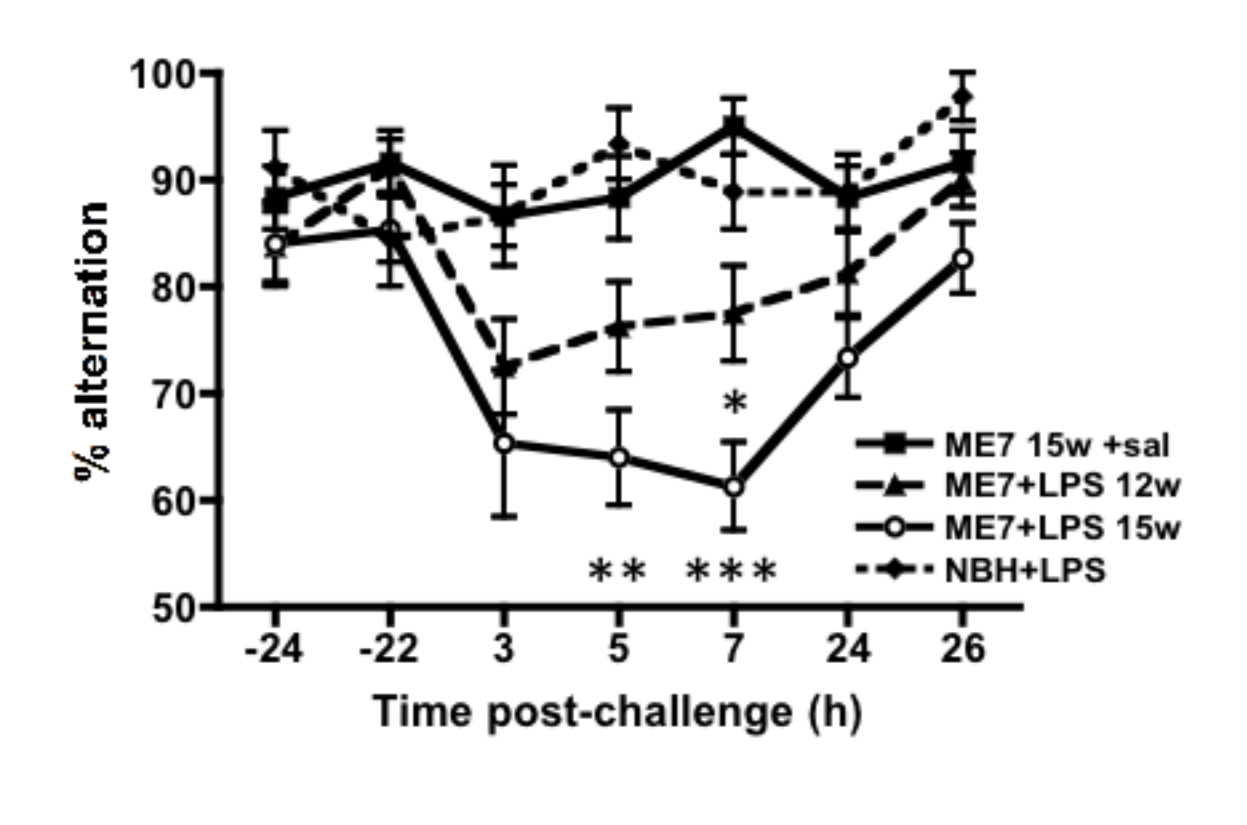
Table 3. Plasma Levels of Inflammatory Markers Before and After Surgery and within (Pre- and Postoperative) and Between (Delirium vs No Delirium) Groups

| | Preoperative | | Postoperative | | |
|---|---|---|---|---|---|
| Inflammatory Marker | Median (IQR) | *P*-Value* | Median (IQR) | *P*-Value* | *P*-Value† |
| C-reactive protein | | | | | |
| Delirium | 0.38 (1.17) | .86 | 18.31 (11.82) | .67 | <.001 |
| No delirium | 0.51 (0.91) | | 15.89 (15.31) | | <.001 |
| IL-1β | | | | | |
| Delirium | 0.40 (0.55) | .57 | 0.4 (0.39) | .86 | .90 |
| No delirium | 0.46 (0.61) | | 0.4 (0.38) | | .05 |
| Tumor necrosis factor alpha | | | | | |
| Delirium | 6.12 (9.28) | .54 | 1.5 (5.01) | .98 | .50 |
| No delirium | 6.2 (9.96) | | 1.5 (8.3) | | .22 |
| IL-6 | | | | | |
| Delirium | 7.95 (8.59) | .65 | 117.39 (148.07) | .14 | <.001 |
| No delirium | 8.27 (8.49) | | 93.18 (99.25) | | <.001 |
| IL-8 | | | | | |
| Delirium | 9.16 (7.02) | .56 | 18.83 (17.3) | .14 | <.001 |
| No delirium | 8.6 (6.51) | | 16.59 (11.25) | | <.001 |
| IL-10 | | | | | |
| Delirium | 1.81 (1.64) | .10 | 3.17 (3.23) | .97 | <.001 |
| No delirium | 2 (1.37) | | 3.18 (3.85) | | <.001 |
| Pro-/anti-inflammatory ratio | | | | | |
| Delirium | 12.44 (9.61) | .18 | 38.06 (27.13) | .049 | <.001 |
| No delirium | 11.14 (5.71) | | 28.31 (26) | | <.001 |

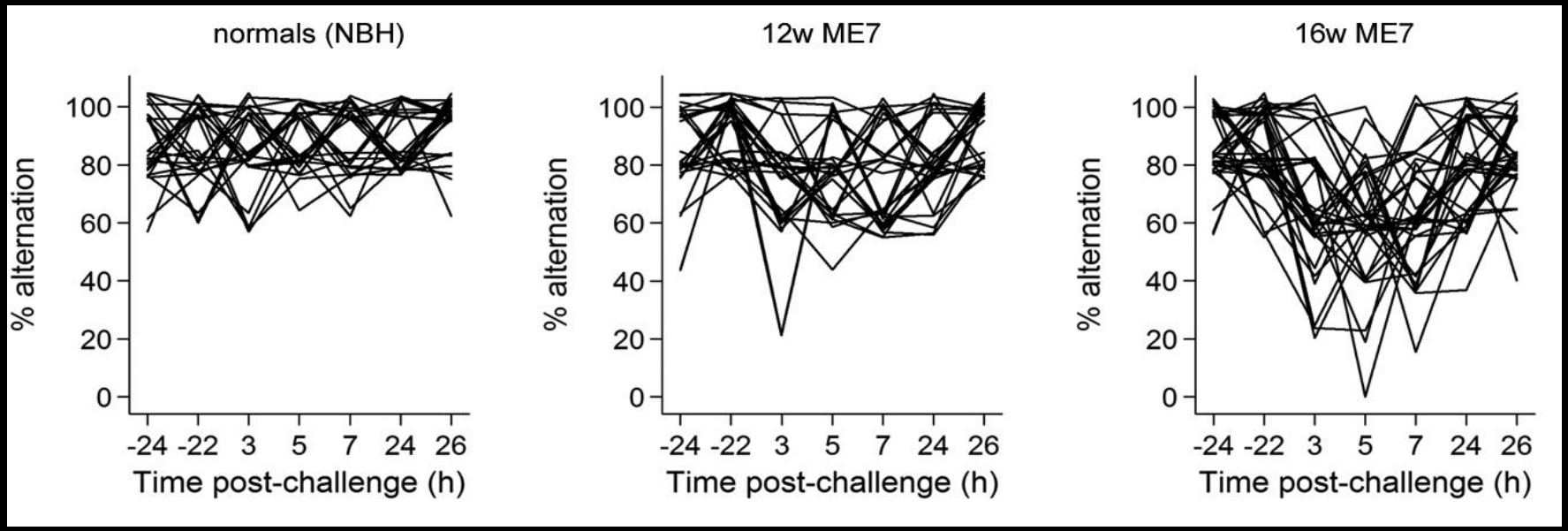
Cerejeira et al., JAGS 2012

Model system 1

# Progressing disease increases risk, severity and duration




Griffin et al., J. Neurosci. 2013




## Fluctuating course

## DSM-IV

**cognitive/attentional**

**acute onset,**
**fluctuating course,**
**not better explained by dementia**

## Davis et al., AJGP (2015)

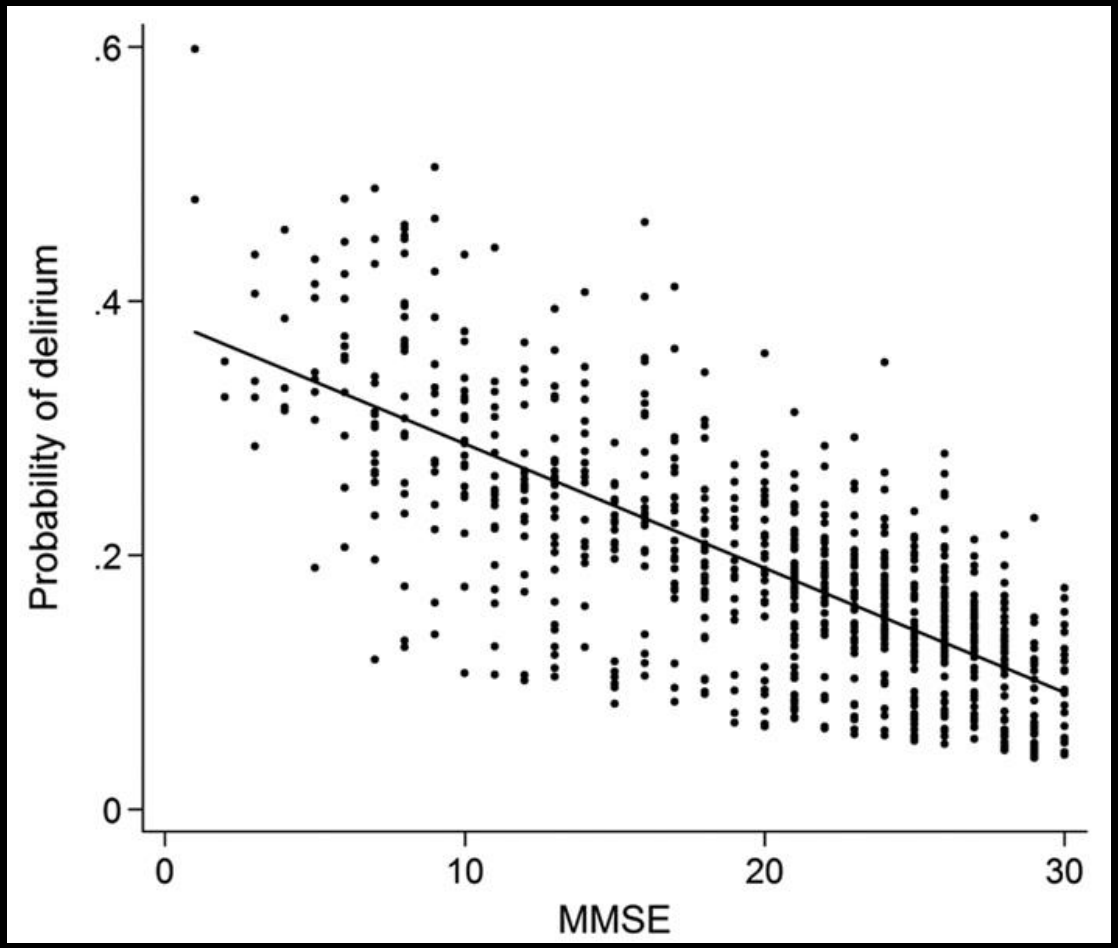
# Mice and men

## Worsening Cognitive Impairment and Neurodegenerative Pathology Progressively Increase Risk for Delirium

*Daniel H.J. Davis, M.R.C.P., Ph.D., Donal T. Skelly, Ph.D., Carol Murray, M.Sc., Edel Hennessy, B.A., Jordan Bowen, M.B., B.S., Samuel Norton, Ph.D., Carol Brayne, M.D., Terhi Rahkonen, M.D., Raimo Sulkava, M.D., David J. Sanderson, Ph.D., J. Nicholas Rawlins, Ph.D., David M. Bannerman, Ph.D., Alasdair M.J. MacLullich, M.R.C.P., Ph.D., Colm Cunningham, Ph.D.*

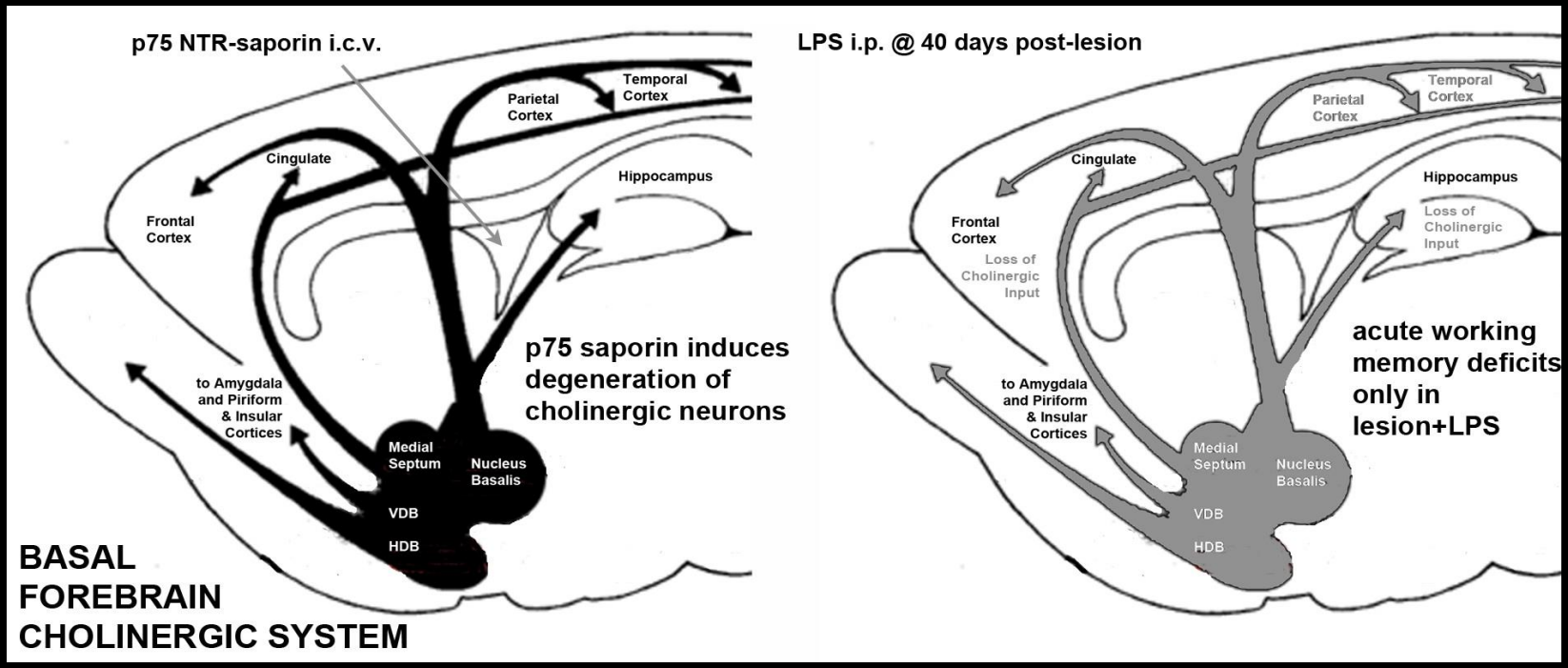
Davis et al., AJGP (2015)

# Mice and men




Davis et al., AJGP (2015)

# **Model system 2:** p75$^{NTR}$-saporin lesion of basal forebrain




ICV SURGERY — T-maze training — LPS & T-maze performance — Perfusion

Recovery — Train to > 80% performance

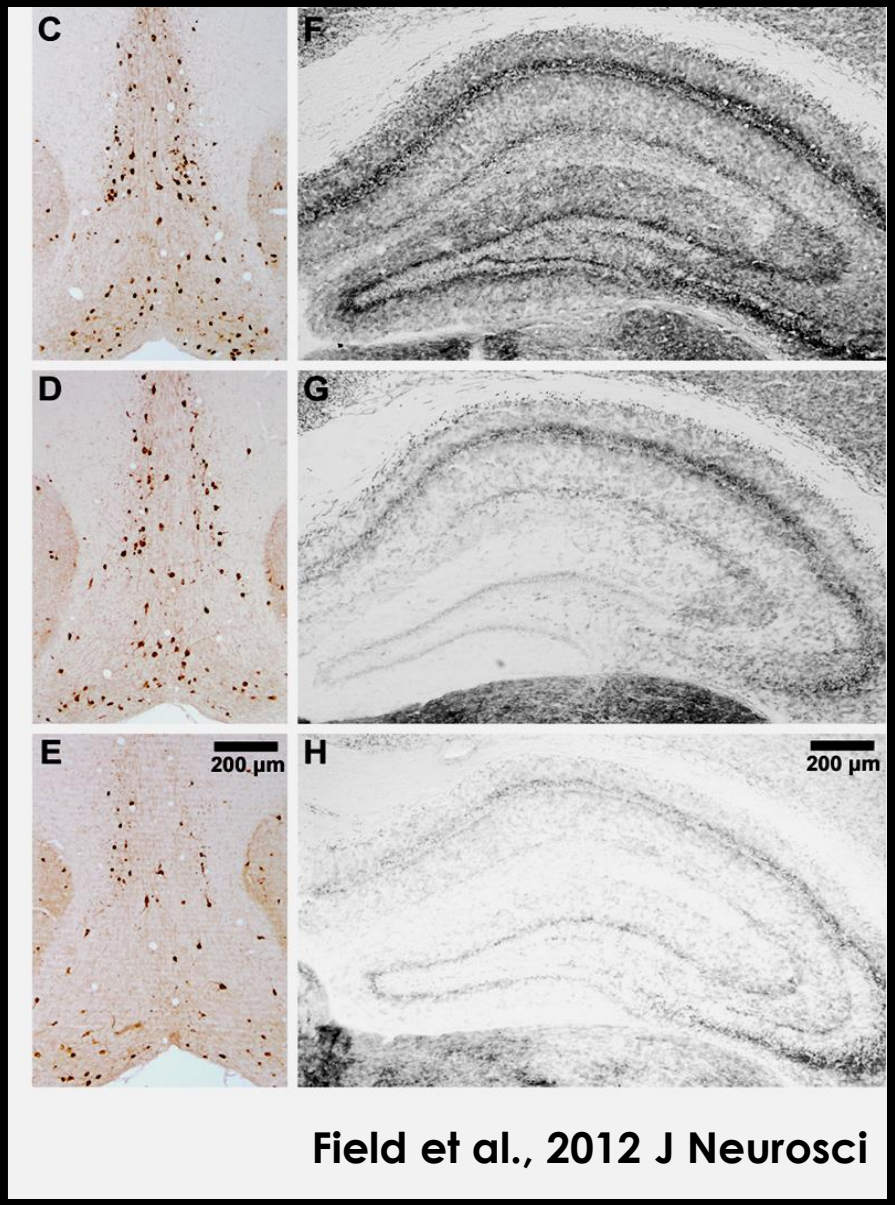
day 1 — day 10 — day 35 — day 40

# p75$^{NTR}$-saporin targets basal forebrain cholinergic neurons

PBS

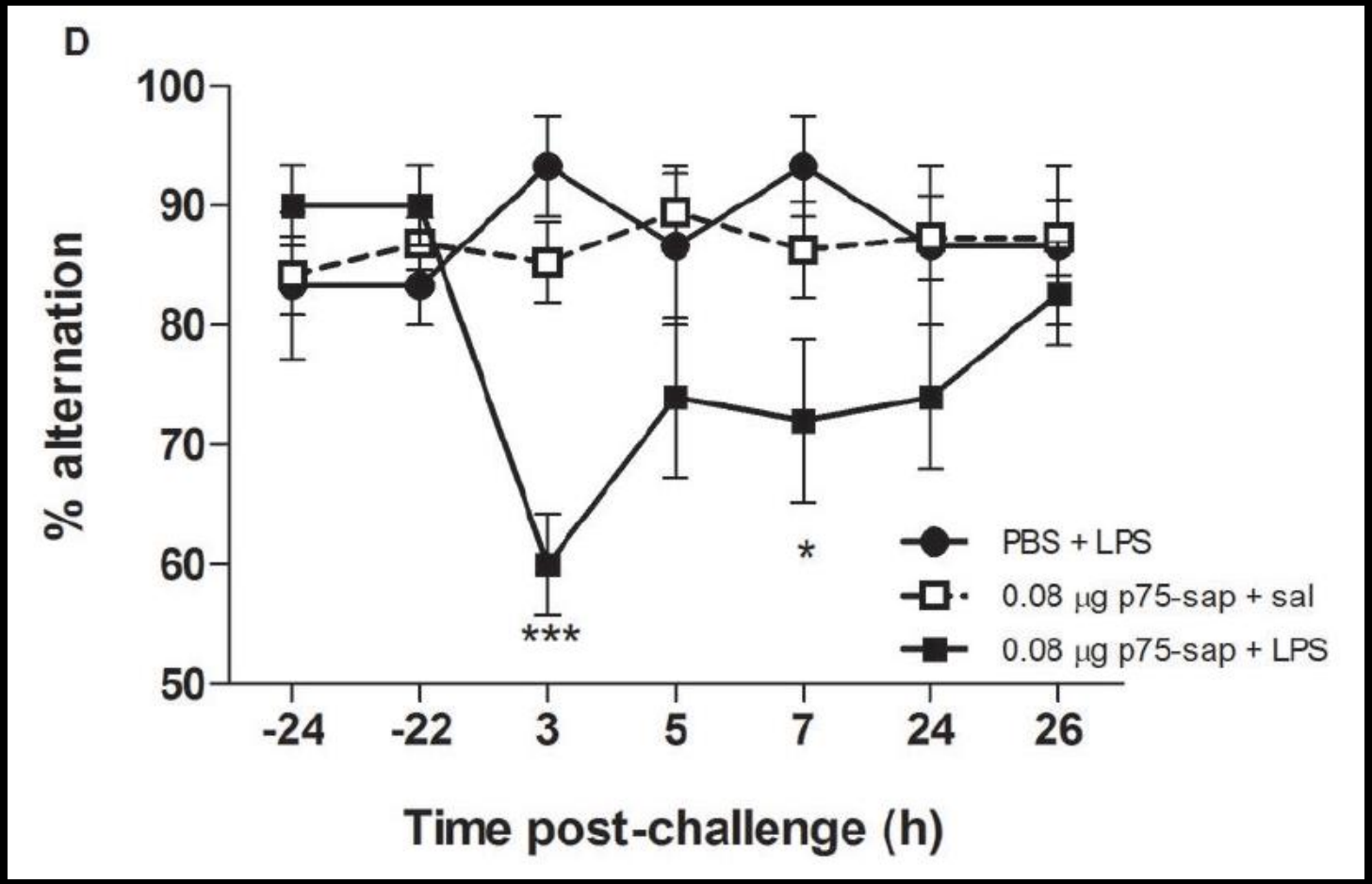
0.08 µg/kg

0.4 µg/kg



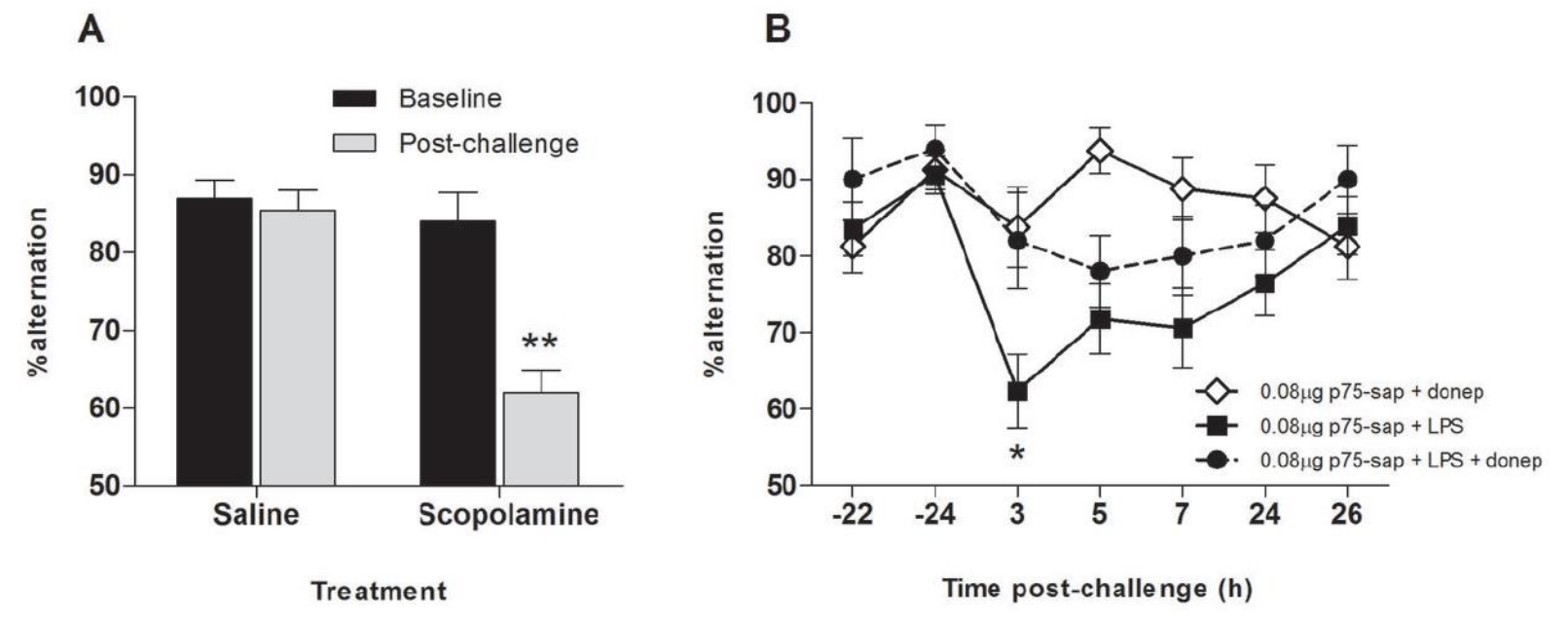

Field et al., 2012 J Neurosci

**Systemic LPS (100 µg/kg) induces acute working memory deficits only in animals with prior hypocholinergia**




Field et al., J Neurosci 2012

# 1) T-maze performance is cholinergic dependent
# 2) Donepezil protects against LPS-induced deficits

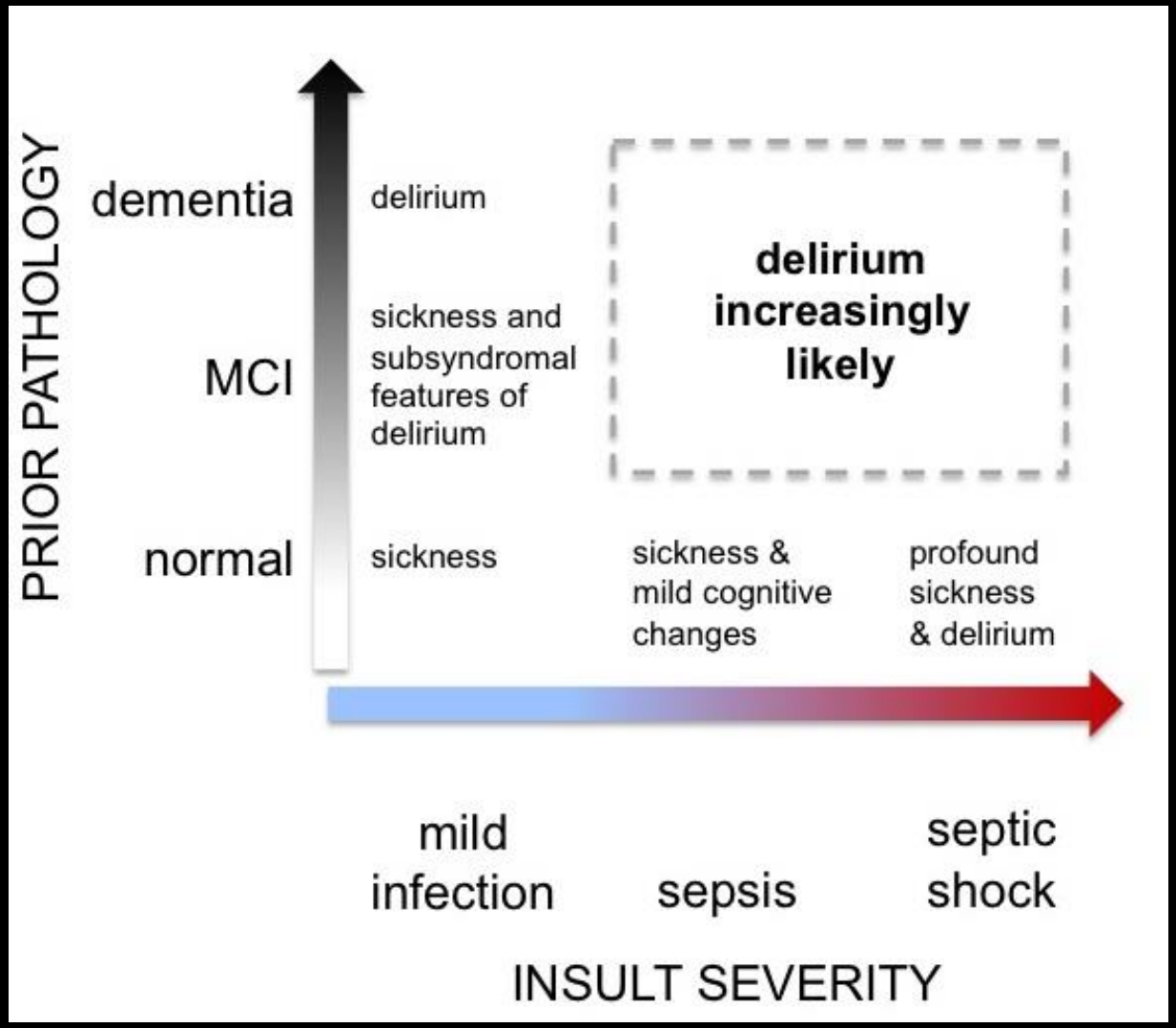



Field et al., J Neurosci 2012

**Reconciling inflammatory and cholinergic hypotheses:**

Cholinergic vulnerability & inflammatory trigger

# Moving towards the tipping point




**Cunningham 2013**, *in* **Brain Disorders in Critical Illness** eds. Stevens, Sharshar & Ely

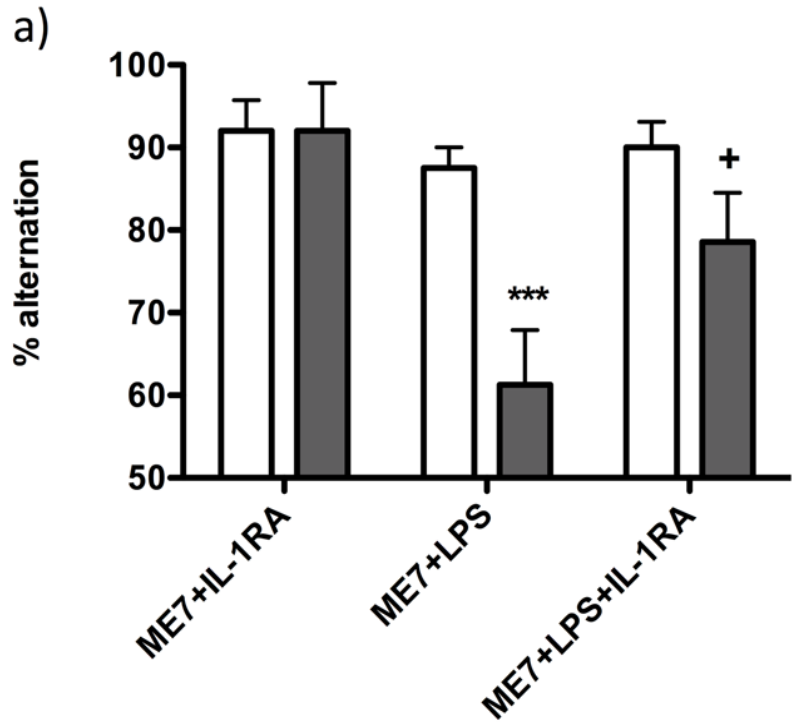
**4 models**

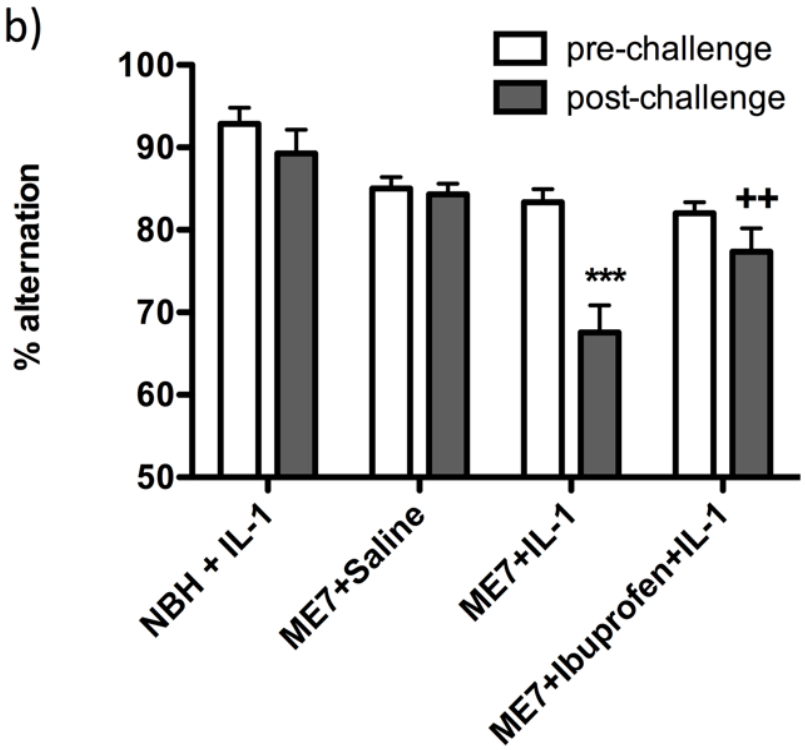
**& MMSE**

**Brain Frailty**

**Failure of frail brain to demonstrate resilience to acute insult**

# 1) Systemic IL-1RA is protective
# 2) IL-1β is sufficient (LPS not necessary)




Griffin et al., J. Neurosci 2013

# Human hip fracture patients & delirium



**Table 2**
Concentrations of CSF markers in patients with delirium pre-operatively (prevalent), postoperatively (incident) and without delirium

| CSF biomarker | Prevalent delirium | Incident delirium | Never delirium | P value |
|---|---|---|---|---|
| IL-1β (pg/ml) | 0.84 (0.49–1.57) N = 8 | 1.74 (1.02–1.74) N = 9 | 0.66 (0.00–1.02) N = 24 | 0.03[a] |
| IL-1ra (pg/ml) | 70.75 (65.63–73.01) N = 3 | 31.06 (28.12–35.15) N = 6 | 33.98 (28.71–43.28) N = 15 | 0.04[a] |
| GFAP (ng/ml) | 0.81 (0.33–1.31) N = 8 | 0.61 (0.46–0.76) N = 9 | 0.45 (0.31–0.86) N = 24 | 0.58[a] |

Results expressed as median (interquartile range).
[a] Kruskal–Wallis test.

**Cape et al., 2014**

## Increased CSF:serum ratio of IL-1β
**(same level of systemic IL-1, but increased brain IL-1)**

Matched blood and CSF will help to address 'microglial priming' and other inflammatory hypotheses.

Sources of CSF cytokine/chemokine ?

**Delirium**
accelerates
Dementia

**Systemic inflammation**
accelerates dementia
(delirium-independent)

Dementia pathology
looks different if previous
episodes of delirium

## Delirium accelerates cognitive decline in Alzheimer disease

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P. Shi, PhD
E.R. Marcantonio, MD, SM
L. Yap, PhD
J.L. Rudolph, MD
F.M. Yang, PhD
D.K. Kiely, MPH, MA
S.K. Inouye, MD, MPH

ABSTRACT

**Objective:** To examine the impact of delirium on the trajectory of cognitive function in a cohort of patients with Alzheimer disease (AD).

**Methods:** A secondary analysis of data collected from a large prospective cohort, the Massachusetts Alzheimer's Disease Research Center's patient registry, examined cognitive performance over time in patients who developed (n = 72) or did not develop (n = 336) delirium during the course of their illnesses. Cognitive performance was measured by change in score on the Information-Memory-Concentration (IMC) subtest of the Blessed Dementia Rating Scale. Delirium was identified using a previously validated chart review method. Using linear mixed regression models, rates of cognitive change were calculated, controlling for age, sex, education, comorbid

## Systemic inflammation and disease progression in Alzheimer disease

C. Holmes, MRCPsych, PhD
C. Cunningham, PhD
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S. Kerr, RGN
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V.H. Perry, PhD

ABSTRACT

**Background:** Acute and chronic systemic inflammation are characterized by the systemic production of the proinflammatory cytokine tumor necrosis factor α (TNF-α) that plays a role in immune to brain communication. Previous preclinical research shows that acute systemic inflammation contributes to an exacerbation of neurodegeneration by activation of primed microglial cells.

**Objective:** To determine whether acute episodes of systemic inflammation associated with increased TNF-α would be associated with long-term cognitive decline in a prospective cohort study of subjects with Alzheimer disease.

**Methods:** Three hundred community-dwelling subjects with mild to severe Alzheimer disease were

doi:10.1093/brain/aws190 Brain 2012: Page 1 of 8 | 1

BRAIN
A JOURNAL OF NEUROLOGY

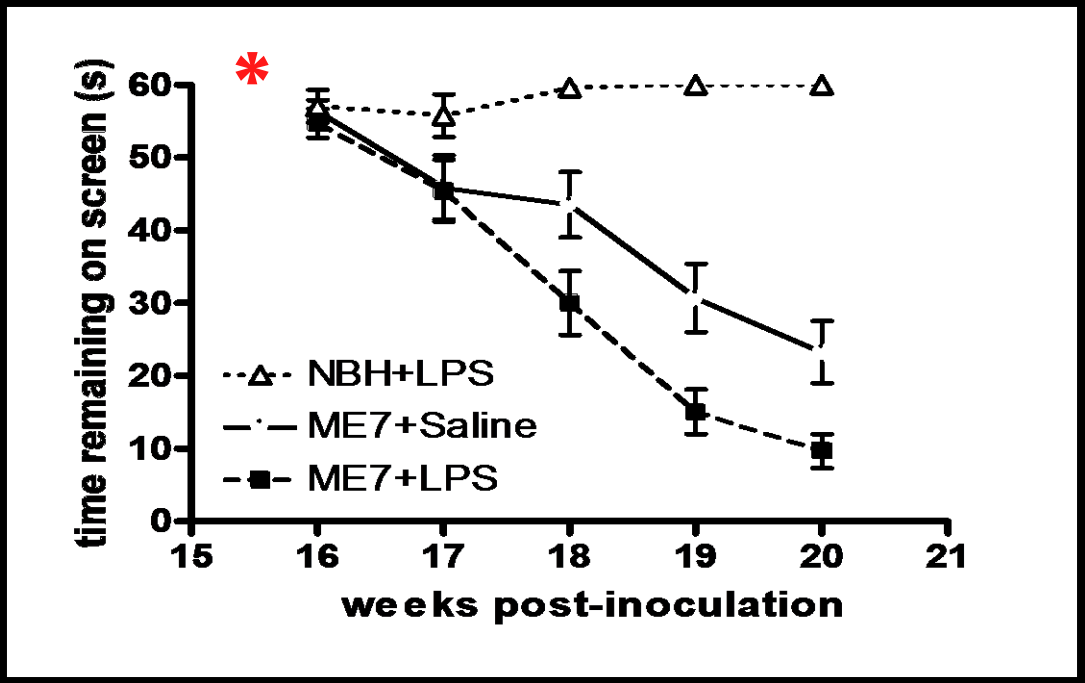
## Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study

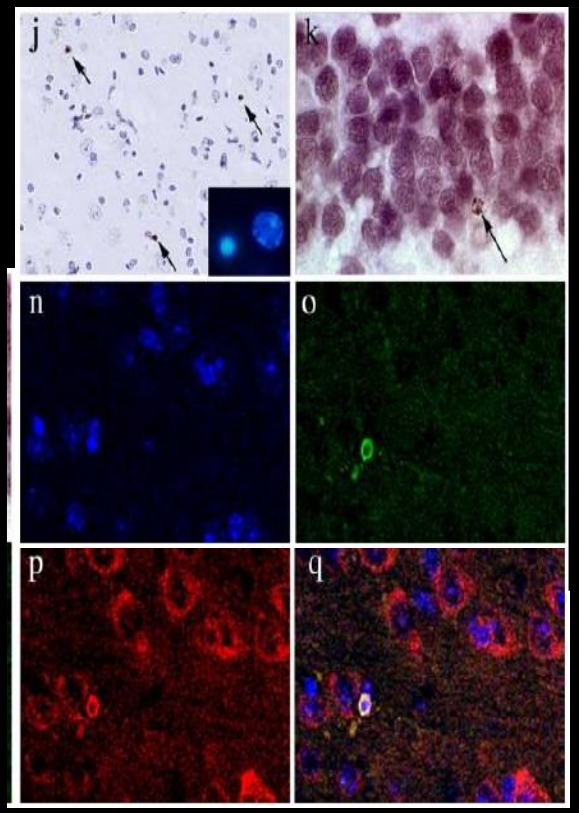
Daniel H. J. Davis,[1,2] Graciela Muniz Terrera,[3] Hannah Keage,[1,4] Terhi Rahkonen,[5] Minna Oinas,[6,7] Fiona E. Matthews,[3] Colm Cunningham,[8] Tuomo Polvikoski,[9] Raimo Sulkava,[10] Alasdair M. J. MacLullich[2,11] and Carol Brayne[2]

# Systemic LPS (500 µg/kg) induces neuronal apoptosis and accelerates decline

**Table 2. Numbers of apoptotic cells[a] counted per coronal section at hippocampal level**

| Animal group | TUNEL-positive cells | Activated caspase-3-positive cells |
|---|---|---|
| NBH | 5.3 ± 0.2 ($n$= 3) | ND |
| ME7 | 26.8 ± 1.6 ($n$= 3) | ND |
| NBH+LPS | 6.8 ± 0.5 ($n$= 5) | 1.4 ± 0.7 ($n$= 5) |
| ME7+LPS | 50.2 ± 2.3 ($n$=9)[b] | 12.2 ± 2.0 ($n$=5)[b] |
| ME7+saline | 27.8 ± 3.0 ($n$= 5) | 6.6 ± 1.3 ($n$= 6) |

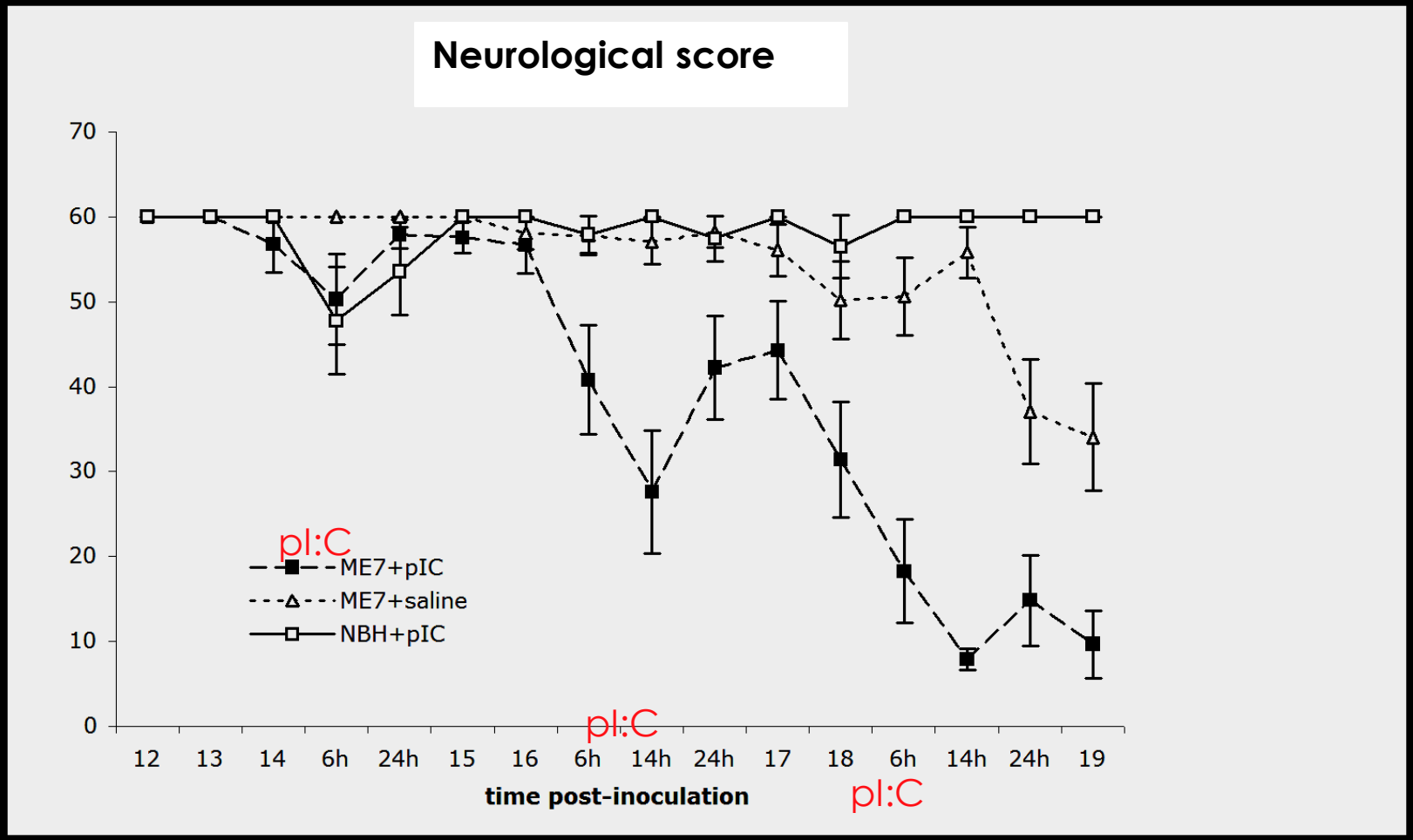



Cunningham et al., J. Neurosci 2005
Cunningham et al., Biol. Psych 2009

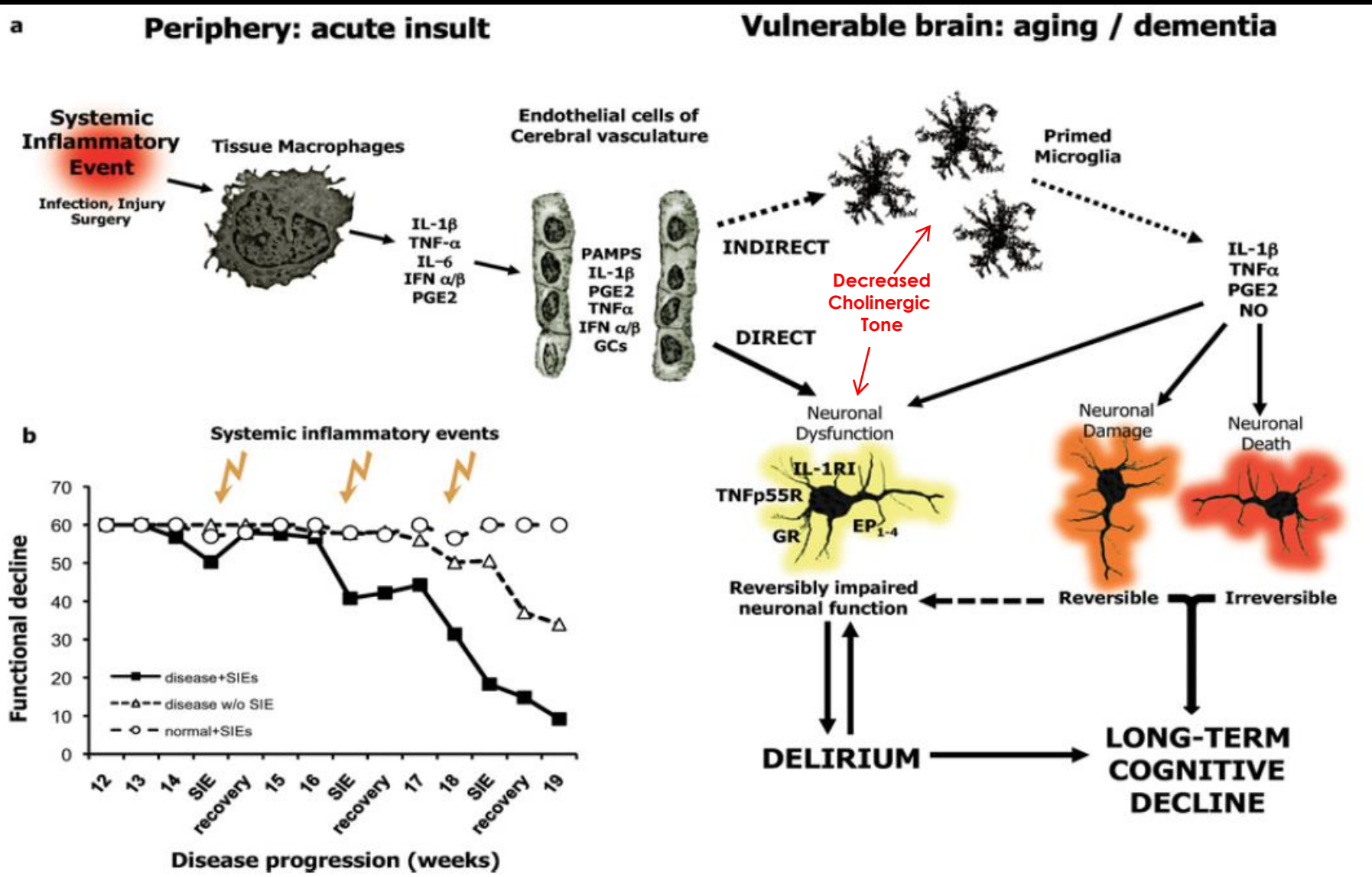
# Poly I:C / TLR3 activation

(systemic TNF-α, IFN-β, IL-6)




Field et al., Brain, Behavior and Immunity, 2010

**The injury remains after the delirium passes**




Cunningham, Biochem Soc Transactions, 2011

# Summary

- Systemic inflammation induces mild reversible and adaptive effects in the normal healthy brain
- When superimposed on the frail (or prior cognitively impaired) brain, if can induce robust 9and reversible) cognitive dysfunction such as delirium and post-operative cognitive dysfunction
- These insults can also cause acute brain injury and significantly contirbute to cognitive decline (including acceleration of dementia)
- Intervening in, or preventing, the acute process may also offer significant benefits against the progression of dementia
- IL-1 and prostaglandins have significant roles in these acute events