

Inflammatory mediators in delirium: Where the neural circuitry of sickness syndrome and dementia meet

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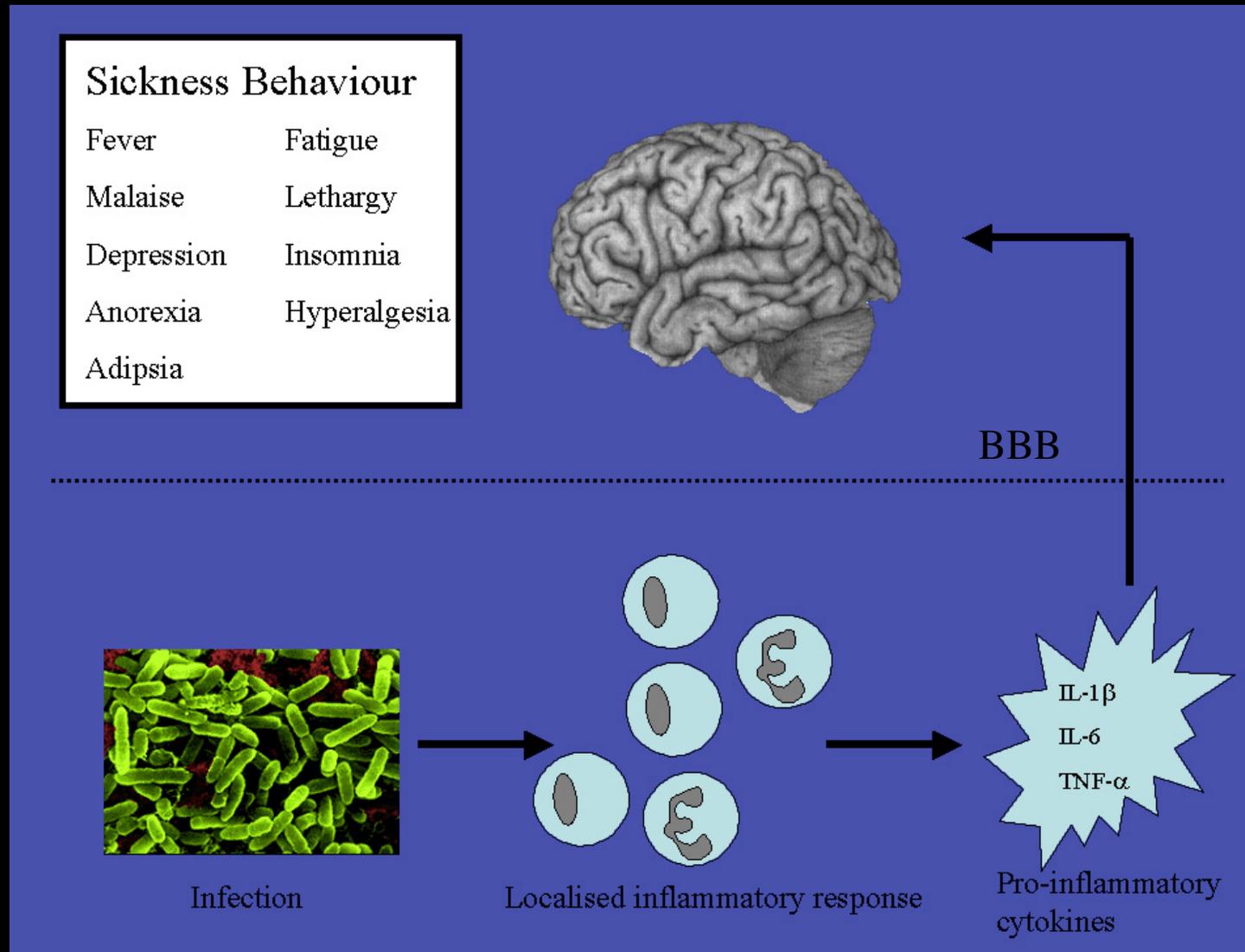
Disclosures

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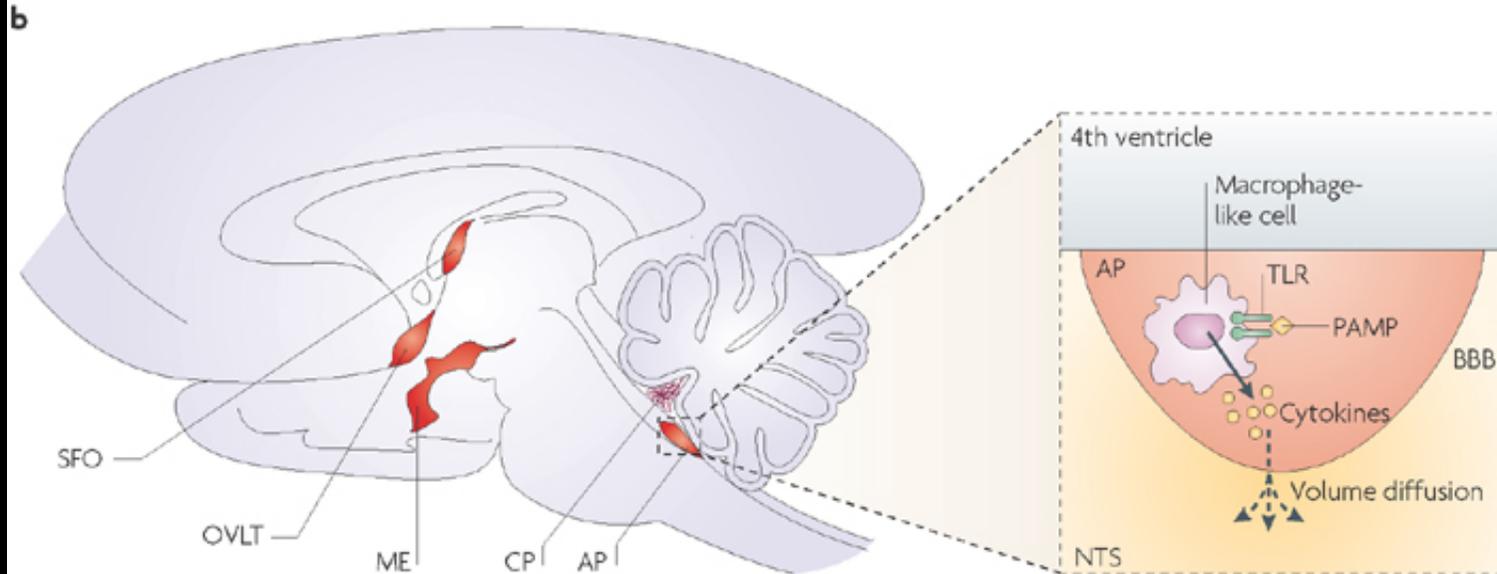
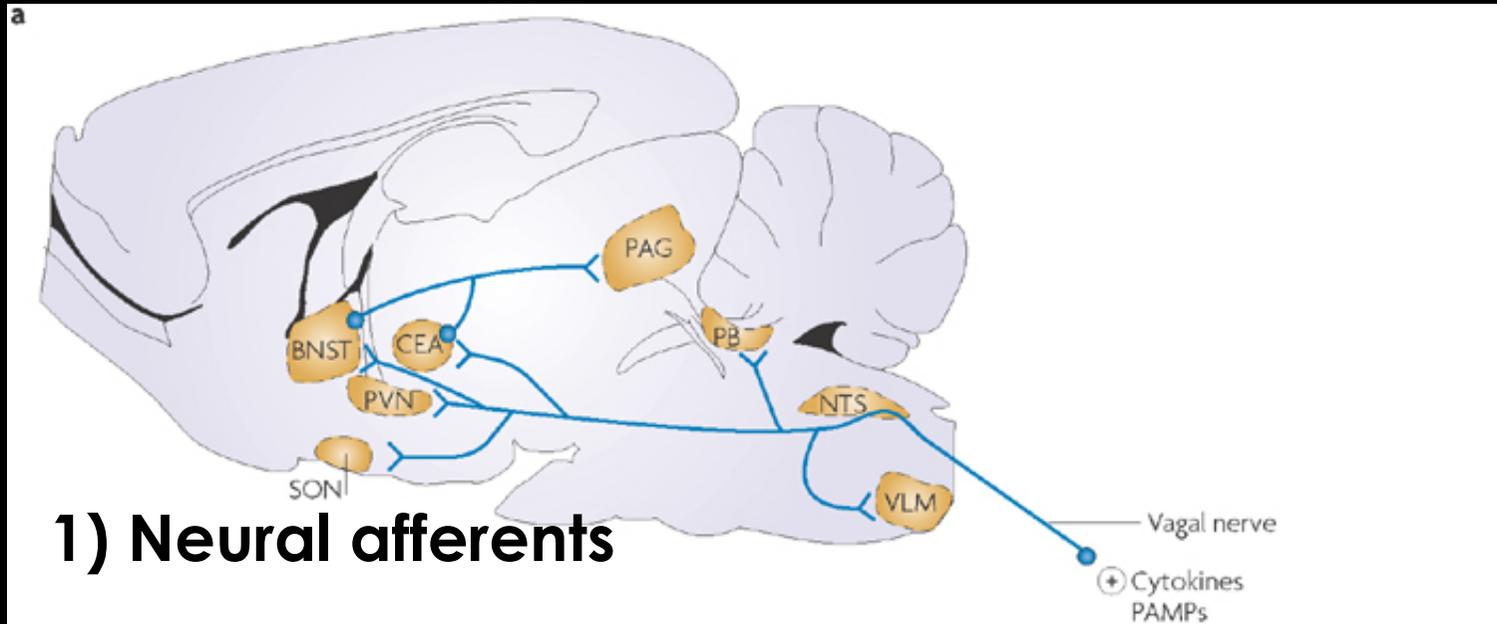
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Systemic inflammation signals to the healthy brain



And can do so across an intact BBB via multiple routes



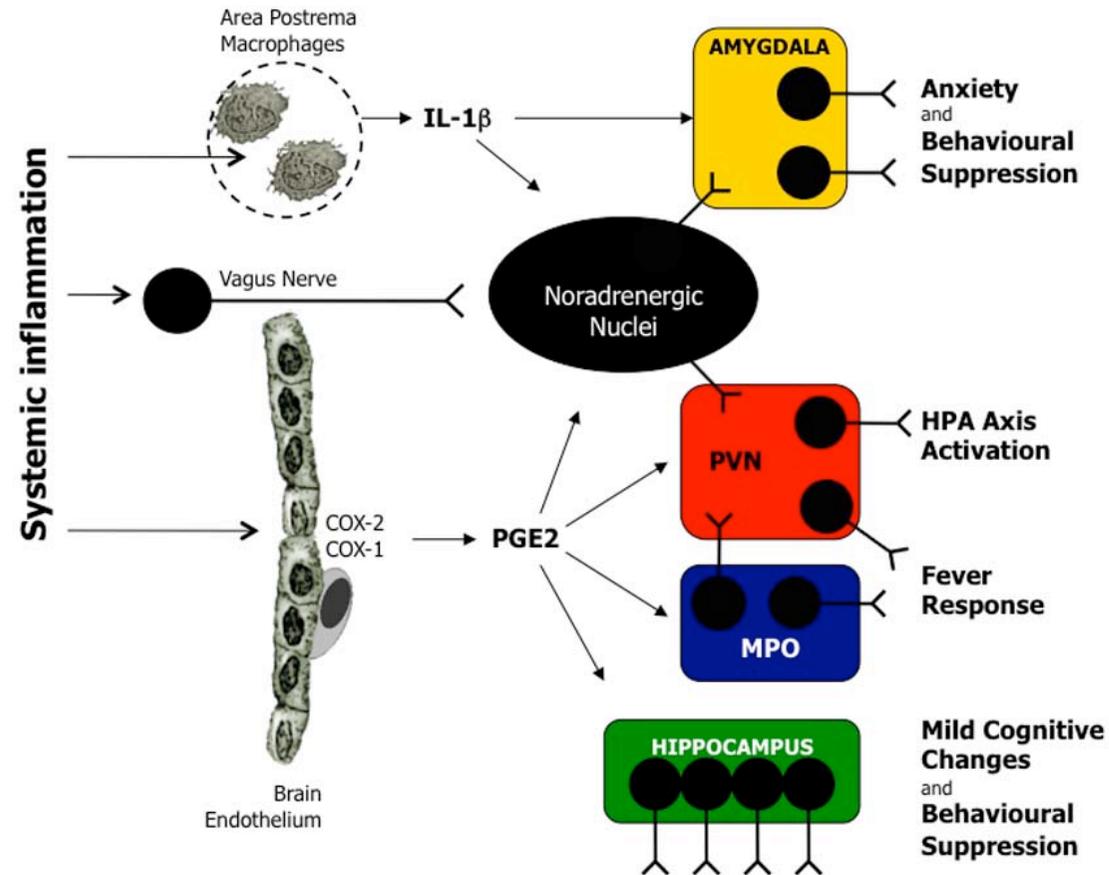
3) Brain endothelium

2)

1)

3)

ADAPTIVE SICKNESS BEHAVIOUR RESPONSE (Rodents)



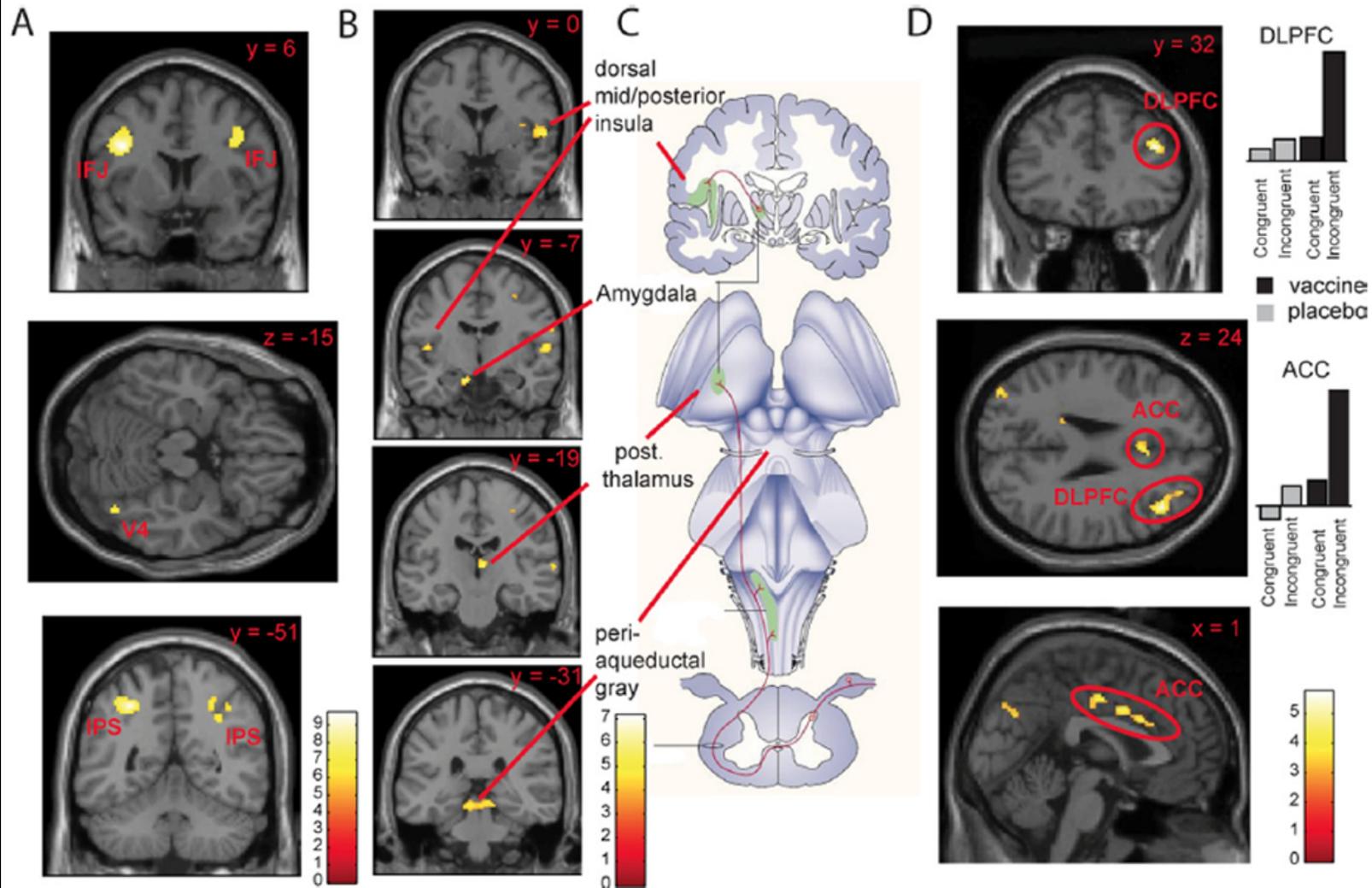
Also Saper, 2012

Cunningham & MacLulich, BBI, 2013

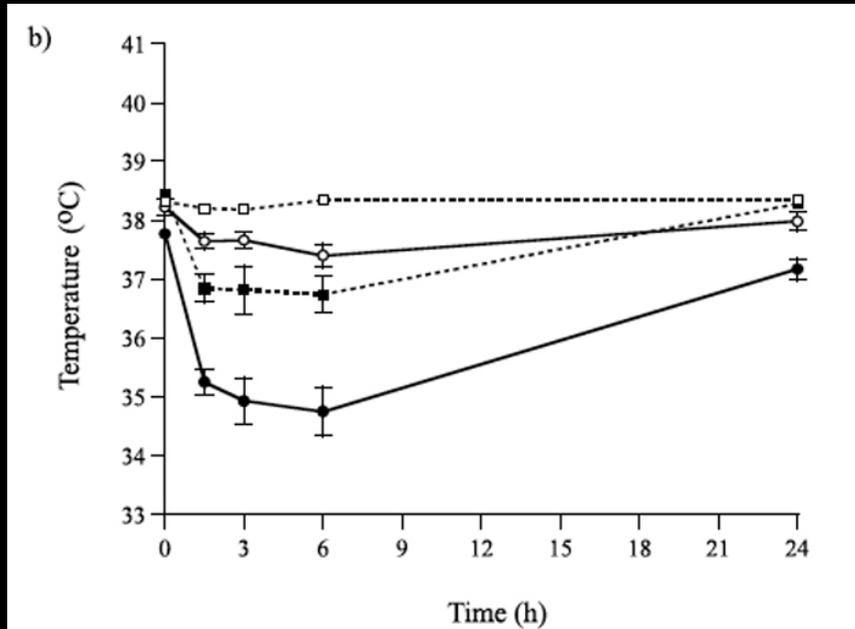
Sickness behaviour neurocircuitry is very similar in humans

N.A. Harrison *et al.*

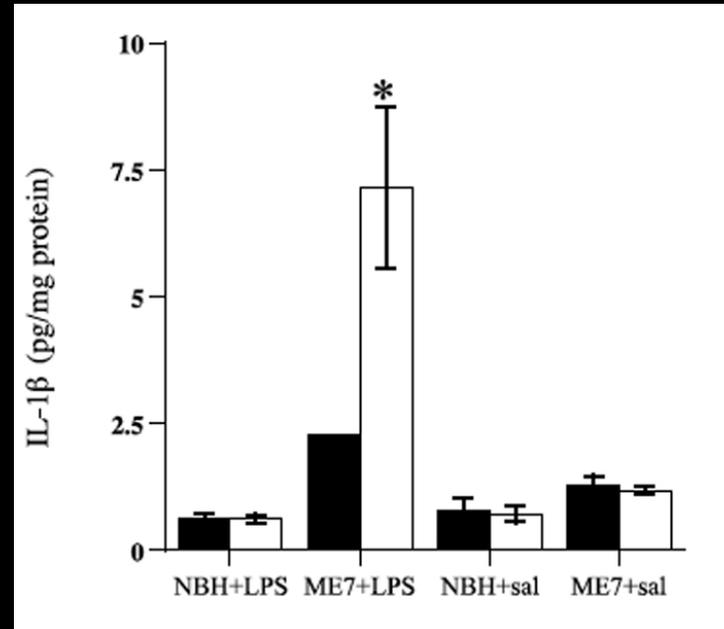
BIOL PSYCHIATRY 2009;66:415–422 419



Sickness responses are exaggerated in animals with prior pathology



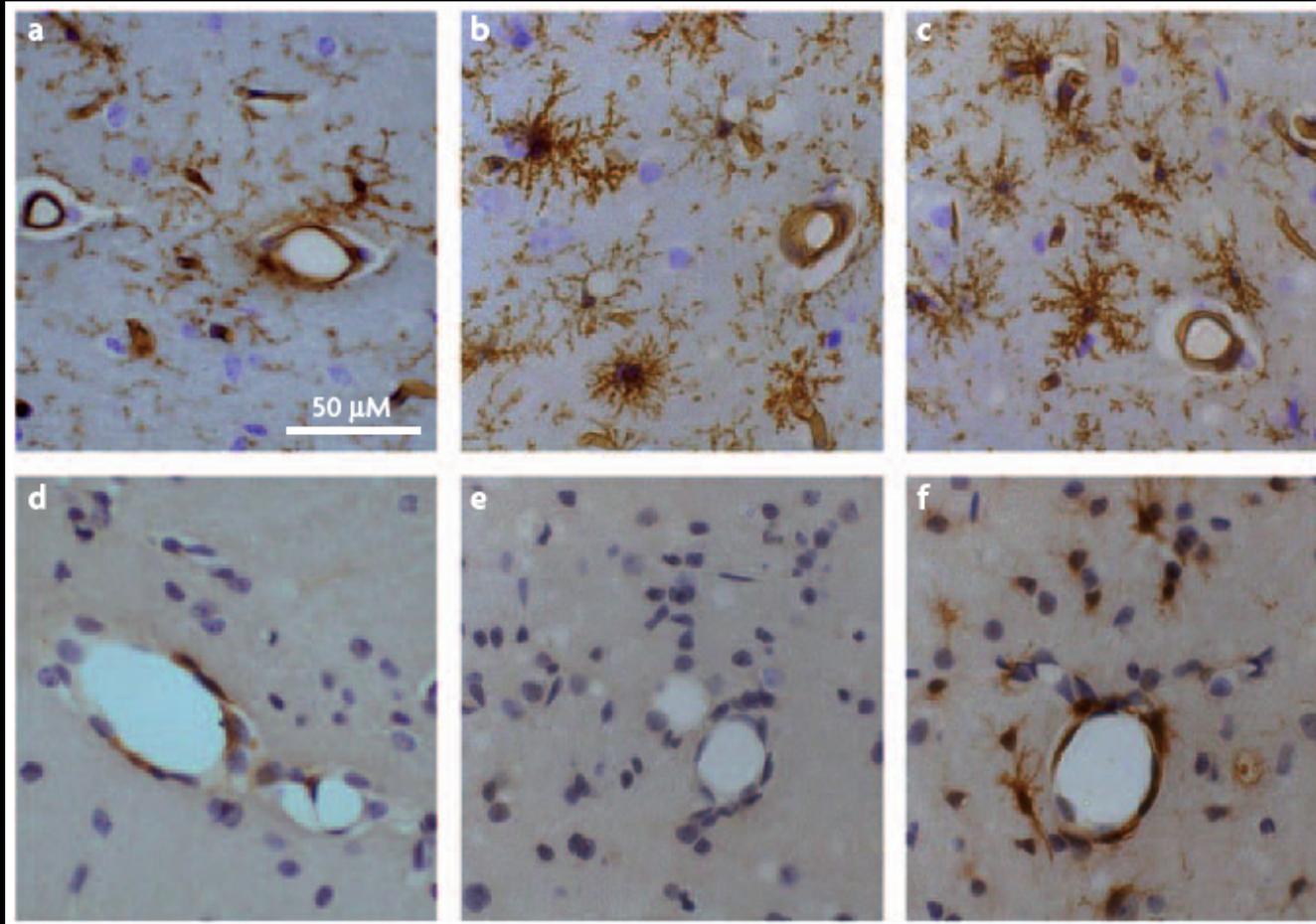
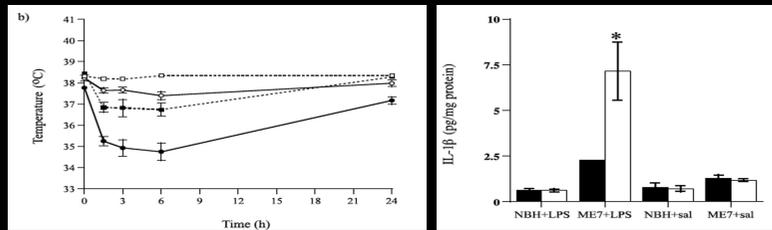
Hypothermia



IL-1 β expression

Combrinck et al., Neuroscience, 2002

Microglial priming

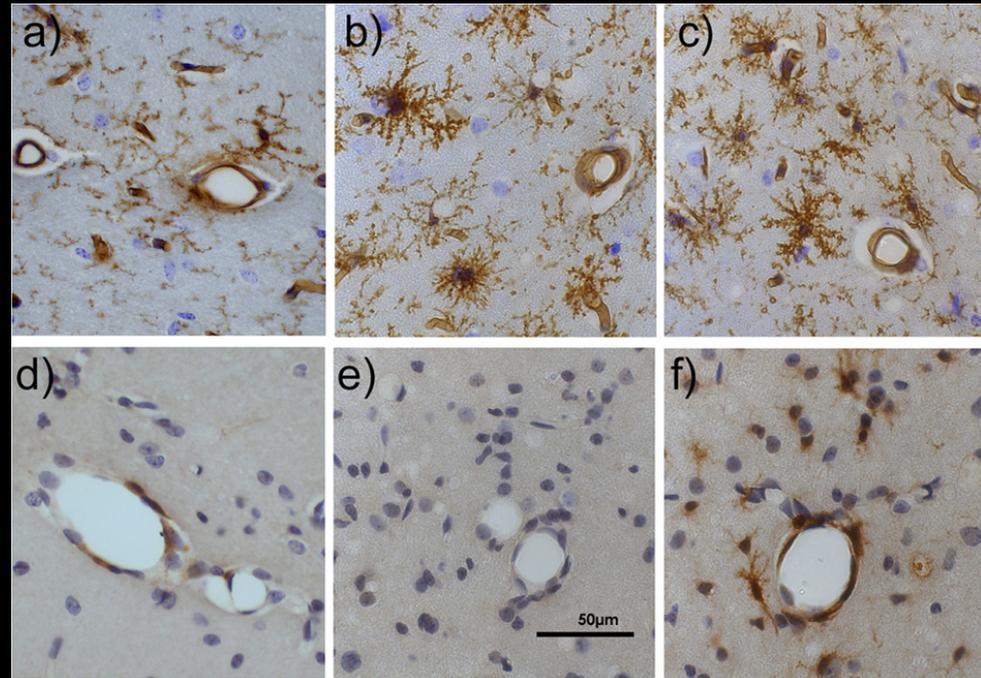


Primed microglial show exaggerated IL-1 responses to subsequent stimulation with either central or systemic inflammation

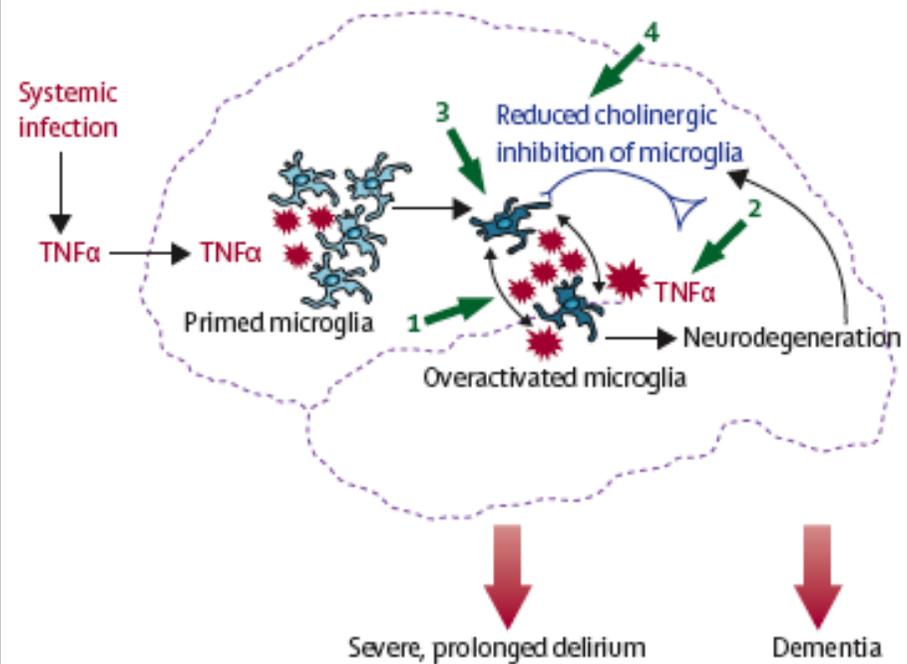
Cunningham et al., J. Neurosci, 2005
Perry et al., Nature Rev. Imm, 2007

Microglial Priming

Cunningham et al.,
J Neuroscience, 2005



Old age, incipient neurodegenerative disease, or anticholinergic drug treatment



Van Gool et al.,
Lancet, February 2010

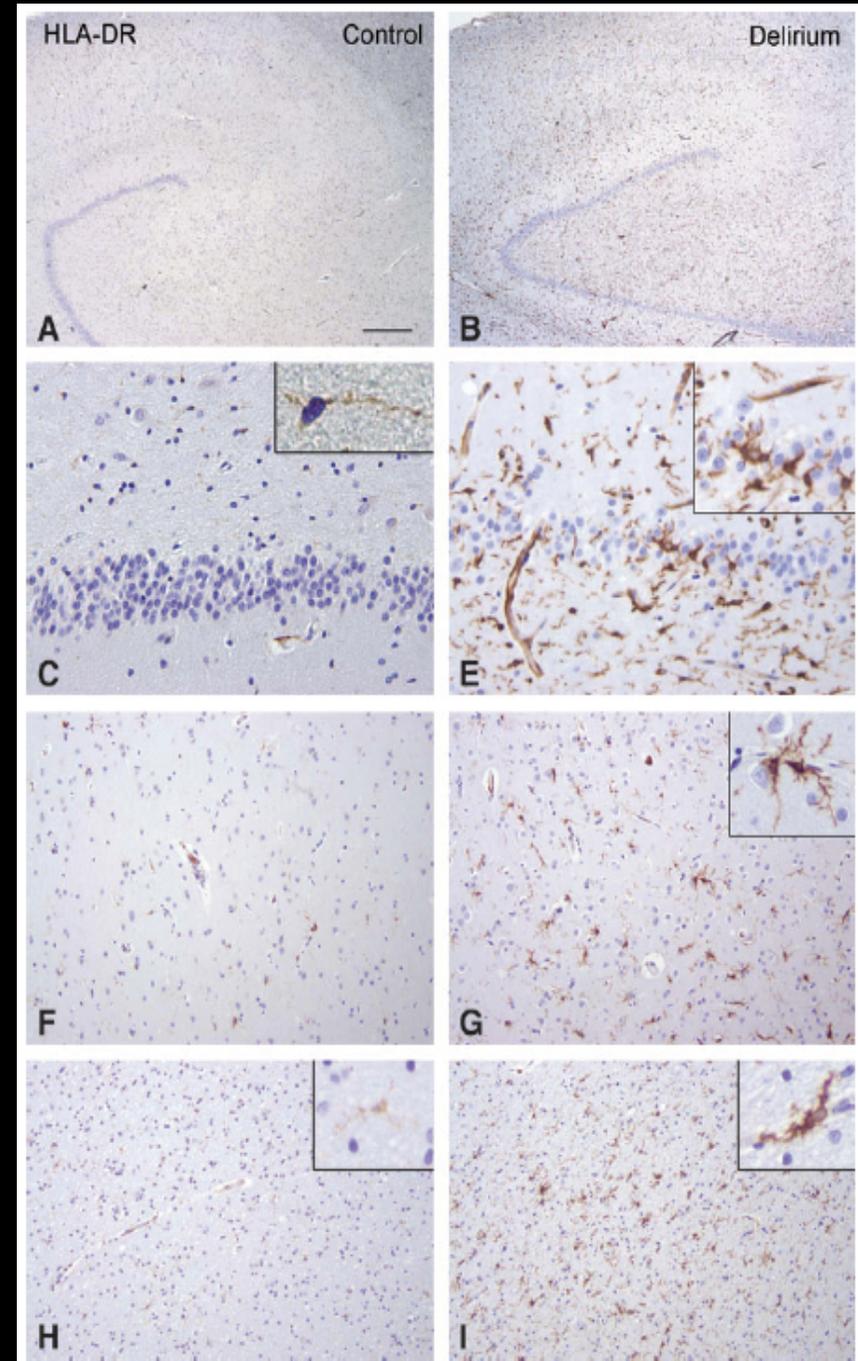
Microglial activation

Is increased in delirium versus non-delirium (multiple etiologies)

Van Munster et al., 2011

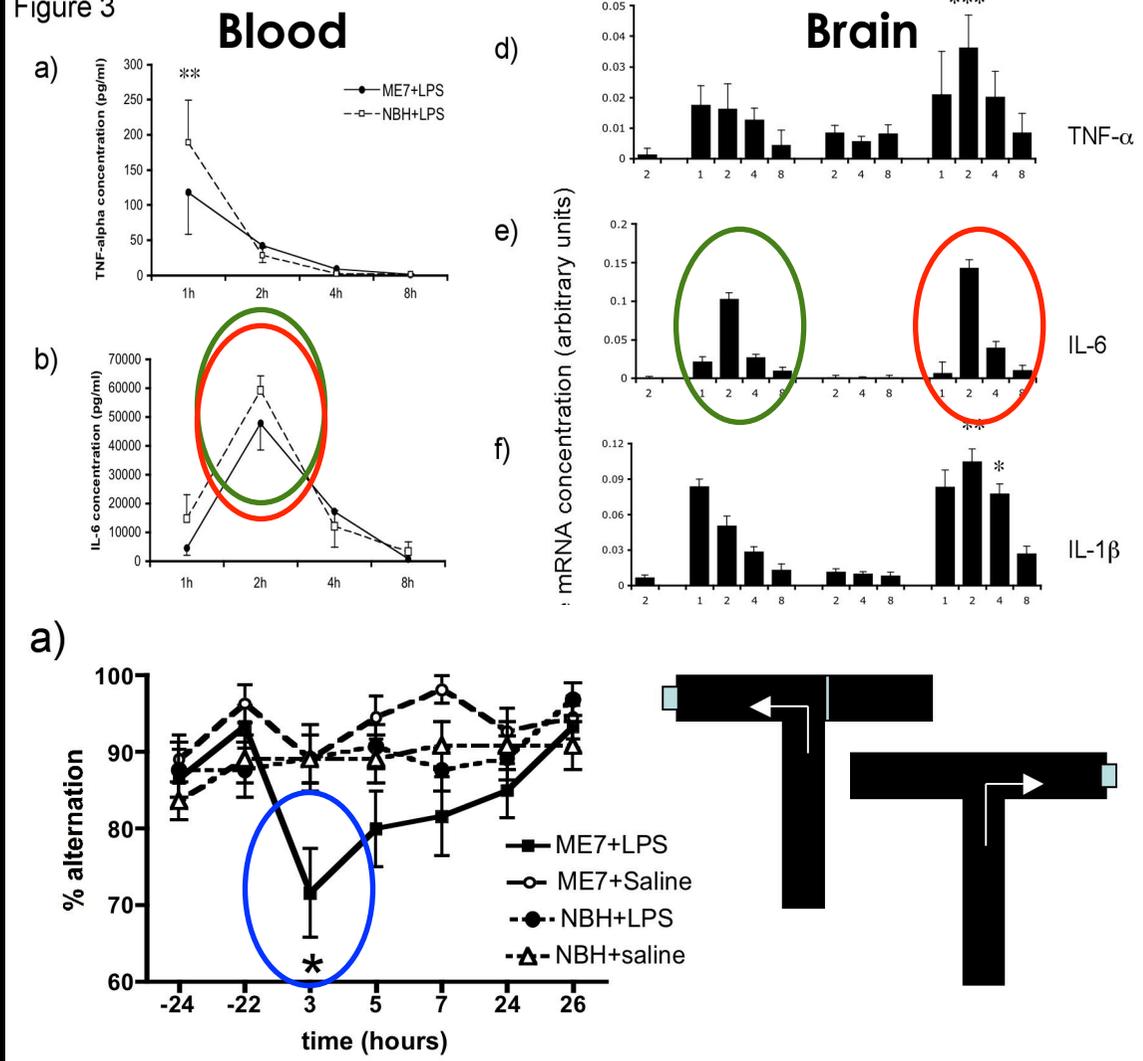
But would like to understand the role of microglia and of inflammatory mediators in delirium

Need model systems!



Model system 1: mild LPS superimposed upon neurodegenerative disease

Figure 3



Here are some data from our First model of delirium during Dementia

Although LPS induces IL-6 equally in **normal** animals and those with **prior neurodegenerative disease** only those with prior degeneration show **acute cognitive deficits** upon LPS challenge.

This is an important prediction made by the model because this sort of weak association between IL-6 and delirium has frequently been observed in the clinical literature.

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

Inflammatory Marker	Preoperative		Postoperative		P-Value [†]
	Median (IQR)	P-Value*	Median (IQR)	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

The prior point is emphasized here: Surgery always induces IL-6 and IL-8 but these are not higher in delirium patients here and are rarely very clearly different in delirium with respect to controls. Therefore I would argue that the prior condition of the brain (IE PREDISPOSITION) is the key factor in whether systemic inflammation induces delirium or not.

Association versus Causation

IL-6, IL-8: Biomarkers or predictors of delirium OR just measures of severity of systemic inflammation ?

Molecules like IL-1 and TNF- α are more potent

Are systemic or central levels more important?

CSF levels of IL-8 associated with delirium

CSF levels of IL-1 associated with delirium

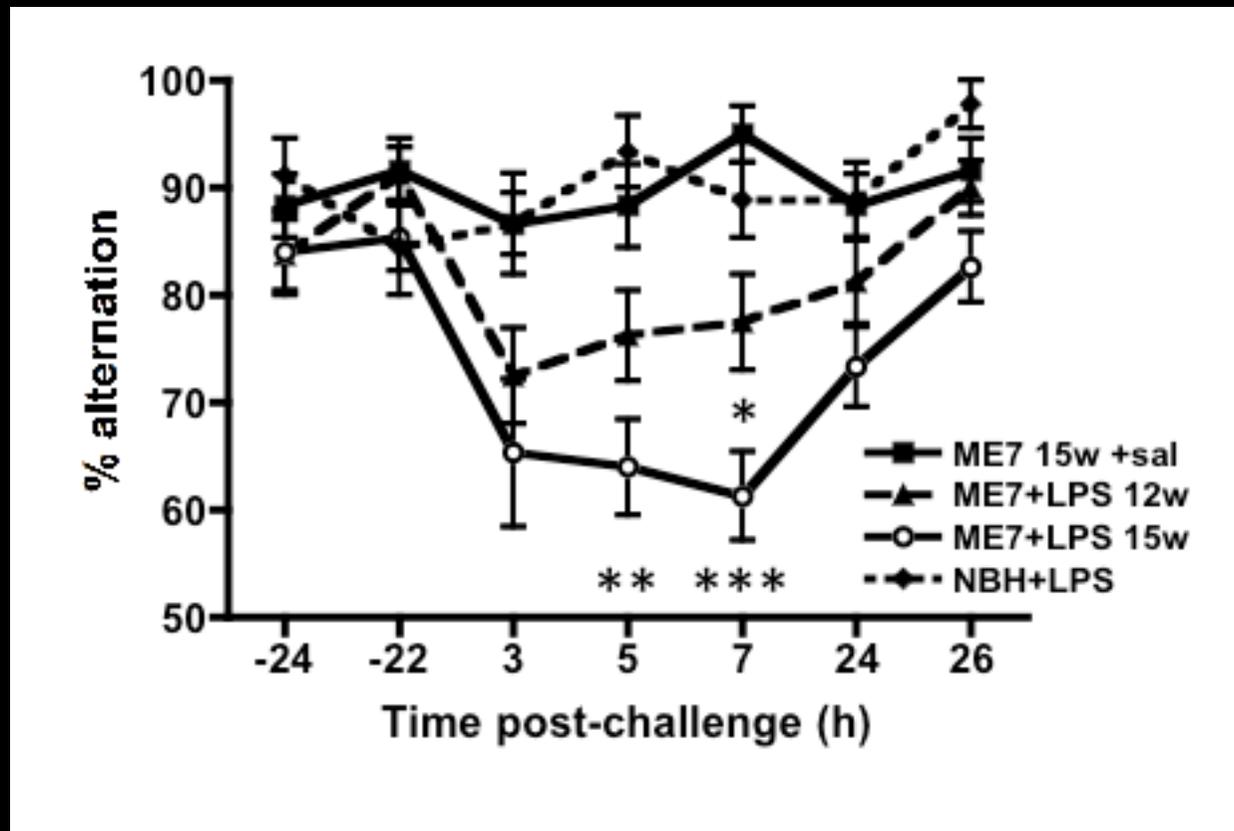
(MacLulich et al., 2011, Cape et al., in revision)

To establish causation: need model systems

(Systemic inflammation impact on vulnerable brain)

Predisposition is the key determinant

Increasing severity of the predisposing factor (underlying degenerative disease), progressively increases risk of acute cognitive dysfunction upon systemic inflammation

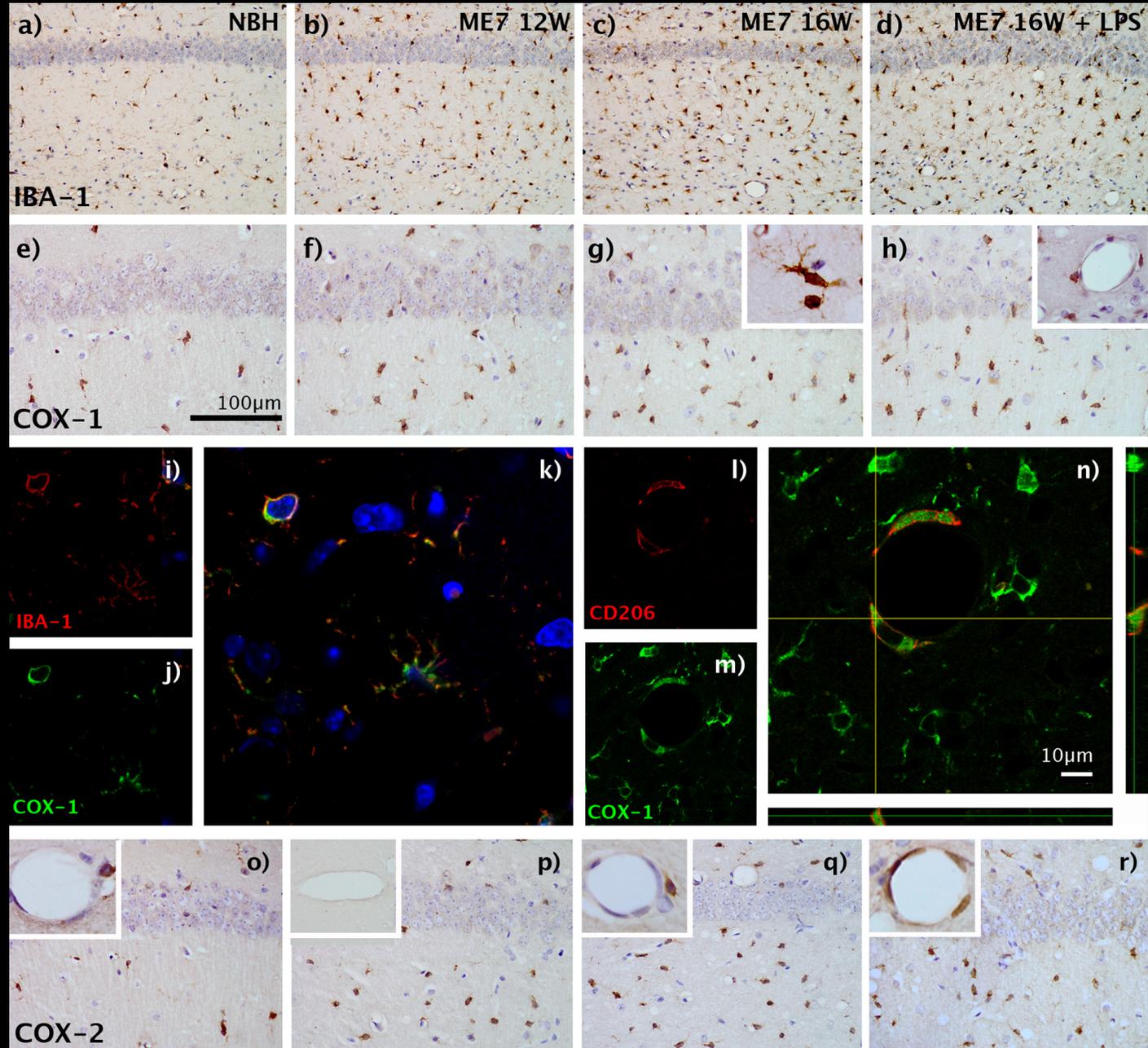


Griffin et al., J. Neurosci 2013

Microgliosis

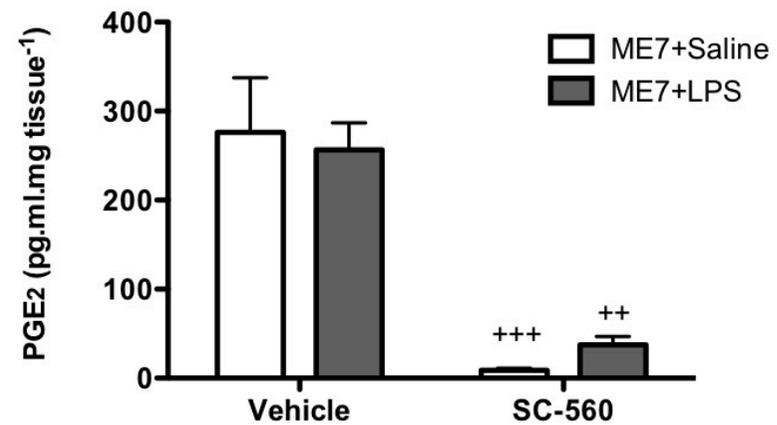
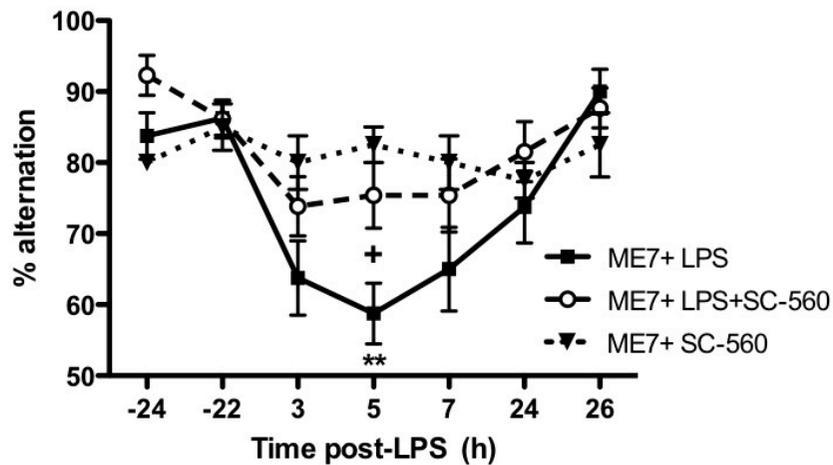
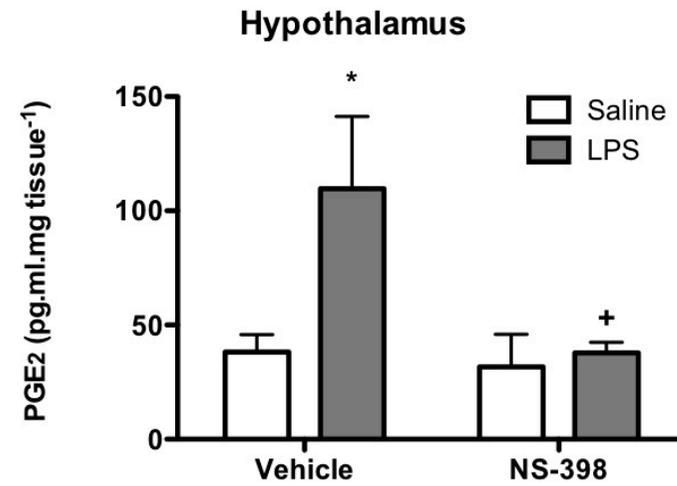
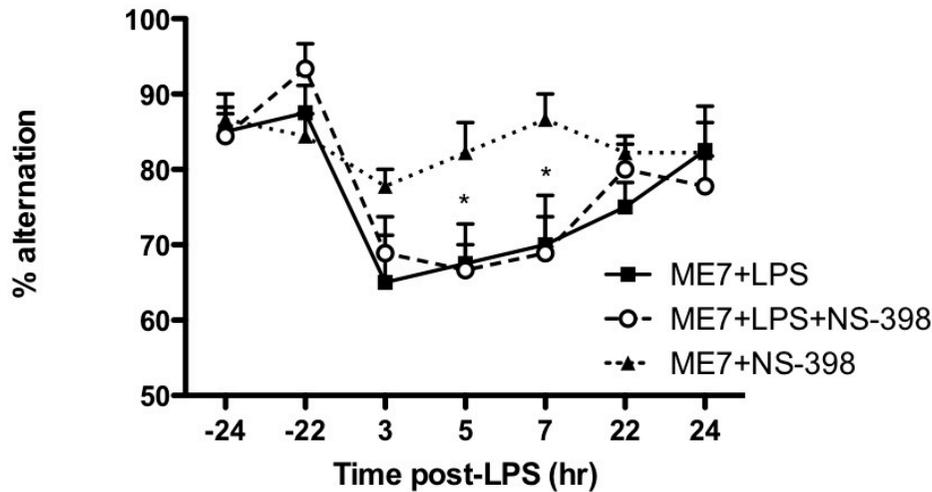
Increases
NBH < 12 < 16w

Disease induces
COX-1 in
microglia

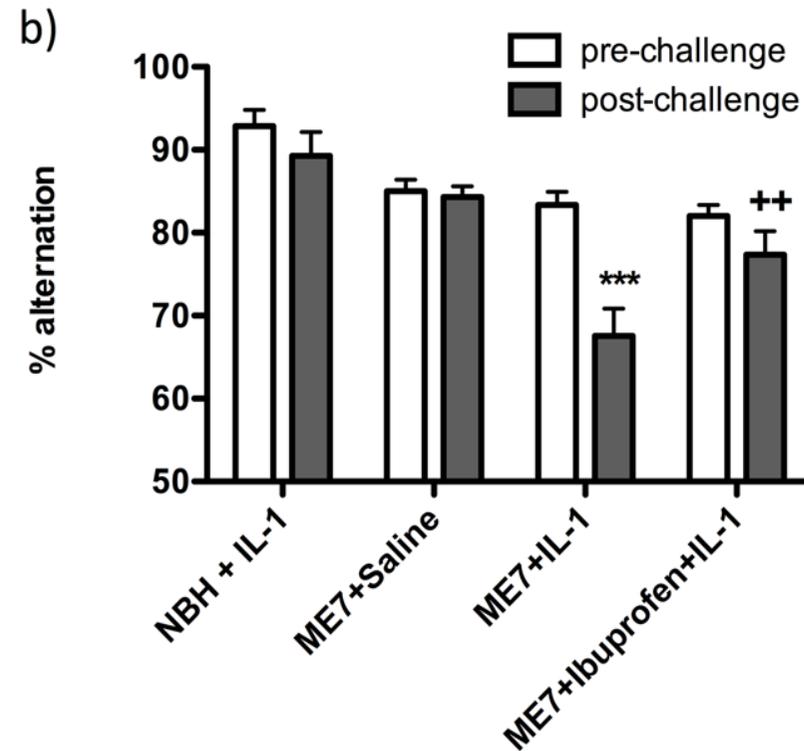
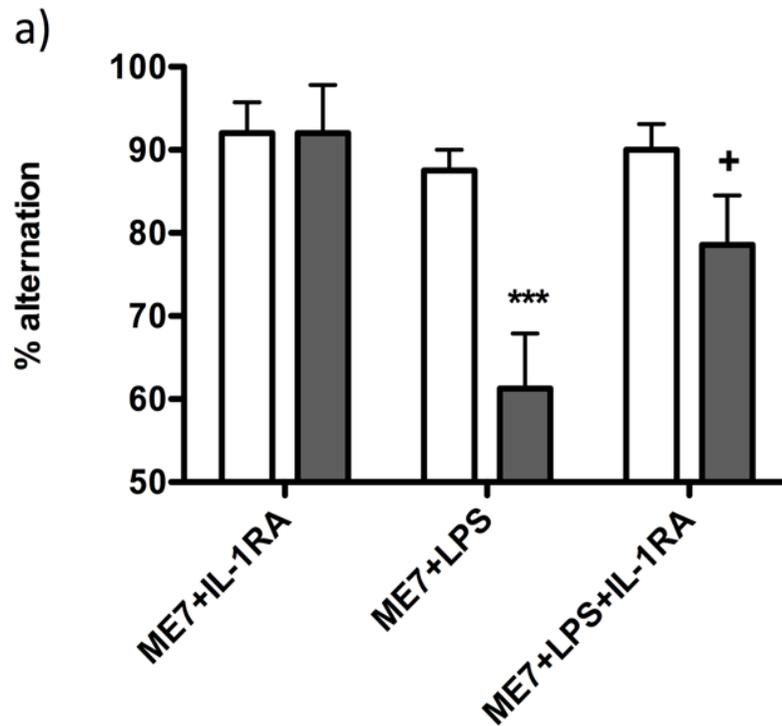


LPS induces
COX-2 at
endothelium

COX-1, but not COX-2 inhibition protects against LPS-induced cognitive dysfunction

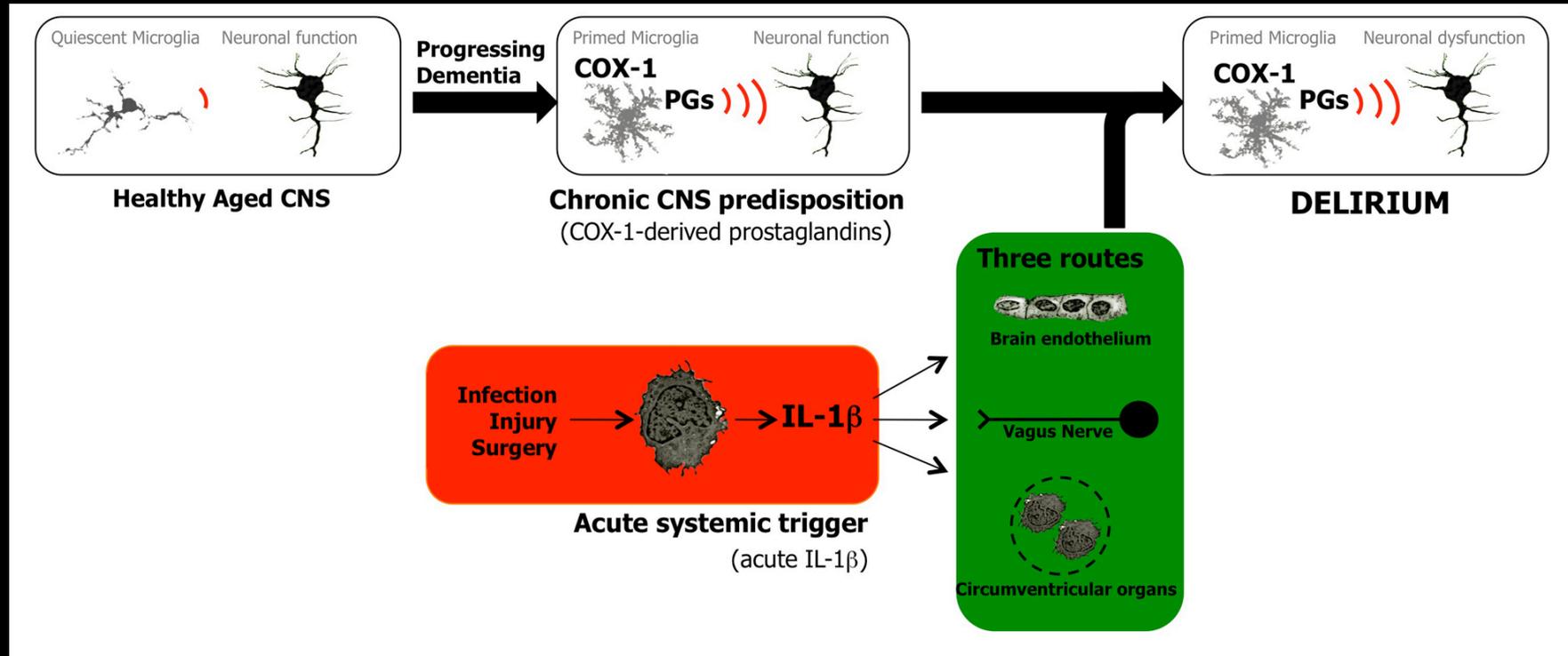


- 1) Systemic IL-1RA is protective
- 2) IL-1 β is sufficient
- 3) Ibuprofen is protective



Griffin et al., J. Neurosci 2013

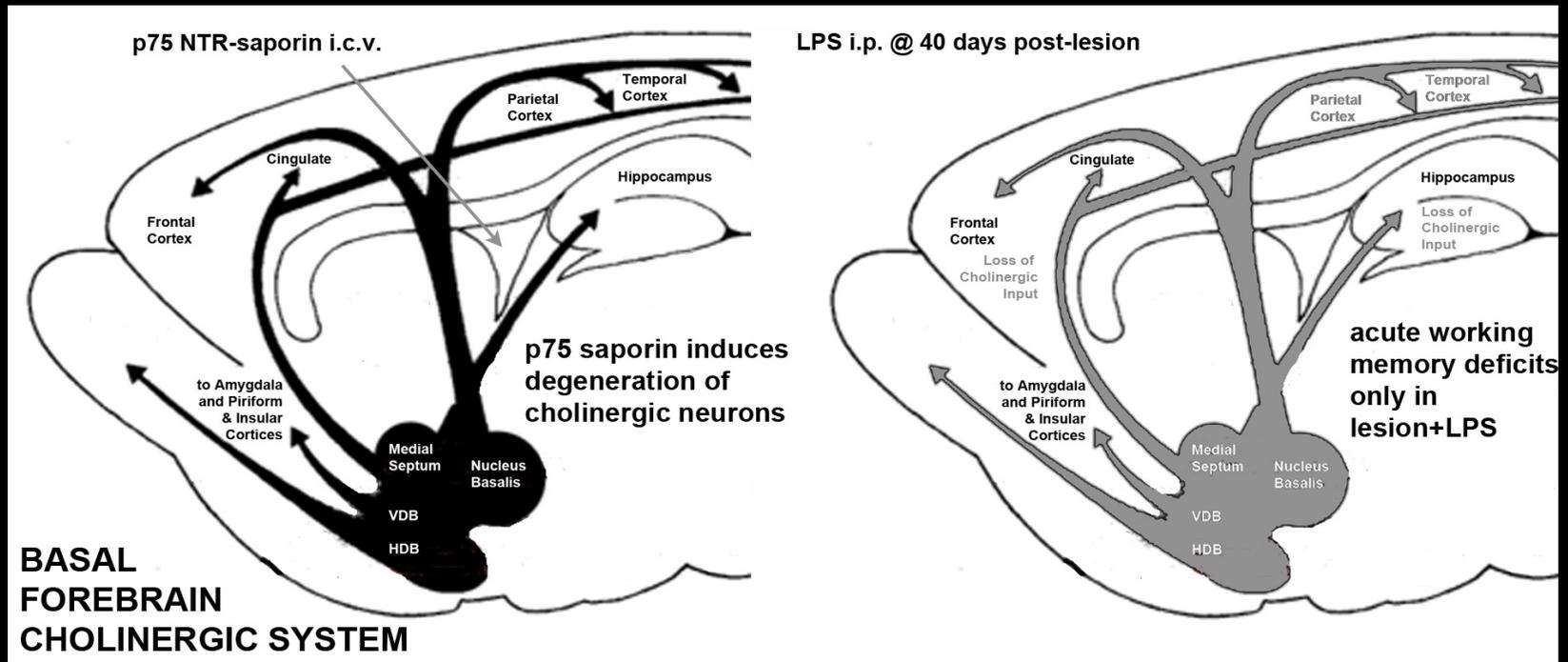
BAD SYNERGY: IL-1 and prostaglandins



Annals of Delirium, November 2013

This is a discussion/digest of Griffin et al., 2013, Journal of Neuroscience written for clinical researchers not familiar with reading mouse inflammatory and experimental psychology studies.

Model system 2: p75^{NTR}-saporin lesion of basal forebrain to produce a hypochoolinergic state. THEN challenge with low dose LPS



ICV SURGERY

T-maze training

LPS & T-maze performance

Perfusion

Recovery

Train to > 80% performance

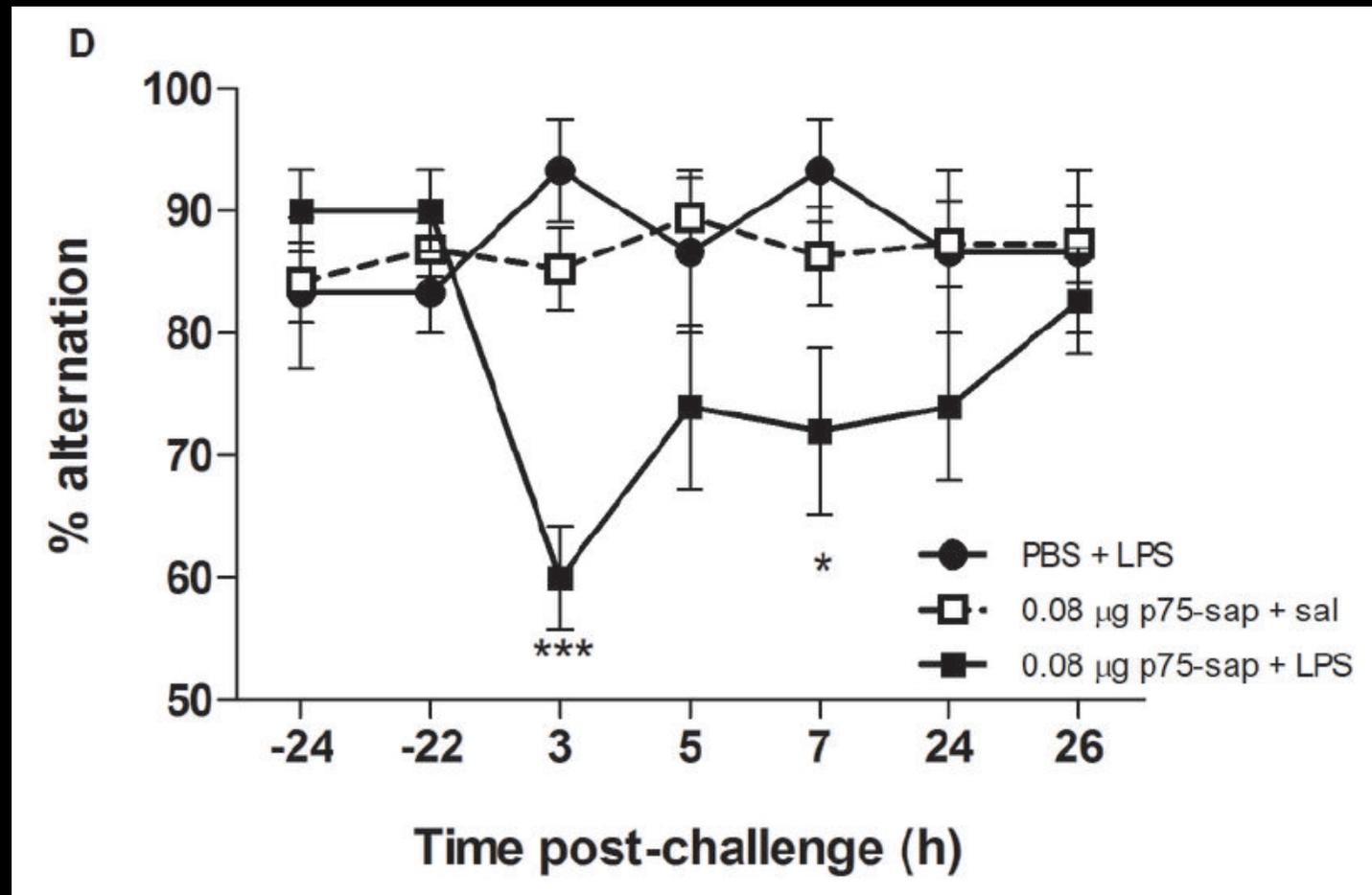
day 1

day 10

day 35

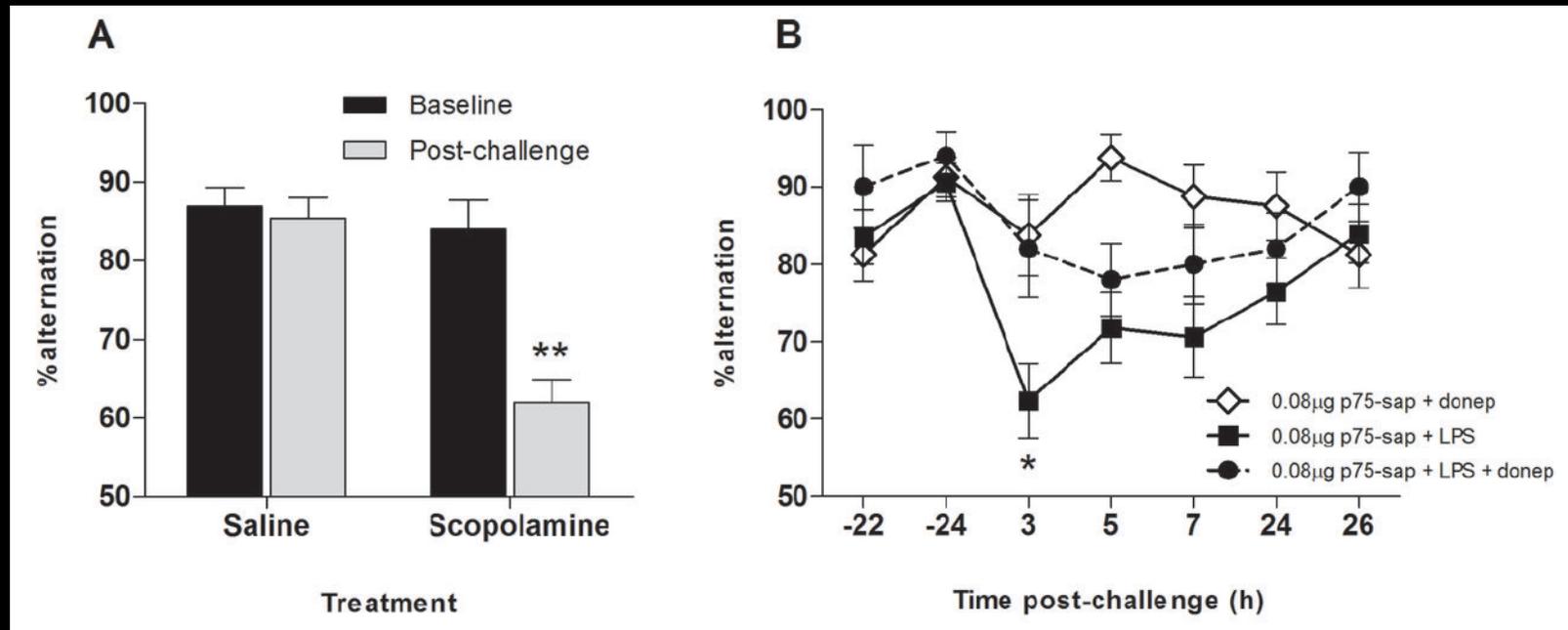
day 40

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



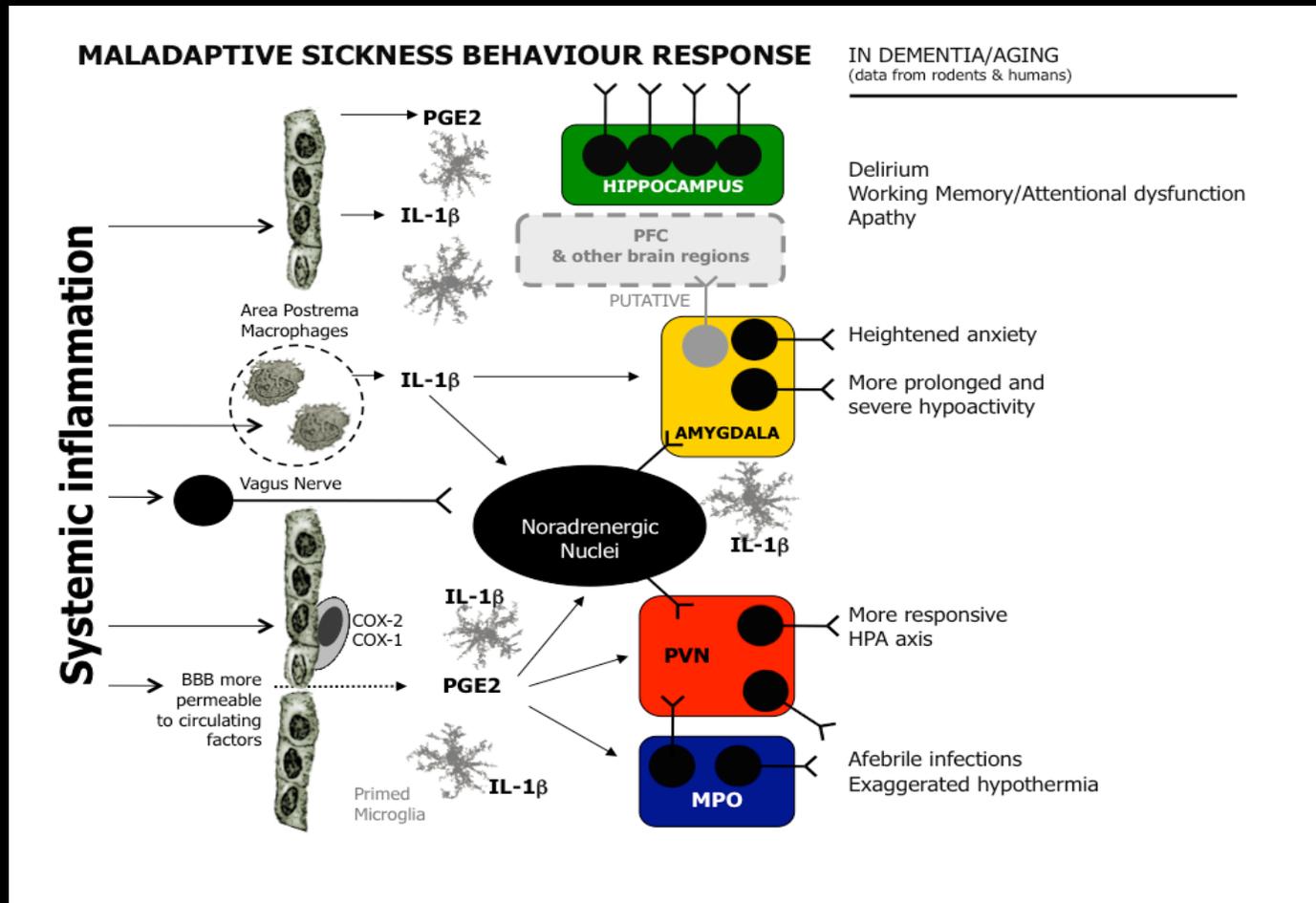
1) T-maze performance is cholinergic dependent

2) Donepezil protects against LPS-induced deficits



Field et al., J Neurosci 2012

Rivastigmine was not protective in ICU delirium but unlikely that those patients had underlying cholinergic deficiency. Once again, we have to be careful about generalising across different delirium etiologies



Cunningham & MacLulich; Brain, Behavior & Immunity, 2013

So, we can return to our schematic depicting sickness behaviour neurocircuitry and update it to show how many of these aspects are exaggerated during aging and neurodegenerative disease AND to emphasise that key mediators such as IL-1b and prostaglandins are CAUSATIVE both in sickness behaviour and in the acute cognitive deficits that I have shown you in our 2 model systems today

Summary

- Delirium is not a single entity - need to study routes to dysfunction in multiple etiologies and not over-generalise
- Can separate PREDISPOSING (COX-1, microglia, loss of ACh tone) vs. TRIGGERING factors (acute IL-1 β , TNF- α , medication changes)
- The neurocircuitry of sickness behaviour syndrome, and its exaggeration in age/dementia, make useful predictions that should be investigated
- Urgent things to do!

Future directions/urgent needs

There is an urgent need to scale up preclinical models to help elucidate delirium pathophysiology in multiple settings.

There is a need to coordinate/reconcile with the HPA axis changes

Have to refine neuroinflammatory hypotheses and test them

Examination of interaction of these systems with drugs/medications and neurotransmitter systems (ACh work begun but need to think about NE, GABA, Glutamate, DA)

Need to disentangle the impact of systemic inflammation on acute cognitive dysfunction from its effects on long-term sequelae.