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

Abstract

It is widely accepted that inflammation plays some role in the progression of chronic neurodegenerative diseases such as AD (Alzheimer's disease), but its precise role remains elusive. It has been known for many years that systemic inflammatory insults can signal to the brain to induce changes in CNS (central nervous system) function, typically grouped under the syndrome of sickness behaviour. These changes are mediated via systemic and CNS cytokine and prostaglandin synthesis. When patients with dementia suffer similar systemic inflammatory insults, delirium is a frequent consequence. This profound and acute exacerbation of cognitive dysfunction is associated with poor prognosis: accelerating cognitive decline and shortening time to permanent institutionalization and death. Therefore a better understanding of how delirium occurs during dementia and how these episodes impact on existing neurodegeneration are now important priorities. The current review summarizes the relationship between dementia, systemic inflammation and episodes of delirium and addresses the basic scientific approaches currently being pursued with respect to understanding acute cognitive dysfunction during aging and dementia. In addition, despite there being limited studies on this subject, it is becoming increasingly clear that infections and other systemic inflammatory conditions do increase the risk of AD and accelerate the progression of established dementia. These data suggest that systemic inflammation is a major contributor to the progression of dementia and constitutes an important clinical target.

Introduction

It has been known for many years that inflammation has a role in the progression of AD (Alzheimer's disease). Patients taking NSAIDs (non-steroidal anti-inflammatory drugs) for the amelioration of rheumatoid arthritis are significantly protected against the subsequent development of AD [1]. These findings, first made more than 20 years ago, have been replicated many times, but prospective studies using these and similar drugs have not had significant beneficial effects for patients [2,3]. Nonetheless, the original findings have launched an enormous field of research into the nature of the CNS (central nervous system) inflammatory response during AD and this field continues apace. This research, unsurprisingly, has been firmly focused on the brain macrophage population, the microglia, since these cells clearly surround the amyloid plaques that become deposited in the brain.

However, one aspect of the rheumatoid arthritis studies that has received less attention is the fact that patients who were protected against development of AD, benefited from a therapy that targeted peripheral inflammation. Whether reducing peripheral inflammation contributed significantly to the protective effects observed has received remarkably little discussion. It is increasingly clear that major risk factors for the development of AD such as aging, obesity, diabetes, hypertension and smoking [4] all comprise a significant increase in systemic inflammatory markers [5]. While such systemic inflammatory activity is unlikely to provide the major explanation for the brain pathology associated with AD, there are good reasons to believe that systemic inflammation contributes to the progression and severity of this pathology.

Perhaps the strongest evidence for this exacerbation of dementia by systemic inflammation lies with the problem of delirium. Delirium is an acute and profound disturbance of thinking, memory, orientation, perception and emotion [6,7]. Dementia and aging are the biggest predisposing risk factors for suffering episodes of delirium and in this population systemic inflammation, caused by infection, injury or surgery, is one of the major triggers [8]. In general, severe stimuli are required to precipitate delirium in healthy populations, whereas much milder inflammatory stimuli can trigger a delirious episode in the elderly and demented [9].

It is now established that an episode of delirium is associated with a higher risk of long-term cognitive impairment [10,11], acceleration of dementia [12] and shortens time to permanent institutionalization and to death [13]. Therefore, if infection superimposed on dementia predicts delirium and delirium during dementia predicts more rapid decline then this suggests that those insults that can cause delirium may directly exacerbate the underlying disease (Figure 1). In recent years, we and our collaborators have used animal
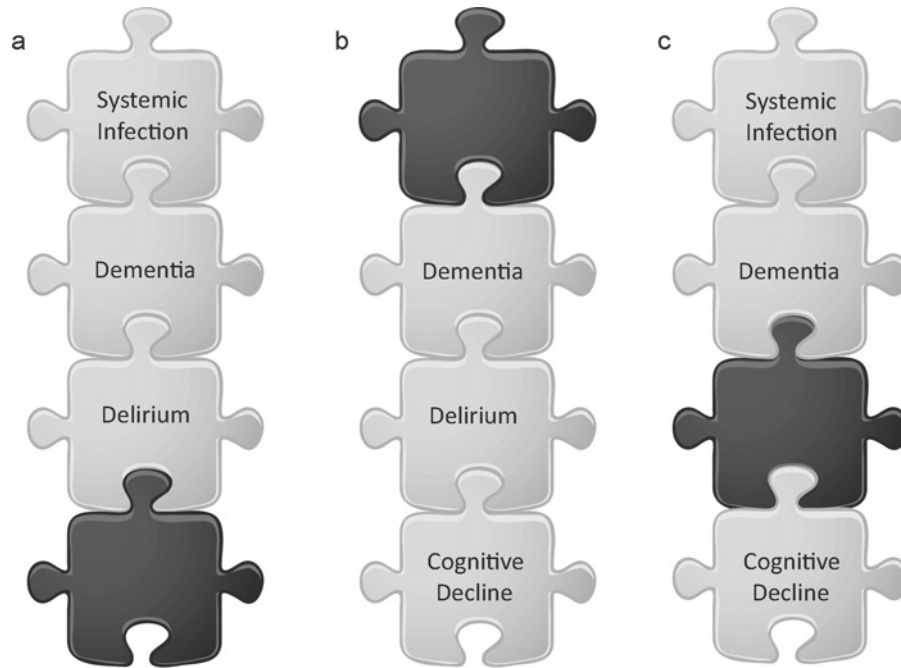
Figure 1 | Systemic inflammation, delirium and cognitive decline

(**a**) It is well established that systemic inflammation in those with dementia frequently leads to delirium. (**b**) It is also established that delirium in demented patients tends to exacerbate disease progression. (**c**) Thus insults that often trigger delirium may accelerate disease, in the presence or absence of the delirious episode. However, little research has addressed this scenario.

models to show that acute systemic inflammatory activation superimposed on existing progressive neurodegeneration can produce acute exacerbation of behavioural and cognitive function, resembling delirium, and can also induce acute neuronal death and accelerate the progression of disease. Similar findings have been made by other groups using various animal models of aging and disease and this nascent field is beginning to provide evidence that this exacerbation of CNS disease by systemic inflammation is a significant phenomenon, and one that requires investigation in clinical populations with AD and other chronic neurodegenerative diseases.

Systemic inflammation affects CNS function

It is well known that systemic inflammation, induced by pathogen-associated molecular pattern stimulators of the Toll-like receptors or by pro-inflammatory cytokines and indeed by surgery, can induce a spectrum of changes in CNS function including decreased locomotor activity, social engagement and feeding and also changes in the sleep–wake cycle. These changes may be collectively described as sickness behaviour and largely describe evolutionarily conserved behavioural and metabolic responses to infection, effected to conserve energy and minimize the spread of infection. This

literature has been extensively reviewed elsewhere [14]. There is also robust evidence that these inflammatory insults have a deleterious effect on the consolidation of new memories in contextual fear-conditioning experiments (see [15] for a review), but these studies do not explain why relatively banal infections such as urinary tract infections in the elderly population produce the profound cognitive changes observed during episodes of delirium, but have limited effects in younger healthy populations.

During the last decade, an emerging literature has begun to attempt to explain this phenomenon of exaggerated CNS effects of systemic inflammation in elderly people and patients with dementia. We have studied the ME7 model of prion disease for many years since it displays robust progressive amyloidosis, microgliosis, synaptic loss, neurodegeneration and progressive affective, cognitive and neurological changes [16–18]. As such, it represents an excellent model system with which to study the natural history of progression of neurodegenerative disease and to examine the impact of environmental influences and insults that are perhaps generic to all chronic neurodegenerative diseases. In 2002, we showed that animals with prior neurodegenerative disease displayed exaggerated sickness behaviour and CNS inflammatory responses to systemic challenge with bacterial LPS (lipopolysaccharide), as a mimic of systemic inflammation [19]. Other groups replicated aspects of these findings in aged rodents [20,21]. The

explanation for this exaggerated CNS inflammatory response appears to lie with the 'priming' of microglial cells, first demonstrated in the ME7 model of prion disease [22]. That is to say, microglial cells are primed by some aspect(s) of neurodegeneration and aging, such that they now show more robust pro-inflammatory responses to subsequent stimulation with bacterial LPS [21,22], bacterial infection [20], double-stranded RNA [23] and perhaps other inflammatory stimuli. Furthermore, it is clear that this priming phenomenon is not specific to prion disease; exaggerated CNS inflammatory responses to systemic inflammatory stimulation have now been demonstrated in several other models of neurodegeneration. These include models of AD [24–26], Parkinson's disease [27,28], brain ischaemia [29], experimental autoimmune encephalitis [30] and Wallerian degeneration [31].

Acute cognitive changes in the presence of prior risk factors: delirium during dementia

One of the first applications of this concept of microglial priming or hyper-reactivity of the aged or diseased brain to subsequent stimulation was in the demonstration that systemic infection with *Escherichia coli* leads to more severe cognitive impairments in the aged compared with the young rodent [20]. These cognitive impairments were chiefly focused on consolidation of memory in contextual fear-conditioning experiments. In this task animals are exposed to a context, which they explore for some time, and are then exposed to an auditory cue (a tone) and a foot shock and are then returned to their home cage. The consolidation of the memory of the context in which they received the shock is impaired by systemic infection induced 4 days prior to, or immediately after, conditioning, as measured by decreased freezing on subsequent exposure to the same context. The authors concluded that some aspect of memory consolidation is affected by systemic inflammation, particularly in the aged rodents [20].

The contextual fear-conditioning task has also recently been used to demonstrate post-operative cognitive dysfunction, a complication that, at least in the immediate post-operative period, shows considerable overlap with delirium. In these experiments, the tibia of rodents was fractured under general anaesthesia, to mimic traumatic surgery, immediately after exposure to the context and the delivery of a foot shock. Once again a failure to consolidate the memory of the context in which the shock was delivered was observed and this impairment was found to be dependent on both TNFα (tumour necrosis factor α) [32] and IL (interleukin)-1β [33]. These experiments confirm and extend previous observations that CNS IL-1β can impair consolidation of contextual memory in rodents [34]. However, the applicability of these data to delirium and post-operative cognitive decline are limited by the fact that the long-term decline observed in post-operative patients, that the authors attempt to model, is not similar to the cognitive impairment actually observed in the rodent studies. The latter is not cognitive decline, but failure to consolidate this memory in the first place. Furthermore, the above rodent studies of POCD (post-operative cognitive dysfunction) have been performed in young healthy animals and this population is certainly much less susceptible to post-operative cognitive decline in the clinic [35]. While it is clear that pro-inflammatory molecules such as IL-6 and IL-8 are associated with post-operative delirium in the clinic, these associations are much weaker than that between prior-cognitive impairment and subsequent delirium [36]. The contextual fear-conditioning task is the best-characterized paradigm in which systemic inflammation has robust effects in healthy young animals (see [15] for a review) and thus appears to be particularly sensitive to inflammatory stimulation. Both memory consolidation and LTP (long-term potentiation; a paradigm for how memory may be consolidated at a molecular level) require new transcriptional and translational events and require hours to be achieved. In addition, there are significant caveats in using the freezing response in contextual fear conditioning to measure learning in animals that may have an issue with maintaining the freezing response, as in the case of tibial fracture [37]. All these factors limit its utility in capturing the acute onset and transient cognitive deficits observed during delirium and the long-term decline sometimes observed in post-operative cognitive dysfunction and post-delirium. Having said that, it is nonetheless significant that older animals are more sensitive than young rodents to memory consolidation deficits induced by LPS in this paradigm, and similar LPS-induced impairments in active avoidance of the context in which a similar foot shock was experienced are also accentuated by aging [38].

Ideally animal models of infection- or surgery-induced delirium should combine relevant risk factors with relevant acute triggers and should assess the impact of this combination on tasks with face validity for the delirium as observed clinically. Dementia and aging are the major risk factors for delirium, and peripheral infections and sterile inflammation induced by insults such as injury and surgery are major triggers for delirium in these populations. Among the core symptoms are inattention and short-term and working memory deficits. In addition, to address delirium, impairments should be of acute onset and reversible (the majority of delirium is transient, although 20 % of cases still show deficits at 6 months [39]). Experiments in spatial and working memory have demonstrated impairments on a serial reversal version of a radial arm maze in aged mice, but not in younger mice [40]. This task requires animals to quickly ignore hidden platform locations learned on the previous day in order to locate the maze exit on the current day's testing and may be thought of as relying on working memory. Systemic LPS (330 μg/kg) induced impairments in performance in this task associated with exaggerated CNS transcription of IL-1β, IL-6 and TNFα in aged compared with young mice.

With a particular focus on dementia, mice with prior neurodegenerative disease made more errors in learning a reference memory Y-maze task under the influence of

systemic LPS (100 μg/kg) than normal animals challenged with LPS, but could clearly remember the location of the exit if learned prior to systemic inflammation [41]. This suggests difficulties in forming new memories when under the influence of systemic inflammatory stimulation. To attempt to specifically address the acute onset and transient changes in orientation, working memory and attention that are observed in delirium during early stages of dementia we have developed a novel water-adapted T-maze alternation task. In this maze animals must retain, for just 30 s, a recollection of the arm that they have just visited to now exit the maze via the opposite arm. Animals in the early stages of neurodegenerative disease can learn and maintain good alternation performance on this task, as can normal animals treated with LPS (100 and 200 μg/kg), but ME7 animals treated systemically with LPS (100 μg/kg) show acute onset and transient working memory deficits [42]. It would appear that prior pathology, in the latter case synaptic loss and microglial priming in the hippocampus, is necessary for the expression of robust working memory deficits after systemic stimulation. Current studies suggest that these deficits are ameliorated by the inhibition of COX-1 (cyclo-oxygenase-1)-mediated PGE$_2$ (prostaglandin E$_2$) production (D.T. Skelly, C.L. Murray and C. Cunningham, unpublished work) and this is consistent with the idea that PGE$_2$ produced by COX-1 can produce hippocampal-dependent cognitive deficits in response to robust IL-1β expression [43].

Although most amyloid transgenic models of AD do not show robust neurodegeneration or synaptic loss they do show some cognitive deficits and these are associated with increased concentrations of low-order amyloid β oligomers [44]. There has been very little work examining the impact of systemic inflammation on acute measures of cognitive function in these animals. However, treatment of normal mice for 7 consecutive days with systemic LPS (250 μg/kg) can actually induce increased Aβ_{1-42} generation and deposition of amyloid plaque material via increased β- and γ-secretase activities [45]. These data are consistent with earlier studies that suggested that systemic LPS altered APP (amyloid precursor protein) processing in C57 mice [25,46]. Cognitive changes in the water maze and passive avoidance tasks, induced by LPS, were partially prevented by the COX inhibitor sulindac [45].

Collectively these results show that systemic LPS or sterile systemic inflammation can induce impairments in memory consolidation in normal animals, but these deficits are exaggerated in aged animals. Furthermore, working memory, which is intact in the normal animal, upon treatment with systemic LPS is acutely and transiently impaired when similar challenges are made in animals with prior age-related or neurodegenerative pathology. It remains likely that pro-inflammatory cytokines such as IL-1β and TNFα as well as prostaglandins have a role, but their involvement in CNS and/or systemic compartments and across multiple cognitive domains has not yet been elucidated. It also should be noted that glucocorticoids may also play some role in acute cognitive deficits, but this area is beyond the scope of this review and has been reviewed elsewhere [8].

Long-term cognitive decline/acceleration of dementia

The mechanisms by which delirium during dementia occurs are critical to unravel since it is clear that these episodes are associated with more rapid long-term functional and cognitive decline (see [13] for meta-analysis). AD patients suffering delirious episodes show accelerated cognitive decline [12], but it is unclear from those studies whether delirium itself, or the triggers that induce delirium, are responsible for altering disease trajectory.

It is important to distinguish between severe systemic inflammation, during sepsis, leading to delirium in critical care patients, and that seen during milder infections that are sufficient to cause delirium in the aged and demented population. It is known that systemic inflammation during sepsis has extremely negative consequences for the brain. In a rodent model, large doses of LPS (10 mg/kg) induced hippocampal and cortical neuronal loss, increased microglial activation, decreased regional blood flow and caused loss of cholinergic innervation. This level of inflammatory stimulation leads to cognitive impairment long after the systemic event [47,48]. LPS-induced long-term cognitive impairments were shown to be dependent on inducible nitric oxide synthase [49]. Similarly, in humans brain lesions can be visualized by MRI (magnetic resonance imaging) after septic shock [50] and microglial activation has also been reported in post-mortem brains after sepsis [51]. Examining the impact of milder infections on disease progression requires a more subtle approach and considerably lower doses of LPS.

There are some studies in chronic disease in which systemic LPS has produced exacerbations of existing disease: Nguyen et al. [52], made repeated challenges with LPS (1 mg/kg every 2 weeks for a 3-month period) to induce markedly more severe axonal pathology and progression of disease in the G93ASOD1 mouse model of ALS (amyotrophic lateral sclerosis). In the triple transgenic model of AD, LPS treatment increased the severity of Tau tangle pathology when administered at 500 μg/kg twice weekly for 6 weeks [53]. LPS-induced tau hyperphosphorylation could be blocked by inhibiting the activity of CDK5 (cyclin-dependent kinase 5). In the ME7 model of prion disease, a single challenge with LPS (500 μg/kg intraperitoneal, from *Salmonella enterica* serotype abortus equi) induced acutely increased neuronal apoptosis in ME7 animals, but not in NBH (normal brain homogenate) controls [22]. This same dose, when administered just once at 15 weeks post-inoculation with disease, was sufficient to cause acute and reversible neurological changes in ME7, but not normal animals. However, even after full recovery from acute deficits, the LPS-treated ME7 animals developed progressive and irreversible neurological impairments earlier and with greater severity than ME7 animals not treated with LPS [41]. In the 6-OHDA (6-hydroxydopamine) model of Parkinson's disease, it was demonstrated that adenovirally mediated systemic expression of IL-1β significantly exacerbated neuronal loss in the substantia nigra and exacerbated motor symptoms when

this expression was insufficient to induce any neuropathology in normal animals [27]. The inhibition of iNOS (inducible nitric oxide synthase) partially protected against IL-1β-induced neurotoxicity in the substantia nigra in these animals. Using another model of Parkinson's disease, induced by intra-nigral injection of LPS, Villaran et al. [28] showed that ulcerative colitis could also significantly exacerbate dopaminergic neuronal loss. Interestingly, infection with the Gram-positive bacterium *Streptococcus pneumoniae* did not exacerbate features of disease in a number of disease models [54]. Although these studies are confounded to some degree by the administration of antibiotics to all infected animals within 24 h of infection it may be of interest that Gram-positive bacteria, lacking LPS, may constitute a less significant insult to the diseased brain. Moreover, disease exacerbating effects have not been observed only with LPS: the acute and longitudinal exacerbation of chronic neurodegenerative disease has been demonstrated after systemic challenge with the double-stranded RNA poly I:C [23]. These animals showed exaggerated CNS IL-1β and also type I interferon (IFN α/β) responses to this mimic of a systemic viral infection. Among the specific type I interferon-responsive genes robustly elevated was PKR (double-stranded-RNA-dependent protein kinase). Increased activity of this kinase has been shown both to induce apoptosis [55] and to impair LTP and consolidation of memory [56]. It is of particular interest to the idea of multiple systemic inflammatory insults triggering delirium and also contributing in a cumulative way to disease progression that poly I:C was administered three times, 2 weeks apart, in the latter study. Each successive challenge produced acute deficits, but these deficits were progressively more severe and less reversible as the challenges were superimposed on disease at more progressed stages [23] (Figure 2). This appears to mimic the fluctuating and variable rate of decline seen in AD patients [57] in the manner that we had previously proposed that this model would [58].

Relevance in human disease

These animal studies raise the question of whether infection has a significant role in the progression of AD. Several studies have examined the association of specific infectious agents with AD. These include HSV-1 (herpes simplex virus-1), *Chlamydia pneumoniae* and spirochaetes (see [59] for a review), but these avenues have not progressed significantly due to a lack of consistent observations. Nonetheless, a review of general practitioner databases revealed that two or more infections over a 4-year period increased the risk of AD 2-fold [60]. Similarly, in a study in elderly patients, MMSE (mini-mental state examination) scores decreased with increasing viral burden, with herpes virus and cytomegalovirus burden being of particular risk [61]. Other studies by the same authors showed that general ill health was significantly associated with cognitive decline [62,63]. Similarly, there is evidence that periodontitis, caused chiefly by infection with the Gram-negative *Porphyromonas gingivalis*, is a significant risk factor for AD [64]. It has also been shown that treating

infection can reduce the risk of development of AD and that vaccination against a number of common diseases can protect against subsequent development of AD [65]. Antibiotic treatment of mild to moderate AD patients with doxycycline and rifampin was also associated with slower decline in the treated group [66]. Interestingly, this did not appear to be associated with effects on *C. pneumoniae*, the rationale for the study.

On the basis of the ME7 animal studies discussed above, we and our clinical collaborators examined the contribution of systemic infection to disease progression in 85 AD patients and showed that elevated serum IL-1β was associated with increased cognitive decline across a 2-month period [67]. In a cohort of 275 AD patients across 6 months, it was found that elevated serum TNFα was highly significantly correlated with accelerated cognitive decline. Indeed those patients with low serum TNFα showed almost no decline across this period. As hypothesized, those with elevated serum TNFα or with reported infection showed greater decline, but those with both elevated TNFα and systemic inflammatory conditions showed the greatest decline in this cohort [68]. Interestingly, many of those with elevated serum TNFα did not suffer acute systemic inflammatory events and this TNFα may arise from a number of other chronic co-morbidities such as obesity, atherosclerosis, diabetes and smoking. Significantly, those patients meeting criteria for delirium were excluded from the analysis of cognitive decline, indicating that inflammation-associated exacerbation of cognitive decline occurred even in the absence of a delirium. Consistent with this are findings that even patients with altered mental status not fulfilling criteria for delirium (often classified as subsyndromal delirium) show evidence of poor outcomes and long-term cognitive impairment and this occurs in both the geriatric [69] and critical care settings [70]. Further studies with the AD cohort discussed above show that these patients do show an exaggerated sickness behaviour response to systemic inflammation, as originally demonstrated in the ME7 model, and now show some symptoms more typical of delirium than of sickness behaviour [71]. Thus, whereas systemic inflammation leads to an adaptive sickness behaviour response in the healthy brain it produces an exaggerated sickness behaviour response in the demented population and this syndrome may now comprise symptomatology not normally associated with these adaptive sickness responses. In more extreme cases, this can present as delirium. It is possible that the delirium syndrome may affect hydration, nourishment, sleep quality and quantity and anxiety, which could influence an underlying condition, but it is apparent that even in the absence of delirium, these systemic inflammatory events are associated with increased pathological burden in individuals with prior pathology. This does not demonstrate causality, but it is plausible that mediators such as IL-1β, TNFα, NO and PGE$_2$ affect neuronal function via neuronal receptors and downstream effects on neurotransmitter release and action, and may also set in motion neurotoxic effects, dependent on the same or different inflammatory mediators, that will ultimately

Figure 2 | **Systemic inflammatory events may trigger delirium and contribute to pathological burden**

(**a**) Systemic inflammatory events trigger the release of inflammatory mediators by tissue macrophages and brain vascular endothelial cells. These mediators may affect neuronal function directly, or via the activation of microglial cells that have become primed by neurodegenerative disease or aging. Inflammatory mediators may cause reversible disruption of neuronal function, perhaps resulting in delirium. These mediators may also induce acute neuronal synaptic or dendritic damage that may be reversible and contribute to delirium or may be irreversible and contribute to long-term cognitive decline. These inflammatory mediators can also bring about neuronal death acutely and these changes are obviously irreversible and contribute to the accumulating damage and neuropathological burden. Thus acute and long-term cognitive effects are likely to occur by both overlapping and distinct mechanisms. (**b**) Successive systemic inflammatory insults induce acute dysfunction, which is progressively less reversible each time, but also contribute to the progression of permanent disability (adapted from [23]). Abbreviations: IL-1RI, interleukin 1 receptor type I; TNFp55, TNFp55 receptor; GCs, glucocorticoids; GR, glucocorticoid receptor; NO, nitric oxide; EP_{1-4}, prostaglandin receptors 1–4; PAMPs: pathogen-associated molecular patterns; $IFN\alpha/\beta$, interferon α/β; SIEs, systemic inflammatory events.
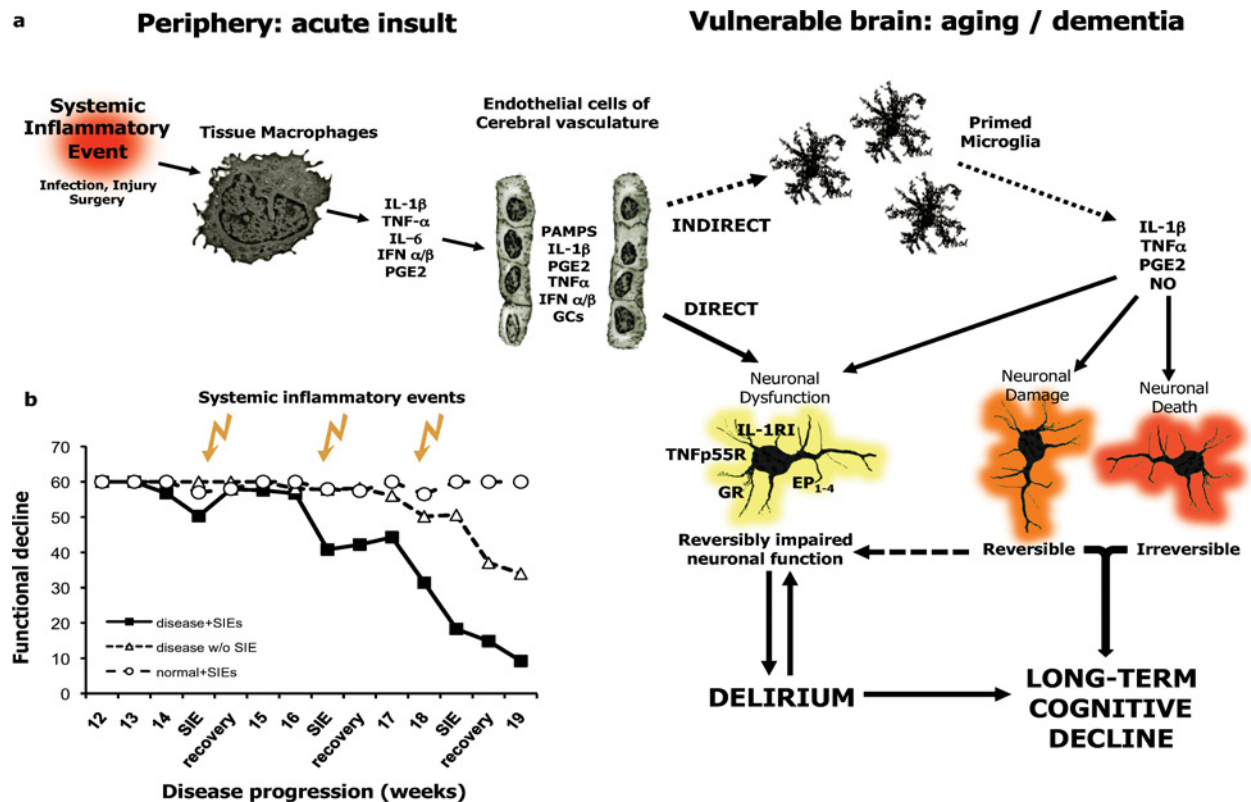
increase pathological burden. Evidence from animal model studies, and possible mechanisms contributing to acute and lasting cognitive dysfunction are illustrated in Figure 2.

Why do anti-inflammatory treatments not help?

It has been shown in several studies that NSAID use can protect against subsequent development of AD [72], but these drugs do not appear to be effective when administered to patients with established AD or even as a primary preventative strategy for those at high risk [3]. While it is possible that these drugs simply target the wrong inflammatory mediators, being primarily directed at inhibition of prostaglandin synthesis, there is intriguing recent evidence that there may indeed be some protection offered by these drugs. Patients already on the cusp of impairment appeared to worsen on treatment with the COX inhibitor naproxen, but those who were not yet impaired showed significant protection at 2-year follow-up [73]. The timing and consequences of inhibiting brain COXs may be crucial since both isoforms of this enzyme are constitutively expressed and have roles in normal brain function, but inhibiting PGE_2 production while the brain still has significant cognitive reserve appears to be beneficial. Returning to the very beginning of the field of inflammation in AD, it is of considerable interest that treatment of rheumatoid arthritis patients with anti-TNFα antibodies has recently been reported to offer very significant protection

against the subsequent development of AD [74]. Thus it seems increasingly likely that pro-inflammatory factors induced during rheumatoid arthritis and other inflammatory conditions, including prostaglandins and TNFα, accelerate disease progression and this is certainly consistent with our recent demonstration that elevated systemic TNFα is associated with more rapid cognitive decline [68]. Therefore blocking these systemic mediators, whether in rheumatoid arthritis or some other condition is likely to block their negative consequences on the brain and slow progression of AD. Furthermore, these data suggest that if we wish to assess the ability of anti-inflammatory drugs to slow or prevent AD, we must do so in populations that do not enforce strict exclusion criteria that exclude those in the population with significant co-morbidity, who it would appear are most likely to demonstrate the importance of systemic inflammation in disease progression.

Conclusion

It is possible that delirium that resolves within days or weeks and long-term cognitive decline are two different manifestations of the same insult, but they may occur by distinct mechanisms or overlapping ones as discussed above. However, on the basis of the growing basic and clinical literature, it seems clear that systemic inflammation has negative consequences for brain function, both acutely and in the long-term. Growing recognition that amyloid-β alone cannot account for progression of dementia across the population [75] increasingly implicates systemic inflammatory conditions as contributors to disease progression, and recent animal model advances are well placed to begin to delineate at least some of the multifactorial influences on disease progression in the real world, where co-morbidity is a feature of aging for most people. In the context of this issue of *Biochemical Society Transactions* on useful models with which to model the progression of dementia, it is significant that models of chronic neurodegeneration, such as the ME7 model of prion disease, which are not reliant on genetic manipulation of amyloid-β levels, have made predictions [41] about the influence of systemic inflammation on disease progression that have successfully translated into the human population [68].

Acknowledgements

Funding

References

1 McGeer, P.L., McGeer, E., Rogers, J. and Sibley, J. (1990) Anti-inflammatory drugs and Alzheimer disease. Lancet **335**, 1037

2 Aisen, P.S. (2002) The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. Lancet Neurol. **1**, 279–284

3 Martin, B.K., Szekely, C., Brandt, J., Piantadosi, S., Breitner, J.C., Craft, S., Evans, D., Green, R. and Mullan, M. (2008) Cognitive function over time in the Alzheimer's disease anti-inflammatory prevention trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch. Neurol. **65**, 896–905

4 Reitz, C., Tang, M.X., Schupf, N., Manly, J.J., Mayeux, R. and Luchsinger, J.A. (2010) A summary risk score for the prediction of Alzheimer disease in elderly persons. Arch. Neurol. **67**, 835–841

5 Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F.A. and Newman, A.B. (2004) The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA, J. Am. Med. Assoc. **292**, 2237–2242

6 American Psychiatry Association (APA) (1994) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th edn, American Psychiatry Association, Washington, DC

7 World Health Organization (1992) The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria for Research, WHO, Geneva

8 MacLullich, A.M., Ferguson, K.J., Miller, T., de Rooij, S.E. and Cunningham, C. (2008) Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J. Psychosom. Res. **65**, 229–238

9 Inouye, S.K. and Charpentier, P.A. (1996) Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA, J. Am. Med. Assoc. **275**, 852–857

10 Jackson, J.C., Gordon, S.M., Hart, R.P., Hopkins, R.O. and Ely, E.W. (2004) The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol. Rev. **14**, 87–98

11 MacLullich, A.M., Beaglehole, A., Hall, R.J. and Meagher, D.J. (2009) Delirium and long-term cognitive impairment. Int. Rev. Psychiatry **21**, 30–42

12 Fong, T.G., Jones, R.N., Shi, P., Marcantonio, E.R., Yap, L., Rudolph, J.L., Yang, F.M., Kiely, D.K. and Inouye, S.K. (2009) Delirium accelerates cognitive decline in Alzheimer disease. Neurology **72**, 1570–1575

13 Witlox, J., Eurelings, L.S., de Jonghe, J.F., Kalisvaart, K.J., Eikelenboom, P. and van Gool, W.A. (2010) Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA, J. Am. Med. Assoc. **304**, 443–451

14 Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W. and Kelley, K.W. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. **9**, 46–56

15 Cunningham, C. and Sanderson, D.J. (2008) Malaise in the water maze: untangling the effects of LPS and IL-1β on learning and memory. Brain Behav. Immun. **22**, 1117–1127

16 Betmouni, S., Deacon, R.M.J., Rawlins, J.N.P. and Perry, V.H. (1999) Behavioural consequences of prion disease targeted to the hippocampus in a mouse model of scrapie. Psychobiology **27**, 63–71

17 Betmouni, S., Perry, V.H. and Gordon, J.L. (1996) Evidence for an early inflammatory response in the central nervous system of mice with scrapie. Neuroscience **74**, 1–5

18 Cunningham, C., Deacon, R., Wells, H., Boche, D., Waters, S., Diniz, C.P., Scott, H., Rawlins, J.N. and Perry, V.H. (2003) Synaptic changes characterize early behavioural changes in the ME7 model of murine prion disease. Eur. J. Neurosci. **17**, 2147–2155

19 Combrinck, M.I., Perry, V.H. and Cunningham, C. (2002) Peripheral infection evokes exaggerated sickness behaviour in pre-clinical murine prion disease. Neuroscience **112**, 7–11

20 Barrientos, R.M., Higgins, E.A., Biedenkapp, J.C., Sprunger, D.B., Wright-Hardesty, K.J., Watkins, L.R., Rudy, J.W. and Maier, S.F. (2006) Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol. Aging **27**, 723–732

21 Godbout, J.P., Chen, J., Abraham, J., Richwine, A.F., Berg, B.M., Kelley, K.W. and Johnson, R.W. (2005) Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J. **19**, 1329–1331

22 Cunningham, C., Wilcockson, D.C., Campion, S., Lunnon, K. and Perry, V.H. (2005) Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J. Neurosci. **25**, 9275–9284

23 Field, R., Campion, S., Warren, C., Murray, C. and Cunningham, C. (2010) Systemic challenge with the TLR3 agonist poly I:C induces amplified IFNα/β and IL-1β responses in the diseased brain and exacerbates chronic neurodegeneration. Brain Behav. Immun. **24**, 996–1007

24 Lee, J., Chan, S.L. and Mattson, M.P. (2002) Adverse effect of a Presenilin-1 mutation in microglia results in enhanced nitric oxide and inflammatory cytokine responses to immune challenge in the brain. Neuromol. Med. **2**, 29–45

25 Sheng, J.G., Bora, S.H., Xu, G., Borchelt, D.R., Price, D.L. and Koliatsos, V.E. (2003) Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid β peptide in APPswe transgenic mice. Neurobiol. Dis. **14**, 133–145

26 Sly, L.M., Krzesicki, R.F., Brashler, J.R., Buhl, A.E., McKinley, D.D., Carter, D.B. and Chin, J.E. (2001) Endogenous brain cytokine mRNA and inflammatory responses to lipopolysaccharide are elevated in the Tg2576 transgenic mouse model of Alzheimer's disease. Brain Res. Bull. **56**, 581–588

27 Godoy, M.C., Tarelli, R., Ferrari, C.C., Sarchi, M.I. and Pitossi, F.J. (2008) Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. Brain **131**, 1880–1894

28 Villaran, R.F., Espinosa-Oliva, A.M., Sarmiento, M., De Pablos, R.M., Arguelles, S., Delgado-Cortes, M.J., Sobrino, V., Van Rooijen, N., Venero, J.L., Herrera, A.J. et al. (2010) Ulcerative colitis exacerbates lipopolysaccharide-induced damage to the nigral dopaminergic system: potential risk factor in Parkinson's disease. J. Neurochem. **114**, 1687–1700

29 McColl, B.W., Rothwell, N.J. and Allan, S.M. (2007) Systemic inflammatory stimulus potentiates the acute phase and CXC chemokine responses to experimental stroke and exacerbates brain damage via interleukin-1- and neutrophil-dependent mechanisms. J. Neurosci. **27**, 4403–4412

30 Serres, S., Anthony, D.C., Jiang, Y., Broom, K.A., Campbell, S.J., Tyler, D.J., van Kasteren, S.I., Davis, B.G. and Sibson, N.R. (2009) Systemic inflammatory response reactivates immune-mediated lesions in rat brain. J. Neurosci. **29**, 4820–4828

31 Palin, K., Cunningham, C., Forse, P., Perry, V.H. and Platt, N. (2008) Systemic inflammation switches the inflammatory cytokine profile in CNS Wallerian degeneration. Neurobiol. Dis. **30**, 19–29

32 Terrando, N., Monaco, C., Ma, D., Foxwell, B.M., Feldmann, M. and Maze, M. (2010) Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline. Proc. Natl. Acad. Sci. U.S.A. **107**, 20518–20522

33 Cibelli, M., Fidalgo, A.R., Terrando, N., Ma, D., Monaco, C., Feldmann, M., Takata, M., Lever, I.J., Nanchahal, J., Fanselow, M.S. and Maze, M. (2010) Role of interleukin-1β in postoperative cognitive dysfunction. Ann. Neurol. **68**, 360–368

34 Barrientos, R.M., Higgins, E.A., Sprunger, D.B., Watkins, L.R., Rudy, J.W. and Maier, S.F. (2002) Memory for context is impaired by a post context exposure injection of interleukin-1β into dorsal hippocampus. Behav. Brain Res. **134**, 291–298

35 Krenk, L., Rasmussen, L.S. and Kehlet, H. (2010) New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol. Scand. **54**, 951–956

36 van Munster, B.C., Bisschop, P.H., Zwinderman, A.H., Korevaar, J.C., Endert, E., Wiersinga, W.J., Oosten, H.E., Goslings, J.C. and Rooij, S.E. (2010) Cortisol, interleukins and S100B in delirium in the elderly. Brain Cogn. **74**, 18–23

37 Maren, S. (2008) Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdala function: cautions and caveats. Eur. J. Neurosci. **28**, 1661–1666

38 Kohman, R.A., Tarr, A.J., Byler, S.L. and Boehm, G.W. (2007) Age increases vulnerability to bacterial endotoxin-induced behavioral decrements. Physiol. Behav. **91**, 561–565

39 Cole, M.G. (2010) Persistent delirium in older hospital patients. Curr. Opin. Psychiatry **23**, 250–254

40 Chen, J., Buchanan, J.B., Sparkman, N.L., Godbout, J.P., Freund, G.G. and Johnson, R.W. (2008) Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav. Immun. **22**, 301–311

41 Cunningham, C., Campion, S., Lunnon, K., Murray, C.L., Woods, J.F., Deacon, R.M., Rawlins, J.N. and Perry, V.H. (2009) Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol. Psychiatry **65**, 304–312

42 Murray, C., Sanderson, D.J., Barkus, C., Deacon, R.M., Rawlins, J.N., Bannerman, D.M. and Cunningham, C. (2010) Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol. Aging, doi:10.1016/j.neurobiolaging.2010.04.002

43 Matousek, S.B., Hein, A.M., Shaftel, S.S., Olschowka, J.A., Kyrkanides, S. and O'Banion, M.K. (2010) Cyclooxygenase-1 mediates prostaglandin E$_2$ elevation and contextual memory impairment in a model of sustained hippocampal interleukin-1β expression. J. Neurochem. **114**, 247–258

44 Ashe, K.H. and Zahs, K.R. (2010) Probing the biology of Alzheimer's disease in mice. Neuron **66**, 631–645

45 Lee, J.W., Lee, Y.K., Yuk, D.Y., Choi, D.Y., Ban, S.B., Oh, K.W. and Hong, J.T. (2008) Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of β-amyloid generation. J. Neuroinflammation **5**, 37

46 Brugg, B., Dubreuil, Y.L., Huber, G., Wollman, E.E., Delhaye-Bouchaud, N. and Mariani, J. (1995) Inflammatory processes induce β-amyloid precursor protein changes in mouse brain. Proc. Natl. Acad. Sci. U.S.A. **92**, 3032–3035

47 Semmler, A., Frisch, C., Debeir, T., Ramanathan, M., Okulla, T., Klockgether, T. and Heneka, M.T. (2007) Long-term cognitive impairment, neuronal loss and reduced cortical cholinergic innervation after recovery from sepsis in a rodent model. Exp. Neurol. **204**, 733–740

48 Semmler, A., Hermann, S., Mormann, F., Weberpals, M., Paxian, S.A., Okulla, T., Schafers, M., Kummer, M.P., Klockgether, T. and Heneka, M.T. (2008) Sepsis causes neuroinflammation and concomitant decrease of cerebral metabolism. J. Neuroinflammation **5**, 38

49 Weberpals, M., Hermes, M., Hermann, S., Kummer, M.P., Terwel, D., Semmler, A., Berger, M., Schafers, M. and Heneka, M.T. (2009) NOS2 gene deficiency protects from sepsis-induced long-term cognitive deficits. J. Neurosci. **29**, 14177–14184

50 Sharshar, T., Carlier, R., Bernard, F., Guidoux, C., Brouland, J.P., Nardi, O., de la Grandmaison, G.L., Aboab, J., Gray, F., Menon, D. and Annane, D. (2007) Brain lesions in septic shock: a magnetic resonance imaging study. Intensive Care Med. **33**, 798–806

51 Lemstra, A.W., Groen in't Woud, J.C., Hoozemans, J.J., van Haastert, E.S., Rozemuller, A.J., Eikelenboom, P. and van Gool, W.A. (2007) Microglia activation in sepsis: a case-control study. J. Neuroinflammation **4**, 4

52 Nguyen, M.D., D'Aigle, T., Gowing, G., Julien, J.P. and Rivest, S. (2004) Exacerbation of motor neuron disease by chronic stimulation of innate immunity in a mouse model of amyotrophic lateral sclerosis. J. Neurosci. **24**, 1340–1349

53 Kitazawa, M., Oddo, S., Yamasaki, T.R., Green, K.N. and LaFerla, F.M. (2005) Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J. Neurosci. **25**, 8843–8853

54 Ebert, S., Goos, M., Rollwagen, L., Baake, D., Zech, W.D., Esselmann, H., Wiltfang, J., Mollenhauer, B., Schliebs, R., Gerber, J. and Nau, R. (2010) Recurrent systemic infections with Streptococcus pneumoniae do not aggravate the course of experimental neurodegenerative diseases. J. Neurosci. Res. **88**, 1124–1136

55 Balachandran, S., Kim, C.N., Yeh, W.C., Mak, T.W., Bhalla, K. and Barber, G.N. (1998) Activation of the dsRNA-dependent protein kinase, PKR, induces apoptosis through FADD-mediated death signaling. EMBO J. **17**, 6888–6902

56 Jiang, Z., Belforte, J.E., Lu, Y., Yabe, Y., Pickel, J., Smith, C.B., Je, H.S., Lu, B. and Nakazawa, K. (2010) eIF2α phosphorylation-dependent translation in CA1 pyramidal cells impairs hippocampal memory consolidation without affecting general translation. J. Neurosci. **30**, 2582–2594

57 Holmes, C. and Lovestone, S. (2003) Long-term cognitive and functional decline in late onset Alzheimer's disease: therapeutic implications. Age Ageing **32**, 200–204

58 Perry, V.H., Cunningham, C. and Holmes, C. (2007) Systemic infections and inflammation affect chronic neurodegeneration. Nat. Rev. Immunol. **7**, 161–167

59 Holmes, C. and Cotterell, D. (2009) Role of infection in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs **23**, 993–1002

60 Dunn, N., Mullee, M., Perry, V.H. and Holmes, C. (2005) Association between dementia and infectious disease: evidence from a case-control study. Alzheimer Dis. Assoc. Disord. **19**, 91–94

61 Strandberg, T.E., Pitkala, K.H., Linnavuori, K.H. and Tilvis, R.S. (2003) Impact of viral and bacterial burden on cognitive impairment in elderly persons with cardiovascular diseases. Stroke **34**, 2126–2131

62 Strandberg, T.E., Pitkala, K.H., Linnavuori, K. and Tilvis, R.S. (2004) Cognitive impairment and infectious burden in the elderly. Arch. Gerontol. Geriatr. Suppl. 419–423

63 Tilvis, R.S., Kahonen-Vare, M.H., Jolkkonen, J., Valvanne, J., Pitkala, K.H. and Strandberg, T.E. (2004) Predictors of cognitive decline and mortality of aged people over a 10-year period. J. Gerontol. A Biol. Sci. Med. Sci. **59**, 268–274

64 Kamer, A.R., Craig, R.G., Pirraglia, E., Dasanayake, A.P., Norman, R.G., Boylan, R.J., Nehorayoff, A., Glodzik, L., Brys, M. and de Leon, M.J. (2009) TNF-α and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J. Neuroimmunol. **216**, 92–97

65 Verreault, R., Laurin, D., Lindsay, J. and De Serres, G. (2001) Past exposure to vaccines and subsequent risk of Alzheimer's disease. Can. Med. Assoc. J. **165**, 1495–1498

66 Loeb, M.B., Molloy, D., Smieja, M., Standish, T., Goldsmith, C.H., Mahony, J., Smith, S., Borrie, M., Decoteau, E., Davidson, W. et al. (2004) A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J. Am. Geriatr. Soc. **52**, 381–387

67 Holmes, C., El-Okl, M., Williams, A.L., Cunningham, C., Wilcockson, D. and Perry, V.H. (2003) Systemic infection, interleukin 1β, and cognitive decline in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry **74**, 788–789

68 Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., Culliford, D. and Perry, V.H. (2009) Systemic inflammation and disease progression in Alzheimer's disease. Neurology **73**, 768–774

69 Cole, M., McCusker, J., Dendukuri, N. and Han, L. (2003) The prognostic significance of subsyndromal delirium in elderly medical inpatients. J. Am. Geriatr. Soc. **51**, 754–760

70 Jones, C., Griffiths, R.D., Slater, T., Benjamin, K.S. and Wilson, S. (2006) Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. Intensive Care Med. **32**, 923–926

71 Holmes, C., Cunningham, C., Zotova, E., Culliford, D. and Perry, V.H. (2011) Pro-inflammatory cytokines, sickness behavior and Alzheimer's disease. Neurology, in the press

72 Vlad, S.C., Miller, D.R., Kowall, N.W. and Felson, D.T. (2008) Protective effects of NSAIDs on the development of Alzheimer disease. Neurology **70**, 1672–1677

73 Laino, C. (2009) In follow-up analysis of clinical trial, NSAIDs seem to preserve cognitive function in patients with healthy brains. Neurol. Today **9**, 21–22

74 Chou, R.C. (2010) Anti-TNF therapies for rheumatoid arthritis could reduce Alzheimer's risk. American College of Rheumatology, http://www.rheumatology.org/about/newsroom/2010/2010_anti_tnf _therapies_for_rheumatoid_arthritis_could_reduce_alzheimers_risk.asp

75 Neuropathology Group. Medical Research Council Cognitive Function and Aging Study (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet **357**, 169–175