33. Gibot, S. *et al.* A soluble form of the triggering receptor expressed on myeloid cells-1 modulates the inflammatory response in murine sepsis. *J. Exp. Med.* **200**, 1419–1426 (2004).
34. Turnbull, I. R. *et al.* DAP12 (KARAP) amplifies inflammation and increases mortality from endotoxemia and septic peritonitis. *J. Exp. Med.* **202**, 363–369 (2005).
35. Pasquier, B. *et al.* Identification of FcαRI as an inhibitory receptor that controls inflammation: dual role of FcRγ ITAM. *Immunity* **22**, 31–42 (2005).
36. Stefanova, I. *et al.* TCR ligand discrimination is enforced by competing ERK positive and SHP-1 negative feedback pathways. *Nature Immunol.* **4**, 248–254 (2003).
37. Takahashi, K., Rochford, C. D. & Neumann, H. Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. *J. Exp. Med.* **201**, 647–657 (2005).
38. Cella, M. *et al.* Impaired differentiation of osteoclasts in TREM-2-deficient individuals. *J. Exp. Med.* **198**, 645–651 (2003).
39. Paloneva, J. *et al.* DAP12/TREM2 deficiency results in impaired osteoclast differentiation and osteoporotic features. *J. Exp. Med.* **198**, 669–675 (2003).
40. Sjolin, H. *et al.* DAP12 signaling regulates plasmacytoid dendritic cell homeostasis and down-modulates their function during viral infection. *J. Immunol.* **177**, 2908–2916 (2006).
41. Blasius, A. L., Cella, M., Maldonado, J., Takai, T. & Colonna, M. Siglec-H is an IPC-specific receptor that modulates type I IFN secretion through DAP12. *Blood* **107**, 2474–2476 (2006).
42. Blasius, A. L. & Colonna, M. Sampling and signaling in plasmacytoid dendritic cells: the potential roles of Siglec-H. *Trends Immunol.* **27**, 255–260 (2006).
43. Samelson, L. E. Signal transduction mediated by the T cell antigen receptor: the role of adapter proteins. *Annu. Rev. Immunol.* **20**, 371–394 (2002).
44. Neel, B. G., Gu, H. & Pao, L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem. Sci.* **28**, 284–293 (2003).
45. Zhang, J., Somani, A. K. & Siminovitch, K. A. Roles of the SHP-1 tyrosine phosphatase in the negative regulation of cell signalling. *Semin. Immunol.* **12**, 361–378 (2000).
46. Hardin, A. O., Meals, E. A., Yi, T., Knapp, K. M. & English, B. K. SHP-1 inhibits LPS-mediated TNF and iNOS production in murine macrophages. *Biochem. Biophys. Res. Commun.* **342**, 547–555 (2006).
47. Fukao, T. & Koyasu, S. PI3K and negative regulation of TLR signaling. *Trends Immunol.* **24**, 358–363 (2003).
48. Fukao, T. *et al.* PI3K-mediated negative feedback regulation of IL-12 production in DCs. *Nature Immunol.* **3**, 875–881 (2002).
49. Guha, M. & Mackman, N. The phosphatidylinositol 3-kinase-Akt pathway limits lipopolysaccharide activation of signaling pathways and expression of inflammatory mediators in human monocytic cells. *J. Biol. Chem.* **277**, 32124–32132 (2002).
50. Kim, A. H., Khursigara, G., Sun, X., Franke, T. F. & Chao, M. V. Akt phosphorylates and negatively regulates apoptosis signal-regulating kinase 1. *Mol. Cell. Biol.* **21**, 893–901 (2001).
51. Gratton, J. P. *et al.* Akt down-regulation of p38 signaling provides a novel mechanism of vascular endothelial growth factor-mediated cytoprotection in endothelial cells. *J. Biol. Chem.* **276**, 30359–30365 (2001).
52. Kagan, J. C. & Medzhitov, R. Phosphoinositide-mediated adaptor recruitment controls Toll-like receptor signaling. *Cell* **125**, 943–955 (2006).
53. Honda, K. *et al.* Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. *Nature* **434**, 1035–1040 (2005).
54. Bave, U. *et al.* FcγRIIa is expressed on natural IFN-α-producing cells (plasmacytoid dendritic cells) and is required for the IFN-α production induced by apoptotic cells combined with lupus IgG. *J. Immunol.* **171**, 3296–3302 (2003).
55. Means, T. K. *et al.* Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. *J. Clin. Invest.* **115**, 407–417 (2005).
56. Vollmer, J. *et al.* Immune stimulation mediated by autoantigen binding sites within small nuclear RNAs involves Toll-like receptors 7 and 8. *J. Exp. Med.* **202**, 1575–1585 (2005).
57. Savarese, E. *et al.* U1 small nuclear ribonucleoprotein immune complexes induce type I interferon in plasmacytoid dendritic cells through TLR7. *Blood* **107**, 3229–3234 (2006).
58. Silverstein, R. D-galactosamine lethality model: scope and limitations. *J. Endotoxin Res.* **10**, 147–162 (2004).
59. Remick, D. G., Newcomb, D. E., Bolgos, G. L. & Call, D. R. Comparison of the mortality and inflammatory response of two models of sepsis: lipopolysaccharide vs. cecal ligation and puncture. *Shock* **13**, 110–116 (2000).
60. Daws, M. R. *et al.* Pattern recognition by TREM-2: binding of anionic ligands. *J. Immunol.* **171**, 594–599 (2003).
61. Makrigiannis, A. P. *et al.* Class I MHC-binding characteristics of the 129/J Ly49 repertoire. *J. Immunol.* **166**, 5034–5043 (2001).
62. Gilfillan, S., Ho, E. L., Cella, M., Yokoyama, W. M. & Colonna, M. NKG2D recruits two distinct adapters to trigger NK cell activation and costimulation. *Nature Immunol.* **3**, 1150–1155 (2002).
63. Diefenbach, A. *et al.* Selective associations with signaling proteins determine stimulatory versus costimulatory activity of NKG2D. *Nature Immunol.* **3**, 1142–1149 (2002).
64. Dietrich, J., Cella, M., Seiffert, M., Buhring, H. J. & Colonna, M. Cutting edge: signal-regulatory protein β1 is a DAP12-associated activating receptor expressed in myeloid cells. *J. Immunol.* **164**, 9–12 (2000).
65. Tomasello, E. *et al.* Association of signal-regulatory proteins β with KARAP/DAP-12. *Eur. J. Immunol.* **30**, 2147–2156 (2000).
66. Kumagai, H. *et al.* Identification and characterization of a new pair of immunoglobulin-like receptors LMIR1 and 2 derived from murine bone marrow-derived mast cells. *Biochem. Biophys. Res. Commun.* **307**, 719–729 (2003).
67. Aguilar, H. *et al.* Molecular characterization of a novel immune receptor restricted to the monocytic lineage. *J. Immunol.* **173**, 6703–6711 (2004).
68. Wright, G. J. *et al.* Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. *J. Immunol.* **171**, 3034–3046 (2003).
69. Mousseau, D. D., Banville, D., L'Abbe, D., Bouchard, P. & Shen, S. H. PILRα, a novel immunoreceptor tyrosine-based inhibitory motif-bearing protein, recruits SHP-1 upon tyrosine phosphorylation and is paired with the truncated counterpart PILRβ. *J. Biol. Chem.* **275**, 4467–4474 (2000).
70. Angata, T., Hayakawa, T., Yamanaka, M., Varki, A. & Nakamura, M. Discovery of Siglec-14, a novel sialic acid receptor undergoing concerted evolution with Siglec-5 in primates. *FASEB J.* **20**, 1964–1973 (2006).

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OPINION

Systemic infections and inflammation affect chronic neurodegeneration

V. Hugh Perry, Colm Cunningham and Clive Holmes

Abstract | It is well known that systemic infections cause flare-ups of disease in individuals with asthma and rheumatoid arthritis, and that relapses in multiple sclerosis can often be associated with upper respiratory-tract infections. Here we review evidence to support our hypothesis that in chronic neurodegenerative diseases such as Alzheimer's disease, with an ongoing innate immune response in the brain, systemic infections and inflammation can cause acute exacerbations of symptoms and drive the progression of neurodegeneration.

We have all, at one time or another, felt ill following an infection of the respiratory tract. These alterations in our metabolic and behavioural state are commonly referred to as 'sickness behaviour' (BOX 1) and have an important role in defence against infection. In recent years, we have learned that this immune-system-to-brain communication is in part dependent on the resident mononuclear phagocyte populations in the brain — the macrophages and microglia.

In the normal healthy brain, the microglia have a quiescent or downregulated phenotype. In chronic neurodegenerative diseases, however, the macrophages and microglia increase in number and change their morphology as well as their cell-surface antigen expression. We have recently shown that a systemic inflammatory challenge in an animal with a chronic neurodegenerative disease leads to exaggerated brain inflammation, exaggerated sickness behaviour and a significant increase in acute neurodegeneration[1,2]. We proposed that the microglia in the diseased or aged brain are 'primed', and switch their phenotype to produce neurotoxic molecules when they respond to systemic inflammatory signals. Therefore, in the diseased or ageing brain, signals from systemic infection or inflammation, instead of signalling to evoke a protective homeostatic response in the host, evoke an exaggerated response that contributes to disease progression. In this article we review

Box 1 | **Sickness behaviour**

Systemic infectious episodes induce a general malaise, with symptoms including lethargy, anhedonia (disinterest in previously rewarding activities), apathy, decreased social interaction and poor concentration. This general malaise can be accompanied by metabolic changes such as altered body temperature (fever or hypothermia), increased somnolence and loss of body weight. However, these symptoms are not merely unpleasant side-effects of infection; together they form an important, evolutionarily conserved, homeostatic mechanism that allows the body to adapt to and combat infection. Through this set of behavioural responses, classically described by Hart[89] and collectively termed as 'sickness behaviour', the body makes conditions suboptimal for microbial replication. It does so through altering body temperature, conserving energy, limiting its exposure to subsequent infection or other insults and limiting the spread of the current infection. These changes are coordinated by the central nervous system (CNS) and peripheral signals must reach particular brain centres to initiate this response. There are a number of routes of communication between the periphery and the brain, but the synthesis of pro-inflammatory molecules in the CNS, such as interleukin-1β (IL-1β), IL-6, tumour-necrosis factor (TNF) and prostaglandins, is thought to be crucial for the initiation of sickness-behaviour responses. The neuroanatomical basis and molecular mechanisms of sickness behaviour have been extensively reviewed elsewhere[3].

evidence from animal models and clinical studies to support this hypothesis, and we discuss the implications for chronic neurodegeneration in general.

Systemic inflammation and the brain

Following injury or infection, in addition to the local inflammatory response, there is a systemic response, which includes the acute-phase response in the liver and the metabolic and behavioural components of sickness that are familiar to us all (BOX 1). The molecular and cellular components that mediate the communication between peripheral inflammation and the brain have been well studied in experimental models. Three major routes of communication are known, all of which lead to the synthesis of cytokines and inflammatory mediators in the brain parenchyma, which are typically associated with tissue injury[3]. First, inflammatory events in the thoracic abdominal cavity are signalled to the brain through vagal-nerve sensory afferents, and in turn the vagal efferent outflow might modify these inflammatory events through acetylcholine secretion[4]. Second, cytokines and inflammatory mediators that are induced at the site of inflammation enter the blood and communicate directly with macrophages and other cells in the circumventricular organs that lack a blood–brain barrier. The signal, communicated by the microglia, then spreads into the parenchyma of the central nervous system (CNS)[5]. Third, the cytokines, inflammatory mediators[5], or indeed the microbial products themselves[6], might interact directly with the brain endothelium, communicating directly across the blood–brain barrier and to perivascular macrophages, possibly through the induction of lipid mediators, in particular, prostaglandin E_2 (PGE_2) (REF. 7). The inflammatory mediators produced in this signalling process do not cause damage to the brain tissue.

Innate inflammation in the brain

Macrophages and microglia (cells of the mononuclear phagocyte lineage) are central to inflammation in chronic neurodegenerative disease. The microglia are characterized in the normal brain by their highly branched morphology and downregulated phenotype[8], which manifests as a low or undetectable expression of cell-surface antigens such as CD45 and MHC class I and class II molecules. These features make microglia a highly atypical population of mononuclear phagocytes (FIG. 1). Although the microglia are phenotypically downregulated, recent imaging studies *in vivo* show that these cells, even in their so-called resting state, are highly active, with their fine processes continually surveying their local microenvironment[9]. The molecular interactions between the microglia and components of the brain parenchyma that result in this downregulated phenotype are beginning to be unravelled; moreover, there is evidence that microglial CD200R (CD200 receptor) recognition of neuronal CD200 (REF. 10), CD45 recognition of neuronal CD22 (REF. 11) and microglial expression of TREM2 (triggering receptor expressed by myeloid cells 2) (REFS 12,13) might have a role. Downregulation of these molecules or their ligands might have a role in the activated microglia phenotype described during ageing or neurodegeneration (see below).

Microglia are exquisitely sensitive to almost any disturbance of brain homeostasis[14], which rapidly causes them to change their morphology and upregulate expression of a range of cell antigens; they are then referred to as 'activated microglia'. It has been proposed that microglia show incremental linear stages of activation and that their functional phenotype might be inferred from their morphology[15] (FIG. 1a), although, in reality, one can conclude very little about microglial function from morphology alone. It is widely recognized that cells of the macrophage lineage exist in many states of activation, including pro-inflammatory, alternatively activated or even anti-inflammatory, following the ingestion of apoptotic cells[16]. It is also apparent that macrophages modify their phenotype during particular stages of an inflammatory response, although the signalling processes involved in these transitions are not known[17]. Moreover, microglia show many states of activation, depending on the nature of the brain injury and the type of tissue degeneration (FIG. 1b). Importantly, they can rapidly switch their phenotype *in vivo* without obvious changes in their morphology (FIGS 1b,2).

Chronic neurodegeneration

To understand how systemic inflammation can alter the microglial phenotype during chronic neurodegeneration, it is necessary to characterize the phenotype before it becomes altered. Suppressing inflammation is now regarded as a leading therapeutic approach in chronic neurodegenerative disease, largely because long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) offers some protection against the development of Alzheimer's disease[18] and Parkinson's disease[19]. Although this protection is relatively modest, it has led to the suggestion that chronic neurodegeneration is accompanied by an inflammatory response that needs to be controlled. However, there is little evidence that this is the case and the mechanism by which these NSAIDs exert their effects is not yet understood.

The available information on inflammatory cells and mediators present in post-mortem brain tissue from patients with Alzheimer's disease has been extensively reviewed[20]. An atypical inflammatory response dominated by cells of the macrophage lineage occurs, with both activation of the resident microglial cells[21] and possible recruitment of monocytes from the blood[22]. As mentioned above, activated microglia adopt a morphologically different phenotype with increased expression of cell-surface antigens[20]; they also surround dense-core (senile) amyloid-$\beta_{1-40/42}$ plaques[23]. The activating stimulus could be either the amyloid itself or the degenerating processes of neurons. *In vitro* studies have investigated how

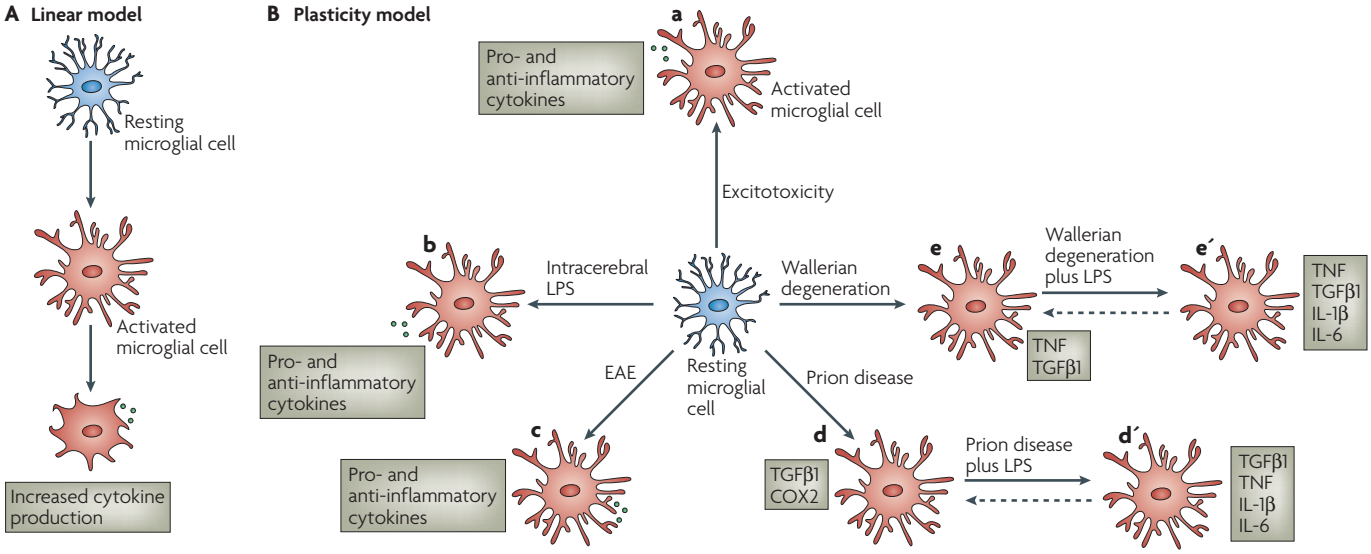

Figure 1 | **Models of activation of microglia.** Microglia in the normal, healthy brain have a highly branched morphology and a downregulated phenotype. In response to injury and disease they rapidly change their morphology and upregulate a number of cell-surface and intracellular antigens — such microglia are generally referred to as activated. **A** | A linear model of activation proposes that resting microglia are activated by a stimulus such that the degree of injury determines the degree of morphological change and pro-inflammatory-mediator production. **B** | By contrast, a plasticity model proposes that cells of the phagocyte lineage are sensitive to the precise nature of the stimulus, its intensity, the time for which it is present and many other factors. Therefore, in different pathological states, activated microglia might synthesize a range of different cytokines. They probably also secrete a different range of other inflammatory mediators and molecules (such as proteases, metalloproteases and acute-phase proteins) that is not illustrated here. The profiles in different forms of injury and disease that are shown are: a model of excitotoxicity (acute neuronal injury) (**Ba**)[90], intracerebral lipopolysaccharide (LPS) challenge (**Bb**)[44], experimental allergic encephalomyelitis (EAE) (**Bc**), prion disease (**Bd**)[44], and Wallerian degeneration (K. Palin, personal communication) (**Be**). It is important to note that these different states are not fixed or immutable, but can be switched between one state and another by a further stimulus, such as an LPS challenge in **Bd** to **Bd′** (REF. 2) and **Be** to **Be′** (K. Palin, personal communication). COX2, cyclooxygenase-2; IL, interleukin; TGFβ1, transforming growth factor-β1; TNF, tumour-necrosis factor.

amyloid-β and disease-associated prion protein (PrP^{sc}) peptides activate macrophages or microglia[24,25] and engage the phagocytic machinery[26,27]. However, the rapid addition of a high concentration of a fibrillar peptide to cultured microglia does not represent the slow and inexorable accumulation of amyloid that is seen in these degenerative diseases. In fact, what is remarkable about the plaques observed in diseased brain is their persistence despite the apparent attentions of activated microglia. It seems that the microglia are not appropriately activated to effect clearance, and that their chronic exposure to the same stimulus, over months, probably downregulates this response, as has been reported for repeated exposure of microglia to lipopolysaccharide (LPS)[28].

Much has been written about the role of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), in Alzheimer's disease[29], but there remains little direct evidence to support it. Although widely referred to as overexpressed, cytokines in most animal models are in fact present at very low levels. Quantification of IL-1β and other cytokines has been inconsistent between laboratories and even between consecutive studies from the same laboratory[30–33]. Furthermore, in these models, animals with cytokine gene deletions have not been shown to be protected against the development of pathology, whereas, in the same models, deletion of the pro-inflammatory complement factor C3 has been shown to exacerbate amyloidosis and to induce neurodegeneration[34]. Together, these data indicate that the inflammatory response in the CNS in animal models of Alzheimer's disease is tightly controlled.

Comparison with other models of chronic neurodegenerative disease is informative. In the G93A-SOD1 model of amyotrophic lateral sclerosis (which primarily affects the lower and upper motor neurons that are crucial for voluntary movement), the pro-inflammatory cytokine expression profile is limited. There are several reports of elevated pro-inflammatory cytokine expression, but the increases are only twofold to fourfold[35]; the protein products of these genes are not generally examined, but where they have been assessed they are elevated less than twofold[36]. It has also been shown that IL-1β expression was not required for normal disease progression[37]. In models of Parkinson's disease, the transcription of pro-inflammatory cytokines is modestly increased[38,39], and both genetic manipulation of cytokines and pharmacological disruption of some aspects of inflammation have shown inconsistent effects[39–41]. In mouse prion disease, low levels of transcription of pro-inflammatory genes and undetectable levels of cytokine protein have been observed in the brain[42,43], whereas clear expression of the anti-inflammatory cytokine transforming growth factor-β1 (TGFβ1) has been observed[44]. Similarly, knockouts of cytokine genes or their receptors have either minor or no effects on disease progression[45–47].

Interestingly, whereas most inflammatory mediators are elevated twofold to fourfold in the CNS, tumour-necrosis factor (TNF) transcription is considerably higher in many models, including those for prion disease, amyotrophic lateral sclerosis and Parkinson's disease, but the expression of the TNF protein is rarely, if ever, detected. It is important to note that TNF is tightly controlled at a translational level by anti-inflammatory molecules such as TGFβ1 and IL-10[48,49], and that high levels of untranslated *TNF* mRNA have been shown to be a feature of primed macrophages in the periphery[50,51]. It is conceivable that this high level of TNF

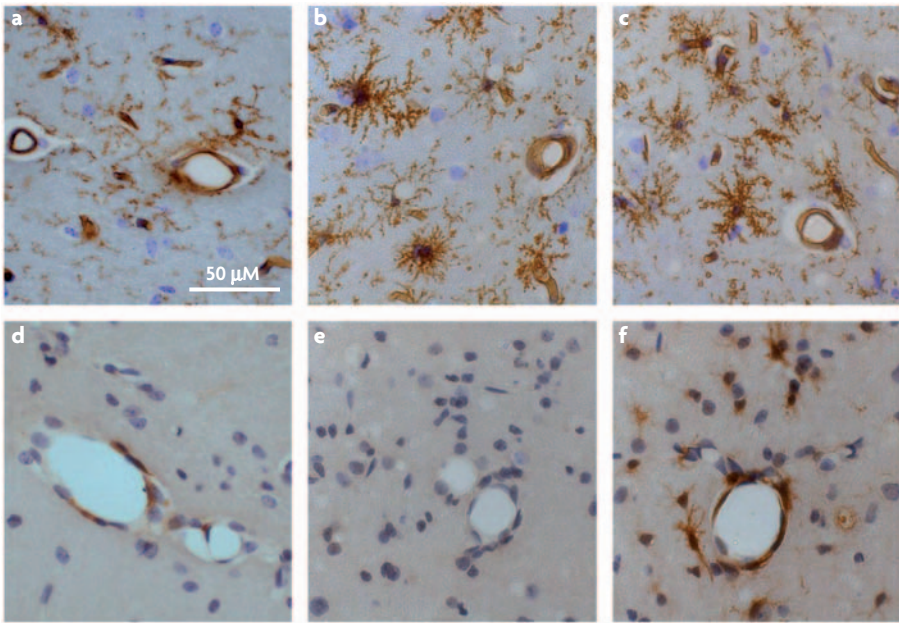

Figure 2 | **Microglial priming and phenotypic switching without morphological change.** The plasticity of 'primed' microglia in mouse prion disease. **a–c** | Photomicrographs of brain sections from animals inoculated with normal brain homogenate and challenged at 18 weeks post-inoculation with lipopolysaccharde (LPS) (**a**), from the ME7 strain of prion disease and challenged at 18 weeks post-inoculation with saline (**b**), and from the ME7 strain of prion disease and challenged at 18 weeks post-inoculation with LPS (**c**). The sections were labelled with tomato lectin, which labels both microglia and the endothelium (stained brown), whereas all nuclei were counterstained blue. Panel **a** shows microglia with a highly branched morphology, whereas panels **b** and **c** show an activated morphology. **d–f** | Similar sections stained with an antibody against the cytokine interleukin-1β (IL-1β), which is known to exacerbate damage to compromised neurons. **d** | Only cells associated with the endothelium are IL-1β positive (stained brown) after intraperitoneal LPS challenge to animals injected with normal brain homogenate. **e** | Despite clear morphological signs of activation of microglia from animals with prion disease seen in panel **b**, when stained for IL-1β, these cells are all negative. **f** | Prion-diseased animals challenged systemically with LPS are morphologically indistinguishable from those not challenged with LPS in panel **b** but synthesize easily detectable levels of IL-1β protein (**f**). This is a clear indication of a phenotypic switch without morphological change.

transcription with minimal translation is a signature of primed microglia in the brain.

The key point here is that, whether described in the literature as elevation of pro-inflammatory cytokines or as a low-level inflammatory response, increases in cytokine expression in mouse models of chronic neurodegeneration are very subtle. Despite a 10–20-fold increase in microglia numbers in models of prion disease or Parkinson's disease, the amounts of cytokines produced are dwarfed by the levels induced by acute microbial challenge[38,42,43]. This indicates that the pro-inflammatory response to neurodegeneration is kept under tight control, probably by appropriate anti-inflammatory mediators such as IL-10, PGE_2 and TGFβ1, and there is evidence that in the ageing brain anti-inflammatory mediators such as IL-10 are decreased[52]. This tight control probably represents the lesser of two evils. The macrophage response to phagocytosis of apoptotic cells is characterized by synthesis of these molecules[49,53], and it seems that chronic neurodegeneration gives rise to a similar anti-inflammatory microglial phenotype[54]. The disruption of this anti-inflammatory state has deleterious consequences for the progression of disease, as blocking TGFβ1 activity by expressing an exogenous inhibitor decorin[55] or deleting IL-10 (REF. 56) both exacerbate the pathology of prion disease.

Microglial priming in animal models

A key point that illustrates the modest degree of microglia activation in animal models of Alzheimer's disease is the improved clearance of amyloid plaques that occurs following secondary challenges such as administration of LPS[57,58], intracranial administration of amyloid-β-specific antibodies[59], and active and passive immunization strategies[60,61].

However, the potential benefits of enhanced or altered activation of the innate inflammatory response in the diseased brain come at a cost. We have proposed that the activated microglia observed in the brains of mice with prion disease, although exhibiting an anti-inflammatory phenotype, are primed by the ongoing pathology, and that their phenotype can be switched by an inflammatory challenge[62]. This phenotypic switching is manifested as an increased production of IL-1β after peripheral LPS challenges (FIG. 2), and increased cytokine production is in turn associated with an increased sickness-behaviour response[1]. We have further shown that the switch in cytokine profile also includes increased *TNF*, *IL6* and inducible nitric-oxide synthase (*iNOS*) mRNA. This cytokine profile is associated with increased numbers of neurons undergoing apoptosis[2] and an accelerated appearance of neurological symptoms associated with later stages of the disease (C.C., unpublished observations). This phenotype switching truly represents microglial priming, as neither prion disease nor intracerebral challenges of normal animals with LPS induces detectable microglial iNOS, but intracerebral challenges of prion-diseased animals with LPS produces readily detectable microglial iNOS[2].

Inflammatory exacerbation is not particular to prion disease: a similar pattern of exaggerated sickness behaviour following LPS challenge has also been observed in aged mice[63] in which the response is accompanied by increased cytokine expression in the CNS. It is known that neurodegeneration occurs during normal ageing, and this is associated with microglial activation[64] and modest increases in pro-inflammatory cytokine expression[65]. An exaggerated pro-inflammatory cytokine response to a cortical stab injury in aged animals has also been reported[66], and more recent studies have shown that hippocampal-dependent learning deficits are induced by peripheral LPS in aged rats but not in younger controls[67]. Blood and brain cytokine levels show that the exaggerated effect occurs only in the brain[67].

In mouse models of Alzheimer's disease, several similar observations have now been made. Increased transcription of cytokines and altered amyloid-β processing in the brain after LPS challenges in the Tg2576 model have been reported[33]. Similar increases in cytokine transcription and also translation of iNOS in the presenilin-1 (PSEN1)-mutation knock-in model of Alzheimer's disease have also been shown[68]. In the triple-transgenic model of Alzheimer's disease, in which the animals have mutations in three key genes that are defective in

Box 2 | **Dementia and delirium**

Dementia of the Alzheimer's type

Dementia is a syndrome resulting from disease of the brain, usually of a chronic and progressive nature, in which there is a disturbance of multiple higher cortical functions including memory and, in most subjects, neuropsychiatric features, such as apathy and depression. Alzheimer's disease is characterized by an insidious onset with a steady progression and is the most common cause of dementia, affecting around 15% of the population over the age of 75 years. The biggest risk factor for Alzheimer's disease is increasing age, with genetic influences becoming less important as the age of onset increases. Diagnosis is largely dependent on the exclusion of other diseases that would otherwise be sufficient to account for the dementia syndrome.

Delirium

Delirium is also a syndrome caused by disease of the brain, usually of an acute, fluctuating and transient nature, in which there is a disturbance of multiple higher cortical functions. Although symptoms can include neuropsychiatric features, the core features are altered consciousness and disturbed attention and concentration. Differential diagnosis from Alzheimer's disease can be difficult and usually depends on acute onset and fluctuating course. The biggest risk factors for delirium are increasing age and dementia, and the most common acute triggers for episodes of delirium in these populations are systemic infections, surgery, stress and drug interactions. Delirium, therefore, often appears superimposed on a background of dementia (as in FIG. 3b), and there might be overlap in the aetiologies of these cognitive disturbances.

patients with early onset Alzheimer's disease (*APP*, *PSEN1* and *TAU*), repeated challenges with LPS were shown to exacerbate CNS inflammation and to cause increased TAU hyperphosphorylation[69], a key step in the formation of neurofibrillary tangles, one of the main features of the pathology of Alzheimer's disease. Repeated systemic challenges with high doses of LPS in the $SOD1^{G37R}$ model of amyotrophic lateral sclerosis also led to the exacerbation of symptoms, the increased loss of motor neurons and a shortened survival time[70].

Therefore, in several animal models of chronic neurodegenerative conditions, it seems that microglia become primed by the ongoing pathology. They are then susceptible to phenotype switching following peripheral inflammatory challenges. This results in elevated expression of cytokines and consequent activation of downstream cascades that are capable of inducing damaging molecules such as iNOS. This has clear consequences for the progression of disease.

Development of Alzheimer's disease

Ageing is accompanied by an age-dependent upregulation of the inflammatory response, due perhaps in part to recurrent or chronic systemic infections that bombard the immune system throughout life. Systemic infections and other systemic inflammatory events are the main cause of delirium in the elderly (BOX 2). Delirium has been shown in several studies to be associated with a significantly increased risk of developing dementia[71,72]. Delirium has many clinical features in common with Alzheimer's disease, including impaired cognition and the development of various neuropsychiatric features. Indeed, the clinical differentiation of dementia and delirium is often difficult to make and is largely dependent on the acute, as opposed to chronic, nature of the confusional state (BOX 2). Patients with dementia are particularly susceptible to developing delirium, indicating similar aetiological pathways[73].

Importantly, the risk of developing Alzheimer's disease is also increased following the development of an infection in the absence of an obvious delirium. In a retrospective general-practitioner database study, the presence of two or more infections over a 4-year follow-up period increased the odds of developing Alzheimer's disease by around twofold[74]. The finding that the risk of developing the disease rose with increasing age is consistent with the known decline in risk related to genetic influences with increasing age. Evidence that systemic inflammation in general is a risk factor for the future development of Alzheimer's disease has been found in a number of studies. Inflammatory proteins in the plasma, notably C-reactive protein and IL-6, were found to be increased 5 years before the clinical onset of dementia in several studies,

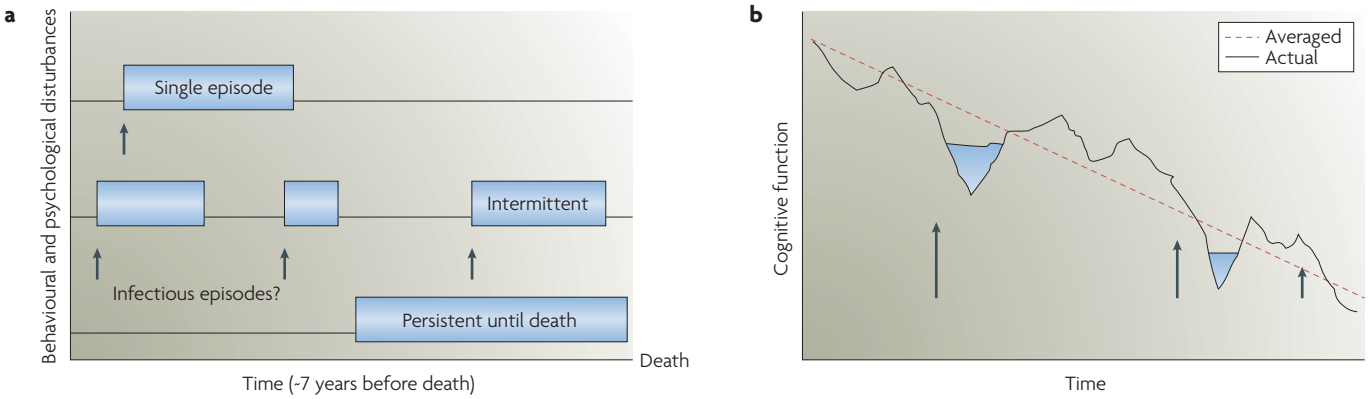

Figure 3 | **Fluctuating symptoms in Alzheimer's disease. a** | The behavioural and psychological problems associated with Alzheimer's disease do not show a simple relationship to cognitive decline, but can show a number of different patterns — a single episode of such problems, intermittent episodes and persistent behavioural and psychological problems until death. It is possible that the onset of these symptoms is associated with systemic inflammation. Instances of systemic inflammation are illustrated schematically by the arrows. **b** | The decline in cognitive function in people with Alzheimer's disease is often shown as a steady, continuous decline (red line). However, we know that the decline is in fact highly variable for each individual. The schematic diagram illustrates how cognition in an individual can vary over time and how systemic infection at particular times (arrows) might induce fluctuations in cognition that are sufficiently severe to meet the criteria for classification as delirium (shaded areas). There is recovery of function as the infection recedes, but the deficit might not be completely reversed. Panel **a** adapted with permission from REF. 82 © (1999) Royal College of Psychiatrists.

compared with age-matched individuals who did not go on to develop dementia[75,76]. Other proposed environmental risk factors for Alzheimer's disease, such as type 2 diabetes[77], depression[78] and head injury[79], have all been associated with an increased systemic inflammatory response.

As described above, sickness behaviour (BOX 1) is a well-recognized consequence of various systemic infections and inflammatory responses[3]. All of these symptoms are commonly present in patients with Alzheimer's disease, but apathy is the most common symptom, with a disease prevalence of around 75% (REF. 80); it has also been shown to be associated with a markedly increased rate of cognitive decline in these subjects[81]. Few prospective studies have followed the natural course of these symptoms in Alzheimer's disease but, in keeping with the hypothesis that they are a consequence of systemic inflammatory events, they are largely non-persistent and periodic in nature, with a highly variable period of duration[82] (FIG. 3a).

There is recent evidence to indicate that symptoms of sickness behaviour precede cognitive decline, which is an essential diagnostic feature of Alzheimer's disease. In a 6-year prospective population-based study of dementia, the greatest risk factor, apart from old age, was the perception of poor health by the subject. Subjects with no evidence of cognitive impairment but with self-perceived poor health were four times as likely to develop dementia as those with self-perceived good health[83]. A recent study, attempting to identify patients with mild cognitive impairment who were at increased risk of cognitive decline, found that 92% of subjects with mild cognitive impairment, who also had symptoms of apathy, developed Alzheimer's disease within 1 year, compared with the 27% of subjects without apathy[84]. Apathy, therefore, might act as an early clinical indicator of elevated pro-inflammatory cytokines in the CNS in subjects with chronic neurodegeneration.

Progression of Alzheimer's disease

Current diagnostic criteria[85] emphasize the gradual progression of amnesia and other cognitive deficits in Alzheimer's disease, as opposed to the fluctuating progressive course of cognitive deficits that is seen in other neurodegenerative diseases (such as dementia with Lewy bodies, which are abnormal cytoplasmic inclusions found in neurons, vascular dementia and delirium). However, marked fluctuation in cognitive performance is also seen in Alzheimer's disease (FIG. 3b), and this is evident from a large number of studies that have examined cognitive performance over short and long periods of time[86,87]. Direct evidence in humans that systemic inflammatory events affect Alzheimer's disease is shown in a 2-month study of subjects with Alzheimer's disease, in which systemic infections and raised plasma levels of IL-1β are both associated with an increased rate of cognitive decline[88].

Conclusions

As the population ages, and the number of individuals with chronic neurodegenerative diseases increases, relatively common systemic infection and inflammation will become significant environmental risk factors for a poor quality of life, with the potential to increase the prevalence of devastating degenerative diseases. The immune-system–brain interface is a crucial route for communication between the brain in health and disease and the pathogens and toxins present in our environment. At present, research on the impact of systemic infection on chronic neurodegeneration seems to involve sporadic studies in various disease models, without mention of similar studies in other models or in the clinical literature. Therefore, this field is still in its infancy. A better understanding of the routes of communication between the peripheral immune system and the brain, and the mechanisms by which microglia switch their phenotype, is essential, if we are to develop strategies to counteract the consequences of systemic inflammation on the brain in an ageing population.

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1. Combrinck, M. I., Perry, V. H. & Cunningham, C. Peripheral infection evokes exaggerated sickness behaviour in pre-clinical murine prion disease. *Neuroscience* **112**, 7–11 (2002).
2. Cunningham, C., Wilcockson, D. C., Campion, S., Lunnon, K. & Perry, V. H. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J. Neurosci.* **25**, 9275–9284 (2005).
3. Dantzer, R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. *Eur. J. Pharmacol.* **500**, 399–411 (2004).
4. Tracey, K. J. The inflammatory reflex. *Nature* **420**, 853–859 (2002).
5. Laflamme, N. & Rivest, S. Effects of systemic immunogenic insults and circulating proinflammatory cytokines on the transcription of the inhibitory factor κBα within specific cellular populations of the rat brain. *J. Neurochem.* **73**, 309–321 (1999).
6. Chakravarty, S. & Herkenham, M. Toll-like receptor 4 on nonhematopoietic cells sustains CNS inflammation during endotoxemia, independent of systemic cytokines. *J. Neurosci.* **25**, 1788–1796 (2005).
7. Ek, M. *et al*. Inflammatory response: pathway across the blood–brain barrier. *Nature* **410**, 430–431 (2001).
8. Perry, V. H. & Gordon, S. Macrophages and microglia in the nervous system. *Trends Neurosci.* **11**, 273–277 (1988).
9. Nimmerjahn, A., Kirchhoff, F. & Helmchen, F. Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. *Science* **308**, 1314–1318 (2005).
10. Hoek, R. M. *et al*. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science* **290**, 1768–1771 (2000).
11. Mott, R. T. *et al*. Neuronal expression of CD22: novel mechanism for inhibiting microglial proinflammatory cytokine production. *Glia* **46**, 369–379 (2004).
12. Daws, M. R. et al. Pattern recognition by TREM-2: binding of anionic ligands. *J. Immunol.* **171**, 594–599 (2003).
13. Schmid, C. D. *et al*. Heterogeneous expression of the triggering receptor expressed on myeloid cells-2 on adult murine microglia. *J. Neurochem.* **83**, 1309–1320 (2002).
14. Kreutzberg, G. W. Microglia: a sensor for pathological events in the CNS. *Trends Neurosci.* **19**, 312–318 (1996).
15. Raivich, G. *et al*. Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res. Brain Res. Rev.* **30**, 77–105 (1999).
16. Gordon, S. Alternative activation of macrophages. *Nature Rev. Immunol.* **3**, 23–35 (2003).
17. Stout, R. D. *et al*. Macrophages sequentially change their functional phenotype in response to changes in microenvironmental influences. *J. Immunol.* **175**, 342–349 (2005).
18. Etminan, M., Gill, S. & Samii, A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ* **327**, 128 (2003).
19. Chen, H. *et al*. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. *Ann. Neurol.* **58**, 963–967 (2005).
20. Akiyama, H. *et al*. Inflammation and Alzheimer's disease. *Neurobiol. Aging* **21**, 383–421 (2000).
21. McGeer, P. L., Itagaki, S., Tago, H. & McGeer, E. G. Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci. Lett.* **79**, 195–200 (1987).
22. Simard, A. R., Soulet, D., Gowing, G., Julien, J. P. & Rivest, S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* **49**, 489–502 (2006).
23. D'Andrea, M. R., Cole, G. M. & Ard, M. D. The microglial phagocytic role with specific plaque types in the Alzheimer disease brain. *Neurobiol. Aging* **25**, 675–683 (2004).
24. Combs, C. K., Karlo, J. C., Kao, S. C. & Landreth, G. E. β-Amyloid stimulation of microglia and monocytes results in TNFα-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. *J. Neurosci.* **21**, 1179–1188 (2001).
25. Brown, D. R., Schmidt, B. & Kretzschmar, H. A. Role of microglia and host prion protein in neurotoxicity of a prion protein fragment. *Nature* **380**, 345–347 (1996).
26. Bamberger, M. E., Harris, M. E., McDonald, D. R., Husemann, J. & Landreth, G. E. A cell surface receptor complex for fibrillar β-amyloid mediates microglial activation. *J. Neurosci.* **23**, 2665–2674 (2003).
27. Koenigsknecht, J. & Landreth, G. Microglial phagocytosis of fibrillar β-amyloid through a β1 integrin-dependent mechanism. *J. Neurosci.* **24**, 9838–9846 (2004).
28. Ajmone-Cat, M. A., Nicolini, A. & Minghetti, L. Prolonged exposure of microglia to lipopolysaccharide modifies the intracellular signaling pathways and selectively promotes prostaglandin E2 synthesis. *J. Neurochem.* **87**, 1193–1203 (2003).
29. Griffin, W. S. & Mrak, R. E. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. *J. Leukoc. Biol.* **72**, 233–238 (2002).

30. Lim, G. P. *et al*. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J. Neurosci.* **20**, 5709–5714 (2000).
31. Lim, G. P. *et al*. Ibuprofen effects on Alzheimer pathology and open field activity in APPsw transgenic mice. *Neurobiol. Aging* **22**, 983–991 (2001).
32. Quinn, J. *et al*. Inflammation and cerebral amyloidosis are disconnected in an animal model of Alzheimer's disease. *J. Neuroimmunol.* **137**, 32–41 (2003).
33. Sly, L. M. *et al*. 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 (2001).
34. Wyss-Coray, T. *et al*. Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proc. Natl Acad. Sci. USA* **99**, 10837–10842 (2002).
35. Hensley, K. *et al*. Temporal patterns of cytokine and apoptosis-related gene expression in spinal cords of the G93A-SOD1 mouse model of amyotrophic lateral sclerosis. *J. Neurochem.* **82**, 365–374 (2002).
36. Hensley, K. *et al*. Message and protein-level elevation of tumor necrosis factor α (TNFα) and TNFα-modulating cytokines in spinal cords of the G93A-SOD1 mouse model for amyotrophic lateral sclerosis. *Neurobiol. Dis.* **14**, 74–80 (2003).
37. Nguyen, M. D., Julien, J. P. & Rivest, S. Induction of proinflammatory molecules in mice with amyotrophic lateral sclerosis: no requirement for proapoptotic interleukin-1β in neurodegeneration. *Ann. Neurol.* **50**, 630–639 (2001).
38. Depino, A. M. *et al*. Microglial activation with atypical proinflammatory cytokine expression in a rat model of Parkinson's disease. *Eur. J. Neurosci.* **18**, 2731–2742 (2003).
39. Sriram, K. *et al*. Mice deficient in TNF receptors are protected against dopaminergic neurotoxicity: implications for Parkinson's disease. *FASEB J.* **16**, 1474–1476 (2002).
40. Rousselet, E. et al. Role of TNF-α receptors in mice intoxicated with the parkinsonian toxin MPTP. *Exp. Neurol.* **177**, 183–192 (2002).
41. Leng, A., Mura, A., Feldon, J. & Ferger, B. Tumor necrosis factor-α receptor ablation in a chronic MPTP mouse model of Parkinson's disease. *Neurosci. Lett.* **375**, 107–111 (2005).
42. Brown, A. R. *et al*. Inducible cytokine gene expression in the brain in the ME7/CV mouse model of scrapie is highly restricted, is at a strikingly low level relative to the degree of gliosis and occurs only late in disease. *J. Gen. Virol.* **84**, 2605–2611 (2003).
43. Cunningham, C., Wilcockson, D. C., Boche, D. & Perry, V. H. Comparison of inflammatory and acute-phase responses in the brain and peripheral organs of the ME7 model of prion disease. *J. Virol.* **79**, 5174–5184 (2005).
44. Cunningham, C., Boche, D. & Perry, V. H. Transforming growth factor β1, the dominant cytokine in murine prion disease: influence on inflammatory cytokine synthesis and alteration of vascular extracellular matrix. *Neuropathol. Appl. Neurobiol.* **28**,107–119 (2002).
45. Felton, L. M. *et al*. MCP-1 and murine prion disease: Separation of early behavioural dysfunction from overt clinical disease. *Neurobiol. Dis.* **20**, 283–295 (2005).
46. Mabbott, N. A. *et al*. Tumor necrosis factor α-deficient, but not interleukin-6-deficient, mice resist peripheral infection with scrapie. *J. Virol.* **74**, 3338–3344 (2000).
47. Schultz, J. et al. Role of interleukin-1 in prion disease-associated astrocyte activation. *Am. J. Pathol.* **165**, 671–678 (2004).
48. Bogdan, C., Paik, J., Vodovotz, Y. & Nathan, C. Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-β and interleukin-10. *J. Biol. Chem.* **267**, 23301–23308 (1992).
49. McDonald, P. P., Fadok, V. A., Bratton, D. & Henson, P. M. Transcriptional and translational regulation of inflammatory mediator production by endogenous TGF-β in macrophages that have ingested apoptotic cells. *J. Immunol.* **163**, 6164–6172 (1999).
50. Schook, L. B., Albrecht, H., Gallay, P. & Jongeneel, C. V. Cytokine regulation of TNF-α mRNA and protein production by unprimed macrophages from C57Bl/6 and NZW mice. *J. Leukoc. Biol.* **56**, 514–520 (1994).
51. Chantry, D., Turner, M., Abney, E. & Feldmann, M. Modulation of cytokine production by transforming growth factor-β. *J. Immunol.* **142**, 4295–4300 (1989).
52. Ye, S. M. & Johnson, R. W. An age-related decline in interleukin-10 may contribute to the increased expression of interleukin-6 in brain of aged mice. *Neuroimmunomodulation* **9**, 183–192 (2001).
53. De Simone, R., Ajmone-Cat, M. A., Carnevale, D. & Minghetti, L. Activation of α7 nicotinic acetylcholine receptor by nicotine selectively up-regulates cyclooxygenase-2 and prostaglandin E2 in rat microglial cultures. *J. Neuroinflammation* **2**, 4 (2005).
54. Cunningham, C. *et al*. Synaptic changes characterize early behavioural changes in the ME7 model of murine prion disease. *Eur. J. Neurosci.* **17**, 2147–2155 (2003).
55. Boche, D., Cunningham, C., Docagne, F., Scott, H. & Perry, V. H. TGFβ1 regulates the inflammatory response during chronic neurodegeneration. *Neurobiol. Dis.* **22**, 638–650 (2006).
56. Thackray, A. M., McKenzie, A. N., Klein, M. A., Lauder, A. & Bujdoso, R. Accelerated prion disease in the absence of interleukin-10. *J. Virol.* **78**, 13697–13707 (2004).
57. DiCarlo, G., Wilcock, D., Henderson, D., Gordon, M. & Morgan, D. Intrahippocampal LPS injections reduce Aβ load in APP + PS1 transgenic mice. *Neurobiol. Aging* **22**, 1007–1012 (2001).
58. Herber, D. L. *et al*. Time-dependent reduction in Aβ levels after intracranial LPS administration in APP transgenic mice. *Exp. Neurol.* **190**, 245–253 (2004).
59. Wilcock, D. M. et al. Microglial activation facilitates Aβ plaque removal following intracranial anti-Aβ antibody administration. *Neurobiol. Dis.* **15**, 11–20 (2004).
60. Bard, F. *et al*. Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nature Med.* **6**, 916–919 (2000).
61. Schenk, D. *et al*. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* **400**, 173–177 (1999).
62. Perry, V. H., Newman, T. A. & Cunningham, C. The impact of systemic infection on the progression of neurodegenerative disease. *Nature Rev. Neurosci.* **4**, 103–112 (2003).
63. Godbout, J. P. *et al*. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *FASEB J.* **19**, 1329–1331 (2005).
64. Perry, V. H., Matyszak, M. K. & Fearn, S. Altered antigen expression of microglia in the aged rodent CNS. *Glia* **7**, 60–67 (1993).
65. Godbout, J. P. & Johnson, R. W. Interleukin-6 in the aging brain. *J. Neuroimmunol.* **147**, 141–144 (2004).
66. Kyrkanides, S., O'Banion, M. K., Whiteley, P. E., Daeschner, J. C. & Olschowka, J. A. Enhanced glial activation and expression of specific CNS inflammation-related molecules in aged versus young rats following cortical stab injury. *J. Neuroimmunol.* **119**, 269–277 (2001).
67. Barrientos, R. M. *et al*. Peripheral infection and aging interact to impair hippocampal memory consolidation. *Neurobiol. Aging* **27**, 723–732 (2006).
68. Lee, J., Chan, S. L. & Mattson, M. P. Adverse effect of a presenilin-1 mutation in microglia results in enhanced nitric oxide and inflammatory cytokine responses to immune challenge in the brain. *Neuromolecular Med.* **2**, 29–45 (2002).
69. Kitazawa, M., Oddo, S., Yamasaki, T. R., Green, K. N. & LaFerla, F. M. 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 (2005).
70. Nguyen, M. D., D'Aigle, T., Gowing, G., Julien, J. P. & Rivest, S. Exacerbation of motor neuron disease by chronic stimulation of innate immunity in a mouse model of amyotrophic lateral sclerosis. *J. Neurosci.* **24**, 1340–1349 (2004).
71. McCusker, J., Cole, M., Dendukuri, N., Belzile, E. & Primeau, F. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. *Can. Med. Assoc. J.***165**, 575–583 (2001).
72. Rahkonen, T., Luukkainen-Markkula, R., Paanila, S., Sivenius, J. & Sulkava, R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: a 2 year follow up study. *J. Neurol. Neurosurg. Psychiatry* **69**, 519–521 (2000).
73. Fick, D. M., Agostini, J. V. & Inouye, S. K. Delirium superimposed on dementia: a systematic review. *J. Am. Geriatr. Soc.* **50**, 1723–1732 (2002).
74. Dunn, N., Mullee, M., Perry, V. H. & Holmes, C. Association between dementia and infectious disease: evidence from a case–control study. *Alzheimer Dis. Assoc. Disord.* **19**, 91–94 (2005).
75. Engelhart, M. J. *et al*. Inflammatory proteins in plasma and the risk of dementia: The Rotterdam Study. *Arch. Neurol.* **61**, 668–672 (2004).
76. Tilvis, R. S. *et al*. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J. Gerontol. A* **59**, 268–274 (2004).
77. Ott, A. *et al*. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**, 1937–1942 (1999).
78. Andersen, K., Lolk, A., Kragh-Sorensen, P., Petersen, N. E. & Green, A. Depression and the risk of Alzheimer disease. *Epidemiology* **16**, 233–238 (2005).
79. Fleminger, S., Oliver, D. L., Lovestone, S., Rabe-Hesketh, S. & Giora, A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* **74**, 857–862 (2003).
80. Craig, D., Mirakhur, A., Hart, D. J., McIlroy, S. P. & Passmore, A. P. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am. J. Geriatr. Psychiatry* **13**, 460–468 (2005).
81. Starkstein, S. E., Jorge, R., Mizrahi, R. & Robinson, R. G. A prospective longitudinal study of apathy in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **77**, 8–11 (2006).
82. Hope, T., Keene, J., Fairburn, C. G., Jacoby, R. & McShane, R. Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease. A longitudinal study. *Br. J. Psychiatry* **174**, 39–44 (1999).
83. Yip, A. G., Brayne, C. & Matthews, F. E. Risk factors for incident dementia in England and Wales: The Medical Research Council Cognitive Function and Ageing Study. A population-based nested case-control study. *Age Ageing* **35**, 154–160 (2006).
84. Robert, P. H. *et al*. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease. A one-year follow-up study. *Clin. Neurol. Neurosurg.* **108**, 733–736 (2006).
85. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* 4th edn (American Psychiatric Association, Washington DC, 1994).
86. Clark, C. M. *et al*. Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer's Disease. *Arch. Neurol.* **56**, 857–862 (1999).
87. Holmes, C. & Lovestone, S. Long-term cognitive and functional decline in late onset Alzheimer's disease: therapeutic implications. *Age Ageing* **32**, 200–204 (2003).
88. Holmes, C. *et al*. Systemic infection, interleukin 1β, and cognitive decline in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **74**, 788–789. (2003).
89. Hart, B. L. Biological basis of the behavior of sick animals. *Neurosci. Biobehav. Rev.* **12**, 123–137 (1988).
90. Blond, D., Campbell, S. J., Butchart, A. G., Perry, V. H. & Anthony, D. C. Differential induction of interleukin-1β and tumour necrosis factor-α may account for specific patterns of leukocyte recruitment in the brain. *Brain Res.* **958**, 89–99 (2002).

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