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At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response

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Abstract

Delirium is a common and severe neuropsychiatric syndrome characterised by acute deterioration and fluctuations in mental status. It is precipitated mainly by acute illness, trauma, surgery, or drugs. Delirium affects around 1 in 8 hospital inpatients and is associated with multiple adverse consequences, including new institutionalisation, worsening of existing dementia, and death. Patients with delirium show attentional and other cognitive deficits, altered alertness (mostly reduced, but some patients develop agitation and hyperactivity), altered sleep-wake cycle and psychoses. The pathways from the various aetiologies to the heterogeneous clinical presentations are hardly studied and are poorly understood. One of the key questions, which research is only now beginning to address, is how the factors determining susceptibility interact with the stimuli that trigger delirium. Inflammatory signals arising during systemic infection evoke sickness behaviour, a coordinated set of adaptive changes initiated by the host to respond to, and to counteract, infection. It is now clear that the same systemic inflammatory signals can have severe deleterious effects on brain function when occurring in old age or in the presence of neurodegenerative disease. Multiple animal studies now show that even mild acute systemic inflammation can induce exaggerated sickness behaviour responses and cognitive dysfunction in aged animals or those with prior degenerative pathology when compared to young and/or healthy controls. These findings appear highly promising in understanding aspects of delirium. In this review our aim is to describe and assess the parallels between exaggerated sickness behaviour in vulnerable animals and delirium in older humans. We discuss inflammatory and stress-related triggers of delirium in the context of new animal models that allow us to dissect some aspects of the mechanisms underpinning these episodes. We discuss some differences between the sickness behaviour syndrome model and delirium in the context of the complexity in the latter due to other factors such as prior pathology, psychological stress and drug effects. We conclude that, with appropriate caveats, the study of sickness behaviour in the vulnerable brain offers a promising route to uncover the mechanisms of this common and serious unmet medical need.

Keywords

Delirium; Sickness behaviour; Dementia; Acetylcholine; Cognitive; Systemic inflammation; IL-1 β ; prostaglandin

Introduction

Delirium is a common and severe neuropsychiatric syndrome characterised by acute deterioration and fluctuations in mental status mainly precipitated by acute illness, trauma, surgery, or the side effects of drugs. The core DSM-IV diagnostic criteria are: (a) a disturbance of consciousness (that is, reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention), (b) a change in cognition (eg. memory impairment) or a perceptual disturbance, and (c) onset of hours to days, and tendency to fluctuate. Delirium is one of the most common acute medical conditions. The overall prevalence in medical inpatients is greater than 10%; in older patients this rises to greater than 20% and in intensive care units and post-operative hip fracture patients the prevalence is greater than 50%. In a typical 1000-bedded hospital, around 120 people will have delirium at any given time. There are currently no licensed treatments.

Although by definition delirium has an acute onset and always involves attentional deficits, it is otherwise heterogeneous, with the variable presence of multiple other neuropsychiatric features. Prominent among these is disturbance in level of consciousness, which ranges from barely responsive to highly agitated. A reduced level of consciousness is termed hypoactive delirium, whereas agitation and increased motor activity is termed hyperactive delirium. Many patients fluctuate between these motoric subtypes. Other neuropsychiatric manifestations include impairments in memory, perception and other cognitive domains, psychosis, and disturbance of the sleep-wake cycle (Fong *et al.*, 2009; MacLulich & Hall, 2011).

The time-course of delirium is highly variable. Delirium has conventionally been described as a transient disorder, and indeed it does resolve in the majority of cases. Some patients may experience only a few hours of the syndrome, while others may have more prolonged episodes lasting days or weeks. Recent research has found that around 20% still exhibit symptoms three or even six months after onset; this is termed 'persistent delirium' (Meagher *et al.*, 2012). Notwithstanding the resolution of most delirium, these episodes have serious long term consequences: it is now known that delirium predicts multiple adverse outcomes, including increased length of stay, morbidity, institutionalisation, and mortality during admission and one year after discharge (Witlox *et al.*, 2010). Moreover, in cognitively normal patients, an episode of delirium is associated with a higher risk of dementia in the years following the episode (MacLulich *et al.*, 2009; Davis *et al.*, 2012). Delirium is also often highly distressing for patients and carers (Fong *et al.*, 2009; MacLulich & Hall, 2011) and may result in post-traumatic stress disorder (Davydow *et al.*, 2008).

Pathogenesis of delirium: direct brain insults versus aberrant stress responses

The precipitants of delirium are legion. So numerous and diverse are they that to conceptualise delirium as a homogeneous pathological entity with a single molecular pathway is untenable. Frequent causes include peripheral and systemic infections, changes in medication, surgery, trauma, pain, psychological stress, acute CNS pathology caused by stroke or head trauma, and metabolic derangements such as hypoglycemia, hypoxia, hyponatremia and liver failure (usually termed acute hepatic encephalopathy). To provide a conceptual framework with which to begin to address why and how such multitudinous aetiological factors can induce delirium, we have previously proposed that these triggers be divided into two broad categories: direct brain insults and aberrant stress responses (MacLulich *et al.*, 2008). The category of *direct brain insults* includes triggers in which the brain is adversely affected by either a direct injury, change in metabolic environment or a drug. For example, it is conceptually very simple to accept that hypoglycemia, a recognised cause of delirium, has wide-ranging effects on the CNS that are severe and of acute onset. Likewise, an overdose of morphine often leads to impairments in brain function that meet criteria for delirium. Conversely, the category of *aberrant stress responses* constitute a group of responses that are somehow deficient or exaggerated in certain individuals such that responses that are typically adaptive under normal circumstances become maladaptive. This mostly occurs where there is susceptibility due to old age or pre-existing brain pathology. It is clear that aging and dementia are the major risk factors for development of delirium (Fong *et al.*, 2009) and as such, while almost any individual can experience an episode of delirium if the stimulus is severe enough, these vulnerable individuals can become delirious even upon relatively mild stimuli. Infection is an excellent example of this: intensive care unit (ICU) patients with severe sepsis commonly develop delirium (often termed septic encephalopathy), but much milder infections, that have trivial effects in a young healthy person, can produce severe delirium in older people with dementia (Fong *et al.*, 2009). Therefore one of the key questions, which our research has begun to address (Field *et al.*, 2012; Murray *et al.*, 2012), is how the factors determining susceptibility interact with the stimuli that trigger delirium?

Sickness behaviour syndrome in health

Peripheral infection can lead to changes in mood, energy, motivation and, consequently, behaviour. These changes were generally seen as direct side-effects of infection until Hart proposed the idea of a coordinated sickness behaviour response (Hart, 1988). This constitutes a reorganisation of priorities by the infected individual, suppressing energy expenditure in activities such as locomotor activity, feeding and social interaction to minimise the risk of predation, to isolate the sick individual from the rest of the herd and to allow the retention of energy to raise a fever, which is metabolically costly. Though it is difficult to prove that the changes in behaviour are beneficial to the host during infection, it is clear that failure to mount a fever response is deleterious to survival (Hart, 1988). These changes in behaviour, which are all coordinated by the CNS, can be seen as adaptive and therefore beneficial to the host. We now know that inflammatory mediators such as

cytokines and prostaglandins can signal to the brain, via several routes (see (Dantzer *et al.*, 2008) for review), to effect changes in neuronal function. Some of these mechanisms are briefly summarised below and in figure 1.

Thermoregulatory responses

The fever, or hyperthermic, response is thought to be dependent on IL-1 β -induced, vascular COX-2-mediated, PGE2 production in the hypothalamus. This PGE2 binds to EP3 receptors in the median preoptic nucleus of the hypothalamus to activate GABAergic signalling in autonomic centres involved in thermogenesis (Nakamura *et al.*, 2005; Lazarus *et al.*, 2007).

Anxiety and the stress response

Systemic LPS or IL-1 β induce neuronal activation in the amygdala, as demonstrated by expression of the immediate early gene, cFOS. Based on microdialysis (Engler *et al.*, 2011) and neuroanatomical tracing (Gaykema *et al.*, 2007) studies, IL-1/LPS is believed to trigger release, in the amygdala, of noradrenaline (NA) originating in brain stem areas such as the nucleus tractus solitarius, ventrolateral medulla and the locus coeruleus. These regions can be readily activated by vagal afferents and also via the circumventricular organs (CVOs: regions such as the area postrema, which lack a patent blood brain barrier). The parabrachial nucleus also innervates the amygdala influencing anxiety and feeding responses to systemic inflammation (Gaykema *et al.*, 2007).

The glucocorticoid response is initiated when systemic IL-1 β or LPS triggers PGE2 release at the brain endothelium in the paraventricular nucleus of the hypothalamus, stimulating secretion of adrenocorticotrophic hormone (ACTH) by corticotropin releasing hormone-containing neurons (see (Furuyashiki & Narumiya, 2009) for review). This ACTH stimulates the adrenal glands to secrete glucocorticoids.

Behavioural depression

Systemic inflammation suppresses locomotor activity and also decreases motivation to engage in rewarding activities (anhedonia) such as investigation of a juvenile conspecific, consumption of sweetened solutions and burrowing. The neuroanatomy of these activities is not fully understood. Pure suppression of activity versus altered motivation have not been teased apart in many studies, but activation of the amygdala and multiple hypothalamic nuclei (Park *et al.*, 2008) and deactivation of the hippocampus are involved. Central inhibition of IL-1 β using IL-1RA can reduce cFOS expression in the central nucleus of the amygdala and in the bed nucleus of the stria terminalis, reducing LPS-induced suppression of social interaction (Konsman *et al.*, 2008). However, there is some evidence that perivascular and systemic IL-1 β have a role in the reduced locomotor activity and vagotomy can also limit the induction of behavioural suppression (Konsman *et al.*, 2000). Systemic inhibition of COX-1 also blocked inflammation-induced suppression of burrowing and glucose consumption (Swiergiel & Dunn, 2002; Teeling *et al.*, 2010).

Cognitive changes

There are many reports of inflammation-induced cognitive deficits (Yirmiya & Goshen, 2011). However, a critical caveat is that the suppressing effects of LPS on locomotor speed,

general activity, motivation by rewards and other features necessary for performance in standard rodent tests of cognitive function may confound many of the studies in this area (Cunningham & Sanderson, 2008). Consolidation of memory for context is impaired by inflammation in contextual fear conditioning experiments, and this involves both IL-1 and PGE2 (Hein *et al.*, 2007; Frank *et al.*, 2010). However, in other paradigms, visuospatial learning and memory and learning appears to cope rather well with even quite robust systemic infection (Jurgens *et al.*, 2012) and it is mental flexibility, rather than visuospatial memory per se, that appears to be most impaired under the influence of systemic inflammation (Sparkman *et al.*, 2006; Jurgens *et al.*, 2012). It seems reasonable to state that facets of cognitive function can be impaired, but that severe, global cognitive impairment is perhaps not a core feature of sickness behaviour syndrome (SBS) in normal animals, and longer-term memories of aversive events may even be enhanced.

Human sickness behaviour

Though the concept has arisen largely in the rodent literature, it is supported by studies in humans. Injections of LPS, typhoid vaccine and interferon- α can cause similar emotional changes and subjective feelings of sickness in humans ((Grigoleit *et al.*, 2011) and references therein). Interestingly, imaging studies in humans have demonstrated similar neural changes underpinning these subjective feelings of sickness (Harrison *et al.*, 2009a; Harrison *et al.*, 2009b; Inagaki *et al.*, 2012). Evidence for systemic inflammation-induced cognitive impairments in healthy individuals is inconsistent (Reichenberg *et al.*, 2001; Grigoleit *et al.*, 2010). Thus, systemic inflammation in rodents can be anxiogenic and can cause affective and cognitive changes, but these are typically short lived and adaptive, and in the case of cognition, these changes are certainly mild in the otherwise healthy individual. The same appears true in healthy, young humans, where moderate doses of LPS induce mild and reversible affective and cognitive changes.

CNS responses in severe systemic inflammation

Severe infections leading to systemic inflammation and shock generally induce more pronounced behavioural changes, including delirium and even unconsciousness. The CNS changes associated with severe sepsis is often known as septic encephalopathy. This can occur in all age groups and even in the absence of prior illness. The evidence would suggest that these extreme changes in behaviour do not fall within the spectrum of adaptive SBS: humans studies show that severe systemic infections are commonly associated with significant brain injury and long-term cognitive impairment in survivors (MacLulich *et al.*, 2009; Iwashyna *et al.*, 2010). Caecal ligation and puncture (CLP), in which rodents are exposed to polymicrobial sepsis, is one of the most clinically relevant models of sepsis and induces significant CNS inflammation, BBB breakdown and pathology (Bozza *et al.*, 2010; Imamura *et al.*, 2011). Likewise, rodents challenged with large doses of bacterial endotoxin (LPS 5 mg/kg) show apoptosis, neuronal loss, glial activation and iNOS activation in several brain regions (Semmler *et al.*, 2005). These pathological changes are associated with spatial working memory deficits in a radial arm maze at 12 weeks post-sepsis (Semmler *et al.*, 2007). There is limited information from animal studies on the confusional state *during* severe sepsis, because the sickness severity in the hours and days post-infection is too great

to allow any significant behavioural analysis beyond assessing suppression of locomotor activity. One study showed that animals trained on passive avoidance immediately before CLP sepsis (Shimizu *et al.*, 1999) showed intact memory when tested 24 hours after sepsis induction but those that were trained *during* sepsis and tested 24 hours post-sepsis induction did show impairments 24 hours later (48 hours post-sepsis induction). Rats undergoing CLP have shown cognitive deficits, using an inhibitory avoidance paradigm, between 10 and 30 days sepsis (Barichello *et al.*, 2005). Therefore in animals we are largely reliant on MRI, EEG and PET imaging studies to inform on early dysfunction during sepsis. These methods have demonstrated vasogenic edema, suggesting blood brain barrier breakdown in the region of the circle of Willis as soon as 6 hours post-CLP. Acute cytotoxicity (Bozza *et al.*, 2010), and decreased glucose utilization and impaired tissue perfusion/blood flow were found in animals 24 hours post-LPS (Semmler *et al.*, 2008). Collectively these studies suggest that decreased blood flow and energy supply might contribute to CNS dysfunction during severe sepsis, and thus direct brain injury through these mechanisms may be a significant cause of the cognitive impairment ultimately observed. As such, severe sepsis could be considered to fit the direct brain insult category discussed above (MacLulich *et al.*, 2008). Thus, we observe a major CNS inflammatory response and cognitive dysfunction as a direct consequence of a profound systemic inflammatory response, often involving high levels of viable bacteria in the blood. It is very important to make a distinction between systemic inflammation of this intensity and the milder infectious episodes that can trigger delirium only in the aged and otherwise vulnerable populations.

Systemic inflammation produces exaggerated CNS inflammation in the susceptible individual

It is now clear that the aged and those with chronic neurodegenerative disease can suffer a more profound CNS inflammation in response to relatively minor systemic inflammation than young healthy controls. Normally this degree of systemic inflammation would only induce adaptive CNS changes. Why is there exaggerated CNS inflammation in certain groups? The basis for this may be explained, at least partly, by the phenomenon of microglial priming. This was first described in an animal model of prion disease (Cunningham *et al.*, 2005b) but has now been observed in multiple models of neurodegenerative injury and disease and in aging (see (Cunningham, 2012) for review). During neurodegenerative disease and ageing, microglia are “primed” by the primary pathology to make them more responsive to subsequent challenge with inflammatory stimuli. In particular, the CNS synthesis of IL-1 β is exaggerated. Crucially, systemic levels of cytokines induced by the peripheral insult are equivalent in normals and aged/diseased animals (Godbout *et al.*, 2005; Murray *et al.*, 2012). This means that the primed microglia act as a CNS amplifier of systemic inflammatory responses. Thus, though the strength of the peripheral inflammatory signal is obviously important, the presence of primed microglia is likely to be the key determinant of the severity of the CNS inflammatory response to this peripheral signal. It should also be noted that increased BBB permeability, as has been reported to occur with aging in humans (Zlokovic, 2011), could also facilitate, increased CNS inflammatory responses in susceptible individuals even when the degree of systemic inflammation is equivalent to healthy controls. Associated with these exaggerated CNS

inflammatory responses in aged and degenerating brains are exaggerated sickness behaviour responses to subsequent peripheral stimulation with LPS (Combrinck *et al.*, 2002; Godbout *et al.*, 2005). Thus aged and diseased animals when challenged with LPS show profoundly suppressed locomotor activity and become more hypothermic than normal animals similarly challenged. Aged animals challenged with the staphylococcal toxin SEA showed prolonged hyponephagia compared to young animals similarly challenged (decreased consumption of a novel food, without effect on consumption of familiar foods: considered a text of anxiety) (Kohman *et al.*, 2009). Aged animals show exaggerated and prolonged 'depressive' responses to systemic inflammation (Godbout *et al.*, 2008), continuing for up to 72 hours after systemic insult. It is of interest that low plasma tryptophan, an important precursor for serotonin synthesis, has been shown to associate with delirium in a number of studies (van der Mast *et al.*, 1991; Robinson *et al.*, 2008). However, rodent studies have shown that systemic LPS or IL-1 β actually lead to increased brain tryptophan and increased turnover of both serotonin and NA (Wieczorek *et al.*, 2005). An alternative proposal is that altered tryptophan metabolism affects mood not via serotonin depletion but via generation of kynurenine by indoleamine 2,3 dioxygenase (Dantzer *et al.*, 2008). Indoleamine 2,3 dioxygenase shows exaggerated induction by LPS in aged animals (Henry *et al.*, 2009) and kynurenine to tryptophan ratio has recently been shown to be associated with delirium in ICU patients (Adams Wilson *et al.*, 2012).

The exaggerated sickness behaviour responses described above, if encompassing anxiety, affective, sleep-wake cycle, stress axis and cognitive aspects, provides a potential conceptual framework through which we might explain the exaggerated responses of the demented and aged to relatively mild systemic infections. As we have shown here, and continue to discuss in the following section, there are data showing dysregulated or exaggerated responses in most of these domains (see figure 2).

Cognitive consequences during exaggerated sickness behaviour and clinical delirium

Although the microglial priming hypothesis has been adopted by researchers in the delirium field (van Gool *et al.*, 2010), clear empirical evidence to support it in clinical populations has not yet been furnished. However, the psychoneuroimmunologists have addressed the hypothesis that systemic LPS stimulation would cause significant cognitive and behavioural impairments in the brains of animals made susceptible by old age or prior neurodegenerative disease. The first of these studies showed that infection with *E. Coli* impaired the ability of aged animals, compared to young animals, to remember and respond appropriately to the visuospatial context in which they previously received a foot-shock (Barrientos *et al.*, 2006). This was associated with a higher CNS IL-1 β response to the systemic infection. This study was an important proof of concept that exaggerated CNS inflammatory responses to equivalent systemic inflammation could produce exaggerated cognitive impairments. However, the contextual fear conditioning (CFC) paradigm appears to be especially sensitive to systemic stimulation (Pugh *et al.*, 1998; Thomson & Sutherland, 2005). Also, it might not be the most informative for the type of cognitive impairment occurring during delirium, which is characterised by attentional deficits. This is because in the CFC task

animals initially ‘attend to’ the context in the absence of an inflammatory stimulus but once inflammation is induced, immediately after the period of exploration, their memory for that context is impaired because IL-1 β interferes with the consolidation of the memory. Surgical and injury induced-trauma are also frequent triggers of delirium and other post-operative cognitive dysfunction (POCD) in the population and this CFC task has also been used to interrogate POCD after tibial fracture in mice (Cibelli *et al.*, 2010; Terrando *et al.*, 2010). These studies have been performed only in young healthy mice and, like the earlier studies with LPS (Pugh *et al.*, 1998; Thomson & Sutherland, 2005), have described a role for IL-1 β in the deficits. These studies have the potential to be relevant to delirium, since they combine inflammatory and surgical elements of delirium risk, but the coupling of the severity of the surgical trauma to a very inflammation-sensitive cognitive task that shows impairments even under mild inflammatory stimulation in young healthy controls may limit the applicability of this paradigm to delirium.

Subsequent studies in aged rodents showed exaggerated impairments in aged animals challenged with moderate LPS in a measure of mental flexibility/working memory (Chen *et al.*, 2008). In this study aged animals showed a reduced ability, with respect to young animals, to learn the new location of a hidden platform which is moved on each day of testing. In the aged animals LPS once again induced exaggerated inflammatory transcripts in the hippocampus, though other regions that are likely involved in the performance of this task were not examined. One interesting feature of the task employed was the daily reconfiguring of the maze: animals appear to learn that the location of the platform will be different each day, but under the influence of LPS, this reorientation process is clearly more difficult. This is consistent with observations we have made in a shallow water Y-maze reference learning task. Animals with prior neurodegenerative disease (ME7 model of prion disease), challenged with LPS (100 μ g/kg), made more errors in learning the location of the exit than did normal animals challenged with LPS. However, if diseased animals had previously learned the location of the exit, LPS had no impact on their ability to remember this location (Cunningham *et al.*, 2009). Thus attention to/retention of new information and mental flexibility are more selectively targeted than visuospatial reference memory. This is consistent with a recent clinical study showing that patients with delirium were able to access previously learned information but showed impairments on tasks involving online processing of novel information, that is, fluid cognitive ability (Brown *et al.*, 2011a). To directly assess whether animals with prior neurodegenerative pathology are more susceptible to working memory deficits, we developed a novel T-maze alternation task. This working memory task showed that normal animals challenged with LPS (100 μ g/kg) performed normally on this task, as did animals in the early stages of neurodegenerative disease. However, diseased animals challenged with LPS showed acute and transient working memory deficits (Murray *et al.*, 2012). It is possible that these animals show an impairment of short-term memory: failing to remember the arm they had visited just 30 seconds earlier. Alternatively, the impairment might represent an attentional deficit: a failure to ‘attend to’ the location just visited. In clinical studies, the ability to maintain attention beyond approximately 30 seconds is known to be particularly badly affected in delirium, in contrast to Alzheimer’s dementia, where performance is similar to non-demented controls (Brown *et al.*, 2011b). Thus there are parallels between the type of cognitive impairments seen in

delirium and those in animals with prior age- or disease-associated vulnerability, and we have proposed the above paradigm (Murray *et al.*, 2012) as a model with which to interrogate aspects of delirium during dementia. Collectively the data above allow us to propose that delirium, at least in its hypoactive form, represents an extreme form of sickness behaviour. However, this is not straightforward for a number of reasons, as we discuss below.

Exaggerated sickness or prior vulnerability?

In classical SBS, as induced by moderate systemic inflammation, affective and motivational changes predominate and cognition is not severely impaired. As discussed above, in the presence of a vulnerable brain, mild or moderate systemic inflammation induces significant cognitive deficits in addition to classical SBS. If the acute cognitive deficits induced by a systemic inflammatory insult superimposed on aging or neurodegenerative disease were a simple case of an exaggerated sickness behaviour response, then one might be able to replicate, in healthy young animals, these acute cognitive deficits by challenging normal/young animals with higher doses of LPS than those administered to 'vulnerable' animals. This would, in theory, induce an equivalent degree of sickness to that experienced in the aged/demented animals and could address the question of whether more sickness *per se* is sufficient to induce the observed cognitive deficit. In the case of aged animals, these experiments with higher LPS doses have not, to the best of our knowledge, been performed. With respect to animals with prior neurodegenerative disease (ME7), normal, aged-matched controls animals were challenged with 200 µg/kg and 500 µg/kg of LPS in the T-maze (Murray *et al.*, 2012) and Y-maze (Cunningham *et al.*, 2009) respectively, without effect on memory function in normal animals, when 100 µg/kg was sufficient to induce the cognitive deficits in diseased animals. This is an important control that verifies that deficits are indeed cognitive and not simply a sickness-related performance deficit. However, this also suggests that, with systemic inflammation, vulnerable brains are prone not only to exaggerated sickness behaviour but also appear particularly vulnerable to cognitive deficits and the results in the ME7 model make the case that the deficits observed when disease and LPS combine result from something more than an amplification of the normal adaptive pathways. The precise pathways by which this occurs remain to be defined, but we propose that prior pathology or other predisposing factors combine with exaggerated SBS to trigger the more global effects on cognition observed in delirium.

Prior pathology as a predisposing factor

In clinical populations, there are now multiple studies showing associations between plasma levels of pro-inflammatory cytokines and chemokines and delirium (Khan *et al.*, 2011). These studies broadly confirm the hypothesis that systemic inflammation increases the likelihood of delirium and that greater severity of systemic inflammation makes delirium more likely. An important caveat is that, apart from old age, prior cognitive impairment is the major risk factor for delirium, and such impairment may also be associated with higher levels of these cytokines (Lee *et al.*, 2009). Indeed, in some studies, associations between proinflammatory cytokines such as IL-6 and delirium are lost when adjusted for prior cognitive impairment (van Munster *et al.*, 2010). These data argue, like those of the ME7

animal model of delirium during dementia (Murray *et al.*, 2012) that, in humans, increased cytokines are associated with delirium but may not be sufficient to induce delirium in the absence of prior vulnerability.

The question therefore arises: does the pattern of baseline pathology predict the degree of vulnerability to developing acute cognitive dysfunction upon acute systemic inflammation and/or the phenotype of the acute dysfunction observed? The ME7 model of prion disease is a model of progressive neurodegenerative disease that is characterised by extracellular amyloidosis (PrP^{Sc} deposition), robust loss of presynaptic terminals and considerable neurodegeneration. At the time in prion disease when LPS challenges were made in the ME7 model there was already significant hippocampal synaptic loss (Murray *et al.*, 2012) but no neuronal death (Cunningham *et al.*, 2003). It is likely that the loss of functional synapses in the dorsal hippocampus makes these animals susceptible to acute dysfunction in this region upon systemic challenge with LPS. More recent work has shown that, as the disease progresses to further deterioration of the hippocampus and marked pathology in the dorsal thalamus (Cunningham *et al.*, 2005a), synaptic density decreases further and these animals become progressively more susceptible to the cognition-interrupting effects of systemic LPS (Skelly & Cunningham, unpublished data). These data argue that as neuronal connectivity degenerates during disease (and perhaps ageing), the susceptibility to acute disruption grows. The clinical evidence suggests that prior cognitive impairment is the biggest risk factor predicting delirium, but studies have not yet addressed the issue of whether patients with dementia of greater severity are more likely to develop delirium than those with more mild impairments. Our data (Murray *et al.*, 2012) rely on a model of prior hippocampal pathology and thus make predictions about subsequent acute hippocampal dysfunction. Those studies do not suggest that delirium consists of a hippocampal deficit. Rather they demonstrate that, and allow us to interrogate how, systemic inflammation and prior pathology, such as loss of synaptic integrity, interact to induce acute working memory deficits in the rodent brain. It is important to be clear that in humans delirium likely represents brain dysfunction considerably more distributed than the hippocampus (Choi *et al.*, 2012). In many cases, delirium may not even include the hippocampus. Working memory is a hippocampal-dependent function in rodents and a frontocortical function in humans. One has to acknowledge this species difference and manipulate these models for the questions they do allow us to address. In this case, the models suggest that patterns of prior pathology influence the risk and nature of acute LPS-induced dysfunction but evidence that particular prior pathologies dictate the overall risk and symptom presentation in delirium (hypoactive/hyperactive, presence of psychotic features) is currently lacking. A systematic review of neuroimaging studies in delirium did report that increased white matter disease appeared to confer a higher degree of overall risk (Soiza *et al.*, 2008). This finding is congruent with evidence suggesting that prior executive dysfunction, which is classically more likely to associate with vascular-type pathology than Alzheimer-type pathology, may particularly predispose to post-surgical delirium (Greene *et al.*, 2009). These human data provide preliminary evidence that the type or region of prior pathology may influence delirium risk.

Recent animal studies also address this issue: it is believed that some delirium may be underpinned by cholinergic hypofunction, perhaps in combination with dopaminergic overactivity (Trzepacz, 2000). This hypothesis is based on the ability of anticholinergic drug treatments to induce delirium in the clinic (Tune *et al.*, 1981). Indeed early animal models of delirium used the muscarinic receptor antagonist atropine to induce cognitive deficits and EEG changes consistent with delirium (Trzepacz *et al.*, 1992). To address the possibility that systemic inflammation can effect dysfunction in the basal forebrain cholinergic system we have recently developed a further model to study aspects of pathophysiology of delirium during dementia (Field *et al.*, 2012). We proposed that, by making limited lesions of the basal forebrain cholinergic system using the ribosomal toxin saporin linked to the p75 neurotrophin receptor (which is enriched on basal forebrain cholinergic neurons), we would make mice susceptible to the impact of LPS on cognitive tasks reliant on the basal forebrain cholinergic system. The novel T-maze working memory task described above was also shown to be cholinergic-dependent but neither animals with approximately 20% neuronal loss in the cholinergic medial septum and diagonal bands, nor normal animals challenged with LPS showed any deficits on this task. However, cholinergic lesioned animals, challenged 40 days later with LPS, showed acute and transient working memory deficits (Field *et al.*, 2012). These deficits could be partially reversed by the administration of the acetylcholinesterase inhibitor donepezil, indicating that systemic inflammation induced impairments via disruption to cholinergic signalling. Thus, prior vulnerability in the cholinergic system made these animals susceptible to cognitive impairments induced by LPS (see figure 3). While there were robust systemic and CNS inflammatory responses in all LPS-treated animals there was no evidence in hypo-cholinergic animals of an exaggerated CNS inflammatory response to the systemic insult (Field *et al.*, 2012). This argues against the deficits being related to an exaggeration of the sickness behaviour response, at least as mediated by conventional inflammatory pathways. If prior pathology/loss of innervation contributes more significantly to delirium susceptibility than 'inflammatory priming', this predicts that patients and animals with prior pathology would also show increased susceptibility to insults that are not inflammatory in nature and this is certainly the case with delirium: old age, cognitive impairment and frailty predispose to all causes of delirium (MacLulich *et al.*, 2008; Fong *et al.*, 2009).

The degree to which delirium is cholinergic-dependent has recently received increased attention in the wake of the clinical trial of the acetylcholinesterase inhibitor, rivastigmine, to treat ICU delirium. The trial was based on the dual role of acetylcholine as a neuromodulator and as an endogenous inhibitor of systemic inflammatory responses to endotoxemia (Tracey, 2007). The trial was stopped early because of increased mortality in the treatment group and those in the treatment group actually had a greater severity and longer duration of delirium (van Eijk *et al.*, 2010). In the light of these data it is tempting to speculate that the cholinergic hypothesis of delirium may be most relevant in those patients with prior vulnerability in the cholinergic system, as predominantly occurs in patients with dementia of the Alzheimer's type (Ballard *et al.*, 2011). Based on our own findings (Field *et al.*, 2012), one might predict that acetylcholinesterase inhibitors, which boost ACh levels, might offer protection against inflammation-induced cognitive deficits, but specifically in these individuals who have a pre-existing cholinergic deficit. Since the ICU patients recently

treated with rivastigmine were unlikely to have prior cholinergic deficiency, this may explain the lack of efficacy of cholinesterase inhibition in that patient group (van Eijk *et al.*, 2010). Much has been written about acetylcholine in delirium (Trzepacz, 2000) and the parallels between Lewy body dementia, which shows marked cortical cholinergic depletion, and delirium are certainly striking (Perry & Perry, 1995). There is evidence that inflammation can directly interfere with ACh release (Taepavarapruk & Song, 2010) and the interaction between systemic inflammation and prior cholinergic depletion to induce acute and transient working memory deficits (Field *et al.*, 2012) suggests a useful model with which to interrogate the pathophysiology of delirium, and the role of ACh after systemic inflammatory insult.

Does aetiology influence the phenotype of delirium or sickness behaviour?

Association studies lead to speculation that particular inflammatory cytokines have a key role in inducing delirium. Whether particular inflammatory mediators contribute to particular presentations of delirium has not been studied in any detail. In a cohort with Alzheimer's disease systemic inflammatory events were found to exacerbate the rate of cognitive decline in these patients in the absence of detectable delirium (Holmes *et al.*, 2009). These patients showed symptoms of sickness behaviour (apathy, anxiety, depression) and these were more frequent in AD patients with raised markers of systemic inflammation. They also had symptoms that often occur during delirium, such as agitation and hallucinations, which are not typically part of the sickness behaviour spectrum (Holmes *et al.*, 2011). These data suggest that sickness behaviour is indeed exaggerated in dementia, as animal models of dementia initially suggested (Combrinck *et al.*, 2002). These data also suggest the possibility that there may be associations between specific cytokines and different symptom profiles: IL-6 was significantly associated with apathy and hallucinations, while TNF- α was associated with agitation, depression and anxiety (Holmes *et al.*, 2011). In the clinical setting, associations between particular inflammatory mediators and specific symptoms can not be elicited without large studies, but it is manifestly the case that some drugs are more likely to cause delirium in which sleepiness and reduced activity predominates (such as benzodiazepines), and other drugs may cause delirium with agitation (such as amphetamine). Studies examining this further would be valuable but are obviously challenging since there are usually many causes of delirium operating in concert.

Hyperactive versus hypoactive delirium

Another issue in evaluating the hypothesis of delirium as exaggerated sickness behaviour is the observation that systemic inflammation tends to induce a marked hypoactive state in animals and therefore may be incompatible with hyperactive delirium. Though a high proportion of delirious patients exhibit the hypoactive subtype, up to 20% of patients with delirium are classed as 'hyperactive'. It is currently unknown if certain aetiologies favour certain subtypes nor if hyperactive delirium has a different neurochemical profile from hypoactive delirium, though there is limited evidence that hyperactivity occurs more readily in drug-induced cases (Meagher *et al.*, 2011). This is a difficult question to answer because many cases of delirium show a mix of hypoactive and hyperactive phases, and some delirium shows no motor abnormalities. Interestingly, hypoactive delirium may be

disproportionately more common in older people (Peterson *et al.*, 2006). Is it possible for infection, which we so often associate with suppressed activity, to induce hyperactive or agitated states? In one study of 614 delirium cases in critically ill patients, less than 2% of these patients showed pure hyperactive delirium, although as many as 55% showed mixed subtype and 44% were hypoactive (Peterson *et al.*, 2006), while another recent study suggested approximately 10% of ICU delirium was hyperactive (van den Boogaard *et al.*, 2011b). In a study of admissions to a geriatric ward, hyperactive delirium was observed in one fifth of cases, while the mixed subtype was once again most common (O’Keeffe & Lavan, 1999). The same study noted, however, that there was no link between infection and any particular subtype. It remains difficult to explain how systemic infections/inflammation, which so often cause hypoactivity in animal models, can induce a hyperactive state in delirious patients. There is some evidence for agitation and hyperactivity as a result of various neurotropic infections in rodents, and systemic challenge with staphylococcal enterotoxins (SEA and B) can produce neuropsychological changes without suppression of activity despite robust synthesis of TNF- α (Kawashima & Kusnecov, 2002). It may be significant that SEA induces significant T-cell-mediated IL-2 synthesis, which has been shown to increase activity in mice (Zalcman *et al.*, 1998) and to induce working memory deficits (Capuron *et al.*, 2001) or indeed frank delirium (van Steijn *et al.*, 2001) when given as a therapy in humans. However, it remains the case that systemic inflammation in rodents almost invariably induces hypoactivity.

Nonetheless, the available evidence does not allow us to state that infection is more likely than other aetiologies to cause hypoactive delirium. Does this invalidate the idea that exaggerated SBS is a valid model of delirium? We would argue that this simply reflects the fact that delirium in humans is more heterogeneous and complex than SBS in animal models. In the first instance, it is worth noting that the vast majority of the sickness behavior literature concerns LPS rather than active infection, thus removing several layers of complexity with respect to immunological profiles. Furthermore there is an absence, in animal models of SBS, of the heterogeneity in pre-existing brain pathology, in which patients can vary from having no pathology (i.e. young patients in intensive care units after trauma) to having various neurodegenerative disease processes present in most older people. In particular, vascular disease leading to white matter damage is almost universal in older people, and appears to be an important risk factor for delirium (Rudolph *et al.*, 2007; Soiza *et al.*, 2008). Yet there are no published studies examining the phenotype of SBS in animal models of vascular disease. It is conceivable that different patterns of prior pathology could alter how the brain responds to inflammatory signalling. Another factor is that in clinical practice, most delirium is multifactorial. Infection and drug side effects are commonly implicated, but there are many other likely factors. Some degree of psychological stress is present in all patients, resulting from pain, thirst, hunger, noise, temperature fluctuations and from being in an unfamiliar environment (MacLulich & Hall, 2011). Psychological stress resulting in HPA axis activation and secondary alterations in CNS neurochemistry modulates cognitive functioning towards a more vigilant, alert and cautious state (discussed below). In some patients this state could override any tendency towards somnolence stimulated by SBS processes. Sleep deprivation is also extremely common, and may persist for days, possibly leading to psychosis. Additionally, because patients with delirium are

usually disorientated, they often struggle to make sense of what is happening to them. Therefore 'agitation', as detected on rating scales, may in some cases reflect a natural reaction to escape what is perceived to be a threatening situation and reach safety.

The hypothalamic-pituitary-axis (HPA) and delirium

An important pathway that may be activated in both hypo- and hyperactive states is the HPA axis. It is well established that systemic LPS or IL-1 β challenge induces HPA axis activation and one recent study in healthy volunteers showed dose-dependent and large increases in plasma cortisol following LPS injection (Grigoleit *et al.*, 2011). Indeed some studies of sickness behaviour and cognitive function have shown efficacy the glucocorticoid antagonists mifepristone (RU486) in reversing LPS-induced impairments (Song *et al.*, 2004). Likewise ageing (Sapolsky *et al.*, 1986) and dementia (de Leon *et al.*, 1988) are associated with abnormalities in the HPA axis, with higher levels, higher trough levels in the circadian rhythm, and prolonged high levels after stress (Magri *et al.*, 2006). Thus, there is an age-related dysregulation of the HPA axis that makes it more responsive to acute stressors. Aside from the impact of this on PFC cortex function (discussed below), this also has interesting consequences for brain inflammation: in recent years it has become clear that increased corticosterone, in rodents, actually sensitizes microglia in the hippocampus and prefrontal cortex to produce exaggerated responses to subsequent challenge with LPS (de Pablos *et al.*, 2006; Munhoz *et al.*, 2006). Age-related priming of microglia can be reduced significantly by adrenalectomy or RU486 treatment (Frank *et al.*, 2012). In health, HPA activation induced by inflammation serves to mobilise energy resources, and also limit the inflammatory response.

However, where the inflammatory stimulus is prolonged or abnormal, the HPA axis may become dysfunctional. This may take the form of very high levels which can persist for weeks and which are associated with worse prognosis (Marik, 2011).

The notion that elevated endogenous cortisol might be important in precipitating delirium was suggested more than 30 years ago (Swigar *et al.*, 1979). This idea has been refined (MacLulich *et al.*, 2008) as we have learned more about HPA dysfunction: ageing and neurodegenerative disease are associated with dysregulation of the HPA axis such that, upon acute stress, cortisol levels take longer to return to basal levels (Otte *et al.*, 2005; Magri *et al.*, 2006). Sustained elevated endogenous cortisol and exogenous treatment with cortisol or analogues are associated with cognitive and/or neuropsychiatric dysfunction particularly in older and other vulnerable populations (Dubovsky *et al.*, 2012). Several studies have directly addressed the association of the stress axis with delirium. These generally show that cortisol levels are elevated in delirium (MacLulich *et al.*, 2008; Pearson *et al.*, 2010; van den Boogaard *et al.*, 2011a) and elevated cortisol levels in the cerebrospinal fluid have also been shown to associate with delirium in hip fracture patients (Pearson *et al.*, 2010). Two further studies showed that elevated cortisol post-dexamethasone (ie failure to suppress cortisol production in the dexamethasone suppression test (DST)) were significantly more likely to show delirium (Olsson *et al.*, 1992). More recent studies, many of which are also small, showed that elevated plasma cortisol was significantly associated with delirium in hip fracture (van Munster *et al.*, 2010; Bisschop *et al.*, 2011), cardiac surgery (Plaschke *et al.*,

2010), coronary artery bypass graft (Mu *et al.*, 2010) and sepsis (Pfister *et al.*, 2008). Interestingly, in one study the association between plasma cortisol and delirium did not withstand adjustment for prior cognitive impairment suggesting the possibility of a strong influence of the association between elevated cortisol and prior dementia or cognitive impairment (van Munster *et al.*, 2010). However, in an earlier study failure to suppress in the dexamethasone suppression test showed that delirium during dementia was nonetheless significantly different to dementia alone (Robertsson *et al.*, 2001). Moreover, higher cortisol in dementia, and an associated elevated response to stress, may be a means by which dementia confers the greater risk of delirium in these patients. Therefore, both explanations for the association are plausible and indeed may coexist. Additionally, as with systemic inflammation, it may be that old age and the presence of neurodegenerative disease render an individual more likely to react adversely to higher levels of cortisol. Notwithstanding the plausibility of the link between increased stress and delirium, causality cannot be inferred from these studies and intervention studies in animal models could usefully address this possibility.

The stress response and delirium: mechanisms

That delirium is mostly precipitated by stress, defined broadly as any form of acute threat to homeostasis, is unarguable. The evidence suggesting that there are associations between activation of stress-responsive systems such as the HPA axis and the immune system and delirium is consistent with this axiom. However, the pathways from stress stimuli to delirium are not yet defined. Given that inattention is the core cognitive feature of delirium, understanding how stress might disrupt attention would seem a reasonable place to start.

The ability of stress to induce hyperactive, inattentive and psychotic states is consistent with an existing literature on the nature of brain regulation of behaviour under conditions of significant psychological stress. Arnsten (Arnsten, 2009) has proposed that when stress pathways in the brain are strongly activated, the usual prefrontal cortex 'top-down' control of attention, monitoring of errors, inhibition of inappropriate responses and regulation of emotionality is disrupted. Instead, cognition and attention change to a 'bottom up' control exerted by the amygdala in which more rapid emotional and instinctive control along with greater vigilance and caution predominates. Activation of the amygdala, as a result of perceived threat, stimulates the basal ganglia and the hypothalamus and evokes higher levels of noradrenaline (NA) and dopamine (DA) release in the PFC. Concentrations of NA and DA modulate PFC functions such as working memory and executive attention through inverted U-shaped dose response curves. With very low concentrations of these catecholamines the PFC is insufficiently activated and there is reduced arousal. Optimal PFC function occurs when NA and DA are in the concentration range where high affinity α_2 -adrenoreceptors are occupied and facilitate arousal and D1 receptors are sufficiently occupied to exert "signal to noise" suppression of inappropriate activity. Under much higher concentrations D1 receptors and α_1 receptors are then fully engaged and there is generalised suppression of PFC activity: instead of DA suppression of 'noise' to improve signal to noise ratio, signal has been suppressed in a generalised way and PFC control of function is diminished. Spatial working memory is impaired in both rodents and primates by increased DA turnover in the PFC (Murphy *et al.*, 1996). A detailed discussion of this important area

is beyond the scope of this review but is discussed in an excellent recent review (Arnsten, 2009). Returning to systemic inflammation, there are elegant animal and human studies showing that systemic LPS can activate the amygdala, increase EEG power and increase release of NA in this area (Engler *et al.*, 2011; Inagaki *et al.*, 2012). Moreover, lesioning of the amygdala is sufficient to prevent the increase of NA and DA in the PFC in response to psychological stress (Goldstein *et al.*, 1996). Consistent with this model, drugs such as amphetamine, cocaine and corticosteroids, which increase PFC monoamines, are all recognised causes of delirium.

Therefore, in amygdala-driven stimulation of catecholaminergic activation of the PFC, we have a common link between systemic inflammation and stress axis activation that is highly relevant to delirium etiology. Furthermore, HPA axis activation can perhaps link multiple stressors: psychological stress, pain, inflammation, to direct pharmacological disruptions in a final common pathway that ultimately results in increased catecholaminergic signalling and diminished PFC influence over brain function. Thus, whether the overall level of arousal is decreased (as is usually the case with systemic inflammation) or increased one may still observe significant attentional and working memory deficits underpinned by HPA axis activation and consequent increases in DA and NA. Since increased dopaminergic tone allied to decreased cholinergic tone constitutes perhaps the most adopted hypothesis of delirium etiology (Trzepacz, 2000) this makes the amygdala driven suppression of PFC activity an attractive explanation of how such a state might come about, particularly when one considers the decreased cholinergic tone apparent in most patients with dementia (Ballard *et al.*, 2011).

However, the data supporting the above formulation mainly pertains to *adaptive* changes in cognition. That is, the brain has evolved to switch to a more rapid and reflexive, less thoughtful, mode of action in situations of acute stress. In health, at least, the changes above would tend to make the organism more awake and active. Most patients with delirium are hypoactive some, or all, of the time and direct evidence for amygdala activation and increased DA and NA in the PFC in delirium or models of delirium is lacking.

Conclusion and future perspective

In this review we have proposed that mapping SBS in vulnerable rodents (aged or with prior neurodegeneration) onto delirium in humans is both plausible and supported by clinical and basic research studies. However, the relationship is not simple: there are key differences between SBS in vulnerable rodents and delirium in humans with respect to aetiologies, varying levels of co-morbidity, varying phenomenology (including hyperactivity), and obviously differences between the rodent and human brains. Put simply, delirium likely results from an acute breakdown of coherent functioning of the CNS. While exaggerated SBS appears to be a prominent underlying mechanism of this phenomenon, there are clearly multiple interacting and alternative pathways that could contribute to this breakdown. These include the effects of drugs, psychological stress leading to elevated cortisol (perhaps leading to PFC/amygdala switching), and direct insults such as hypoxia, all superimposed onto heterogeneous prior pathologies. However, we believe that despite the complexities of the problem, developing a better understanding of these mechanisms and pathways is

feasible. The focus of this article, studying SBS in vulnerable models, provides an exemplar of a tractable approach to one probable major class of delirium pathophysiology. Future research combining systemic inflammation, psychological stress and indeed systemically administered stimulant drugs with well described prior pathologies could also begin to address the hyperactive behavioural phenotype seen in some patients with delirium.

It will also be important in the coming years to formalise measures of SBS in patients and to develop methods and clinical study designs that allow us to assess the CNS inflammation occurring during delirium in patients and to directly test the microglial priming hypothesis. A small number of studies have already provided evidence that elevated CNS IL-8 (MacLulich *et al.*, 2011) and microglial activation (van Munster *et al.*, 2011) are associated with delirium, but these are small studies and need to be expanded in size and scope. The paucity of research in delirium belies its enormous economic and medical importance, and the field of basic research, in particular, is in its infancy. At the extreme end of the psychoneuroimmunological spectrum seems like a sensible place to start.

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DELIRIUM CASE HISTORY

An 82-year-old man with a history of mild dementia, ischaemic heart disease and osteoarthritis who lived with his wife was taken to the emergency department with confusion and agitation, and productive cough and fever for 2 days. He had resisted being brought to the hospital initially but had then become drowsy and had to be lifted onto the ambulance trolley. Upon arrival he became agitated, saying that he didn't want to be 'locked up', and he tried to get off the trolley to leave the hospital. With reassurance from his wife he became calmer. A few minutes later he was drowsy again. On examination he was able to say his name on request but did not respond meaningfully to other questions and only intermittently obeyed simple commands such as 'lift up your arms'. The pulse was raised at 98 and the blood pressure was 108/64. Oxygen saturations were normal and the temperature was elevated at 37.8 degrees C. Chest examination revealed signs of a pneumonia but chest X-ray was not possible because the patient could not tolerate the procedure. Blood tests showed a raised white cell count and evidence of mild acute kidney injury. The patient was treated with antibiotics and intravenous fluids and within one day was less agitated. His vital signs all become normal. He became more compliant with treatment and had no further episodes of agitation. However, he remained drowsy and at times was too sleepy even to exchange a few words. When awake his speech was intermittently coherent but he was unable to sustain meaningful communication for more than a few seconds at a time. He was disorientated and unable to count backwards from 20 down to 1. His wife stated that his mental status was much worse than normal. After three more days he was more consistently awake but remained unable to sustain normal conversation. He was also unsteady when walking and required assistance to do this safely. Seven days after admission he was transferred to a rehabilitation facility, and after a further two weeks his mental and physical status had improved sufficiently such that he was discharged home. However, when visited by the general practitioner two weeks later his wife reported that though he was improving he was still sometimes disorientated, and also considerably more passive and apathetic than he had been before his illness.

Urinary Tract Infection and Delirium

Urinary tract infections, predominantly gram-negative *E. Coli* infections in humans, are a very frequent trigger of delirium in older people. The reasons for this are not clear. These infections can often cause bacteremia, but this is estimated to occur in only about 15% of cases (Bahagon *et al.*, 2007) and in many cases of UTI, there may not be a classical systemic inflammatory response (Ginde *et al.*, 2004). In animal models of uropathogenic infection, intravenously inoculated *E. Coli* became systemically disseminated (Smith *et al.*, 2010). However, when LPS was administered to the bladder via a catheter, inflammatory products such as iNOS were detectable in the bladder but not the kidney (Olsson *et al.*, 1998). Thus UTI does not necessarily produce systemic inflammation and indeed UTI-induced delirium does not necessarily require clinically apparent systemic inflammation. It is unclear whether there is a specific neural mechanism of inflammatory sensing in the urinary tract, though afferents in the urothelium may potentially serve this purpose (Birder *et al.*, 2010). It is well known that such a pathway exists to signal visceral inflammation to the brain, via activation of vagal afferents: behavioural suppression induced by systemic LPS or IL-1 β can be prevented by prior subdiaphragm transection of the vagus (Konsman *et al.*, 2000). Another possibility is that even minor infections or trauma causing macrophage activation may lead to release of circulating mediators at levels not easy to detect but which nevertheless elicit CNS change. Increased permeability of the blood brain barrier seen with ageing and in neurodegenerative disease (Zlokovic, 2011) and the priming of microglia by prior pathology (Cunningham *et al.*, 2005b) may both contribute to a pathological CNS amplification of the signal from circulating messengers. Given the importance of UTIs as a cause of delirium in older people, the study of this interaction may provide valuable insights.

ADAPTIVE SICKNESS BEHAVIOUR RESPONSE (Rodents)

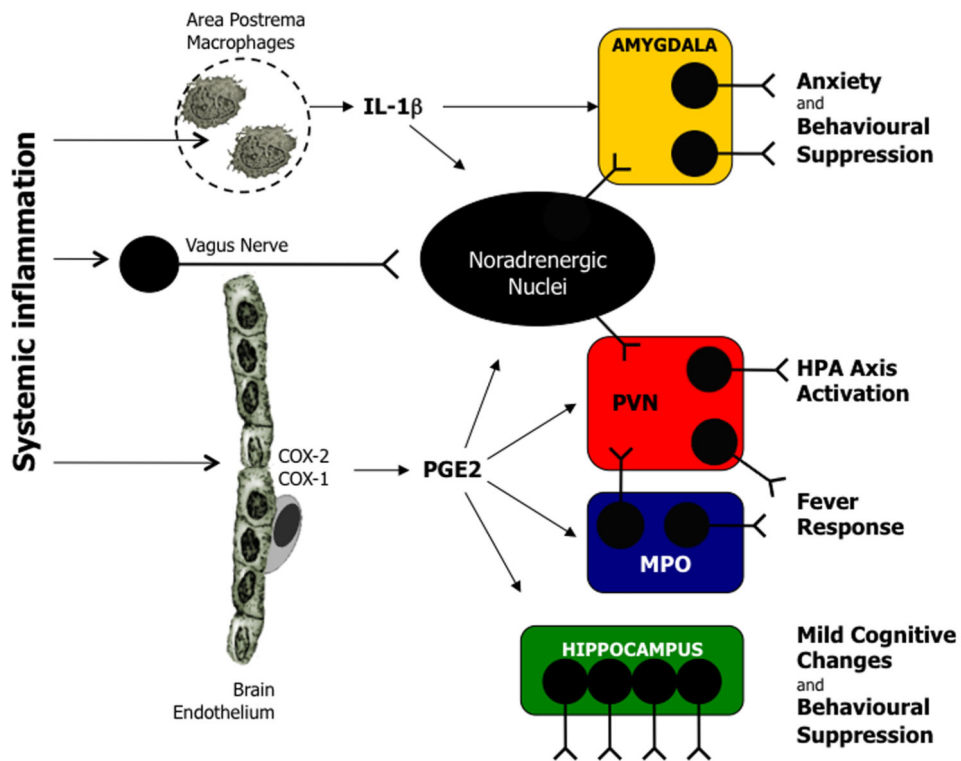


Figure 1.

Adaptive Sickness Behaviour Response: This scheme simplifies and summarises current knowledge of the sickness behaviour response as elucidated in rodents. Systemic inflammation is signalled to the brain via activation of the brain endothelium, the vagus nerve or circumventricular organs, such as the area postrema. The endothelial cells and perivascular macrophages express COX2 and COX1 to synthesize PGE2 and other prostanoids. PGE2 is known to activate hypothalamic centres (MPO: blue, PVN: red) via EP3 and EP1 receptors to drive fever and stress responses. Anxiety responses are mediated by the amygdala (yellow), which is activated directly by both IL-1 β and brainstem noradrenaline release (indirect neuronal activation by the parabrachial nucleus detailed in main text). The hippocampus (green) can be activated by both IL-1 β and PGE2 contributing to disengagement from the environment and cognitive changes. Abbreviations: PGE2: prostaglandin E2, IL-1 β : interleukin-1 β ; COX: cyclooxygenase; HPA: hypothalamic pituitary adrenal; PVN: paraventricular nucleus; MPO: medial preoptic nucleus.

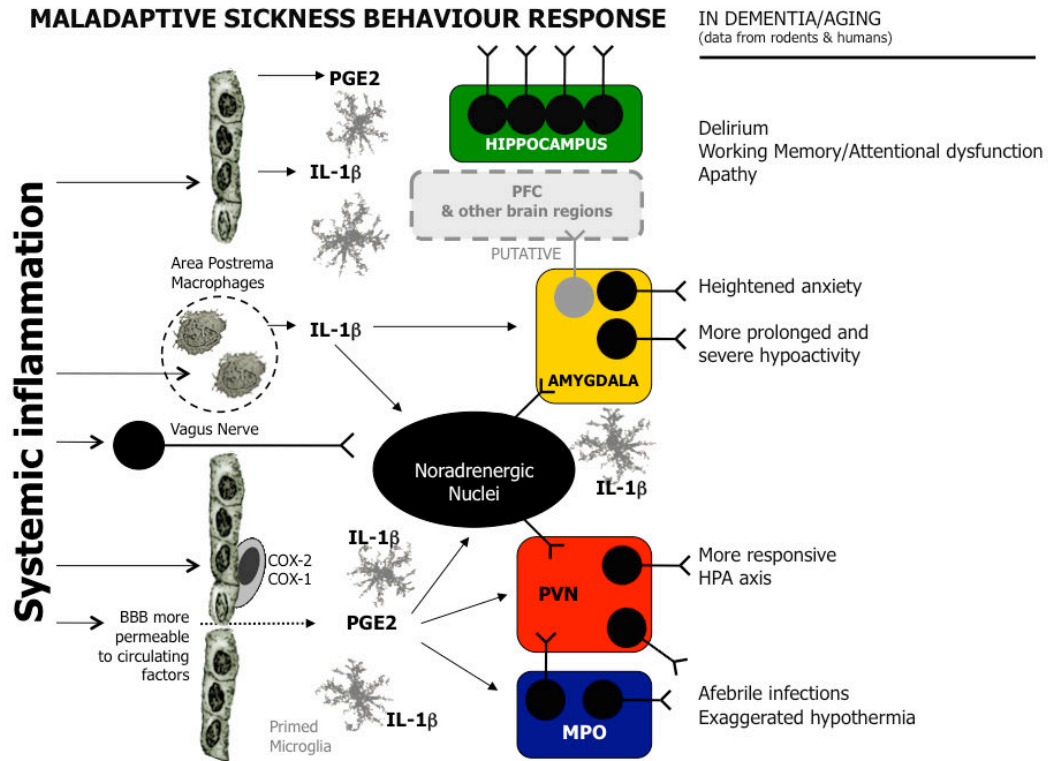


Figure 2.

Maladaptive Sickness Behaviour response: This scheme superimposes observations from the rodent and clinical literature onto the broadly accepted model of sickness behaviour to propose ‘maladaptive sickness behaviour’. The pathways are largely as described in figure 1 with the following exceptions: increased blood brain barrier permeability may facilitate increased access of serum factors to the brain parenchyma, primed microglia (shown in grey) may cause amplified CNS responses to systemic inflammation, dysregulated HPA function may allow excessive stress responses. Putatively, altered HPA and amygdala responses, in addition to elevated inflammatory mediators may also have robust effects on the prefrontal cortex or other areas likely to be important in delirium in humans. Coupled with these changes, prior pathology in brain areas such as the cholinergic basal forebrain, the noradrenergic brainstem or the dopaminergic midbrain may have significant impacts on the presentation of inflammation-induced sickness behaviour. While the idea that delirium is compatible with an elevated and maladaptive sickness behavioural response remains speculative, evidence exists for marked hypoactivity and apathy (humans and rodents), dysregulated HPA function (humans and rodents), afebrile infections (humans) and exaggerated hypothermia (rodents), delirium (humans) and robustly impaired working memory/mental flexibility (rodents). Abbreviations: PGE2: prostaglandin E2, IL-1 β : interleukin-1 β ; COX: cyclooxygenase; HPA: hypothalamic pituitary adrenal; PVN: paraventricular nucleus; MPO: medial preoptic nucleus.

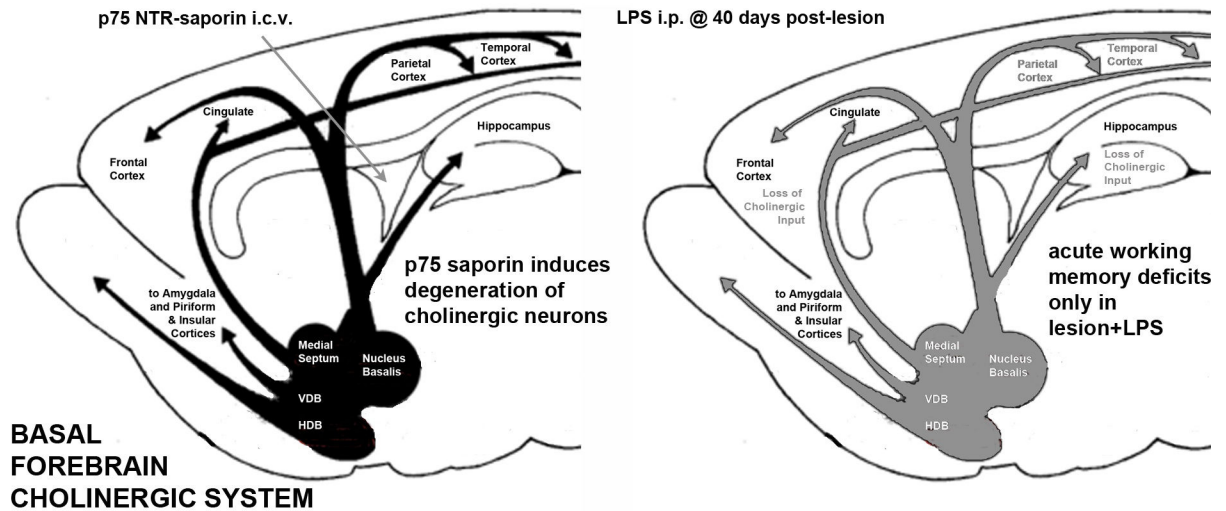


Figure 3.

Prior pathology and superimposed systemic inflammation interact to produce acute and transient working memory deficits: towards reconciling cholinergic and inflammatory hypotheses of delirium. This scheme shows the basal forebrain cholinergic nuclei (BFCN), illustrating the septohippocampal pathway, the ventral diagonal band projections to the amygdala and piriform and insular cortices and the nucleus basalis projection to the frontal, parietal and temporal cortices (after Wolff 1991). Intracerebroventricular injection (left panel) of the ribosomal toxin saporin, linked to an antibody against the p75 neurotrophin receptor, which is enriched on BFCN cells, induces selective neuronal death in these regions. This approach facilitates targeted, selective and limitable lesioning of this area and consequently decreased cholinergic tone (shown in grey, right panel) in these projection fields. In lesioned animals, LPS induces acute and transient working memory deficits, resembling delirium. Neither lesion nor LPS alone were sufficient to induce such deficits. LPS-induced CNS inflammatory responses were equivalent in lesioned and non-lesioned animals and the acetylcholinesterase inhibitor donepezil could block these deficits (Field et al., 2012). This model serves as a useful exemplar of how systemic inflammation in ‘vulnerable’ animals may be used to interrogate aspects of delirium pathophysiology.