Who understands delirium?

“Thousands of tiny little creatures, some on horseback, waving arms, carrying weapons like some grand Renaissance battle,” were trying to turn people “into zombies.” Their leader was a woman “with no mouth but a very precisely cut hole in her throat.”

This New York Times article on Pulitzer Prize-winning historian Justin Kaplan’s experience of delirium [1] provided welcome publicity of this enormously impactful but historically neglected syndrome. Nevertheless, the remarkable scarcity of such exposure in the mass media speaks to what is perhaps the most significant obstacle to progress in delirium research and practice: its invisibility.

Why has delirium remained so obscure? There would appear to be several reasons. Patients rarely speak of their experiences of delirium, perhaps because of embarrassment or bewilderment; currently, there are no specific charities or patient advocacy groups. Healthcare staff use a wide variety of informal words and phrases to describe delirium. This diagnostic ambivalence and imprecision greatly hinders the implementation of formal methods of improving care.

Another likely factor is that delirium is very challenging: it is heterogeneous in its precipitants, symptomatology, severity and course. The mixture of mental status abnormalities and complex medicine means that healthcare professionals require multiple skills to manage delirium. Indeed, these skills may be lacking: a recent survey of UK junior doctors suggested that there are serious deficiencies in knowledge of the diagnostic criteria [2].

However, there have been major advances over the last three or four decades that ought to be more widely disseminated [3]. We know that delirium is common and that it has several adverse consequences, including loss of independence, acceleration of dementia and death [3–5]. The clinical predisposing and precipitating factors are now well documented [3]. Recent work has shown that delirium persists for months in around 20% of cases [6]. The significance of delirium in critically ill patients and in palliative care settings is now far clearer [7–9]. Crucially, it is now established that multi-component prevention strategies are effective, and should be introduced into standard health-care practice [3].

What might be the current priorities for research? Direct brain insults such as oxygen deprivation, hypoxaemia and adverse drug effects are common causes of delirium, and in many such cases, the routes to disruption of cognitive processes are clear. In contrast, the mechanisms by which peripheral illness such as urinary tract infection can cause acute, severe mental deterioration over periods of as little as a few hours are poorly understood. Recent experiments in animal models and humans have found that in older individuals peripheral stimuli can induce adverse inflammatory and stress system responses in the central nervous system, with resultant maladaptive behavioural change including delirium [10–12]. Delirium could thus represent an exaggeration of the sickness behaviour syndrome (a set of normally adaptive behavioural responses to illness including sleepiness, fatigue, anhedonia and impaired concentration), but may also simply be due to the effects of pathologically sustained high cortisol levels [10]. These leads in dissecting the ‘indirect’ causes of delirium may suggest potential new treatments. The role of stress mediators is also relevant to the patient experience of delirium: studies in animal models suggest that chronic unpredictable psychological stress over periods of days can cause marked brain damage [13]. Patients with delirium are often in a comparable position, suffering pain, fear, an unpredictable environment and strangers undertaking invasive activities. All of this is exacerbated by the inability of the patient’s mind to fully comprehend what is happening to them. The implications here are that effective psychological care of patients with delirium may be particularly important, not simply to relieve distress, but to protect the brain.

Detection is a pre-requisite for good care, but the problem of achieving acceptable levels of recognition of delirium has not yet been solved. This partly reflects the lack of validated brief screening tools that do not require special training and that discriminate delirium from dementia [14, 15]. Another need is for methods of recording the status of conscious but untestable patients, that is, those too drowsy to undergo cognitive testing or even a brief interview. Such patients are overwhelmingly likely to have a diagnosis of hypoactive delirium, but are often left without any label and resultant management plan. More broadly, further research on the neuropsychology of delirium is essential to the development of better testing instruments for screening and diagnosis in clinical practice and in research. There are many challenges here, not least because of the range of mental status change, from stupor to relatively mild deficits in attention. Subsyndromal delirium, where there are one or more features of delirium but in which full DSM-IV criteria are not met, has recently been shown to have diagnostic significance [16]. Despite this, its neuropsychology is all but unexplored. The clinical role of other methods of assessment, such as neuroimaging, plasma biomarkers and lumbar puncture, also remain greatly under-researched. A recent systematic review of the literature on neuroimaging findings in delirium found that though there may be some relationships between white
matter lesions and cerebral atrophy with delirium, no recommendations on clinical utility could be made based on the available evidence [17].

There are currently no papers that unequivocally show the efficacy of any drugs as treatments for delirium. This may be because most studies are too small; there are very few randomised trials of sufficient size. Most studies have focused on antipsychotic drugs or cholinesterase inhibitors. The evidence suggests that there is unlikely to be a final common pathway for delirium [10], but it is conceivable that correction of frequently occurring neurotransmitter or neuromodulator disturbances could benefit some patients. An alternative approach might be to target different elements of the symptoms or mechanisms of delirium—for example, cognitive impairment, hyperactivity, psychosis, apathy, sleep-wake cycle disturbance [18], excess cortisol or neuroinflammation. Therapies aimed at neuroprotection may also be worth considering if it emerges that delirium is associated with acute and ongoing brain damage, which appears a strong possibility [5, 19].

Currently, there is consensus that the treatment of delirium involves considering multiple precipitants, amelioration of predisposing factors and the management of symptoms of delirium. Yet, there remain many unresolved fundamental issues in general care. For example, adequate provision of macro- and micronutrients is obviously compromised in many patients, but how these deficiencies might contribute to poor outcomes is not known. Should all older, frail patients with delirium receive comprehensive nutritional support to avoid potentially damaging deficiencies, for example of thiamine? Likewise, periods of low blood pressure and hypoxia are commonly observed in patients with delirium, often resulting from the practical difficulties in caring for delirious patients. It is plausible that these processes might contribute to adverse outcomes, yet few studies have aimed to assess the effects of maintaining brain oxygen delivery [20].

Specialised delirium units, partly modelled on acute stroke units, could provide the comprehensive and intensive brain care that patients with delirium need. However, changes of environment can be harmful to patients with delirium, and delirium differs from stroke in that it is more common and more variable in duration and severity. Thus, specialist units will likely only have a role for a relatively small number of severe and sustained cases. For other patients, perhaps specific actions triggered by the diagnosis, including strategies to optimise brain functioning (for example, avoid hypoxia, hypotension etc.), elicit precipitating and predisposing factors, rationalise drug treatments, search for underlying dementia, seek and manage distress, ensure good hydration and nutrition etc., would be an appropriate aim. One might assume that these measures should obviously be part of normal practice, but widespread implementation could only be stimulated with good trial evidence.

Because delirium often occurs in patients with dementia, and because most dementia patients lack a diagnosis, it is reasonable that older patients with delirium should be screened for dementia. Furthermore, because those who develop delirium without prior dementia are at high risk of developing future dementia, there is a strong case to be made that such patients should be monitored. Yet there remain important unanswered questions regarding the timing of such attempts to detect current or future dementia. As Cole et al. have suggested, some of the cognitive impairment detected months after the delirium episode may represent persistent delirium rather than dementia [16]; if cognitive tests alone are used in long-term follow-up, it is not possible to make this distinction. Long-term natural history studies of delirium involving detailed mental status assessments are essential.

In conclusion, though substantial progress has been made in delirium research in the last few decades, daunting challenges lie ahead. Addressing these will require a massive increase in research at all levels, from neural mechanisms to the methods of implementation of best practice. Alongside research, delirium care needs to be given appropriate prominence in clinical practice, through expanded educational programmes, audits of performance, independent quality assurance and so on. We would argue that to underpin the above increased engagement with healthcare staff, the public, policy-makers, scientists and health service leaders is the most urgent step. New organisations focused on delirium will be critical to this. The recent founding of two major professional bodies, the European Delirium Association and the American Delirium Society, will help us to focus and strengthen the efforts of those working to improve the care of patients with this devastating condition.

Conflicts of interest
A.M.J.M. holds patents on instruments for assessment of attentional deficits in delirium.

Funding
A.M.J.M. is supported by grants from the Medical Research Council. R.J.H. is supported by a British Geriatrics Society Research into Ageing Clinical Research Fellowship. A.M.J. M. and R.J.H. are members of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative. Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged.

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Acute non-invasive ventilation in older patients: medical evolution and improvement in survival of the un-fittest

In the current edition of ‘Age and Ageing’, Nava et al. have confirmed the clinical value of non-invasive ventilation (NIV) [1] in very elderly patients (mean age of 81 years) with chronic respiratory conditions [(largely but not exclusively) chronic obstructive pulmonary disease (COPD)] with acute hypercapnic respiratory failure (Type 2 respiratory failure). In this randomised control trial, the primary endpoint was the achievement of criteria for endotracheal intubation. The secondary endpoints comprised mortality rate, arterial blood gases and respiratory rate. Only 7% (3 out of 41) patients from the NIV group met the criteria for intubation as against 63% (26 of 41) from the control group who received standard medical therapy. The odds for ratio for mortality in the NIV group was 0.4 (95% confidence intervals 0.19–0.83: \( P = 0.014 \)), and subsequent analysis showed that this difference was preserved even in patients with ‘Do not incubate’ orders who received NIV as rescue therapy. The authors concluded that NIV should...