Delirium mouse model helps researchers understand the condition's causes

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A new mouse model of delirium developed by Wellcome Trust researchers has provided an important insight into the mechanisms underlying the condition, bringing together two theories as to its causes. Details of the research are published today in the *Journal of Neuroscience*.

Delirium is a profound state of mental confusion which can include hallucinations and severe mood swings. According to the Royal College of Psychiatrists, one in ten hospital patients will experience a period of delirium.

Dr Colm Cunningham, a Wellcome Trust Senior Research Fellow at Trinity College Dublin explains: "Delirium is an extremely common condition, particularly amongst the elderly, and it is extremely distressing both for the individuals themselves and for their families. The long-term outcomes for these individuals are often poor. Yet we know very little about its underlying mechanisms and have very few animal models with which to study the condition."

Delirium can arise in many situations, for example, as a result of infection or after surgery. This has led to the "neuroinflammatory hypothesis", which proposes that systemic inflammation arising in the body as a result of infection or injury induces inflammation in the brain, causing a disturbance of brain function. Delirium can also arise as the result of changes in medication, particularly those medications targeting a chemical known as acetylcholine. Acetylcholine is a chemical

messenger that allows signals to be transmitted between nerve cells and is thought to be involved in learning, memory, and mood. The 'cholinergic hypothesis' of delirium suggests that the condition results from decreased action of this chemical, whether resulting from the loss of brain cells that normally synthesize this chemical, the cholinergic cells, or other acute disruptions of its release or action, such as anticholinergic medication.

Dr Cunningham and colleagues have now published findings that for the first time begin to reconcile these 'cholinergic' and 'neuroinflammatory" hypotheses.

The researchers developed a mouse model of the condition and showed that systemic inflammation triggers a robust disturbance of short-term memory, one of the key symptoms of delirium, but only in animals that have already lost cholinergic cells. Importantly, neither inflammation nor cholinergic cell loss individually were sufficient to cause this disturbance.

"Our work shows that both inflammation and prior damage to the cholinergic cells can combine to produce the delirium-like state," adds Dr Cunningham. "We also found that the effects could be partially reversed by treatment with donepezil, a drug that slows the breakdown of acetylcholine and is used to treat mild cases of Alzheimer's. However, this approach may only be effective in those patients with this vulnerability in the cholinergic system."

The research has been welcomed by Professor Alasdair MacLullich, Professor of Geriatric Medicine at the University of Edinburgh and President of the European Delirium Association. "Delirium causes enormous suffering and costs billions of pounds, but it is hardly researched and there are no treatments. Dr Cunningham's exciting study provides critical new knowledge on the mechanisms explaining how two

causes of delirium well known to clinicians, cholinergic deficiency and inflammation, may combine to produce this devastating syndrome. This is an important step forward and takes the field closer to developing drug treatments."

Dr John Williams, Head of Neuroscience and Mental Health at the Wellcome Trust said: "Understanding the brain is one of the Trust's five strategic priorities. "Animal models are essential in helping us understand how disease occurs in humans and how it may be treated. Dr Cunningham's work provides us with one of the surprisingly few models for delirium and should help further our understanding of this distressing and yet very common condition."

More information: *Journal of Neuroscience*; e-pub 2 May 2012

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