Worsening Cognitive Impairment and Neurodegenerative Pathology Progressively Increase Risk for Delirium

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Background: *Delirium is a profound neuropsychiatric disturbance precipitated by acute illness. Although dementia is the major risk factor this has typically been considered a binary quantity (i.e., cognitively impaired versus cognitively normal) with respect to delirium risk. We used humans and mice to address the hypothesis that the severity of underlying neurodegenerative changes and/or cognitive impairment progressively alters delirium risk.* **Methods:** *Humans in a population-based longitudinal study, Vantaa 85+, were followed for incident delirium. Odds for reporting delirium at follow-up (outcome) were modeled using random-effects logistic regression, where prior cognitive impairment measured by Mini-Mental State Exam (MMSE) (exposure) was considered. To address whether underlying neurodegenerative pathology increased susceptibility to acute cognitive change, mice at three stages of neurodegenerative disease progression (ME7 model of neurodegeneration: controls, 12 weeks, and 16 weeks) were assessed for acute cognitive dysfunction upon systemic inflammation induced by bacterial lipopolysaccharide (LPS; 100 μg/kg). Synaptic and axonal correlates of susceptibility to acute dysfunction were assessed using immunohistochemistry.* **Results:** *In the Vantaa cohort, 465 persons (88.4 ± 2.8 years) completed MMSE at baseline. For every MMSE point lost, risk of incident delirium increased by 5% ($p = 0.02$). LPS precipitated severe and fluctuating cognitive deficits in 16-week ME7 mice but lower incidence or no deficits in 12-week ME7*

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and controls, respectively. This was associated with progressive thalamic synaptic loss and axonal pathology. **Conclusion:** *A human population-based cohort with graded severity of existing cognitive impairment and a mouse model with progressing neurodegeneration both indicate that the risk of delirium increases with greater severity of pre-existing cognitive impairment and neuropathology.* (Am J Geriatr Psychiatry 2015; 23:403–415)

Key Words: Delirium, dementia, neurodegeneration, neuropathology, synaptic, axonal, thalamus, hippocampus, basal forebrain, ageing, cognitive decline, systemic, inflammation, susceptibility, neuroinflammation

Delirium is a severe neuropsychiatric syndrome characterized by acute cognitive deficits and inattention arising as a consequence of generalized illness.[1,2] It affects 10%–31% of older hospitalized patients.[3] Even higher prevalence has been reported in settings associated with frailty (e.g., nursing homes) or critical illness (e.g., intensive care units).[4] As well as being profoundly distressing for patients, relatives, and care staff,[5] delirium is associated with multiple poor outcomes: higher mortality, longer hospital stay, and increased institutionalization.[6,7]

Dementia is a strong risk factor for developing delirium,[8] but the pathophysiology of this relationship is not well established. Part of the difficulty in investigating this in clinical samples is disentangling biological and neuropsychiatric constructs related to delirium (i.e., the acute precipitating disturbance) from the underlying dementia (i.e., the chronic predisposition). Hospital studies have usually relied on duration of dementia diagnosis[9] or informant scales (e.g., Informant Questionnaire on Cognitive Decline in the Elderly or informant component of the Clinical Dementia Rating Scale) as ways of quantifying pre-existing cognitive deficits.[10,11] Though these studies have reported that delirium was more likely in persons with apparently more severe prior cognitive impairments, it is difficult to be conclusive about the reliability of such retrospective measures. One prospective study in hospitalized patients showed that severity of dementia progressively increases delirium risk.[12]

Separately capturing pre-existing cognitive function from incident delirium is heuristically (and probably mechanistically) important, but the ability to do this is limited in hospital samples for the reasons outlined above. Here, we present two different approaches (with different strengths and limitations) that together may offer new perspectives. Firstly, we use observational data from an epidemiologic cohort study, where the risk of incident delirium can be more reliably related to baseline cognitive function. This generates hypotheses that can then be tested in an experimental mouse model in which pre-existing cognition and pathology can be controlled more precisely. Interrogation of the contribution of specific features of neurodegenerative pathology to cognitive frailty may add to understanding the basis of delirium risk associated with prior cognitive impairment. Although neither analytic method can directly demonstrate causation, there may be an argument for a degree of coherence between the two approaches.

We hypothesized that severity of pre-existing brain dysfunction progressively increases delirium risk and wanted to investigate this prospectively. We approached this by considering older humans from a population-based cohort[13,14] who had been assessed with the Mini-Mental State Examination (MMSE).[15] In parallel, we tested the hypothesis that severity of underlying neurodegenerative pathology would predispose to acute cognitive deficits using mice with none, intermediate, or severe neurodegenerative pathology upon challenging them with systemic inflammation or vehicle control (Table 1). We predicted increased susceptibility to acute dysfunction even before disease-associated cognitive impairment had emerged. We assessed the incidence of delirium in humans and delirium-like cognitive dysfunction in mice at follow-up.

The findings of this investigation would provide important information on severity of cognitive decline as a graded risk factor in a true representative elderly population and a possible validation of a small animal model for delirium pathophysiology research. The overall purpose of these analyses is to broaden the methods available for addressing the