Hippocampal neurofibrillary tangle changes and aggressive behaviour in dementia
Mitchell K.P. Lai\textsuperscript{a,b}, Christopher P. Chen\textsuperscript{a,b}, Tony Hope\textsuperscript{c} and Margaret M. Esiri\textsuperscript{d}

Neuropsychiatric behaviours occur frequently in Alzheimer's disease and other dementias and are thought to arise from the neurodegenerative process. However, it is unclear whether neurodegenerative changes in the hippocampus are associated with neuropsychiatric behaviours such as aggression. In this study, semiquantitative measurements of cell loss, atrophy, neuritic plaque and neurofibrillary tangle load in the postmortem hippocampus were taken for dementia patients, prospectively assessed for neuropsychiatric behaviours. It was found that increased tangle load, but not other hippocampal neuropathological variables, was associated with increased severity of aggressive behaviours and presence of chronic aggression. This study suggests a pathogenic link between neurofibrillary tangle load and aggressive behaviours in the hippocampus of dementia patients. NeuroReport 21:1111–1115 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: aggression, Alzheimer's disease, dementia, hippocampus, neurofibrillary tangles, neuropsychiatric behaviours

\textsuperscript{a}Department of Neuropathology, John Radcliffe Hospital, Oxford, UK
\textsuperscript{b}Correspondence to Dr Mitchell K.P. Lai, PhD, Neurochemistry, Molecular Pathology and Biomarkers Discovery Theme, MACC, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Kent Ridge, Singapore, \textsuperscript{b}Department of Psychiatry, Warneford Hospital and \textsuperscript{d}Department of Neuropathology, John Radcliffe Hospital, Oxford, UK

Received 19 August 2010 accepted 10 September 2010

Introduction
In addition to cognitive impairments, people with Alzheimer’s disease and other dementias also frequently exhibit noncognitive, neuropsychiatric behaviours including aggression, depression, overactivity and psychosis [1,2]. Together, these behavioural and psychological signs and symptoms of dementia (BPSDs) [3] contribute disproportionately to caregiver distress and cost of care associated with institutionalisation [4,5]. Of the BPSDs identified by instruments such as the Present Behavioural Examination [6], aggressive behaviours and overactivity are particularly prevalent, occurring in 40–60% of patients [2,7]. Although another well-established instrument (the Neuropsychiatric Inventory) uses the terms ‘agitation’ and ‘aberrant motor behaviour’ [8], operationally they seem to refer to the same spectra of behaviours [6,8]. There is mounting evidence that BPSDs are a consequence of the neurodegenerative process, which includes intercellular neuritic plaques (NP), intracellular neurofibrillary tangles (NFT), neurovascular changes and cortical atrophy suggestive of extensive neuronal loss and associated neurochemical perturbations [9]. For example, earlier clinicopathological studies have correlated tangle load in the frontal cortex with agitation and aberrant motor behaviour [10], whereas disturbances of neocortical cholinergic and serotonergic neurotransmission have been implicated in aggression and overactivity [11,12]. However, it is not known whether other brain regions are involved in the occurrence of these BPSDs. It is also unclear whether the neuropathological changes reported earlier in BPSDs are specific pathological correlates of behaviours or are indicators of more generalised neurodegenerative processes.

The hippocampus, along with associated structures in the temporal lobe, is particularly vulnerable to Alzheimer’s disease and shows significant pathology even in early stages of disease [9,13]. In addition to the well-established roles in learning and memory formation, the hippocampus is also known to be involved in aggressive behaviours and trait [14,15]. It is at present unclear whether the hippocampus plays a part in overactivity. In this study, we measured a range of neuropathological changes in the postmortem hippocampus of a cohort of longitudinally followed-up dementia patients. We then correlated these neuropathological measures with clinical assessments of aggression and overactivity.

Materials and methods
The 27 patients included in this study were from a community-based cohort of patients from Oxfordshire, UK who were recruited into a prospective, longitudinal study of behaviour in dementia [2], and are now part of the Thomas Willis Oxford Brain Collection. Institutional review board approval for the recruitment and study of patients had been obtained from the Oxford Psychiatric Sector Research. All patients were assessed with the Cambridge Mental Disorders of the Elderly Examination

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Website (www.neuroreport.com).

0959-4965 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

DOI: 10.1097/NWR.0b013e3283407204