Insight 46: the NSHD neuroscience sub-study

In collaboration with the UCL Institute of Neurology

Introduction

Approximately 800,000 people in the UK are estimated to be living with dementia, the most common form of which is Alzheimer's disease (AD). The dementias:

- are a leading cause of death and a major cause of disability and residential care placement
- are calculated to cost the UK economy over £23bn per year (more than the cost of cancer and heart disease combined)
- are likely to become ever more prevalent with increasing life expectancy
- currently have no effective treatments

Most dementias have a long pre-symptomatic phase, during which molecular pathology gradually accumulates. This leads to brain cell damage, which then becomes self-perpetuating once established

Therefore effective therapies should be applied at the earliest stage of this process, before significant irreversible damage occurs. This necessitates the earliest detection of relevant disease markers

Fig 1: Hypothesized biomarker changes in AD

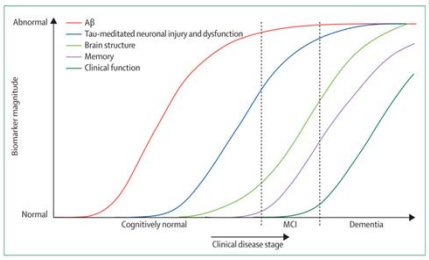
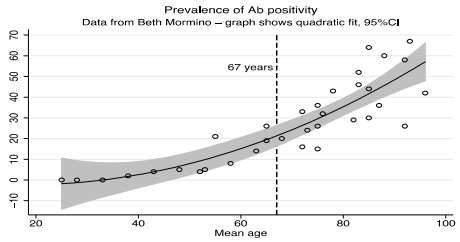


Fig 2: Prevalence of β-amyloid positivity in ageing



There is evidence that this neuropathology predates symptoms (Fig 1); that a significant proportion of healthy older people have β–amyloid (Fig 2); and that healthy amyloid-positive individuals have increased rates of brain shrinkage and cognitive decline.

What we do not know is which factors lead to these changes; and which factors influence whether these lead to brain damage. NSHD can uniquely answer these questions.

Key aims

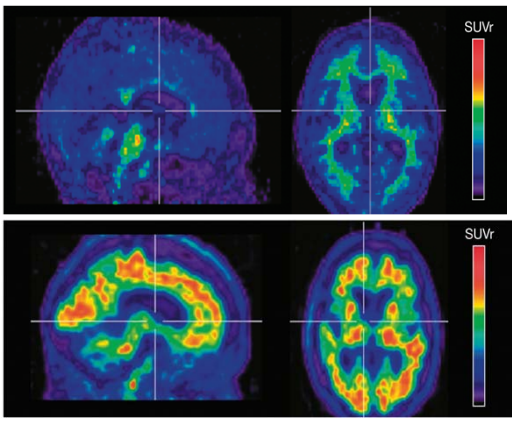
- To identify the prevalence of neuropathology at the beginning of the 8th decade, before this is likely to have caused significant irreversible damage
- To test life course predictors of this neuropathology, including genes, lifetime cognition and mental health, cardiovascular function and risk factors, physical capability and early motor function
- To repeat scans after 2 years: identify changes in neuropathology, and whether these changes predict clinical outcomes

Methods

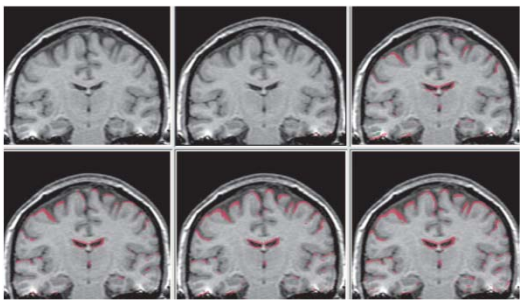
A random sub-sample of 500 NSHD study members is being invited to undergo neuroimaging at the Leonard Wolfson Experimental Neurology centre at UCL. We are using the UK's first combined PET-MRI device, a highly sensitive scanner that will enable early detection of brain anatomical and biochemical features that may signpost risk of Alzheimer's disease; and detailed cognitive assessment

At the same time study members also have a neurological examination, and undergo an enhanced cognitive assessment, sensitive tests of vision, hearing and smell, and a detailed assessment of walking speed and pattern

These scans will be repeated 2 years later to assess change in these features over time, and how they interact with each other. Combined with the extensive life course data already obtained from study members, this will provide vital information about the causes and consequences of normal and abnormal brain ageing



Representative florbetapir PET images for an amyloid-negative (A[beta]-) cognitively normal subject (top panel) and an amyloid-positive (A[beta]+) patient with AD (bottom panel). Colour scale is shown in standardized uptake value ratio (SUVr)



Six serially acquired T1-weighted MRI scans from an initially asymptomatic patient destined to develop familial Alzheimer's disease. Scans were acquired over 4 years before criteria for dementia were met; the first symptoms were reported between scans 4 and 5. Each scan has been positionally matched (registered) to the baseline scan; red overlay represents tissue loss compared with baseline.

Conclusions

Determining the causes and consequences of normal and abnormal brain ageing is of vital importance. Collaboration between the NHSD and the UCL Institute of Neurology unites an unparalleled level of expertise to lever this goal, linking the unprecedented life course data and epidemiological skills of the former with state of the art scanning techniques and expertise of the latter

This will be the first ever investigation of prospectively-measured lifetime risk of early asymptomatic β–amyloid deposition, and by far the largest amyloid PET scanning project ever undertaken in the UK. This will provide the platform for the UK to undertake pre-symptomatic trials to test therapies aimed at preventing the development of impairments due to Alzheimer's disease

The Insight 46 team includes Jonathan Schott, Nick Fox, Marcus Richards, Sebastian Crutch, Sebastien Ourselin, John Hardy, Henrik Zetterberg, Chris Lane, Tom Parker, Michelle Byford, Andrew Wong, Dave Cash, Jose Bras, Nikhil Sharma and Diana Kuh