**FINAL REPORT**

**Project title:** Significance of TDP-43 in the population in relation to dementia

**Funding Scheme:** Programme PEOPLE - Call ID FP7-PEOPLE-IIF-2008 - Panel SOC - Proposal N°235694

**Period covered: from** 03 April 2009

**to** 31 January 2011 (including 18 weeks maternity leave)

**Fellow:** Dr Hannah Keage

**1. Work carried out**

The Fellow, Dr Keage, worked on a large database – Epidemiological Clinicopathological Studies in Europe (EClipSE; www.eclipsestudy.eu) – to investigate the behavioural and biological correlates of a diagnosis of clinical dementia in late life and factors which affect its progression. Investigations made use of existing data within the EClipSE resource and new neuropathological data created during the Fellowship. This later neuropathological work was detailed in the original application. Further funding was required and successfully obtained from the Addenbrooke’s Charity Trust, UK. Staining for, and scoring of, a new protein aggregate neuropathology of dementia, TDP-43, was carried out and results are soon to be reported in a series of papers in 2012.

Notably, on paper published under this Fellowship (published in the journal *Brain*), received world-wide media attention including BBC TV and radio and Scientific American (over 250 online articles according to Google). This paper investigated how education in early life allows individuals to compensate for the presence of damage to the brain.

**2. Overview of results**

- Individuals who complete more education in early life are at lower risk of dementia in late life. This is not because they have fewer neuropathologies in their brain at death but rather, they are able to cognitively cope with the presence of these neuropathologies (EClipSE Collaborative Members, 2010).

- A genetic polymorphism within the APOE gene is associated with cognitive decline over a long 10-year follow-up (Keage et al., 2010).

- There is a complex relationship between obesity and dementia risk. Midlife obesity is strongly associated with dementia onset in late life, however late life obesity is protective (Keage et al., 2011).

- Neuropathologies typically disregarded in terms of their importance to dementia in late life, along with rare pathologies thought to only play a role in rare early-onset dementias, contribute to the manifestation of clinical dementia in late life. The underlying neuropathology of late life dementia is more complex than originally thought (Keage et al., 2012).

- Some sleep characteristics, particularly napping and excessive day time sleepiness, are predictive of cognitive decline in late life over a ten year time period (Keage et al., in press).

- The significance of the new TDP-43 pathology to dementia in late life, associated symptomatology and neuropathology cannot be reported publically here as is under review at various scientific journals.

**3. Conclusions**

The underlying biology of late life dementia is complex, and is not simply due to the accumulation of amyloid and tau protein within the brain or vascular dysfunction. Further, although dementia only manifests in late life, its onset and progression is affected by health and behaviours over the entire life course.

**4. Socio-economic impacts of the project**

Results will improve our understanding of the pathological basis of late life dementia. Findings will feed most immediately into clinical diagnostic and prognostic applications, as well as in the development of biomarker and neuropathological diagnostic methods and new pharmacological treatments for late life dementia. Given our global aging population, this will be critical if we are to reduce the economic and social burdens of dementia in late life.

**5. Scientific outputs (published and in press thus far)**

Keage, H.A.D., Banks, S., Yang, K.L., Morgan, K., Brayne, C., & Matthews, F.E. on behalf of

the MRC Cognitive Function and Ageing Study. (in press). What sleep characteristics predict cognitive decline in the old? Sleep Medicine

Keage, H.A.D., Matthews, F.E., Ince, P.G., Wharton, S., & Brayne, C. (2012). Impact of less

common and “disregarded” neurodegenerative pathologies on dementia burden in a population-based cohort. *Journal of Alzheimer’s Disease*, 28(2), 485-93.

Keage, H.A.D., Gupta, S., & Brayne, C. (2011). Risk for dementia and age at measurement.

*International Journal of Geriatric Psychiatry*, 26(3), 329-30.

EClipSE Collaborative Members\*. (2010). Education, the brain and dementia:

 neuroprotection or compensation? *Brain*, 133(8), 2210-2216.

Keage, H.A.D., Matthews, F.E., Guo, L., Rubinzstein, D., McKeith, I.G., McCracken,

C., Yipp, A., & Brayne, C.E.G. (2010). APOE and ACE polymorphisms and dementia risk in the older population over prolonged follow-up: ten years of incidence in the MRC CFA Study.  *Age and Ageing*, 39, 104–111.

\*EClipSE Collaborative Members includes (in alphabetical order):

Professor Carol Brayne (lead PI), Professor Paul G Ince, Dr Hannah AD Keage, Professor Ian G McKeith, Dr Fiona E Matthews, Dr Tuomo Polvikoski and Professor Raimo Sulkava. For all EClipSE papers, Fellow Keage carried out all analyses and wrote the draft paper, and is corresponding author.

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