Neuroinflammatory and morphological changes in late-life depression: the NIMROD study

L. Su, Y. O. Faluyi, Y. T. Hong, T. D. Fryer, E. Mak, S. Gabel, L. Hayes, S. Soteriadess, G. B. Williams, R. Arnold, L. Passamonti, P. Vázquez Rodriguez, A. Suresdanathan, R. W. Bevan-Jones, J. Coles, F. Aigbirhio, J. B. Rowe* and J. T. O’Brien*

Summary
We studied neuroinflammation in individuals with late-life depression, as a risk factor for dementia, using [11C]PK11195 positron emission tomography (PET). Five older participants with major depression and 13 controls underwent PET and multimodal 3T magnetic resonance imaging (MRI), with blood taken to measure C-reactive protein (CRP). We found significantly higher CRP levels in those with late-life depression and raised [11C]PK11195 binding compared with controls in brain regions associated with depression, including subgenual anterior cingulate cortex, and significant hippocampal subfield atrophy in cornu ammonis 1 and subiculum. Our findings suggest neuroinflammation requires further investigation in late-life depression, both as a possible aetiological factor and a potential therapeutic target.

Declaration of interest
J.T.O.’B. consulted for GE Healthcare, Servier and Bayer Healthcare and has received honoraria for talks from Pfizer, GE Healthcare, Eisai, Shire, Lundbeck, Lilly and Novartis.

Copyright and usage
© The Royal College of Psychiatrists 2016. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) licence.

Late-life depression is known to be associated with specific clinical features, such as cognitive impairments, it typically has a poor outcome and is a risk factor for dementia. Vascular factors have been implicated in its aetiology,1 but neuroinflammation has not been well studied despite being a highly plausible mechanism and potentially tractable target. We have previously shown an increase in inflammatory cytokines in the blood in older individuals with depression.2 In the current study we aimed to show whether we could demonstrate an increase in central (brain) inflammation in vivo using [11C]PK11195 positron emission tomography (PET) imaging. [11C]PK11195 is a radioligand that selectively binds to the translocator protein (TSPO), a receptor expressed on activated microglia. Increased binding has been found in stroke, traumatic brain injury and some neurodegenerative diseases, such as Alzheimer’s disease.3 We also investigated vascular and structural changes in late-life depression using multimodal magnetic resonance imaging (MRI).

Method
Within the Neuroimaging of Inflammation in Memory and Other Disorders (NIMROD) study, we recruited five participants with depression aged 65–78 years (depression group) from secondary care National Health Service (NHS) psychiatry services, who had met DSM-IV criteria for major depression (assessed using the Structured Clinical Interview for DSM Disorders)4 and 13 controls aged 65–78 years (depression group 10.0, control group 4.0; P = 0.065). The two groups did not differ in age, gender ratio, education or global cognition (Mini-Mental State score5) but the depression group had a trend in Montgomery–Åsberg Depression Rating Scale score (depression group 10.0, control group 4.0; W = 13.5, P = 0.065). Although largely recovered from their depression at time of imaging, at the group level, participants with depression had...
significantly higher $[^{11}C]PK11195$ BP$_{ND}$ compared with controls in left subgenual anterior cingulate cortex (mean BP$_{ND}$: depression group 0.1103, control group 0.0246; $W=54$, $P=0.035$), and right parahippocampus (depression group 0.1225, control group 0.0490; $W=53$, $P=0.046$); these are substantiated by the voxel-wise results given in Fig. 1 and online Fig. DS5. Using the individual-level Monte Carlo randomisation test, all five individuals in the depression group showed a significant increase of $[^{11}C]PK11195$ BP$_{ND}$ in the aforementioned brain regions, confirming the group-level statistical inference.

The depression group showed trends for more extensive WMH in both periventricular (depression group 7.33 ml, control group 3.74 ml; $W=13$, $P=0.059$) and deep (depression group 1.85 ml, control group 0.73 ml; $W=15$, $P=0.095$) white matter. We found a significant reduction of CA1 area in the coronal plane ($W=22.9$ mm$^2$, control group 24.90 mm$^2$; $W=52$, $P=0.019$) and subiculum thickness (depression group 1.73 mm, control group 1.95 mm; $W=56$, $P=0.004$) in the depression group. (See online supplement DS2 for additional demographic, cognitive, WMH and volumetric results.)

Discussion

We found evidence of both central and peripheral inflammation in older individuals with depression, including changes in the anterior cingulate and medial temporal lobe, which play a key role in the regulation of mood and cognitive functioning. Damage in these areas is linked with an elevated risk of dementia. Increased $[^{11}C]PK11195$ binding in people with depression could be associated with cerebrovascular disease and white matter lesions, reported in the current and previous studies, although some controls also had a similar burden of WMH with normal levels of $[^{11}C]PK11195$ binding in subgenual anterior cingulate cortex and parahippocampus (online Fig. DS5). It is notable that $[^{11}C]PK11195$ BP$_{ND}$ showed the greatest effect size compared with other modalities, with a 300% increase from controls (v. 150% for WMH and 10% for hippocampal atrophy), suggesting a strong biomarker potential for late-life depression.

There was no major cognitive impairment in our cohort, although the depression group showed significant atrophy in the hippocampus and subcicum, which have been shown to correlate with greater risk of cognitive impairment and Alzheimer’s disease. In addition, the hippocampus is a key component in the hypothalamic–pituitary–adrenal (HPA) axis. Increases in cytokine levels can lead to increases in oxidative stress and glucocorticoid as well as decreases in serotonin and other neurotransmitters in HPA resulting in impaired mood and cognition.

Our results were not corrected for multiple comparisons, and further replication is required in a larger cohort. However, the large effect size of $[^{11}C]PK11195$ was in keeping with our principal hypothesis and was supported by both a primary group-level test and secondary individual statistical tests. Cross-sectional studies provide limited information about whether neuroinflammation was the cause or consequence of neuronal damage in affected brain areas, so future longitudinal studies are needed. In conclusion, we suggest that neuroinflammation may be an important mechanism in late-life depression and merits further investigation as a potential target for novel therapeutics in a condition that responds poorly to conventional antidepressant therapy.

Funding

The study was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre and Biomedical Research Unit in Dementia based at Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. J.B.R. is supported by the Wellcome Trust (103838). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Chartson M. "Vascular depression" hypothesis. Arch Gen Psychiatry 1997; 54: 915–22.
2. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O’Brien JT. Increase in interleukin-1β in late-life depression. Am J Psychiatry 2005; 162: 175–77.
3. Stelmasiak I, O’Brien J. Imaging of neuroinflammation in dementia: a review. J Neurol Neurosurg Psychiatry 2016; 87: 21–8.
4. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. Structured Clinical Interview for DSM-IV Axis I Disorders. Research Version, Patient Edition. American Psychiatric Press, 1997.
5. Yassa M, van Berckel BN, Scheltens A, Hinz R, Turkheimer FE, Tomas G, et al. Optimization of supervised cluster analysis for extracting reference tissue input curves in [R11]PK11195 brain PET studies. J Cereb Blood Flow Metab 2012; 32: 1600–8.
6. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
7. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382–9.
8. Bae JN, MacFall JR, Krishnan KR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. Biol Psychiatry 2006; 60: 1356–63.
9. Taylor WD, McQuoid DR, Payne ME, Zananas AS, MacFall JR, Steffens DC. Hippocampal atrophy and the longitudinal course of late-life depression. Am J Geriatr Psychiatry 2014; 22: 1504–12.
10. Sexton CE, Le Masurier M, Allain CL, Jenkinson M, McDermott L, Kalu UG, et al. Magnetic resonance imaging in late-life depression: vascular and glucocorticoid cascade hypotheses. Br J Psychiatry 2012; 201: 46–51.
11. Apostolova LG, Dutton RA, Dinov ID, Hayashi K, Toga AW, Cummings JL, et al. Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. Arch Neurol 2006; 63: 693–9.
12. Sapolisky RM, Krey LC, McGeein BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocrinology 1986; 7: 284–301.
13. Dantzer R, O’Connor JC, Freund GG, Jonson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008; 9: 46–56.