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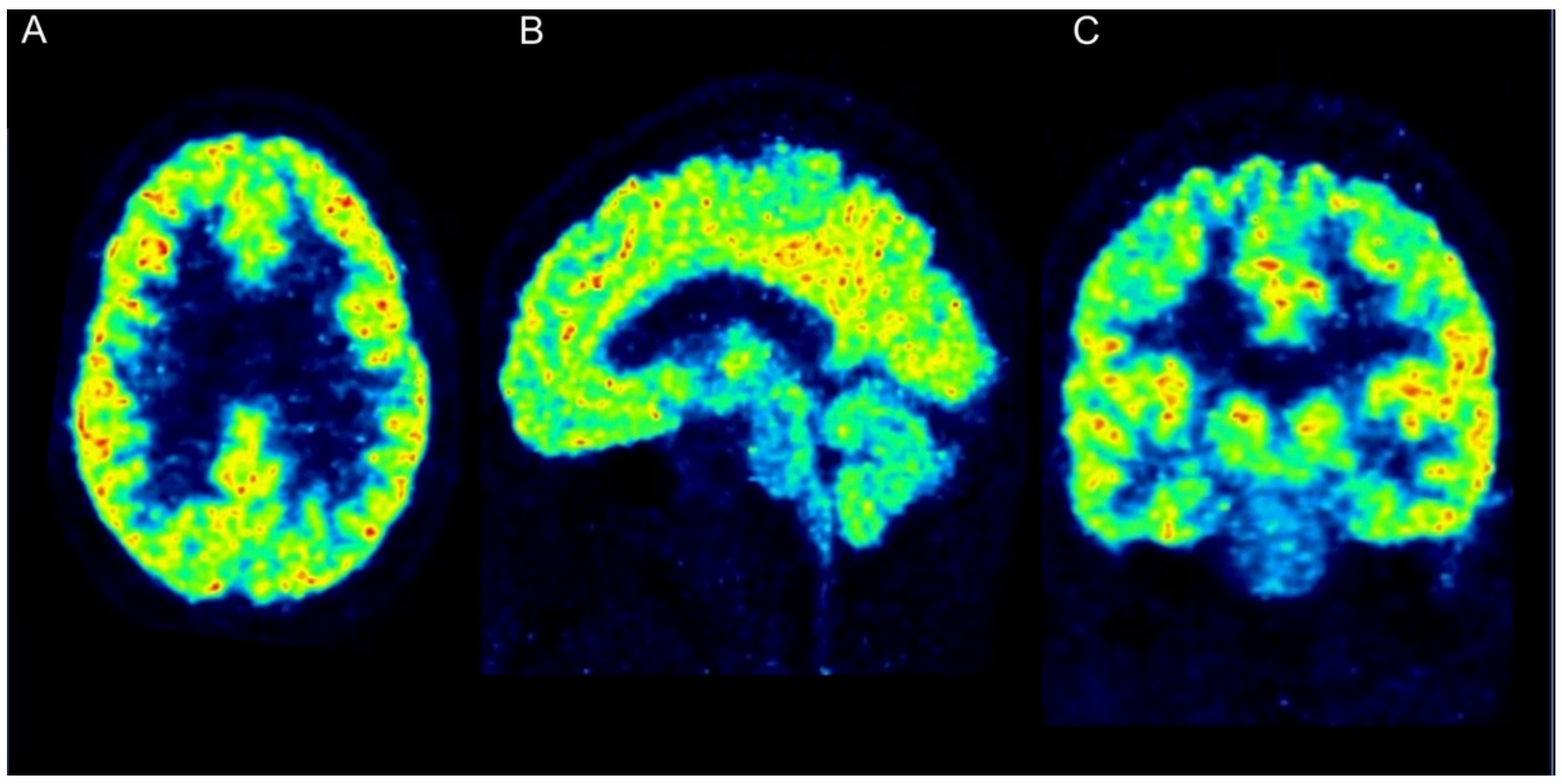
PNC DISTINGUISHED LECTURES

A talk by Federico Turkheimer
(King's College London, UK)

IMAGING THE INTERACTION BETWEEN SYSTEMIC AND BRAIN IMMUNITY AND ITS RELEVANCE IN MAJOR DEPRESSIVE DISORDER



The relationship between peripheral and central immunity and how these ultimately may cause depressed behavior has been the focus of a number of imaging studies conducted with Positron Emission Tomography (PET). These studies aimed at testing the immune-mediated model of major depressive disorder (MDD) that proposes a direct effect of peripheral cytokines and immune cells on the brain to elicit a neuroinflammatory response via a leaky blood-brain barrier and ultimately MDD. However, the studies conducted so far have demonstrated mild inflammatory brain status but no correlation between central and peripheral immunity. Hence the mystery remains on how these two systems communicate in MDD.

To gain a better insight into the relationship between heightened peripheral immunity and neuroinflammation, we estimated blood-to-brain and blood-to-CSF perfusion rates on data collected in two separate studies, one large clinical study of neuroinflammation in MDD cohorts and a second mechanistic study where peripheral inflammation in healthy controls was induced via subcutaneous injection of interferon (IFN)-. In both studies we observed a consistent negative association between peripheral inflammation and radiotracer perfusion into and from the brain parenchyma and CSF.

These results support a different model of peripheral-to-central immunity interaction whereas peripheral inflammation does not exert a direct neuroinflammatory "flare-up" but instead causes a "stiffening" of the BBB with consequent reduction of small molecule trafficking to and from the blood into the brain and CSF. This effect, on the long term, is likely to disrupt brain homeostasis and induce depressive symptoms. Moreover, given the molecular similarity between the TSPO ligands and antidepressant, this phenomenon may underlie treatment resistance in MDD cohorts with heightened peripheral status. This model has been further supported by recent clinical and pre-clinical work.

At the same time, further analysis of these rich data-sets generated a surprise finding, e.g. the unexpected role of the skull marrow as a further locus of interaction between systemic and central immunity and brought together a novel transdiagnostic mechanism linking body-brain immunity, MDD, pain and migraines.

Federico Turkheimer is an electronic engineer by training, and holds a PhD in Nuclear Medicine. He has worked in PET and neuroscience for the past 20 years holding appointments at the National Institute of Mental Health (Bethesda. USA), the University of Cambridge, the MRC Cyclotron Unit (then Imanet Ltd.) at Hammersmith Hospital. From 2002 to 2012 he was Reader in Mathematical Neuroscience at the Imperial College London and Head of the PET Methodology Group at the MRC Clinical Science Centre. Currently, he is Professor in Neuroimaging (Analysis & Statistics) at the King's College London and Theme Co-Lead for Neuroimaging at the NIHR Maudsley Biomedical Research Centre.

Federico Turkheimer's main interest is in the application of mathematics and statistics to problems in neuroscience, particularly in imaging and genomics. The aim of his work is to develop in-vivo imaging markers of brain function. Together with his group, he uses Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) to model brain physiology in health and disease. They are focused on brain immunity and its' relationship with the peripheral immune system, brain myelination and glymphatic function. They are also interested in constructing precise models of drug pharmacodynamics and pharmaco-kinetic action.