Introduction: In recent years, there has been much interest in variant Creutzfeldt-Jakob disease (vCJD), shown to be caused by the same prion strain as that causing Bovine Spongiform Encephalopathy (BSE). With recent reports of blood transfusion associated transmission, the disease remains an important public health issue. For diagnosis, histopathologists often examine only the frontal cortex where the hallmarks of vCJD: spongiosis, gliosis and deposition of the abnormal prion protein (PrPSc) in the form of multiple rounded amyloid plaques are evident. However, whilst bilateral thalamic high signal on T2W and FLAIR MRI in the pulvinar nuclei are reported with sensitivities of 78-100%, cortical changes on MRI have not been extensively characterised. Magnetic resonance microscopy (MRM) at 9.4T with an in-plane spatial resolution of 78µm can resolve the horizontal lamination of the isocortex. The purpose of this study was to exploit this technology to see whether prion protein plaques can be detected in vCJD.

Methods: 2 formalin-fixed specimens from the frontal cerebral cortex of a patient who had died from vCJD and a control specimen from a patient who had died from sporadic CJD were imaged at 9.4T (Varian Inc, Palo Alto, CA) before and after passive staining with 10 mM Omniscan (gadodiamide solution - Nycomed Imaging, Oslo, Norway). The gadolinium solution was used to reduce the MR relaxation times of the tissue so that maximum signal intensity would be achieved using a fast 3D gradient echo experiment. Typical T1 relaxation time constants of 1.1s and 1.2s for white and grey matter respectively decreased to 150ms and 90ms respectively while typical T2 time constants of 20 and 30 ms for white and grey matter respectively decreased to 10 and 7 ms. The tissue samples were placed in fomblin (Solvay Solexis, Milan, Italy) during scanning to minimise artefacts arising at the air-tissue interface. A high resolution (58 micron isotropic voxels) 3D gradient echo sequence was used (TR 20, TE 5 ms, FOV 30 x 30 x 15 mm, matrix 512 x 512 x 256 and 16 averages) with a total acquisition time of 12 hours. Following MR imaging, the fixed tissue was incubated in 98% formic acid for 1 h and following further washing for 24 h in 10% buffered formal saline, tissue samples were processed, paraffin wax-embedded, cut and stained with haematoxylin (Harris’ haematoxylin) and eosin (0.5%, Merck). Immunohistochemical staining, was performed with ICSM-33 to visualize prion protein (PrP) deposition and Aβ 1-42 to reveal Aβ deposits. All MR images were visually assessed for hypointense foci and inhomogeneity of the cortex.

Results: Visual inspection of high resolution gradient-echo MRI images of the frontal cortex in the vCJD specimens revealed multiple hypointense foci in the cortex of the vCJD specimens whereas the only the normal laminar pattern of the cortex was seen in the sCJD control sample (Figure 1). PrP immunohistochemistry revealed multiple rounded amyloid plaques (composed of PrPSc) with a dense eosinophilic core and a pale radiating fibrillary periphery in the cortex of the vCJD specimens with no plaques in the white matter (Figure 2). No plaques were seen in the sCJD control sample and none of the samples were positive for Aβ 1-42. On further analysis, the hypointense foci tended to be in the central layers of the cortex, corresponding to the greatest density of the PrP-amyloid plaques (Figure 2) and probably correspond to aggregates of the plaques rather than individual plaques.

Conclusions: Post mortem MRI at 9.4T can depict prion plaques in the cortex of patients with vCJD. The exact cause of the gradient-echo hypointensity will form the focus of further research. As higher field strength systems with improved RF receive coils enter clinical practice, in vivo high resolution MRI of the cerebral cortex may be valuable for earlier diagnosis and more sensitive monitoring of vCJD.