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In situ characterization and mapping of iron compounds in Alzheimer's disease tissue

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Abstract. There is a well-established link between iron overload in the brain and pathology associated with neurodegeneration in a variety of disorders such as Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) diseases [1]. This association was first discovered in AD by Goodman in 1953 [2], where, in addition to abnormally high concentrations of iron in autopsy brain tissue, iron has also been shown to accumulate at sites of brain pathology such as senile plaques [3]. However, since this discovery, progress in understanding the origin, role and nature of iron compounds associated with neurodegeneration has been slow. Here we report, for the first time, the location and characterisation of iron compounds in human AD brain tissue sections. Iron fluorescence was mapped over a frontal-lobe tissue section from an Alzheimer's patient, and anomalous iron concentrations were identified using synchrotron X-ray absorption techniques at 5 μm spatial resolution. Concentrations of ferritin and magnetite, a magnetic iron oxide potentially indicating disrupted brain-iron metabolism, were evident. These results demonstrate a practical means of correlating iron compounds and disease pathology *in-situ* and have clear implications for disease pathogenesis and potential therapies.

Keywords: Iron, neurodegeneration, ferritin, magnetite, alzheimer's disease, x-ray

1. Introduction

Iron in the brain, as in the rest of the body, is normally stored within ferritin: a 12 nm-diameter hollow protein shell which contains a ferrihydrite-like ($5Fe_2O_3 \cdot 9H_2O$) core. This allows iron to be stored predominantly in the less reactive ferric (Fe^{3+}) valence state [4, 5]. However, iron can be present in a variety of forms in brain tissue and despite decades of research, the form and role of the excess iron in neurodegenerative tissue is not well understood. Though recent work has resulted in the identification of ferrous (Fe^{2+}) iron associated with AD, appropriate techniques for the *in situ* characterization and mapping of anomalous iron compounds has been lacking [6,7]. In addition to ferritin and other common biological iron compounds, such as heme iron, the presence of biogenic magnetite (Fe_3O_4), a magnetic iron compound containing alternating lattices of ferrous and ferric iron is also present in human brain tissue [8,9]. Although the concentration of magnetite appears to represent a tiny fraction of total brain iron, recent quantification of magnetite levels in brain tissue revealed that levels of magnetite were significantly higher in autopsy tissue from AD patients than in the controls [10]. This may indicate that magnetite is a marker of the disease or potentially plays a role in pathogenesis. Recent electron microscopy investigations conducted on ferritin from AD tissue suggested the presence of a cubic magnetite-like structure in some of the iron cores, and a dominant crystalline

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