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USING SYNCHROTRON RADIATION TO MAP THE METALLO-MAZE TO MEMORY LOSS

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Transition metals such as Fe, Cu, Zn are essential for brain function, because they enable energy production, metabolism, and neurotransmitter synthesis. Disturbed brain metal homeostasis has been observed in the ageing and degenerating brain (e.g., Alzheimer's disease). Elevated levels of Fe, Cu, Zn are frequently observed in to spatially associate with markers of brain pathology (e.g. elevated metal content within amyloid plaques). Due to the redox active nature of Fe and Cu (e.g., classic Fenton Chemistry pathways) there is much interest in the role metal ion catalyzed free radical production and oxidative stress may hold in driving cognitive decline. There is extensive literature studying possible roles for Fe and Cu overload during natural ageing and neurodegeneration; yet in our studies at the XFM beamline of the Australian Synchrotron we have not observed any direct increase in Fe or Cu concentration within hippocampal neurons, in rodent models of natural ageing or dementia. Indeed, under certain conditions we have observed apparent decreases in neuronal metal ion concentration during ageing or neurodegeneration. This finding has led our research group to investigate differences in the sensitivity and specificity of direct elemental mapping techniques compared to histochemical methods to detect metal ions in brain tissue (e.g., Perl's Fe stain). We have also examined at length, how multiple aspects of sample preparation may affect the metal ion concentration, distribution, and chemical form in brain tissue.

Our findings appear to indicate that there are unique differences in the handling of metal ions by different brain cells. Specifically, brain cells of glial lineage (oligodendrocytes, macrophages, astrocytes) appear to be capable of accumulating Fe and Cu metal ions, while concomitantly neurons may become metal ion deficient. On the basis of our results, we suggest that neuronal metal ion deficiency may occur in the ageing and degenerating brain, possibly as a result of excessive metal ion accumulation in glia. If this is correct, metal ion deficiency would result in impaired energy metabolism and reduced neurotransmitter synthesis, which could be a potent driver of cognitive decline and memory loss. Our results suggest that future studies are needed to specifically investigate the mechanisms through which neuronal metal ion deficiency can occur, which may identify new opportunities for therapeutic intervention.

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