Metrology for metallomics

Discovering the roles of metals in brain disorders

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How we use synchrotron x-rays to study metal elements in the brain – and why!

Iron nanoparticle chemistry in pathology

Super-resolution approaches to speed up XRF imaging of tissue samples

Understanding how MRI signal is affected by iron in neurodegenerative diseases
Metal elements are essential to normal brain function

Fig. 2. Schematic overview of brain regions and distribution of Fe, Cu, Mn, Zn, and Se highlighting areas of TE enrichments under physiological conditions. Illustrated is a schematic longitudinal section of the brain with its five main brain regions. Additionally, shown are the respective subsections for each main brain region with their particular TE enrichment. A detailed summary of the different TE brain concentrations is reviewed in Grochowski et al. [31,105].

Wandt et al, Redox Biology 2021, 41, 101877
Transport & storage of metals is disrupted in some disorders

How to measure what is happening?

Alzheimer’s amyloid plaque

Iron accumulation in Parkinson’s

Figure 3 from Collingwood et al, Journal of Alzheimer’s Disease 2005, v7, pp267-272

Figure 2A from Oakley et al, Neurology, 2007, v68, pp1820-1825
Non-destructive imaging & analysis – synchrotron X-ray spectromicroscopy

What is the relationship between brain iron and MRI contrast?

Dependence of MRI on iron at 9.4T in human Alzheimer's and control brains:

- \( R_2 = 0.072 \text{[Fe]} + 20 \)
- \( R_2' = 0.340 \text{[Fe]} + 37 \)
- \( R_2'' = 0.260 \text{[Fe]} + 16 \)


Synchrotron X-ray spectromicroscopy of Alzheimer’s amyloid plaque cores


Plaque core (533.8 eV)
- Protein (532.1 eV)
- Carbonate (533.8 eV)
- Fe (710 eV)

Composite

STXM
Scanning Transmission X-ray Microscopy

X-ray Magnetic Circular Dichroism (XMCD)

(a) 709.5 eV
(b) Fe map

(c) X-ray absorption (arb. units)
(d) XMCD (arb. units)

XAS
X-ray absorption spectroscopy

81% Fe$_3$O$_4$
11% Fe$^{3+}$
8% Fe$^{2+}$

61% Fe$_3$O$_4$
39% Fe$^{3+}$
65% Fe$^{3+}$
24% Fe$^{2+}$
10% Fe$_2$O$_3$

100% Fe$^{3+}$
Biogenic metallic elements in the human brain?

James Everett²,³, Frederik Lermyte²,³, Jake Brooks³, Windy Tjendana-Tjin³, Germán Plascencia-Villa³, Ian Hands-Portman⁵, Jane M. Donnelly⁷, Kharmen Billimoria⁵,⁶,⁷, George Perry⁴, Xiongwei Zhu⁸, Peter J. Sadler⁸, Peter B. O’Connor⁹, Joanna F. Collingwood², Neil D. Telling¹∗
Finding melanin pigment in human brain with X-ray microscopy

Optical microscopy as the first step to find brain cells (neurons) containing neuromelanin

Brooks J et. al., Angewandte Chemie, 2020
Conclusion

Metal elements are essential to normal brain metabolism, but are not all easy to picture in detail with staining methods in the lab.

Need more sensitive and accurate ways of looking at brain tissue samples.

Some metal elements, particularly iron, give contrast in certain clinical scanning methods, particularly Magnetic Resonance Imaging.

Patterns of change in the brain, & impact of treatment, could be imaged in people.

Synchrotron X-ray microscopy is extremely sensitive and accurate to allow metal elements to be identified.

Documenting change and discovering what is happening to metal distributions and metal chemistry.
THANK YOU!

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