Brain Iron Deposition

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The brain uses iron for many essential processes (1-4). The extent of iron utilization is heavily dependent on local functional requirements, leading to significant variations in tissue iron concentrations throughout the brain (5-7). This was graphically illustrated nearly a century ago in the first colour illustrations of the differential distribution of iron throughout the brain architecture, obtained by Spatz (8) using Perls staining (9).

This early histochemical study was subsequently replicated, confirming that the observed patterns are reproducible in normal healthy brains, and that iron revealed by Perls stain is concentrated more highly in the grey matter, with negligible staining in the white matter. Subsequent studies quantifying iron in bulk tissue samples revealed that iron concentrations in some white matter regions are similar to those in grey (e.g. as reviewed in 10), demonstrating that conventional Perls staining is not equally sensitive to all forms of brain iron.

Iron in the brain can be categorized as either haem iron (including the iron in haemoglobin, which is required for transport of oxygen), or non-haem iron, which is present in a variety of forms, and required for roles ranging from neurotransmitter synthesis to cellular aerobic metabolism. The valence state of iron can switch between ferric (Fe^{3+}) and ferrous (Fe^{2+}) under in-vivo conditions, and this property is exploited in the mechanisms of iron uptake, transport, and storage (1).

It is understood that the significant majority of brain iron is bound; in other words, there is very little free (labile) iron in the tissues under normal circumstances. Unbound or accumulated iron may play a toxic role by catalyzing the formation of radical species, for example via Fenton chemistry (1,11,12). There is extensive evidence of a sophisticated and complex system to regulate iron uptake, transport and storage in the brain (6-7,13-15); however, while our understanding of the mechanisms has developed significantly in recent years, aspects of the process still remain to be understood (3).

With the development of MRI in the 1980s came the discovery that iron in tissue may influence MRI mechanisms to provide clinically observable contrast. Since the observations of Drayer et al in 1986 (16), an active, challenging and exciting research field has emerged (10,17-18), with a variety of MRI techniques being employed to explore the scope for quantifying brain iron in vivo, and for tracking changes in brain iron status as a function of age and disease (e.g. 19-32). This is particularly relevant for certain neurodegenerative disorders where changes in brain iron are observed; typically in conjunction with pathologic protein deposition or regions of tissue atrophy (e.g. 33-44). If we can reliably quantify brain iron in-vivo, this opens up possibilities for improved detection and diagnosis of these diseases (45), as well as the potential for assessing the impact of therapeutic interventions.

In this session we will learn about iron deposition at various levels in the brain architecture, including regional non-haem iron in areas of the cortex and basal ganglia, and cellular-level distribution in neurons and glia (46). We will discuss the various forms of non-haem iron that have been observed in post-mortem brain tissue (47-48), alongside consideration of the techniques used to identify them (49-52). We will also consider recent approaches to in-vivo detection of brain iron with MRI, and how the various bound forms of brain iron may impact specific measurement parameters in MRI (e.g. 53-55). The relevance of this approach will be illustrated with reference to neurodegenerative disorders where there is significant deposition of iron in the brain (19,40-41,56), and also those where more subtle brain iron changes are implicated in disease pathology (12).

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