BIOGENIC MAGNETITE PARTICLES IN ALZHEIMER’S DISEASE BRAIN TISSUE

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ACKNOWLEDGEMENTS

Dimitri Hautot, Ian Mortimer, Wisdom Beyhum
– UCL Physics & Astronomy

Nadeem Khan – Institute of Psychiatry

Roger Ordidge – UCL Medical Physics

Charlie Davie, Rupert Page – Royal Free and UCH

Gill Bates, Ben Woodman – Guy’s Hospital

Jon Dobson – Keele

Andy Curtis, Chris Morris, John Burn – Newcastle
Alzheimer’s disease (AD) is the most common form of senile dementia, affecting millions of people across the world every year.

After correcting for longevity, 60% of AD sufferers are women and 40% are men – the origin of this gender difference is not known.

Tiny magnetic particles are present in all human brains, at very low levels, which we can measure using new methods.

In our study we found that two-thirds of the women suffering from AD had abnormally large levels of magnetic particles in their brains.

This draws attention to the role of iron in AD, and offers a potential diagnostic role for MRI brain scans.
Our hypothesis is:
‘that the presence of magnetic biominerals in the brain can provide a diagnostic indicator of neurological diseases’

Our approach is:
To locate and characterise the magnetic material:
- Established – histopathology (sectioning, staining, microscopy)
- Current – in vitro SQUID magnetometry
- Future? – in vivo magnetic resonance imaging (MRI) or magneto-encephalography (MEG)

Our immediate goal is:
to establish whether magnetic materials are present in abnormal concentrations using in vitro SQUID magnetometry
Perls’ stain for iron in an AD shows an association of iron with the neurofibrillary tangles and plaques that characterise AD.
Recent work on magnetic extractions from the human hippocampus shows up magnetite/maghemite nanocrystals.
SQUID MAGNETOMETRY

- Superior temporal gyrus samples, preserved by freezing at -80 °C, ca. 1 gram by weight, supplied by MRC London Brain Bank.
  - First cohort: six samples, all female.
  - Second cohort: twenty samples, ten male, ten female.
- Tissues very dilute – ca. 200 ng/g magnetic material.
  - Measure using an ultra-sensitive superconducting quantum interference device (SQUID) magnetometer.
  - Months of testing to arrive at a reliable measurement protocol.
• M-H curves dominated by the diamagnetic response of the tissue.

SQUID MAGNETOMETRY

\[ \text{Magnetisation (emu/g)} \]

\[ \text{Field (G)} \]

150 K
Model the M-H curves as a sum of three magnetic contributions.

- Diamagnetic tissue
  - linear, negative slope
- Superparamagnetic ferritin
  - constrained to that of human spleen ferritin
- Ferrimagnetic magnetite
  - fitted, ignoring the small coercivity

\[
\text{Magnetisation (M)} \quad \text{Field (H)}
\]
M(T) shows a ferrihydrite blocking transition at 12 K.
IRM shows the presence of magnetite and/or maghemite.
SQUID MAGNETOMETRY

- Extracted M-H curves – fitted as ferritin plus magnetite.
Even without case-by-case scrutiny, AD females clearly have more magnetite/maghemite than the others.

- **Statistical analysis:** Mann-Whitney rank sum test.

- No differences between AD and control males, \( p = 0.286 \), nor between the male and female controls, \( p = 0.788 \).

- Significant differences between AD and control females, \( p = 0.005 \), and between the male and female AD subjects, \( p = 0.030 \).
There is a measurable and quantifiable differentiation between the pathogenesis of AD in men and women.

There is a potential role for disrupted iron homeostasis in AD.

There is support for the hypothesis that a malfunction in the iron biomineralisation cycle undertaken by the iron storage protein ferritin may be a significant factor in AD pathogenesis.
Across all tissue samples – male, female, AD and controls – see a correlation between the total magnetite concentration and the percentage of magnetite that is nanoscale i.e. < 50 nm in size.

![Graph showing the correlation between mass fraction of magnetite and percentage blocked across different groups.](image-url)
A possible answer to a 50 year old conundrum: why does the iron content increase in diseased tissue whereas the amount of ferritin does not?

- Propose the *accelerated growth* of nanoscale magnetite

- Conversion of the 8 nm sized ferrihydrite cores of the storage protein ferritin
MRI SCANS

- New 4.7 T, 90 cm bore fast spin echo system at UCL.
  - Resolution: 400 microns x 500 microns.
  - Relaxation Parameters: TE = 66 ms, TR = 3.5 s.
  - Scan Time: 17 slices (2 mm thick) in 6 minutes.
MRI SCANS
We have started tests with ping-pong balls filled with different concentrations of water and ferritin.
CONCLUSIONS

- Alzheimer’s disease:
  - we find a measurable, statistically significant difference between magnetic nanoparticles in AD men and women
  - we propose an accelerated growth of nanoscale magnetite and/or maghemite in ferritin, and an increase in iron loading

- Further work:
  - further work on HD transgenic mice
  - continuing MRI studies
  - much more to learn from cross-disciplinary communicating
FINAL THOUGHTS

- So what have we learned?
  - *that biogenic magnetism is worth paying attention to, and may be an important clue to iron metabolisation malfunctions in the body*

- What is the scope for medical improvements?
  - *there may be diagnostic or even therapeutic implications, as evidenced by recent work on vitamins for AD treatment*

- What else is there to do?
  - *we have barely scratched the surface: there have been very few studies of biogenic magnetism*
  - *what happens to the ferritin in the liver, spleen or blood?*
  - *do anaemia sufferers get AD?*