Alzheimer's (or Parkinson's) -- hypothesis for an *attractive* cause

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ABSTRACT

The basis of this hypothesis is the presence of organelles, called *magnetosomes**, in all human brain cells, a fact discovered fifteen years ago. As a natural occurrence, brain cells die of apoptosis at a slowly increasing, but very critical rate. The dead brain cells are dissolved by enzymes liberating the insoluble core elements of these magnetosomes, i.e., tiny magnets, which then aggregate as magnetic clumps. Depending upon the aforementioned apoptotic rate of brain cell death, the following chain reaction would occur: these clumps would magnetically bind nearby ferritin, withholding this essential brain cell nutrient. Other brain cells, thus deprived of ferritin, also die releasing yet more clumps of magnetite, thus triggering this exponential brain cell death. This process defines Alzheimer's, and could possibly be implicated in Parkinson's disease. The literature is replete with numerous reports of magnetite crystals, anomalous ferritin and beta amyloid plaque in the brains of Alzheimer's cadavers. * familiar to specialists studying animal navigation using magnetic fields

Alzheimer's disease (AD) affects over 5 million persons in the U.S alone. It has so far defied attempts by medical researchers to explain its origin. Without a full understanding of the underlying mechanism, it will be difficult to derive therapies, develop medication or implement prevention strategies for AD.

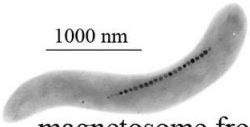
A possible cause is suggested herein, together with simple laboratory procedures to test the relevance of the proposed causative mechanism. This hypothesis is based upon the known presence of organelles, called magnetosomes, in all human brain cells. Brain cells die, naturally, of apoptosis, i.e. programmed cell death, at a rate which slowly increases with age. Enzymes liberate the insoluble core elements of these magnetosomes, i.e., biogenic, permanently-magnetized magnetite crystals. These crystals then aggregate in magnetic clumps. They magnetically bind with and withhold ferritin, an essential brain cell nutrient. Deprived of ferritin, other brain cells die, triggering a chain reaction, thereby defining the onset of Alzheimer's.

Magnetosomes are present in many if not all animal species. Present in a unique prokaryotic organelle inherited from bacteria more than a billion years ago, these magnetosomes contain crystals of the mineral *magnetite*. These crystals, when configured, constitute the magneto-responsive element that forms the 'magnetic compass' needle that, under certain conditions, assists some species of animals to navigate (magnetotaxis) using the earth's magnetic field. (See, for example, R.B. Frankel, R.P. Blakemore, and R.S. Wolfe, Magnetite (1979) in Freshwater Magnetic Bacteria. Science 203, 1355-1357)

Magnetite, in its inorganic form is a common mineral comprised of ferrous and ferric oxide, Fe_3O_4. It is vary hard, relatively *inert*–and *ferrimagnetic* in the presence of an ambient magnetic field. These last two characteristics (and the differences between inorganic and biogenic forms) are critical in the proposed hypothesis. Magnetite is a very common accessory mineral in granitic and volcanic rocks and is sometimes mined as iron ore. Dipping a common magnet in the water at the seashore or the bank of a stream will attract small grains of magnetite. These grains, weakly magnetic in the presence of an ambient field, are not in themselves, magnetic. That is, they are not permanently magnetized. Magnetic domains, microscopic regions several tens of nanometers (nm) in size, comprise ferrimagnetic material. They are randomly oriented and require external ambient magnetic fields to exhibit their magnetic behavior.

In bacteria and higher order animals, magnetite is formed by biological processes and is called *biogenic magnetite – forming 30 to 40 nm cubic crystals each comprised of a single magnetic domain*. Therefore, unlike inorganic magnetite crystals, these crystals are permanently and fully magnetized when formed. In order for these crystals to act as a compass needle and produce sufficient torque to sense the ambient earth's magnetic field, tens of such crystals are lined up with their magnetized vectors all aligned, constrained against clumping, by a cyto-scaffold to keep the crystals aligned. This line of magnetite crystals is then attached via cytoskeleton ligatures to the external bilayer lipid protein membrane, or housing, the whole unit representing a single magnetosome, or magnetic compass

'needle' whether in humans, insects or bacteria. **(**See, for example, Kirschvink, JL, et al (1992) Magnetite biomineralization in the human brain. Proc. Natl. Acad. Sci., USA, 89: 7683-7687)



magnetosome from Magnetospirillum magnetotacticum

As brains cells die, various enzymes dissolve cells or other non-functioning materials—including the lipid protein, the cytoskeleton and scaffolding. But, biogenic or inorganic magnetite such as found in the environment, survives millions of years: resisting acids, ultraviolet and mechanical abrasion. Therefore, biogenic magnetite crystals from tens of millions of cells, liberated from their protective membranes, should form clumps and resist the actions of any natural enzyme to dissolve them or remove them from the body. Their magnetic properties will then act, even at a distance, on molecules of ferritin being delivered to brain cells.

Brain tissue collected from AD cadavers always contain anomalous amounts of iron* though the iron compounds are not always specified. Under the subject hypothesis, it should contain small amounts of magnetite and considerably more concomitant ferritin. In fact, such evidence has been widely observed, but without accompanying explanation. (See excerpts of abstracts from these papers below.) Another recent paper** suggests that high frequency electromagnetic fields (EMF), simulating use of cell phones, actually *improved* cognitive behavior in Alzheimer's-bred transgenic mice. One explanation for this surprising find could be that such EMF interferes with the ability of magnetite crystals to attract ferritin, which is weak. See below. *Dobson J, (2004) Magnetic iron compounds in neurological disorders. Ann. NY Acad Sci, Mar; 1012:183-92. **Arendash, GW, et al Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimer Dis (2010) Jan;19(1):191-210.

Based upon the above, our working hypothesis is: *at a certain rate of brain cell death what was linear becomes exponential, rapidly destroying critical regions of brain tissue, thereby defining early or mid-stage Alzheimer's disease.* A variant of this could be related to brain tumors or Parkinson's Disease.

From the literature, there appears to be some connection between AD and the apolipoprotein E4 gene (Apo E4) and/or tau tangles in the entorhinal cortex. The subject hypothesis suggests that there might be a mechanism for a greater than normal rate of programmed cell death—apoptosis or other—to initiate the triggering exponential phase. A natural variation among individuals in the apoptotic rate, whether Apo E4-controlled or not, might explain why AD occurs in some individuals and not others. Possibly, there may be tests to confirm if such putative AD subjects have a significantly earlier onset of brain cell death, compared to controls.

Consider this numerical example for the process: Assume that for the above magnetite-induced chain reaction, the threshold is 5,000 brain cell deaths (BCD) per day (numbers and description are merely placeholders for purposes of example). A 60 year-old person not genetically predisposed for AD exhibits a BCD rate of 2,000/day, increasing at a rate of 50 BCD/day/year. At 100 years old, this person will still only have a BCD of 4000, and not symptomatic of AD. Another 60-year-old person with no AD symptoms but carrying the Apo E4 gene, has the same BCD of 2,000 as the above non-AD person, but with a *rate of change* of BCD of 200/day/year (due to something associated with the Apo E4, tau or other known AD indicator). This person, will, by 75, attain a BCD of 5,000 and thus exhibit symptoms of AD.

Ferritin is weakly paramagnetic and should be attracted to a magnet, but not strongly. Even a weak attraction might be just enough to affect the supply of ferritin. An elementary laboratory test of this hypothesis would begin with a test confirming how effective is the attraction between clumps of biogenic magnetite and ferritin in appropriately simulated conditions.

Another key experiment could involve transgenic mice bred for AD symptoms. By applying magnetic field gradients to the brains of the test group, one might be able to drive the magnetite crystals to an outlying location near the skull, where a small subcutaneous magnet could safely sequester them.
(Does apoptosis in mice exist and does that affect this animal model?) Like these animal tests, routine hour-long (??) sessions every few years wearing a headdress bearing a magnetic field gradient is, in

fact, the prophylaxis suggested for human purposes, perhaps once every few years after a certain age and at greater frequency with age. Since it is not known whether these magnetic clumps can be induced to move through brain tissue and between brain sections, it might be that if the clumps were merely moved, say, out of the hippocampus and into another region, that the clumps would be out of harm's way and either prevent the onset of AD or defer its progression.

Alternatively, a form of iron, other than ferritin, could be developed and administered or ingested that is metabolically suitable for brain cells or all cells but that does not exhibit magnetic properties in the presence of a magnet. Or, a benign substance or condition could be introduced that decreases the already-weak magnetic attraction between the ferritin and the magnetite clumps. Combinations of the above could lead to prevention, therapy or mitigation of AD—or, perhaps--PD symptoms.

For diagnostic purposes, it may be possible to measure and differentiate between distributed and clumped magnetite in AD patients and a control group using a sensitive SQUID magnetometer in a magnetically-shielded room.

The already proven presence of magnetite particles in all normal individuals and its anomalous presence together with anomalous ferritin in AD cadavers must be explained. While animal models might shed light on some of these unanswered questions, there may be non-invasive methods applied to humans to prove or disprove the subject hypothesis, especially when various tests now under development become available for confirming the diagnosis of AD in living individuals years before symptoms appear.

Excerpts from abstracts citing magnetite and ferritin in the brains of deceased Alzheimer's patients (in particular, read the text-- ***in bold***--from the following dozen papers found on PubMed)

For more info, use this link below to access all papers

http://dl.dropbox.com/u/6088957/Links%20to%20magnetite%2C%20ferritin%20in%20AD.pdf)

A study of the magnetic properties of superior temporal gyrus brain tissue from 11 Alzheimer's disease (AD) and 11 age-matched control subjects demonstrates an exponential correlation between the concentrations of the Fe;{2+}-ion-containing iron oxide, magnetite (Fe{3}O{4}), and the fraction of those particles that are smaller than 20 nm in diameter. These data provide circumstantial evidence in favor of their genesis within the 8 nm diameter cores of the iron storage protein ferritin. **We also show, for the first time, that the total concentration of biogenic magnetite is generally higher in the AD brain (in some cases as much as 15 times greater than controls)** . . .

Pankhurst Q, Hautot D, Khan N, Dobson J Increased levels of magnetic iron compounds in Alzheimer's disease. J Alzheimers Dis. (2008) Feb;13(1):49-52.

(http://www.ncbi.nlm.nih.gov/pubmed/18334756?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

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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** . . .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

Collingwood JF, et al In situ characterization and mapping of iron compounds in Alzheimer's disease tissue. J Alzheimers Dis. (2005) Aug;7(4):267-72

(http://www.ncbi.nlm.nih.gov/pubmed/16131727?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=1&log$=relatedarticles&logdbfrom=pubmed)
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Elevated iron levels are associated with many types of neurodegenerative disease, such as Alzheimer's, Parkinson's and Huntington's diseases. However, these elevated iron levels do not necessarily correlate with elevated levels of the iron storage or transport proteins, ferritin and transferrin. As such, little is known about the form of this excess iron. It has recently been proposed that some of the excess iron in neurodegenerative tissue may be in the form of the magnetic iron oxide magnetite (Fe(3)O(4)). We demonstrate, for the first time to our knowledge, using highly sensitive superconducting quantum interference device (SQUID) magnetometry, that the **concentrations of magnetite are found to be significantly higher in three samples of Alzheimer's disease tissue than in three age- and sex-matched controls.** These results have implications, not only for disease progression, but also for possible early diagnosis.

Hautot D, Pankhurst QA, Khan N, Dobson J. Preliminary evaluation of nanoscale biogenic magnetite in Alzheimer's disease brain tissue. Proc Biol Sci. (2003) Aug 7;270 Suppl 1:S62-4.
http://www.ncbi.nlm.nih.gov/pubmed/12952638?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=2&log$=relatedarticles&logdbfrom=pubmed
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Previous studies of the structure of core nanocrystals of ferritin (Ft) in the brains of patients with Alzheimer's disease (AD) have shown differences in the mineral compound in comparison with physiological Ft. Both Ft cores have a polyphasic composition but whereas the major phase in physiological Ft is hexagonal ferric iron oxide (ferrihydrite), the major phases in brain AD Ft are two cubic mixed ferric-ferrous iron oxides (magnetite and wÃ¼stite). cytes. Ft was particularly abundant in myelinated axons in association with oligodendrocyte processes. **These findings provide new arguments to support the hypothesis of a dysfunction of ferritin, Ft, (with eventual degradation to hemosiderin (Hm) in AD resulting in an increase of toxic brain ferrous ions that may contribute to the production of free radicals that induce both cellular oxidative stress and aged-related myelin breakdown associated with cognitive decline and AD**

Quintana C, et al Study of the localization of iron, ferritin, and hemosiderin in Alzheimer's disease hippocampus by analytical microscopy at the subcellular level. J Struct Biol. 2006 Jan;153(1):42-54. Epub (2005) Dec 1
(http://www.ncbi.nlm.nih.gov/pubmed/16364657?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=3&log$=relatedarticles&logdbfrom=pubmed)
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One of the characteristics of many neurodegenerative diseases is the disruption of normal iron homeostasis in the brain. Recent experimental work indicates that nanoscale magnetic biominerals **(primarily magnetite and maghemite) may be associated with senile plaques and tau filaments found in brain tissue affected by these diseases.** These findings have important implications for our understanding of the role of iron in neurodegenerative disease as well as profound implications for their causes. In addition, the presence of biogenic magnetite in affected tissue should also provide improved mechanisms for early detection through the modification of MRI pulse sequences.

Dobson J Nanoscale biogenic iron oxides and neurodegenerative disease. FEBS Lett. (2001) May 4;496(1):1-5
(http://www.ncbi.nlm.nih.gov/pubmed/11343696?dopt=abstractplus)
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Mammalian cellular iron is stored inside the multisubunit protein ferritin, normally taking the structure of a ferrihydrite-like mineral core. **It has been suggested that biogenic magnetite, which has been detected in the brain and may be related to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, could initially form in ferritin. Indeed, as ferritin is present in the brain, the ferrihydrite core could be a precursor for biogenic magnetite formation--particularly in cases where the normal functioning of the ferritin protein is disrupted.**

Gossuin Y, et al. Looking for biogenic magnetite in brain ferritin using NMR relaxometry. NMR Biomed. (2005) Nov;18(7):469-72. (http://www.ncbi.nlm.nih.gov/pubmed/16177954?dopt=AbstractPlus)
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Oxidant-mediated damage is suspected to be involved in the pathogenesis of several neurodegenerative disorders. Iron promotes conversion of hydrogen peroxide to hydroxyl radical and, thus, may contribute to oxidant stress. We measured iron and its transport protein transferrin in caudate, putamen, globus pallidus, substantia nigra, and frontal cortex of subjects with Alzheimer's disease (n = 14) and Parkinson's disease (n = 14), and in younger adult (n = 8) and elderly (n = 8) normal controls. Although there were no differences between control groups with regard to concentrations of iron and transferrin, **iron was significantly increased ($p < 0.05$) in Alzheimer's disease globus pallidus and frontal cortex** and Parkinson's disease globus pallidus, and transferrin was significantly increased in Alzheimer's disease frontal cortex, compared with elderly controls. . . .(Pearson's correlation coefficient) in elderly controls than in Alzheimer's and Parkinson's disease. **The altered relationship between iron and transferrin provides further evidence that a disturbance in iron metabolism may be involved in both disorders.**

Loeffler DA, et al Transferrin and iron in normal, Alzheimer's disease, and Parkinson's disease brain regions. J Neurochem. (1995) Aug;65(2):710-24 (http://www.ncbi.nlm.nih.gov/pubmed/7616227?dopt=AbstractPlus)
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The magnetic properties of human hippocampal tissue from 23 subjects (15 epilepsy patients and eight cadavers with no neuropathology) were analysed and tissue concentrations of magnetic material were calculated. The biogenic iron oxide magnetite (Fe(3)O(4)) is the dominant source of magnetisation in the tissue. Analysis of the group as a whole revealed no significant trend towards either increasing or decreasing magnetite concentration with age. **Separate analysis of male and female subjects, however, reveals a trend towards increasing magnetite concentration with age in males.** This trend is not seen in females and may have implications for iron metabolism and neurological disorders associated with disruptions in normal iron homeostasis.

Dobson J. Investigation of age-related variations in biogenic magnetite levels in the human hippocampus. Exp Brain Res. (2002) May;144(1):122-6. Epub 2002 Mar 12.
(http://www.ncbi.nlm.nih.gov/pubmed/11976766?dopt=AbstractPlus)

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The amount of loosely bound iron was measured in frontal cortex and cerebellum from autopsy brain samples from Alzheimer's patients and from non-demented, age matched controls. **It was found that the amount of total iron and of ferric iron in Alzheimer's brain tissues was significantly higher compared to control samples in both regions studied.** Neither the ferrous nor the ferrous to ferric ratio were found to be changed. **Since it is the loosely bound iron that is responsible for free radical reactions in vivo, these results are consistent with an increased free radical burden in Alzheimer's disease** that leads to the progressive neurodegeneration seen in this disorder.

Kala SV, Hasinoff BB, Richardson JS. Brain samples from Alzheimer's patients have elevated levels of loosely bound iron. Int J Neurosci. (1996) Sep;86(3-4):263-9.
(http://www.ncbi.nlm.nih.gov/pubmed/8884397?dopt=AbstractPlus)

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Ferritin is the primary iron storage protein in the brain. It consists of a 12nm diameter spherical protein shell with an 8nm cavity capable of storing up to 4500 iron atoms in the form of ferrihydrite. Ferrihydrite is superparamagnetic at body temperature and it exists in varying degrees of crystallinity in the human body. In addition to ferritin, biomineralization of ferrimagnetic magnetite is known to occur in a number of organisms including animals [e.g. 1]. Recent investigations have revealed the presence of biogenic magnetite in human brain tissue as well [2,3,4,5]. **The presence of magnetite in the brain has been established using a variety of magnetic and electron microscopic techniques. In addition, anomalous concentrations of iron are known to be associated with virtually all neurodegenerative diseases, however, since this relationship was first discovered 50 years ago, very little progress has been made in understanding their composition, origin or role in disease processes.**

Goodman, L Alzheimer's disease - a clinicopathologic analysis of 23 cases with a theory on pathogenesis. J. Nerv. Ment. Dis. (1953) 118: 97-130