Alzheimer’s Disease, Part III: Further Imaging and Treatment

Our memories form the collective essence of ourselves. They create the framework of our contemplative and imaginative abilities. But what molecular arrangement stores these experiences, where are they held, and how are they retrieved? What cascade of events marks some memories for long-term storage and not others?

Imagine looking into a lens that shows structures on an ever-smaller scale. Envision the anatomy of memory by viewing the brain’s parenchyma, then the cellular circuitry, the micro-environmental, the molecular, and finally the subatomic basis of memory, its electromagnetic energy. What comprises these pieces? And how does this anatomic memory network function?

It is this fundamental understanding that will help unlock clues to protecting memories from the destructive force of Alzheimer’s disease (AD). While answers to many of these questions remain an undiscovered frontier, imaging has afforded insight into some of them. This week’s WCC Note examines some of the applied and experimental literature about memory gone awry in the anatomy and physiology of Alzheimer’s. This issue, the third in a three-part series, concludes with an overview of attempts at AD treatment and prevention.

What Are the PET and SPECT Findings in Alzheimer’s Disease?

To evaluate AD, PET scans can be performed with (18F)-2-fluoro-2-deoxy-D-glucose (FDG-PET) to image the brain’s glucose metabolic rate or, more recently, with specific agents to directly image amyloid plaques.

1. FDG-PET

   a. FDP-PET in AD demonstrates a pattern of abnormality, with decreased FDG in the parietotemporal cortex and posterior cingulate cortex. (1) The severity of decreased metabolism correlates with the degree of cognitive impairment. Frontal-lobe abnormality frequently develops as the disease advances.

   b. Different patterns of FDG-PET characterize other causes of dementia, helping to differentiate between AD and frontotemporal dementia (decreased uptake in frontal, anterior temporal, and medial temporal cortices), pseudodementia caused by depression (normal scan), and vascular dementia (patchy defects of the central white matter and cortex). Dementia with Lewy bodies (DLB) can show a pattern similar to AD, but DLB has frequent association with Parkinson’s disease, which involves the occipital lobes that are spared in AD. (1)
c. FDG-PET scans show changes years before clinical AD, according to a recent study. The research imaged cognitively normal elderly people who subsequently displayed Alzheimer’s disease symptoms, and who underwent post-mortem exams. The subjects’ FDG-PET scans had shown progressive loss in cerebral metabolic rate for glucose in the hippocampus to the parietotemporal and posterior cingulated cortices. (2)

2. **Amyloid plaques** can be visualized directly by positron emission tomography (PET) using a radioactive ligand bound to them. Those currently under scrutiny include carbon 11-labeled Pittsburgh Compound B (PIB-PET), developed at the University of Pittsburgh (3), and 18F-(2-(1-{6-[2-[18F]fluoroethyl]}(methyl)amino)-2-naphthyl)ethylidene) (FDDNP-PET). (4) Studies of these agents concluded that:

a. PIB-PET and FG-PET both can diagnose early cognitive impairment with similar accuracy, but PIB-PET better distinguishes between amnestic and nonamnestic MCI, according to authors from The Mayo Clinic. The authors theorize that PIB-PET may reflect early amyloid deposits before cerebral metabolism becomes disrupted. (5)

b. A study that performed PIB-PET mapping of amyloid toxicity with volumetric MRI in AD subjects concluded that the medial temporal lobe may be more susceptible to amyloid toxicity than neocortical areas. (6)

c. The severity of dementia significantly associates with PIB-PET uptake, according to a study from Munich, Germany. The authors propose that PIB-PET could be a potential surrogate marker for dementia severity. (7)

d. Using FDDNP-PET as a molecular imaging probe for plaques and tangles, in association with MRI cortical surface models, researchers at UCLA found PET results correlated with cognitive performance. (8)

e. A recent report evaluating these two tracers in AD, MCI, and controls found that PIB-PET showed higher binding in AD than controls or MCI. The FDDNP-PET uptake was higher in AD than controls, but MCI proved indistinguishable. (9)

3. **SPECT**

a. Single-photon emission CT (SPECT) shows altered brain perfusion similar to the metabolic changes reflected at PET. (1) According to a review by Coleman, SPECT findings, in general, tend to display less sensitivity and accuracy compared to FDG-PET. (1)

b. Regionally distinct patterns of hypoperfusion on SPECT or PET can help distinguish AD from vascular dementia, and dopaminergic loss in the basal ganglia can discriminate dementia with Lewy bodies (DLB) from AD. (10)
What Other Experimental Imaging Work Is Being Done on AD, Molecular and Otherwise?

1. **Time-lapse imaging of astrocytes** in a mouse model of Alzheimer’s disease showed that amyloid β plaques caused widespread effects on astrocytes beyond just the local region. To do this, researchers at Massachusetts General Hospital used multiphoton calcium imaging, a technique that uses fluorescence and microscopy. (11, 12)

2. **MRI spectroscopy in AD** showed significant correlation between myo-inositol/N-acetylaspartate (ml/NAA) ratio and cognitive decline, according to a recent report. (13) The study performed exams at 3T and evaluated different limbic regions in AD and MCI subjects.

3. **Imaging mapping studies report:**
   a. *Tensor-based morphometry*, a method that maps regions on images and statistically analyzes their differences (14), can demonstrate three-dimensional brain changes in AD over time. Serial MRI brain scans can track the disease in 3-D, according to imagers at UCLA working with the Alzheimer’s Disease Neuroimaging Initiative. The authors examined patients with AD and MCI, as well as healthy elderly controls, and reported temporal-lobe atrophy occurred significantly faster in MCI subjects who converted to AD. (15)
   b. A *fully automated mapping system* was used on the hippocampus in very mild AD. (16)
   c. *Diffusion tensor imaging* and *cortical thickness analyses* may serve as markers to discriminate MCI from normal aging. (17)

4. **Functional MRI studies include:**
   a. 4T functional MRI performed on subjects with MCI showed different regions of brain decreased and increased activation, finding lower hippocampal activation during memory retrieval the most significant correlate for severity of memory loss. (18)
   b. 4T functional MRI performed on healthy controls, and subjects with MCI and AD, reported that as subjects displayed increasing memory impairment, exams showed decreasing activation of the medial temporal lobe and increasing activation in the posterior-medial cortices – the precuneus and posterior cingulate gyrus in particular. (19)

5. **Diffusion-Tensor imaging (DTI):**
   a. DTI assesses the magnitude and direction of microscopic water movement in the brain. Therefore, AD-related damage to myelin sheaths or axonal membranes can change brain/water dynamics. (20)
   b. A review article about DTI states that it can serve as an adjunct to support the clinical impression of AD. (21)

6. **In vivo imaging of brain serotonin 4 receptors**, which are involved in learning and memory, has been achieved with a novel marker using PET. (22)

How Has Imaging Advanced Our Global Understanding of Memory’s Anatomy?

A recent, elegant review of the anatomy of the *hippocampal-parahippocampal network* (23) discusses neuronal circuitry and connections of memory, then elaborates on their functional implications. These include memory formation, ability to navigate, and synchronization of the neuron firing that is probably needed for memory consolidation.

Much of the information about these neuronal pathways was discovered using neuroanatomical tract tracing and imaging live rats’ brains. Cells underwent labeling with techniques such autofluorescent dyes, so that they could be visualized with light, electron, or confocal microscopy.
What AD Treatment Approaches Are Possible, How Have They Fared, and What Else Is Being Tried?

1. Four medications currently carry FDA approval for treating AD symptoms and are being prescribed, according to the National Institutes of Health. (24) These drugs all try to stimulate areas of damaged brain (3), but afford marginal help. (25) The agents include three cholinesterase inhibitors used for mild to moderate AD:
   a. **Razadyne** (galantamine). This agent both stimulates more brain acetylcholine release and prevents its breakdown.
   b. **Exelon** (rivastigmine).
   c. **Aricept** (donepezil), which also can be used in moderate to severe AD.

The first approved agent, **Cognex** (tacrine), lacks current wide usage because of safety issues. The theory behind these drugs rests in the requirement of acetylcholine for memory and thinking. As AD advances and the brain makes less acetylcholine, these medications may cease working.

For moderate to severe AD, **Namenda** (memantine) can be given. This is an N-methyl D-aspartate (NMDA) antagonist and is thought to regulate glutamate, which when overproduced may cause brain-cell death.

2. No drugs now available can “stop, slow, or prevent the disease.” (26)

3. Recent investigational drug failures included two targeting amyloid β (26):
   a. **Tarenflurib** (Flurizan), which modulated γ-secretase. (26, 3)
   b. **Tramiprosate** (Alzhmed), which bound to amyloid β. (26, 3)

4. Other recent drug trials have involved (26):
   a. **Bapineuzumab**, a humanized monoclonal antibody made for removing brain amyloid β, which resulted in a mixed response.
   b. **Semagacestat**, a γ-secretase inhibitor.
   c. **BPT2**, which interferes with amyloid β interaction with zinc and copper.
   d. **Methylthioninium chloride**, which targets tau aggregation and showed promising Phase II results.
   e. **Dimebon** (Medivation), which provided subjects with improved cognition and memory, and appeared safe and well-tolerated, according to a report last year in *Lancet*. (27)
   f. **Gammagard**, an intravenous immunoglobulin.
   g. **Methylene blue**. (3)

5. **Vaccines** developed and tested so far have attempted to get a person’s immune system to perceive amyloid protein as foreign and attack it. Last year, long-term follow-up of an amyloid β 42 immunization trial reported that although autopsies showed decreased plaque, most of these subjects died with severe dementia. (3, 28) It is possible that the vaccine was given too late in the disease process. (29)

6. Potential strategies to thwart AD include:
   a. **Blocking cyclophilin D**, since amyloid β interacts with it, which may lead to mitochondrial dysfunction and neuronal death. (30)
   b. **Targeting serum amyloid P (SAP)**, which binds to amyloid deposits and prevents their proteolytic degradation and may also be directly neurotoxic. A compound called CPHPC depletes SAP. (31, 32)
   c. **Targeting Orphan G protein receptor**, a modulator of amyloid β production in neurons. (33, 34).
Conclusion: PET imaging in Alzheimer's disease patients shows decreased FDG uptake in the parietotemoral cortex and posterior cingulate cortex; helps distinguish between dementia types; can reflect AD prior to symptoms; and can image amyloid directly. Molecular and other imaging techniques advance our understanding of memory anatomy and AD, which is crucial to treating and preventing this devastating disease for which no prevention or cure yet exists.

Alzheimer's disease is the sixth leading cause of death in the United States. (24) The diagnosis of Alzheimer's disease today is made with a high degree of confidence, but the disease progresses in a manner unique to each person. (1) Efforts to develop better treatments for Alzheimer's disease are critically needed. (25)

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PET scans have long been used to image brain activity in patients with Alzheimer's disease. (1) PET scans are performed using a tracer called (18F)-2-fluoro-2-deoxy-D-glucose (FDG), which can be visualized using a PET scanner. (18F)-FDG accumulates in areas of increased metabolic activity. (1)

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