Final report

Alzheimer's disease (AD) is the most common and most feared form of dementia. It is characterized by progressive brain dysfunction, thought to be due to continuous degeneration of the central nervous system. Episodic *memory* impairment is typically one of the earliest and most prominent domains of cognitive impairment, with eventual deterioration of other cognitive skills leading to restricted ability to perform daily activities. Amyloid is one hallmark pathology of Alzheimer's disease (AD), but is present in many clinically normal individuals. In addition, although the past decade has seen remarkable advances in our understanding of the basic pathobiology of AD, we still lack a complete mechanistic account of exactly how the early accumulation of Aβ pathology relates to the emergent clinical syndrome of memory impairment in humans. Thus, this knowledge could not only give insights into the disease pathology during the early stages of the disease but also help in finding reliable biomarkers for individuals at high risk of impending clinical decline (e.g. individuals with *Mild Cognitive Impairment* (MCI)).

This multimodal neuroimaging project, involving functional neuroimaging, investigated memory function in older adults with and without significant amyloid burden. We used data from a novel neuroimaging technique using the tracer Pittsburgh Compound B with positron emission tomography (PIB-PET) to measure the level of amyloid present in the brains of healthy, clinically normal older adults (see example in figure 1 demonstrating increased amyloid burden particularly in the posteromedial cortex of one representative subject from the study), MCI and patients with AD, PIB-PET was introduced for use in humans in 2004 and has rapidly become an important and cutting-edge research tool for distinguishing individuals without any clinical symptoms of dementia who might nonetheless be at risk for developing AD because of the high level of amyloid burden in their brains. To probe memory function we used a novel encoding/retrieval functional magnetic resonance imaging (fMRI) task paradigm involving a face-name association task. With this paradigm we recently demonstrated that successful encoding and subsequent retrieval of face-name associations in a group of young subjects are dependent on activity of the posteromedial cortices (see figure 2A; Vannini et al., 2011, *Cerebral Cortex* and Vannini et al., 2012, *Human Brain Mapping*).

Using a multimodal approach, by combining this fMRI paradigm and PET amyloid imaging (using PiB), we could further demonstrate that cognitively normal older individuals with high levels of amyloid burden had aberrant functional neuronal response in the posteromedial cortex (see figure 2B; Vannini et al., 2011, *Neurobiology of Aging* and Vannini et al., 2012, *Cerebral Cortex*). These results are potentially very important because it marks the memory processes in the posteromedial cortex as a very early indicator of dysfunction related to amyloid pathology, indicating that testing memory function with fMRI could provide a useful diagnostic marker of dysfunction that could be used in conjunction with amyloid imaging and other tests to identify individuals in a preclinical (that is, asymptomatic) stage of AD.

Fig 1. PiB-PET maps

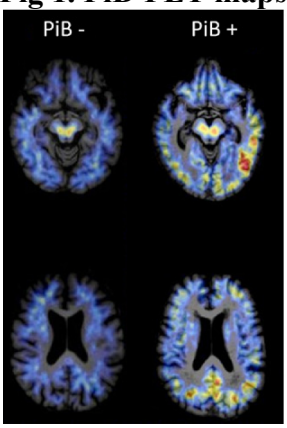

Fig 2. fMRI maps

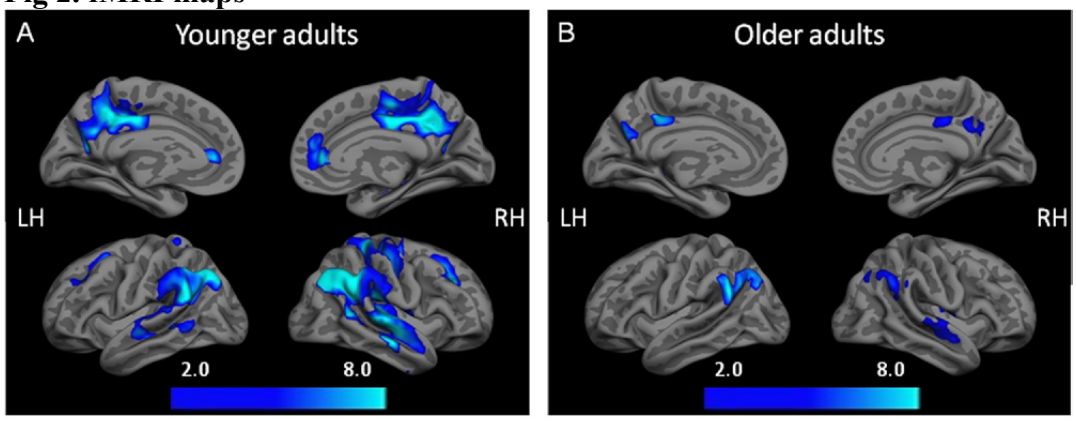

Figure 1 (left). Amyloid deposition in older individuals

Maps displaying high amount of amyloid deposition in the posteromedial cortex in one representative subject (PiB +) from the study and one representative subject (PiB -) with negligible amounts of amyloid depositon in these brain regions. (Color scale from blue=low to pink/red=very high levels of PiB retention).

Figure 2 (right). Functional activation maps in young and older adults during successful encoding.

Significant neuronal deactivation in the posteromedial cortex was found in young subjects (A) during successful encoding of face-name associations. (B) Older adults demonstrate less functional deactivation whereas older adults with high amounts of amyloid demonstrate dysfunction in this area.

The incoming phase of the Marie Curie fellowship built on these previous findings from the outgoing phase and aimed to validate our main hypothesis that altered functional memory processes in the posteromedial cortex in cognitively normal older adults is an early indicator of progressive decline towards AD dementia due to increased Aβ pathology. Thus, we combined Aβ imaging (using PiB-PET) with fMRI studies of memory processes (encoding and retrieval) in a sample of cognitively healthy older individuals, MCI and AD patients to improve our understanding of the pathophysiological mechanisms behind the memory decline seen in AD patients. Our results indicate that the individuals with neurodegenerative changes (MCI and AD patients) demonstrate similar aberrant functional neuronal response in the posteromedial cortex that we had observed in our cognitively healthy older individuals with increased Aβ pathology (see Fig 3). These results are exciting as they suggests that the functional alterations that we have previously observed over the course of normal aging can indeed be used to better discriminate age-related changes from pathological neurodegenerative processes.

The results are potentially of great significance to the field of aging and age-related neurodegenerative diseases due to the fact that today the diagnosis of AD is based on multiple sources of information that are considered simultaneously. The reason for this is that no single biological marker exists for AD. An important challenge for the clinicians is to identify subjects with developing AD in the preclinical phase of the disease. There are several reasons why this is of great interest, the most important one perhaps being to facilitate the intervention of therapeutic agents to slow down or prevent the disease progression. However, the affected individual and their caregivers may also benefit from counseling on how to handle the cognitive impairment. The estimated number of people with dementia living in the European Union is between 5.3 and 5.8 million people. This means that between 1.14% and 1.27% of citizens in the European Union are living with a form of dementia. Dementia is the leading cause of institutionalization among the elderly; prevalence among elderly nursing home residents is estimated to be 60 to 80%. Thus, this makes it even more important to elucidate the functional alterations that occur in the course of normal aging, to better discriminate age-related changes from pathological neurodegenerative processes. In the long run, this will decrease the amount of individuals that needs to be institutionalized, leading to decreased costs for the society. In addition, given that amyloid-modifying therapies for AD has entered clinical trials, this knowledge may give new insights in elucidating the relationship between amyloid burden and clinical outcome measures used in trials (such as episodic memory) and help in assessing response to treatment, especially in "Proof of Concept" trials.

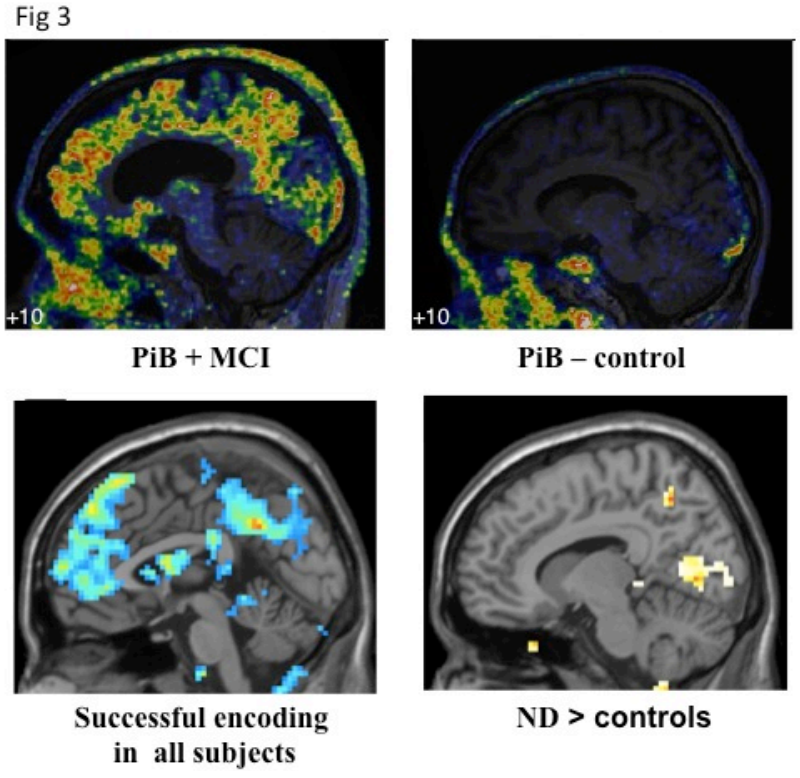

Figure 3 (top). Amyloid deposition in an individual with MCI and control subject
Maps displaying high amount of amyloid deposition in the medial cortex in one representative MCI individual using [^{11}C]AZD2184 PET and one representative subject (PiB -) with negligible amounts of amyloid deposition in these brain regions. Color scale from blue=low to pink/red=very high levels of PiB retention).

Figure 3 (bottom). Functional activation maps in all subjects during successful encoding.
(right) Significant neuronal deactivation in the posteromedial cortex was shown when analyzing all subjects (A) during successful encoding of face-name associations. (B) Individuals with neurodegeneration (MCI and AD patients) demonstrate dysfunction in the posteromedial cortex as compared to cognitively healthy individuals.