sporadic AD, studies have shown that early perfusion frames of amyloid imaging with [11C]-Pittsburgh Compound B PiB (ePiB) correlate well with glucose metabolism (Rostomian et al., 2011). Here, we evaluated whether ePiB is a reasonable surrogate marker for synaptic dysfunction, in comparison to glucose metabolism hypometabolism, and how ePiB changes with the disease progression. **Methods:** DIAN participants (n=110), including 65 asymptomatic and symptomatic mutation carriers (MC), underwent full dynamic PiB-PET and also had [18F]-fluorodeoxyglucose (FDG) PET and volumetric brain MRI. The MRI was used to register the PET images. A standardized uptake value ratio (SUVR) from MR segmented PiB and FDG regions. An ePiB image with 1-9 min time frames was selected. Voxel-wise spatial correlation between FDG and ePiB was performed for each participant. The mutation and cognitive status were taken into account in the analyses. For each imaging modality, relationship with EYO was evaluated with linear mixed models on specific regions such as inferior parietal and precuneus cortices. **Results:** FDG and ePiB were visually similar and showed high spatial correlation with an average of 0.8 ± 0.04 regardless of the mutation or cognitive status. As we have previously found, the association between FDG and EYO significantly differs between MC and non-carrier groups (p-value<0.001 and p-value<0.01 for inferior parietal and precuneus, respectively). However, these associations were not significant between ePiB and EYO. **Conclusions:** Our findings show that ePiB is strongly correlated with FDG within the same individual. However, ePiB does not display the same sensitivity as FDG to reflect disease progression in this population. Further studies are needed to fully determine the utility of ePiB measurements in clinic.

IC-03-03 AN EARLY ALZHEIMER'S DISEASE FUNCTIONAL IMAGING MARKER: OLFACTORY DEFICITS IN ALZHEIMER'S DISEASE AND MCI REFLECT DEGENERATION OF CENTRAL OLFACTORY SYSTEM

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Background: Olfactory deficits are present in early AD and MCI (1-4). It is critical, however, to determine whether these deficits are due to degeneration of the central or peripheral olfactory system. We investigated involvement of the central olfactory system in AD and MCI with an implicit olfactory associative learning paradigm. **Methods:** Sixty-three subjects (15 AD, 21 MCI and 27 age-matched CN) were studied with cognitive tests, the University of Pennsylvania Smell Identification Test (UPSIT) and fMRI. The olfactory associative learning paradigm (Fig. 1) consisted of visual cues paired with lavender odor (visual+odor) followed by the same visual cue without an odor (visual-only). **Results:** Visual-only cue activated in the primary olfactory cortex (POC) and hippocampus as did the preceded visual+odor cue for each group ($p<0.05$), suggesting a rapid implicit olfactory associative learning under this paradigm (Fig. 2). The CN subjects had greater activated volume in hippocampus and POC during both visual+odor and visual-only conditions than either the MCI or AD subjects ($P < 0.05$). Both conditions correlated with the cognitive and olfactory tests. **Conclusions:** The activation by visual-only cue in POC and hippocampus is likely a result of implicit learning/memory since it occurs only when preceded by the visual cue paired with odor. The significant decline in brain activation under this condition suggests that the central olfactory processing contributed the olfactory dysfunction in AD and MCI patients, which could lead a sensitive functional imaging marker for AD.

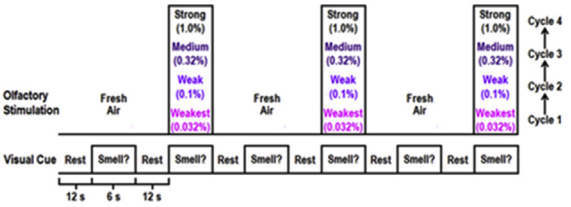

Figure. 1. The fMRI paradigm. The visual cue, the words "Smell?", was paired with lavender odor and then odorless air with a "Rest" in between. When "Smell?" is given, the subject responses with left hand button press if no smell and right hand if they smelled the stimulus. Four odorant concentrations were presented incrementally to offset the olfactory habituation.

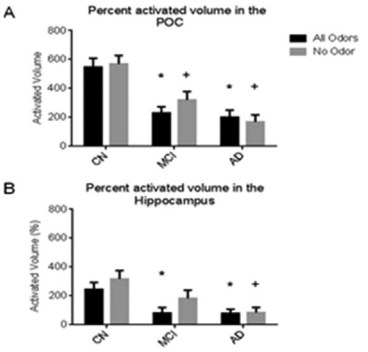

Figure. 2. Activated volume in POC and hippocampus (mean ± standard error) during visual + odor and visual- only conditions. The activated volume in the POC (A) and hippocampus (B) in MCI and AD) was decreased by more than 50 percent than that of the cognitively normal controls (CN) during odor presentation. Notes: * $P \leq 0.05$, ANOVAwhen compared to CN-AII Odors
$^{+}$ $P < 0.05$, ANOVAwhen compared to CN-No Odor.

JULY 18, 2015
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-04
NOVEL APPROACHES

IC-04-01 CORTICAL CAPILLARY DYSFUNCTION IN PATIENTS SUSPECTED OF ALZHEIMER'S DISEASE

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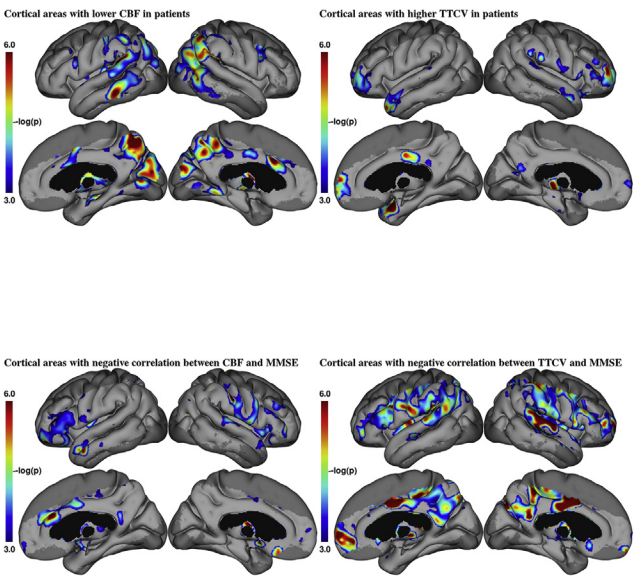
Background: Vascular risk factors are suspected to play a role in the etiology of Alzheimer's disease. Recently, a model that relates capillary dysfunction to the development of AD was proposed [1]. The model predicts that capillary dysfunction in form of increased capillary transit time heterogeneity (CTH) leads to inefficient oxygen extraction and eventually to tissue hypoxia. In this study we investigated regional cerebral blood flow (CBF) and CTH in cortical gray matter of AD patients and controls using dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) and surface based statistics. **Methods:** Sixteen patients with clinically suspected possible or probable AD (MMSE:24.8±2.7, age:70.4±6.3) and 19 cognitively normal (MMSE≥28) agematched (age:67.5±7.2) and healthy controls were scanned using DSC and T1-weighted (T1w) MRI. From the DSC-MRI we measured CBF, mean transit time (MTT), and CTH using a parametric model assuming a gamma distribution of the capillary transit times [2]. Capillary dysfunction was evaluated as the flownormalized CTH, the transit time coefficient of variation: TTCV=CTH/MTT. Cortical perfusion estimates were mapped onto a surface fitted to the middle layer of the subject's individual cortex using the T1w images [3] and mapped to a standard surface in MNI space [4]. Surface based linear regression was performed to examine patient/control differences and the association between MMSE and perfusion. Age and gender were used as covariates in the analyses. **Results:** Cortical CBF was significantly reduced bilaterally in the precuneus and parietal and temporal lobes in patients (Fig.1). Capillary dysfunction as measured by TTCV was significantly higher bilaterally in the frontal lobe, the temporal pole, and posterior cingulate gyrus in patients (Fig.1). In parts of the frontal and temporal lobes and the right cingulate gyrus we found a negative association between CBF and MMSE in patients (Fig.2). Finally, we found widespread negative correlations between TTVC and MMSE in all major lobes except the occipital lobe (Fig.2). **Conclusions:** Our findings are consistent with the capillary dysfunction hypothesis of AD of increased capillary transit time heterogeneity in patients. We found a negative association between CBF and MMSE. We speculate that, in these areas, CBF is increased to compensate for the rising CTH and thus the imminent capillary dysfunction.



IC-04-02 THE RELATIVE IMPORTANCE OF IMAGING MARKERS FOR THE PREDICTION OF ALZHEIMER'S DISEASE DEMENTIA IN MILD COGNITIVE IMPAIRMENT: THE CURSE OF DIMENSIONALITY

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Background: Selecting a set of relevant markers to predict conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) has become a challenging task given the wealth of regional pathologic information that can be extracted from multimodal imaging data. **Methods:** We used regularized regression approaches with an elastic net penalty for best subset selection of multiregional information from AV45-PET, FDG-PET and volumetric MRI data to predict conversion from MCI to AD. The study sample consisted of 127 MCI subjects from ADNI-2 who had a clinical follow-up between 6 and 31 months. Additional analyses assessed the effect of partial volume correction on predictive performance of AV45- and FDG-PET data. **Results:** Predictor variables were highly collinear within and across imaging modalities (see Figure 1). Penalized Cox regression yielded more parsimonious and neurobiologically plausible prediction models compared to unpenalized Cox regression. Within single modalities, time to conversion was best predicted by increased AV45-PET signal in posterior medial and lateral cortical regions, decreased FDG-PET signal in medial temporal and temporobasal regions, and reduced gray matter volume in medial, basal, and lateral temporal regions. Logistic regression models reached up to 72% cross-validated accuracy for prediction of conversion status, which was comparable to cross-validated accuracy of non-linear support vector machine classification. Regularized regression outperformed

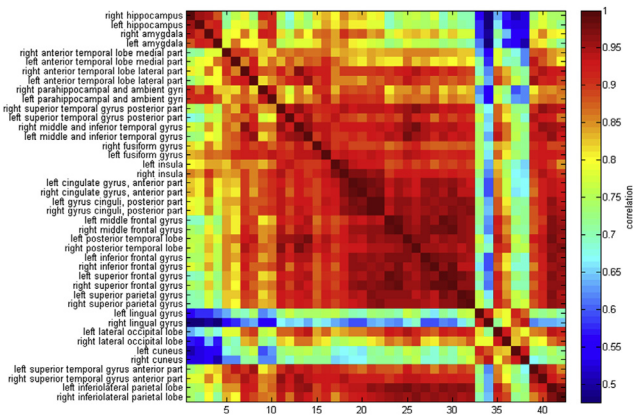

Figure 1. Cross-correlation matrix across AV45-PET regions