ORAL SESSIONS: O3-08 DIAGNOSIS AND PROGNOSIS: AMYLOID AND COGNITIVE IMPAIRMENT

O3-08-01 THE PREVALENCE OF AMYLOID PATHOLOGY IN HEALTHY INDIVIDUALS AND INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT: A META-ANALYSIS OF AMYLOID-PET STUDIES

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Background: Amyloid pathology in nondemented individuals might reflect an early-stage of Alzheimer's disease (AD) development. Prevalence estimates of amyloid pathology differ widely across studies. We aimed to estimate the prevalence of amyloid pathology in cognitively healthy individuals and subjects with mild cognitive impairment (MCI) as assessed by amyloid-PET imaging with a meta-analysis. We also examined the effect of study characteristics on prevalence estimates. **Methods:** We searched the MEDLINE and Web of Science databases. The search terms used were 'PET' and 'amyloid' or 'abeta' or 'amyloid beta' and 'Pittsburgh' or 'PiB' or 'florbetapir' or 'florbetaben' or 'flutemetamol'. The searches resulted in 520 hits. Titles and abstracts were reviewed and all relevant studies were further analyzed. Pooled estimates of the prevalence were obtained using random-effects models. Relationships with the study averages of age, gender, APOE-ε4 status and global cognitive functioning as measured by the Mini Mental State Examination (MMSE) were assessed using meta-regression on study level. **Results:** We selected 25 PET studies of healthy controls (HC), including 1679 subjects and 13 PET studies of subjects with MCI, including 433 subjects. The prevalence of amyloid pathology in HC was 18.9% (95% CI 13.3 to 24.5) and in subjects with MCI 57.2% (95% CI 51.3 to 63.1, p-value difference < 0.001). Meta-regression showed that the prevalence in the HC group increased with higher age and lower MMSE score. After exclusion of 3 studies that included only subjects below age 40 of which none had amyloid pathology, the prevalence estimate in HC was 21.4% (95% CI 16.2 to 26.6). In the MCI group, study prevalences were not related to study characteristics. **Conclusions:** About 60% of the subjects with MCI and 20% of cognitively normal subjects have evidence of amyloid pathology as assessed by amyloid-PET. Assuming that these individuals are on the path to AD dementia, this study indicates that AD is a major health problem.

O3-08-02 LONGITUDINAL EVALUATION OF BASAL FOREBRAIN ATROPHY AND ITS ASSOCIATION TO BETA-AMYLOID BURDEN AND HIPPOCAMPAL VOLUME IN ALZHEIMER'S DISEASE

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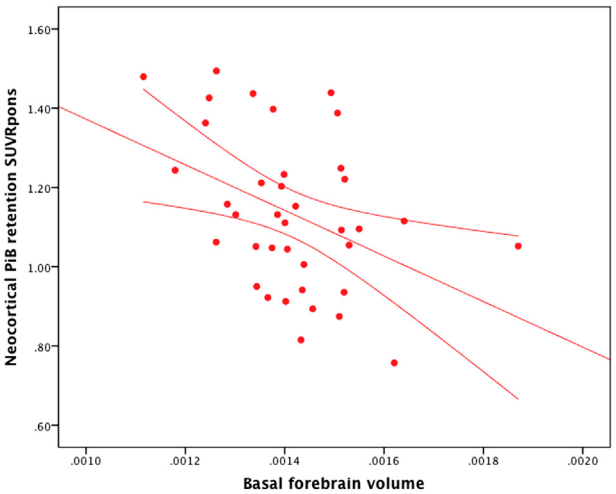
Background: The basal forebrain (BF) is believed to be one of the earliest regions affected by Alzheimer's disease (AD). In this study we used magnetic resonance imaging (MRI) to investigate the degeneration of the BF and its relationship to amyloid level as measured with Pittsburgh compound B (PiB)-PET, and hippocampal atrophy. **Methods:** From the AIBL study, longitudinal PiB and T1W MRI images of AD, mild cognitive impaired (MCI) and healthy control (HC) subjects from two time points (baseline: 156 HC, 40 MCI, 38 AD subjects; 18 month: 133 HC, 22 MCI, 19 AD) were used. From the ADNI study, T1W MRI images of 26 HC, 94 MCI and 9 AD were used. A BF mask was delineated using published coordinates of the BF and constrained to areas that undergo atrophy in Alzheimer's disease (when comparing HC and AD subjects), resulting in a BF mask of AD-specific change. The BF, hippocampus, pons and grey matter (GM), white matter (WM) and CSF were segmented from the MR images. Volumes were normalized by intracranial volume. The PiB images were standard uptake value ratio (SUVR) normalized (pons WM) with PiB+ defined as SUVR > 0.71 and neocortical PiB uptake calculated within the GM. **Results:** The average BF volume of AD subjects was significantly decreased compared to HC subjects in both AIBL ($p<0.001$) and ADNI ($p<0.05$) studies. In addition MCI subjects showed a significantly smaller BF volume compared to HC subjects (PiB+: $p<0.01$; PiB-: $p<0.001$). The BF volume was correlated to the PiB uptake in the neocortex ($r^2=0.39$; $p<0.05$) in AD subjects (Fig. 1), and also correlated to hippocampal volume in all subject groups (HC: $r^2=0.46$; $p<0.001$; aMCI: $r^2=0.62$; $p<0.001$; AD: $r^2=0.58$; $p<0.01$). Furthermore, using longitudinal data from the AIBL study, we found that the rate of atrophy of the BF was greater in AD subjects compared to the rate of atrophy in other groups (aMCI: $p<0.05$; HC PiB+: $p<0.05$; HC PiB-: $p<0.01$). **Conclusions:** The basal forebrain undergoes significant atrophy in AD and MCI compared to HC subjects. Small basal forebrain volumes were associated with high amyloid burden as well as small hippocampal volumes.



O3-08-03 DISCLOSING AMYLOID IMAGING RESULTS IN MCI: WHAT DO PATIENTS AND FAMILIES WANT, AND WHY?

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Background: Growing evidence suggests that PET amyloid imaging may provide useful prognostic information in mild cognitive impairment (MCI). Yet, discussing amyloid imaging with patients is challenging because amyloid positivity connotes a risk, not diagnosis, of Alzheimer's disease. Communicating such nuanced information requires particular care given that a) disclosing one's risk of progressing to clinical dementia may be psychologically harmful, and b) MCI-related deficits may impede comprehension and appreciation of results. **Methods:** Following on our previous report of receptiveness to and understanding of amyloid imaging results, we held a focus group to elicit in-depth feedback from 4 MCI patients and 4 care partners (age range: 55-92; mean education: 14 years) who received information about amyloid imaging, but were not scanned. Participants previously underwent mock disclosure sessions returning fictitious but realistic results regarding the patient's hypothetical brain amyloid status, and an explanation of how results impact dementia risk. The focus group guide consisted of a brief review of amyloid imaging in MCI and

12 open-ended questions designed to augment previously collected satisfaction and comprehension data. Specifically, participants were invited to consider what additional information and support would be beneficial for those contemplating amyloid imaging. Qualitative content analysis was used to analyze focus group transcripts. **Results:** Focus group data reinforced findings of high satisfaction with explanations provided during disclosure sessions, and included 6 recommendations for practice: 1) offer pre-test counseling, 2) use clear graphics, 3) review patient's own brain images during disclosure sessions, 4) offer take-home materials describing follow-up options, 5) call patients post-disclosure to address emerging questions, and 6) communicate seamlessly with primary care providers. Further analysis revealed that both patients and care partners understood the limitations of amyloid imaging, but nevertheless viewed the prospect of learning a patient's amyloid status as valuable and empowering. This prominent theme was exemplified by statements like, "I want to know everything I can know," "knowledge is strength," and "you need the knowledge." **Conclusions:** Patients and families may find value in amyloid imaging irrespective of whether results are clinically actionable. Researchers and clinicians disclosing amyloid imaging results should consider the patient and caregiver-generated recommendations reported above.

O3-08-04 PREFRONTAL HYPOMETABOLISM IN ALZHEIMER'S DISEASE IS CAUSED BY LONGITUDINAL AMYLOID ACCUMULATION IN REMOTE, FUNCTIONALLY CONNECTED BRAIN REGIONS

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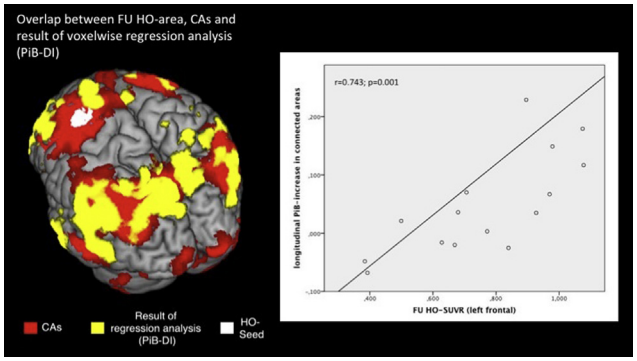
Background: In Alzheimer's disease (AD) patients, prominent hypometabolism may occur in brain regions with minor amyloid load. Such hypometabolism only areas (HO) cannot be explained as direct consequence of local amyloid-toxicity. In a recent cross-sectional study we reported correlations between metabolism in prefrontal HO and metabolism in remote, but functionally connected areas (CAs) (as defined by resting-state fMRI), suggesting an association between prefrontal HO and AD-pathologies in remote CAs, e.g., via disconnection (1). Based on our previous findings we now investigated the longitudinal relationships between metabolism in peak HO-areas and local as well as remote amyloid-accumulation, in order to establish a causal link. **Methods:** 15 mild probable AD-patients underwent baseline (BL) and follow-up (FU) [11C]PiB- and [18F]FDG-PET (mean FU-period 2y). PVE-corrected PiB-SUVR-difference images (PiB-DI) were created using the formula: FU- minus BL-PiB)/FU-period. PiB-DIs are supposed to represent longitudinal amyloid accumulation over time. BL-& FU-HO and CAs were created as previously described (1). Voxelwise regressions and ROI-based correlations were calculated between PiB-DIs and FDG-SUVRs in BL-& FU-HO and remote brain areas ($p<.05$; 2-tailed). **Results:** Positive voxelwise and ROI-based correlations between HO-SUVRs (BL&FU) and PiB-DIs were found in several AD-typical brain regions. Strongest correlations were found between FU-left prefrontal HO-SUVR and PiB-DIs in temporoparietal and prefrontal cortex (r=.743). **Conclusions:** Strongest positive correlation has been demonstrated between left prefrontal HO at the end of the observation period and amyloid-accumulation over time in remote brain regions in the temporoparietal and frontal cortex. This indicates that hypometabolism in brain regions not strongly affected by amyloid-pathology represent a temporally delayed consequence of amyloid-increases in remote CAs, supporting a causal relationship.



O3-08-05 *IN VIVO* PATTERN OF TAU AND BETA-AMYLOID DEPOSITION IN THE BRAIN MIGHT DISTINGUISH HEALTHY CONTROLS FROM PRECLINICAL ALZHEIMER'S DISEASE

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Background: Tau deposition in Alzheimer's disease (AD) follows a stereotypical pattern. The introduction of tau imaging with 18 F-THK523, a novel tau imaging ligand displaying high selectivity and specificity for PHF-tau pathology, has allowed the *in vivo* evaluation of the regional distribution of PHF-tau in the brain. **Methods:** Twenty participants -10 elderly healthy controls (HC) and 10 AD patients- underwent neuropsychological examination, MRI, 18 F-THK523 and 11 C-PiB-PET. Standard uptake value ratios (SUVR) at 60-90 min and 40-70 min post injection were calculated for 18 F-THK523 and 11 C-PiB respectively, using the cerebellar cortex as the reference region. Images were corrected for partial volume effects. **Results:** Significantly higher 18 F-THK523 cortical retention was observed in the temporal, parietal, orbitofrontal and hippocampus of AD patients when compared to HC. The pattern of 18 F-THK523 retention followed the known distribution of PHF-tau in the AD brain (higher in posterior areas than frontal) and it did not correlate with the cortical retention of 11 C-PiB. Furthermore, 18 F-THK523 retention was correlated with cognitive parameters and unlike 11 C-PiB, 18 F-THK523 hippocampal retention was highly correlated with hippocampal atrophy. Cognitively unimpaired individuals with high beta-amyloid in neocortical areas, already presented AD-like levels of tau deposition in the mesial temporal cortex, but not in isocortex. **Conclusions:** 18 F-THK523 retention follows the known distribution of PHF-tau in the brain and does not bind to beta-amyloid *in vivo*. Significantly higher cortical 18 F-THK523 retention in association with cognitive parameters and hippocampal volume, indicates that 18 F-THK523 selectively binds to PHF-tau in the AD brain. Furthermore, our results suggest that cognitively unimpaired individuals with high hippocampal tau and high neocortical beta-amyloid deposition might truly represent preclinical AD and may benefit most from disease-specific therapies aimed at reducing or eliminating beta-amyloid and/or tau from the brain, before irreversible neuronal or synaptic loss occurs. Longitudinal follow up studies will allow determination of the sequence of cortical tau deposition associated with progressive cognitive impairment.

O3-08-06 ALTERATIONS IN STRUCTURE AND PERFUSION IN ALZHEIMER'S DISEASE–RELATED BRAIN AREAS DEPEND ON BETA-AMYLOID ACCUMULATION IN HEALTHY CONTROLS AND MCI PATIENTS

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