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Ageing and dementia 1

EP1101

Neuronal correlates of anosognosia for memory impairment in Alzheimer's disease: the role of posterior cingulate cortex

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Introduction: Anosognosia for memory deficits has major impact on caring for Alzheimer’s disease (AD). However, the neural mechanisms of anosognosia in AD remain unclear. The aim of this study was to acquire multimodal brain imaging in a sample of patients, to search for brain regions that differ between patients and elderly controls and to evaluate the contribution of brain regions to anosognosia in AD.

Methods: We compared 31 patients with probable AD and 19 cognitively intact healthy volunteers using Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). Participant’s awareness of current memory functioning was assessed with the memory awareness rating scale (MARS). We used statistical parametric mapping (SPM8) to compare both groups in each modality and to correlate brain imaging measurements and anosognosia scores in AD patients, controlling for dementia severity, age, gender and education.

Results: In the group comparison, we found a significant hypometabolism of the posterior cingulate cortex (PCC) and parieto-frontal associative cortices in Alzheimer patients with PET. Additional analysis with voxel based morphometry (VBM) also showed cortical atrophy of the PCC and the medial temporal regions. Finally, in Alzheimer patients, correlation between anosognosia scores and hypometabolism extending from ventral to dorsal PCC was evidenced.

Conclusions: The PCC is a hub region of the default mode network, notably involved in self-referential processing. In addition to confirming the vulnerability of the PCC in AD, these results suggest that the disturbance of the PCC is implicated in loss of self-knowledge in AD.

Disclosure: Nothing to disclose

EP1102

An fMRI graph theory study of the effect of gender and aging on topology of functional brain networks

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Introduction: To analyze age- and gender-related effects on large-scale functional brain networks using a graph theory approach.

Methods: Graph theoretical analysis was applied to resting state (RS) fMRI data from 132 healthy controls (62 men and 70 women, mean age=40.6 years, range=8-84 years). The global topology of functional networks was examined by computing the average degree, clustering coefficient, characteristic path length, global and local efficiency, hierarchy and assortativity. Regional network properties, including the integrated degree and local efficiency of each network node, were also assessed. The effects of age, gender and “age x gender” interactions on global functional network measures were assessed by using linear regression models.

Results: Significant age-related abnormalities (i.e., lower degree, clustering coefficient, local and global efficiency and hierarchy; and higher path length and assortativity) were detected in both genders. Males showed higher average network values than females. Both genders experienced a significant age-related decline of nodal degree and local efficiency of several regions of the frontal lobe (including the bilateral anterior cingulate cortex, middle and superior frontal gyrus, orbitofrontal cortex, precentral gyrus and supplementary motor area), temporal regions, posterior cingulate cortex/precuneus and deep gray matter nuclei. No significant “age x gender” interaction was found for global and regional network metrics.

Conclusions: Age-related decline of functional network measures were detected in both genders. The effect of aging was more severe in regions of the frontal lobes and the basal ganglia than in the other brain areas. Gender does not influence such an altered network connectivity with aging.

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EP1103

[18F]FDG-PET evidence of selective medial temporal lobe dysfunction in prodromal Alzheimer’s disease

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Introduction: [18F]FDG-PET imaging is a fundamental prognostic marker in mild cognitive impairment (MCI), supporting the presence of Alzheimer’s Disease (AD) pathology by the evidence of the typical temporo-parietal pattern. A limbic-predominant AD subtype has been defined on the basis of the prevalent distribution of neurofibrillary tangles in the hippocampus compared with the cortex. In this study, we evaluated [18F]FDG-PET brain metabolic changes and hippocampal volume in a sample of amnestic MCI subjects with long-term disease course (range 3-7 years).

Methods: Within a large series of MCI subjects, we selected 13 cases with persistent, selective long-term memory impairment. Optimized voxel-based statistical parametric mapping (SPM) procedure was used to assess brain metabolic changes in single subjects. Medial temporal lobe atrophy was measured with voxel-based morphometry (VBM). Clinical-neuropsychological features and CSF profile were also obtained.

Results: The majority of cases showed an unusually selective medial temporal hypometabolism. None showed the typical AD pattern. VBM analysis showed significant atrophy in the hippocampal structures, less extended than the hypometabolic pattern. Low CSF A-beta42 values supported the diagnosis of prodromal AD.

Conclusion: In this MCI group with predominant episodic memory deficits and very slow rate of progression of memory impairments, [18F]FDG-PET and VBM findings suggest a specific and more limited anatomo-functional pattern, in comparison to the typical prodromal AD, compatible with the pathological limbic-predominant subtype. Single-subject [18F]FDG-PET imaging can be useful in revealing MCI subtypes with more favourable prognosis and in subject selection for clinical trials.

Disclosure: Nothing to disclose

EP1104

Clock drawing test: validation studies with multiple forms of dementia

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Introduction: The Clock Drawing Test (CDT) is a classic instrument preferably used for the assessment of constructive/visuospatial functions. Its clinical and investigational use has shown potential for the detection of cognitive impairment in populations with dementia, especially Alzheimer’s disease (AD).

Methods: We selected patients with a clinical diagnosis of mild stage AD, frontal variant frontotemporal dementia (fv-FTD), vascular dementia (VaD), dementia with Lewy Bodies (DLB) and Parkinson’s disease (PD). All subjects were assessed with the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Clinical Dementia Rating scale and the CDT. The CDT was scored according to three scoring systems: Rouleau et al., 1992; Cahn et al., 1996; and Babins et al., 2008.

Results: We included 557 subjects (225 AD, 102 fv-FTD, 126 VaD, 51 DLB and 53 PD), 50.6% female. The results showed the existence of significant differences between the several diagnoses, for the three scoring systems, with the following pattern of results: AD,DLB< fv-FTD,VaD. Once we controlled the effects of cognitive screening test scores and age, only the Cahn scoring system was able to significantly discriminate AD and DLB patients from fv-FTD and VaD patients. This particular discriminatory capacity was due to the qualitative analysis of the clock drawing errors, namely stimulus-bound response and conceptual deficit, both considered typical of AD patients.

Conclusions: Our results support the CDT potential as a cognitive screening measure particularly sensitive to AD pathology and similar cognitive deficits, a fact more evident for the Cahn scoring system.

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Disclosure: Nothing to disclose
EP1105
Cross-sectional clinical, neuropsychological, neuroimaging, and neurophysiological characterization of mild cognitive impairment patients in WP5 PharmaCog/E-ADNI study


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Introduction: Workpackage5 of PharmaCog (E-ADNI) is a serial multicenter European study aimed to identify new cognitive, neuroimaging, neurophysiological, and biochemical biomarkers of disease progression in patients with amnestic mild cognitive impairment (aMCI).

Methods: We report cross-sectional data of the 147 patients enrolled in 13 memory clinics in Italy (Brescia, Genoa, Naples, Perugia, Rome, France (Marseille, Toulouse, Lille), Spain (Barcelona), Germany (Essen, Leipzig), Greece (Thessaloniki), and The Netherlands (Amsterdam). Patients underwent clinical and neuropsychological evaluation, high resolution 3T MRI with MPRAGE, T2*, FLAIR, resting state, and DTI acquisitions, EEG with resting state and auditory P300 recording, lumbar punctures assessing Abeta42, tau and p-tau, and blood samples. Patients were divided into Abeta positive (CSF-POS) and negative (CSF-NEG) based on CSF Abeta42 levels.

Results: CSF-POS have worse performance relative to CSF-NEG patients on visual memory (delayed matching to sample test 72.0±15.1 vs 62.7±16.9 respectively, p=0.002 and spatial recognition memory 67.5±12.5 vs 58.8±12.9 respectively, p<0.0005), and working memory (spatial working memory score 48.3±21.3 vs 39.4±20.8 respectively, p=0.02). Moreover, CSF-POS have reduced volumetric (hippocampus, caudate, putamen, pallidum and lateral ventricles), thicknesses (entorhinal, fusiform and parahippocampal gyrus), and diffusion (splenium of the corpus callosum) measures, and a specific EEG pattern of cortical sources relative to CSF-NEG patients.

Conclusions: We found significant clinical, neuroimaging, and neurophysiological differences between aMCI patients with high and low CSF Abeta42 levels, suggesting that these two populations show different underlying pathology. Longitudinal data acquisition is ongoing and will clarify the impact of these biomarkers in predicting progression of the disease.

Disclosure: Nothing to disclose

EP1106
Retinal plaques in Alzheimer’s disease
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Objectives: To evaluate the existence of pathologic retinal deposits in patients with possible Alzheimer’s Disease (AD).

Methods: We examined 20 patients with mild cognitive impairment, 10 of whom had family history of AD. Also, 10 patients with no complaints were examined. The age range was between 45 and 86. We performed fundus auto-fluorescence (FAF) test and optical scanning tomography (OCT) test on all of them. The retinal regions with hypofluorescent and hyperfluorescent images were taken into consideration and OCT was also performed through these lesions to detect the layer of the abnormality. Patients with diabetic retinopathy and vascular occlusions were excluded.

Results: In 16 patients with mild cognitive defects we were able to find abnormal accumulations in the ganglion layer and nerve fiber layer. Some of the accumulations were hypofluorescent and others were hyperfluorescent on FAF. In the other group of patients who had no complaints, only drusen on the pigment epithelium layer could be seen.

Conclusions: We believe that abnormal retinal deposits (possibly containing beta amyloid protein) can be observed in the ganglion and retinal fiber layers in patients who have high risk for AD. Retinal examination can be very helpful in the evaluation of these patients.

Disclosure: Nothing to disclose.
Cognitive impairment in healthy Filipino adults with MRI white matter hyperintensities
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Introduction: White matter hyperintensities (WMH) are frequently seen in MRI of patients presenting with stroke or dementia, but are also observed to be present in healthy adults with no neurologic or cognitive impairment. Are they radiological findings of uncertain clinical significance? Or are they pre-clinical signs of dementia and cognitive decline. This paper studies the relationship of WMH and cognitive function of healthy Filipino adults with normal hippocampal volume and with no previous history of strokes.

Methods: 202 Filipinos with MRI hippocampal volumetry, neurocognitive screening tests and normal metabolic parameters were studied. Hippocampal volume was determined using NeuroQuant®, a software utilized by US-NIH studies for dementia. Those with low hippocampal volume and evidence of stroke were excluded. MRI were reviewed and WMH were graded using Fazekas scale. 51 patients were included in the final sample. Correlational statistics was used to determine relationship of WMH to neurocognitive scores.

Results: The higher the age, the greater is the Fazekas Score and WMH (p=0.004). There is a clinically significant decrease in Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) Scores with the greater WMH. Most significant drop in scores between Fazekas 2 and 3.

Conclusions: This paper to the best of our knowledge is the first to use hippocampal volumetry to exclude subjects with Alzheimer’s and vascular dementia. Our results show that there is a clinically significant drop in neurocognitive scores with increasing WMH in healthy adults with no apparent clinical signs of dementia but only has WMH on MRI.

Disclosure: Nothing to disclose
EP1108
Factors that predict cognitive decline in patients with subjective cognitive impairment
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Introduction: Current evidence supports the concept of a preclinical phase of Alzheimer’s disease (AD) where pathological and imaging changes are present in asymptomatic individuals. Subjective cognitive impairment (SCI) may represent the earliest point on the continuum of AD. A better understanding of the baseline characteristics of this group of patients will enhance our knowledge of the very early disease process and facilitate preventive strategies, early diagnosis, timely follow-up and treatment. The aim of this study was to investigate which factors in SCI predict cognitive decline defined as a progression to a diagnosis of amnestic mild cognitive impairment (aMCI) or dementia at follow-up.

Methods: A retrospective observational study comparing baseline characteristics of patients with SCI who declined cognitively and those who did not.

Results: Patients who declined took significantly more medications for physical illnesses at baseline, were older by 9.78 years (p=0.001) and reported that the onset of their memory problems was 10.3 years later than those that did not decline (p=0.001). There were significant differences in test scores on the Trail Making B test and CAMCOG-R (attention subscale). Survival analysis demonstrated significant cut off points on key variables that predicted later decline (age of onset, age at first assessment, trail making test B and NART score). These cut-offs suggest differences in executive function, attention and cognitive reserve even at the stage of SCI.

Conclusions: Knowing which factors and test results in SCI predict conversion to aMCI or dementia can facilitate early detection, decision about frequency of follow-up and timely treatment.

Disclosure: Nothing to disclose

EP1109
Study of Alzheimer’s disease patients in a cohort of aged adults on the island of Crete, Greece suggests genetic predisposition for the disease
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Introduction: The aim of this project was to investigate the clinical, epidemiological and genetic characteristics of a cohort of aged adults on the island of Crete, Greece diagnosed with Alzheimer’s disease (AD), mild cognitive impairment (MCI) and depressive disorder (DD).

Methods: A total of 3200 adults over 65 years of age visiting selected primary care physicians in the town of Heraklion, Crete and nearby villages were tested using a detailed questionnaire. Individuals scoring less than 23 or 24 (if <6 or >6 years of education, respectively) on the MMSE test were referred to the second phase physicians of the study (neurologists, psychiatrists, and geriatricians) and underwent neuropsychological evaluation. An interim analysis was performed in the first 138 consecutive patients diagnosed with AD (NINCDS/ADRDA criteria; n=45), MCI (IWG criteria; n=71) or DD (n=22).

Results: Mean age (years) was 77.4, 77.2 and 76.2 for patients with AD, MCI and DD, respectively. The majority in all groups were females (60.0%, 73.2% and 86.4% for AD, MCI and DD, respectively). The mean MMSE was lower for AD (19.8) than for MCI (21.6) and DD (20.7) patients. The 3 groups were comparable concerning history of hypertension, diabetes mellitus, arthritis, osteoporosis and dyslipidemia. In this cohort, 46.5% of AD patients had history of dementia in a first degree relative, compared with 16.9% of the MCI and DD patients examined together (p=0.001).

Conclusion: The high frequency of dementia in first degree relatives of AD patients suggests a genetic component for the disease in our cohort.

Disclosure: Nothing to disclose
EP1110
The Retzius-Cajal neuron in Alzheimer’s disease
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Introduction: Retzius-Cajal neuron is the prominent neuron of the layer I of the brain’s cortex. This is a large multipolar solitary neuron, mostly surrounded by astrocytes.

Methods: The structural morphology of the layer I of the temporal and occipital areas of the cortex of twenty cases of Alzheimer’s disease was studied in rapid Golgi staining, Golgi-Nissl method and electron microscopy.

Results: In case of Alzheimer’s disease Cajal-Retzius neuron, was dramatically reduced in comparison with normal controls brains of the same age. The electron microscopy revealed alterations of dendritic branches, decrease in spine density and morphological alterations of the mitochondria in the soma, the dendrites and the dendritic spines of Retzius-Cajal neurons. Tau pathology in the form of paired helical filaments were very rare in Retzius-Cajal neurons.

The synapses between the Retzius-Cajal neurons and the corticopetal fibers were dramatically reduced.

Conclusions: Retzius-Cajal neurons serve mainly in the development of horizontal connections in the cortex. Their loss in Alzheimer’s disease may result in substantial alteration of the local functional fields of the cortex.

Disclosure: Nothing to disclose

EP1111
Five-line fluency test is brief and effective screening for mild Alzheimer’s disease - norms and cut-offs
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Introduction: Figure fluency test may be a visual analogy of word fluency tasks and may briefly detect new distinct deficits in Alzheimer's disease different from those measured by common tests. We aimed to establish norms for senior population and to find out cut-offs for mild AD patients.

Methods: We asked 645 normal elderly people (NEP) (the Mini-Mental State Examination (MMSE) 28±2 points) and 46 patients with mild dementia due to Alzheimer's disease (AD) (MMSE 23±3 points) fulfilling NIA-AA recommendations to draw as many different figures using exactly five lines as possible within three minutes (five-Line Fluency Test, LIFT).

Results: Mild AD patients produced significantly less figures than NEP in several aspects: total numbers (average: 9 vs 13), repeating figures (2 vs 3), repetition rate (16 vs 26%), wrong figures (0 vs 3) and original correct numbers (4 vs 11) (all p<0.01). The optimal cut-off of 6 correct figures yielded sensitivity 83 % and specificity 85 % with area under curve of receiver operating characteristic 0.9.

LIFT scores in NEP are not influenced by gender, but they are significantly, yet poorly associated with age (r=-0.15) and education (r=0.2).

Conclusions: LIFT is a short, simple, yet complex cognitive test that can be useful in everyday screening for AD with pencil and paper only. We provide normative data for the elderly which may be easily used in other countries due to non-verbal nature of the test.

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EP1112

The use of biomarkers for the etiologic diagnosis of mild cognitive impairment in Europe: a survey of the European Alzheimer’s disease consortium

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Introduction: Revised diagnostic criteria for Alzheimer’s Disease (AD) acknowledge a key role to imaging and biochemical markers for the early diagnosis of AD. We aimed to investigate the use of AD biomarkers in the European Alzheimer’s Disease Consortium (EADC) centres and assess perceived usefulness for the etiologic diagnosis of mild cognitive impairment (MCI).

Methods: We surveyed the availability, the frequency of use, and the confidence in diagnostic usefulness of markers of brain amyloidosis (cortical amyloid burden on PET and CSF Abeta levels) and neurodegeneration (medial temporal atrophy [MTA] on MRI, temporoparietal and posterior cingulate hypometabolism on FDG-PET, and CSF tau levels). Questionnaires were filled by physicians of EADC centres in charge of patient care.

Results: The most frequently used biomarker is visually rated MTA (75% of the 37 responders using it “always” or “frequently”), followed by CSF markers (22%), FDG-PET (16%) and amyloid PET (3%) (Figure 1). Although MTA is reported in clinical reports by 89% of centres, only 45% of them perceive it as contributing to diagnostic confidence, and contribution is rated as “moderate”. Seventy-nine percent of responders feel “very” or “extremely” comfortable delivering a diagnosis of MCI due to AD when both amyloid and neuronal injury biomarkers are abnormal (p<0.02 versus any individual biomarker) (Figure 2).

Conclusions: EADC Memory Clinics make fairly extensive use of biomarkers for the etiologic diagnosis of MCI. Responders largely agree that a combination of amyloidosis and neuronal injury biomarkers is a persuasive AD signature.

Disclosure: Nothing to disclose

EP1113

Crossed aphasia in a dextral patient with nonfluent/agrammatic variant of primary progressive aphasia

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Introduction: To describe a case of “crossed” nonfluent/agrammatic variant of primary progressive aphasia (nfv-PPA) evolving to an extrapyramidal syndrome.

Methods: We collected clinical/cognitive and neuroimaging data over 2 years from a 55-year-old right-handed lady presenting with language disturbances, including 18F-FDG PET, 123I-DaTscan, and structural MRI. fMRI during verbal fluency generation was also performed to establish language hemispheric dominance, and diffusion tensor MRI was applied to evaluate the language network relative to controls.

Results: The patient presented with motor speech impairment characterized by slowness, difficulty on initiation with frequent stuttering, prosodic changes, hypophonia and frequent pauses. Mild agrammatism and difficulties in complex sentence comprehension were also present. 18F-FDG PET and structural MRI revealed a selective involvement of the right middle and inferior frontal gyri (Broca’s area). The clinical picture was highly suggestive of nfv-PPA. Over 2 years, language deficits worsened evolving to a full apraxia of speech with an overlapped mixed dysarthria. The patient developed a left-sided mild extrapyramidal bradykinesic-rigid syndrome. 18F-FDG PET and structural MRI at year 2 showed a progression of brain damage to the right dorsolateral frontal cortex, frontal operculum, caudate nucleus and putamen. Homologous regions on the left hemisphere were mildly involved. DaTscan showed a decreased right putamen 123I uptake. FMRI demonstrated a left hemispheric language dominance. Tractography showed a right superior longitudinal fasciculus severe damage.

Conclusions: Functional and structural imaging indicate a nondominant hemisphere-related degeneration in patient with nfv-PPA. The occurrence of a left-sided extrapyramidal motor syndrome might suggest an underlying corticobasal degeneration.

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