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ABSTRACTS

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Abstracts

Longitudinal patterns of brain atrophy in frontotemporal lobar degeneration: clinical syndromes compared with Alzheimer's disease

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Objective: To investigate grey (GM) and white matter (WM) volume contraction in patients with frontotemporal lobar degeneration (FTD) syndromes and Alzheimer's disease (AD) using tensor based morphometry (TBM).

Background: Structural MRI is known to provide relevant information for the phenotypic characterization and diagnosis of FTD syndromes and can aid the differential diagnosis with AD.

Methods: T1-weighted MRI scans were obtained at baseline and follow-up (range interval: 12-36 months) from 7 patients with probable behavioural variant of frontotemporal dementia (bvFTD, age: 60 ± 7; CDR-SB: 4 ± 3), 7 patients with semantic variant of primary progressive aphasia (SV; age: 65 ± 8; CDR-SB: 3 ± 2), and 13 patients with probable AD (age: 69 ± 7; CDR-SB: 5 ± 1). TBM was used for image processing and statistical analysis.

Results: BvFTD patients showed a progression of GM atrophy in the orbitofrontal cortex, thalamus, middle and posterior cingulum, and angular gyrus bilaterally, and WM atrophy in the genu of the corpus callosum, posterior parahippocampal regions, brainstem and regions in the vicinity of the primary motor cortices. SV patients showed a progression of GM atrophy in the parahippocampal gyrus, posterior cingulum and thalamus bilaterally, and WM atrophy progression in the splenium of the corpus callosum and midbrain bilaterally. AD patients showed a progression of GM atrophy in the frontal gyrus, anterior and posterior cingulum, and hippocampus bilaterally, and WM atrophy in the entire corpus callosum and regions in the vicinity of the precentral gyri.

Conclusions: Structural MRI is able to detect longitudinal changes in patients with FTD clinical syndromes and AD. The spread of atrophy (posteriorly in FTD and anteriorly in AD) is consistent with the evolution of cognitive deficits in these syndromes. Furthermore, in all patients WM atrophy progression involved the motor system. These patterns provide information about disease evolution in the FTD syndromes and AD that is of both clinical and neurobiological relevance.

Assessing brain system dysfunction in amnesic mild cognitve impairment through MRI-based connectomics

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Objective: To investigate the topological organization of functional brain network connectivity in patients with amnesic mild cognitive impairment (aMCI).

Background: Brain networks supporting complex cognitive processes are specifically and progressively impaired over the course of AD. Brain connectomics may be sensitive to early network changes in aMCI.

Methods: Graph theoretical analysis was applied to resting state functional MRI data from 45 aMCI patients and 32 age-matched healthy controls. Functional connectivity between 90 cortical and subcortical brain regions was estimated using bivariate correlation analysis and thresholded to construct a set of undirected graphs. Measures of global and local network organization were obtained.

Results: Small-worldness was verified in patients and controls. Functional brain networks in aMCI patients were characterized by a significantly higher hierarchy compared with healthy subjects. Compared to controls, aMCI patients did not show hub regions in the right hippocampus, anterior cingulate and calcarine cortices bilaterally, and left putamen and caudate nucleus. Compared with controls, aMCI patients showed a pattern of increased betweenness centrality in the posterior cingulate cortex bilaterally, left angular, inferior parietal and supramarginal gyri, and right superior medial frontal cortex.

Conclusions: The global organization of functional networks is relatively preserved in aMCI patients, except for an increased hierarchy of the brain functional networks. High hierarchy suggests a high sub-modular decomposition of the functional networks, which is thought to be negatively related with the span of control acted by the central module. On the contrary, local functional network organization is altered in aMCI patients showing a loss of major hubs in the regions typically hit by the disease and evidence for increased connectivity locally within the parietal and frontal lobes. Graph analysis provides additional insights into the physiology of early changes in Alzheimer's disease.

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Validation of Italian Revised Memory and Behavior Problem Checklist Scale (RMBPC): a useful and reliable tool for assessing behavioural problems in people with dementia

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Background: Behavioural and Psychological Symptoms (BPSD) affect almost of 90% dementia patients.

Objective: The aim of this study was to translate and validate the complete Revised Memory and Behavior Problem Checklist Scale (RMBPC) for evaluating patients' symptoms and caregivers' distress in Italian-speaking population.

Methods: RMBPC was translated using a back-translation procedure. This Italian version of RMBPC was evaluated with 111 consecutive recruited patient-caregiver dyads (F=57; 76.3±.1 years). Cronbach's coefficient was used to asses reliability. Concurrent and discriminant validity were computed using correlation (Spearman's Rank correlation coefficients - RSp) with validated tools (Mini Mental State Examination -MMSE-, Neuropsychiatric Inventory -NPI- total score, disruption and NPI depression).

Results: As in the American population in which the scale was originally validated (Teri et al, 1992), and in the Spanish population in which the scale was recently validated (Gonzales Salvia et al, 2011) our results showed that memory symptoms were the most prevalent. The Cronbach's coefficient displayed good internal consistency for the whole scale (0.83 for total frequency; 0.89 for total reaction) and subscales (0.89 for memory; 0.60 for disruption; 0.81 depression). RMBPC subscales showed a positive correlation with all their respective validated tools of the patients' symptom scales. Memory and depression RMBPC subscales were correlated to MMSE scores (RSp –0.49, $p<0.001$) and NPI depression (RSp 0.66, $p<0.001$) (concurrent validity) but not to disruption measures (Discriminant validity). Conversely, disruption RMBPC subscale was associated with NPI disruption (RSp 0.32, $p<0.001$) but also with NPI depression (RSp 0.19, $p<0.05$) and MMSE scores (RSp –0.20, $p<0.05$).

Conclusions: We conclude that the Italian version of RMBPC scale is a reliable and valid tool for the clinical assessment of BPSD in patients with dementia. The self administered format of the scale makes its use in clinical settings very easy and inexpensive.

Non-pharmacological therapies for people with Alzheimer (PWA): which PWA characteristics predict a positive response?

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Background: The lack of medical treatments able to modify the dementia course have awoken the interest in non-pharmacological (nP) therapies for people with Alzheimer (PWA). Recent data support the notion that these nP-treatments have significant effects in improving PWA cognitive-behavioral status by restoring neural functioning. However, little is known about the characteristics of PWA, which may predict a more positive response to nP-therapies.

Objective: This study sought to investigate which factors may predict positive response to rehabilitation protocols.

Methods: We retrospectively analyzed 101 PWA (mean age 75±7 years; 8.3±4 years of education; 21.2±3.4 Mini Mental State Examination -MMSE- scores) followed in our Centre during group rehabilitation programs (a multidimensional approach that involved cognitive stimulation, physical, recreational, and occupational activities). Neuropsychological (MMSE) and neurobehavioral (Neuropsychiatric Inventory -NPI-) scores were considered as outcome

measures. Moreover, contributing factors (age, sex, education, MMSE and NPI baseline levels) that predicted change in outcomes were examined. An interval regression was devised for each scale in order to understand which independent factor could have positively affected efficacy of interventions in cognitive and behavioural areas.

Results: Data showed that training on cognitive outcome was influenced by baseline levels of MMSE (OR 0.72, 95%CI 0.60-0.87, $p=0.001$); while behavioural outcome was influenced by age (OR 0.91, 95%CI 0.86-0.97, $p=0.003$), education (OR 0.88, 95%CI 0.79-0.98, $p=0.024$) and NPI frequency at baseline (OR 0.91, 95%CI 0.88-0.99, $p=0.016$).

Conclusions: In line with Aguirre and colleagues (Aguirre et al, 2011) and with well-known data about disease progression, our data show that nP-treatment is potentially more beneficial for older people. Interestingly, gender were not associated with increased cognitive and behavioral benefits from the intervention. Whereas, lower MMSE at baseline and higher education seem to play a role on behavioral response. Although these data need to be explored further in future trials, it's our belief that these findings could be useful to support clinical decision in the current economical context.

Frontotemporal lobe degeneration: a new phenotypic variant?

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Background: Frontotemporal lobe degeneration (FTLD) includes several phenotypic variants. In life behavioural variant of FTD syndrome (bv-FTD) can be associated to aphasic syndromes or motoneuron disease. It has never been associated to Progressive Supranuclear Palsy (PSP). On the other hand some behavioural disturbances are described in patients with PSP, but they are never a prominent symptom of the syndrome nor a clinical variant such as Corticobasal Degeneration-PSP or Progressive Nonfluent Aphasia-PSP.

Case report: D.G., a 69-year old woman, came to our attention for a two year progressive behavioural syndrome characterized by loss of embarrassment, irritability, disinhibition, social avoidance and neglect of personal hygiene. Her relatives also noticed eating behavior changes: hyperphagia and tendence to steal food from other's plates. Both simple motor and verbal stereotypies together with complex motor routines were reported. Furthermore, a postural instability and a progressive walking impairment with frequent falls was reported. Hallucinations, delusions and disorientation in space and time were not present and no memory problems were noticed. Her past history revealed persistent atrial fibrillation and dyslipidemia, both in pharmacological treatment. Neurological examination documented an axial rigidity and retrocollis with an uninstable gait. Conjugate movement in the vertical direction of gaze was severely impaired. A brain MRI documented a diffuse mild cerebral atrophy. PET scan revealed frontotemporal hypometabolism prominent in the right brain. Neuropsychological tests revealed a severe frontal cognitive-behavioral syndrome with impairment in critique and judgment, reduced logical-deductive ability, concreteness and impaired categorization and motor planning, with frequent motor perseverations. She did not showed language problems.

Conclusions: For the first time association of frontal bv-FTD with PSP was documented. This case supports the great phenotypic variability of FTLD.

Pragmatic language in myotonic dystrophy type 1

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Objective: The present study is aimed to evaluate pragmatic language in patients with myotonic dystrophy type 1 (DM1).

Methods: We recruited 12 patients with DM1 who did not show a cognitive profile keeping with dementia or oligophrenia. A deep evaluation of language by means of the BADA battery was performed in order to exclude a primary language problem. Pragmatic language was examined by means of the Language Right Hemisphere Battery (BLED). The BADA and the BLED batteries were administered to a group of 15 healthy subject sharing similar demographic variables (age, education and sex) with the DM1 group.

Results: While both groups obtained performance within normal limits in the BADA battery, in BLED battery DM1 patients obtained lower performance than the control group ($p<0.01$) in subtests exploring different aspects of pragmatic language (metaphors, inferences and humor).

Conclusions: It is demonstrated that patients with DM1 show problems in understanding pragmatic language in absence of primary language problem, dementia or oligophrenia.

Prevalence of cognitive impairment and dementia in a population based study in Southern Italy: The Great Age study

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Background: The prevalence of cognitive impairment (CI) has been studied mainly in clinical setting. Most of the studies in population-based setting have been conducted outside Italy.

Methods: subjects over 65 years were recruited in Castellana Grotte, Southern Italy, as part of the fourth wave of a cohort study named MICOL, started in 1986. All subjects underwent a complete neurological and neuropsychological examination as a part of a multidisciplinary assessment. Dementia diagnosis was made according to Diagnostic and Statistical Manual of Mental Disorders - V edition. Diagnosis of dementia subtypes was made according to the current international diagnostic criteria. Neuropsychological assessment evaluated global cognitive function, memory, attention, language, executive functions and visuospatial skills by means of standardized tests. The cognitive performance was considered impaired if less than 2 SDs from the mean of the general population.

Results: We enrolled 514 subjects (312 males and 202 females, mean age of 72.84 ± 6: 12, mean years of school education 6: 59 ± 3.63). Fifty subjects (10%) were diagnosed as having Subjective Memory Complaints. CI was diagnosed in 150 subjects (29.4%). The 5.9% ($n = 30$) was amnesic MCI ($n = 13$ single domain impaired; $n = 17$ multiple domains impaired). The 23.5% ($n = 120$) was non-amnesic MCI ($n = 83$ single domain; $n = 37$ multiple domains). Cognitive performance was impaired for 10.5% in visuospatial abilities, for 9.8% in attention, for 5.3% in language and for 4.3% in executive functions tests. Twenty-five patients (5%) received a diagnosis of dementia (n. 17 Alzheimer disease and n. 8 other types of dementia).

Conclusions: These preliminary results showed a lower prevalence of dementia and a higher prevalence of CI compared to previous studies.

CSF p-Tau181/Tau ratio as biomarker for TDP pathology in Frontotemporal Dementia

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Objectives: To evaluate the CSF phospho-Tau/total-Tau (p/t-Tau) ratio to distinguish between the two main forms of frontotemporal lobar degeneration (FTLD): FTLD with TAR DNA-binding protein 43 (TDP-43) immunoreactive inclusions (FTLD-TDP) and FTLD with Tau inclusions (FTLD-Tau).

Methods: Differences in the CSF p/t-Tau ratio were examined in a multi-center testing cohort, in patients with predictable Tau ($n = 18$, affected by Progressive Supranuclear Palsy or carriers of mutations within MAPT gene) and TDP-43 ($n = 22$, carriers of mutations within Granulin, C9orf72, TARDBP genes or affected by FTD with motor neuron disease) neuropathology. Cut-off values were determined to achieve highest sensitivity and specificity according to ROC curve analysis. Cut-off values were tested in a separate multi-center validation cohort consisting of subjects with FTLD-TPD ($n = 22$), FTLD-Tau ($n = 17$). Included patients were randomly assigned to either the testing or the validation cohorts.

Results: In the first validation cohort, we found significantly reduced CSF p/t-Tau ratio in FTLD-TDP relative to FTLD-Tau. The ROC analysis for p/t-Tau ratio was 0.875 and the comparison of FTLD-TDP with FTLD-Tau showed 81.8% sensitivity and 88.9% specificity. Analysis in the second validation cohort showed CSF p/t-Tau ratio < 0.136 to distinguish FTLD-TDP from FTLD-Tau with 85% specificity and 63.6% sensitivity. The positive predictive value of detecting TDP neuropathology was 82.4%.

Conclusions: A reduced CSF p/t-Tau ratio represents a viable and reproducible biomarker to correctly identify FTLD-TDP, whilst a ratio within normal range does not allow to clearly define FTLD neuropathology. Detecting an on-going TDP pathological

process in FTLD has several implications for defining distinctive therapeutic approaches, guiding genetic screening and helping in patients' selection in future clinical trials.

A case of atypical familial early-onset dementia carrying the C9orf72 hexanucleotide expansion

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Background: Hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (C9orf72) gene is responsible for a significant fraction of fronto-temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Recently, the C9orf72 mutation has been shown to explain a small proportion of patients with a clinical presentation indistinguishable from Alzheimer's disease (AD), highlighting the necessity of screening C9orf72 gene in clinical AD cases with strong family history.

Case report: We here describe the case of a 64-year-old woman who presented severe cognitive impairment with a beginning with psychiatric disturbances including confusional state, confabulation, worry and severe agitation, delusions and rapid deterioration which led to a complete loss of autonomy in less than six months. The family history has been confirmed, with a sister, an uncle and a cousin affected by AD. Routine laboratory investigations resulted normal. Infectious and tumoral disease were ruled out. A neuropsychological examination was not possible to administer due to the severe cognitive impairment. Cerebrospinal fluid analysis, with determination of beta-amyloid, P-Tau e total Tau was normal, 14.3.3 protein resulted negative. Electroencephalography, magnetic resonance imaging of the brain and positron emission tomography scanning with the fluorodeoxyglucose (18FDG-PET) were no indicative for a specific neurodegenerative disorder. Genetic testing revealed no mutation in APP, PS1 and PS2 genes and Apolipoprotein E (APOE) genotype was 2/3. The analysis of C9orf72 showed large hexanucleotide repeat expansion.

Conclusions: This case report highlights the need to consider mutations in the FTD-associated genes when a strong familial disorder is suggested and neuroimag-

ing studies reveal findings atypical of an AD pathophysiological process and rapid deterioration of cognitive decline.

Italian Network For Autosomal Dominant Alzheimer's Disease and Frontotemporal Lobar Degeneration (ItalianDIAfN): definition of protocols for data collection and genetic counselling

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Background: The ItalianDIAfN project was launched in 2012 to create an Italian network of centres of excellence with the capabilities to recruit and assess subjects with familial autosomal dominant Alzheimer's disease [fAD] (genes: APP, PSEN1, PSEN2) and frontotemporal lobar degeneration [fFTLD] (MAPT, GRN, C9ORF72).

Objective: The first phase of the project aimed to develop standard protocols for data collection and genetic counselling of families with fAD and fFTLD.

Methods: We surveyed the international and local protocols for data collection (clinical, neuropsychological, neuroimaging, molecular imaging, biological, and neurophysiological) and the local genetic counselling protocols. Differences and commonalities among protocols were identified and discussed among the ItalianDIAfN partners to reach consensus.

Results: The following procedures for data collection were agreed:
(i) disease-specific and internationally compliant protocols for clinical, neuropsychological and neuroimaging data: the DIAN protocols for fAD cases and the GenFi protocols for fFTLD cases;
(ii) a specific amyloid-PET protocol (only for fAD cases);
(iii) a common, DIAN compliant, FDG-PET protocol;
(iv) a common protocol for biosamples (DNA, RNA, sierum, plasma, lymphoid cells, CSF, urine, fibroblasts), representing a synthesis between DIAN and GenFi protocols;

(v) a common, IMI-Pharmacog compliant, protocol for neurophysiological data;

(vi) a common registry for fAD and fFTLD cases and common procedures for biosample storage in a national Biobank.

A common protocol was defined for genetic counselling of symptomatic subjects with fAD and fFTLD and/or their at-risk-relatives, provided by multidisciplinary team (a geneticist, a psychologist/psychiatrist, and a neurologist/geriatrician). Moreover, we developed a decision tree for genetic testing, guided by the following hierarchical information: CSF Aß levels (if available), clinical phenotype, age at onset.

Conclusions:These defined protocols will now be validated on 12 families with a known pathogenic mutation for fAD or fFTLD. The procedures will be disseminated to reach academia, medical societies, and the public at large and exploited for clinical trials.

RT-QuIC of olfactory neuroepithelium brushings as an intravital diagnosis for Creutzfeldt-Jakob disease

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Background: Definite diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) in living patients remains a challenge. Real time quaking induced conversion (RT-QuIC) testing of cerebrospinal fluid (CSF) has allowed identification of sCJD patients with 80-90% sensitivity. However, because CJD is transmissible, untreatable and fatal, it is important to eliminate missed diagnoses. Previous work identified abnormal prion protein (PrP) in olfactory neuroepithelium of sCJD patients, prompting us to investigate whether RT-QuIC analysis of easily accessible nasal brushings might improve CJD diagnosis.

Methods: We tested olfactory neuroepithelium brushings from 20 CJD and 30 non-CJD patients using RT-QuIC, which is an ultrasensitive, multiwell plate-based fluorescence assay involving prion-seeded polymerization of recombinant PrP into amyloid fibrils.

Results: We observed strong positive RT-QuIC reactions seeded with nasal brushings from 20 of 19 probable CJD patients, but none of 30 negative controls, providing sensitivity 95% and 100% specificity. By comparison, 5 out of 20 CSF samples from the same group of CJD patients was RT-QuIC-positive, giving 75% sensitivity. Quantitative RTQuIC showed that olfactory brushings contained ~10 5-10 7 prion seeds.

Conclusions: Nasal brushing-based RT-QuIC may markedly facilitate and strengthen diagnosis of CJD. Moreover, the high levels of prion seeding activity found in these samples raises concerns about transmissible CJD prion shedding from olfactory mucosa.

Sporadic, familial, genetic Alzheimer's Disease patients: long-term effects of Cholinesterase Inhibitors

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Background: Few long-term and/or naturalistic studies exist on progression of cognitive deficits in Alzheimer Disease (AD) patients assuming Cholinesterase-Inhibitors (ChEIs). No data in patients with genetic cause or familial trait.

Objective: The aim of the study was to determine long-term, real-life effects of ChEIs on progression in genetic, familial and sporadic AD patients and to individuate predictors of pharmacological response.

Methods: A retrospective analysis of 647 AD patients (age onset 74.1 ± 9.3 years) has been performed: 13 patients Met1146LeuPS1-mutated (gAD), 143 patients with 1stdegree-relative affected (fAD), 335 patients affected by sporadic (sAD), and 156 patients without familial data. Data were obtained from baseline interview. Cognitive status was measured (Mini Mental State Examination -MMSE-) at the baseline and after every 6 months.

A loss of ≥ 5 points at MMSE respect to the baseline values was considered as an indicator of disease progression. Time to progression was calculated in months from the baseline to the visit when the loss occurred (survival curves by Kaplan-Meier's). Age,

education, basal MMSE, gender, family history, ChE-I's type and dosage studied were considered as predictors of pharmacological response (Cox's proportional hazard models).

Results: During follow-up time (42.4±25.6 months), 287(44.5%) patients experimented a disease progression. Median time to progression was 22.2 months. At 20 months, 417 (80%) patients didn't experiment disease progression, while this number decresed after 40 months, when 387(60%) patients didn't experiment disease progression.

Early onset patients (≤59 years) with 6 years of education had the fastest progression while subject with onset 80-84 years experimented the slowest decline; gAD patients had the fastest progression rate compared to fAD and sAD groups (*p*=0.000). Progression rate was greater in fAD group than sAD group, but no statistical differences. Type or dosage of ChE-I didn't influence progression rate.

Conclusions: Despite the new pharmacological perspectives, at present ChEIs administered in long-term naturalistic settings seem to represent the most effective treatment to reduce progression in the majority of AD patients. The most beneficial effects, independently of dosage, regarded older patients (80-84 years), while gAD patients showed the worse outcomes.

Experimental web-portal to support integrated care models for dementia in Calabria

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Background: Dementia is a growing emergency worldwide because of the high disability and the social costs related to the disease. "Network oriented" integrated care models appear to be needed in order to ensure effective care to patients. Currently, two pilot projects focused on dementia advanced care are being tested in Calabria. One of these is based on an advanced version of the Chronic Care Model (CCM), whereas the other project focuses on creating a network between the Alzheimer Assessment Units (UVAs) of the region ameliorating clinical diagnosis – assistance and care of patients and families.

Objective: The aim of the study is to provide integrated and multidisciplinary interventions in order to ensure the quality and effectiveness of a patient centred care.

Methods: A hub-spoke structure was organized: the governance function was attributed to the CRN (Regional Centre of Neurogenetics) and the role of satellite units was attributed to the local Dementia Assessment Centres (CVD), formerly called UVA.

Results: The activities of CVD and other professionals involved in dementia care (general practitioner, i.e.) were integrated with the implementation of the web-portal www.univacalabria.it, allowing epidemiological analyses, clinical research and the experimenting of advanced models of care (Home-care and Tele-Care). Moreover, the web application supports an active "virtual community" by forum users'. The web portal allows the integrated management of the patient sharing clinical and social information in a safe medical record available by Internet.

Conclusions: This experience is in progress in Calabria and represents an innovation for the Italian context because of the relevant synergy between medical care and clinical engineering in favour of translational research.

The qualitative scoring of the MMSE pentagon test may distinguish prodromal Lewy bodies disease from Alzheimer's disease

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Background: Visual-constructional apraxia is a prominent feature of dementia with Lewy bodies (DLB) that may contribute to distinguish DLB from Alzheimer's Disease (AD). Some previous studies suggested that the analysis of the pentagon copy included in the MMSE could be a promising tool for the diagnosis of DLB since its early stages (Ala et al. 2001).

Objectives: To assess the pentagon copy performance in prodromal stage of DLB with the Qualitative Scoring MMSE Pentagon Test (QSPT) (Caffarra et al., 2013).

Methods: Thirty patients with non-amnestic-Mild Cognitive Impairment (MCI) diagnosed as prodromal DLB and 25 patients with amnestic-MCI diagnosed as prodromal AD were enrolled. All patients obtained MMSE score=26/30. The diagnosis of DLB and AD

was confirmed at 3-year follow-up visit according to established criteria. Each MMSE test was examined with the QSPT which is based on the assessment of different parameters of the pentagon drawing, such as the number of angles, distance/intersection, closure/opening, rotation and closing-in. A broad standard neuropsychological assessment was also performed in order to correlate the performances at the QSPT with those of single cognitive domain.

Results: Data showed that 50% of MCI-DLB and 12% of MCI-AD obtained wrong performances at the QPST in the subitem considering the number of angles ($p = 0.005$). There were no differences between the two groups in the other QSPT subitems. Attention and executive functions and visuo-spatial abilities were worse in MCI-DLB (TMT-A, Digit Span Backward, Clock Tests), while episodic memory impairment was greater in the MCI-AD group. The number of angles of the QSPT correlated negatively with the TMT-A performance in both groups (DLB: $r = -0.45$; $p = 0.010$; AD: $r = -0.57$; $p = 0.003$).

Conclusions: The number of angles in the QPST is the parameter firstly impaired in DLB. The results suggest an earlier loss of the whole visuo-spatial mental image in prodromic DLB patients with respect to AD.

Neurocognitive correlates of metaphoric language: evidence from frontotemporal dementia

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Background: Behavioural variant of FTD is characterized by subtle behavioural changes in absence of primary language problem. At the same time there is evidence that these patients are more likely to show problems in understanding pragmatic language.

Objective: To explore metaphoric language in early behavioral variant of Frontotemporal Dementia (bvFTD).

Methods: Fourteen patients affected by early bvFTD were enrolled in the study. A group of 31 healthy subjects, matched with the patients for demographical characteristics, served as reference group. All subjects were administered an experimental battery (Italian Battery for Right Emisphere Language - BLED) exploring figurative metaphors and written metaphors. Patients underwent positron emission tomography (PET) and they were classified in right and left bvFTD according to the prevalence of the hypometabolism showed in the PET scan.

Results: The t test revealed a significantly lower performance ($p < 0.001$) of FTD patients in both tasks in comparison with controls, with tendency to choice literal distractors. The performance on the tasks correlated significantly to hypometabolism in frontal lobe showed by the PET imaging. Performance in figurate metaphors were significantly worse in the FTD patients with prominent right hypometabolism.

Conclusions: Our data suggest that alterations of metaphoric language represent an early feature of bvFTD and may offer new insights on the cognitive changes underpinning this neurodegenerative disease.

Route learning in Semantic Dementia and Alzheimer's Disease

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Background: Driving is a highly complex task which entails many cognitive functions to be intact. Dementia represents the most frequent neurological disease that invariably leads to loss of driving abilities with the possible presence of topographical disorientation (TD).

Objective: To verify the occurrence of TD and to identify the neuropsychological dysfunctions associated with TD in Semantic Dementia (SD) and Alzheimer's Disease (SD).

Methods: Ten patients with SD and ten patients with AD, in the mild stages of the disease, were enrolled in the study. A group of 16 healthy subjects, matched with the patients for demographical characteristics, served as reference group. They were administered an experimental Route Learning Task (RLT), requiring the subjects to learn a real route showed in a video.

Results: In the RLT test the SD group showed performances similar to healthy controls while the AD group showed lower performances than controls and SD ($p < 0.001$).

The performance of the AD group on the RLT correlated significantly to spatial tasks in the background neuropsychological examination ($p = 0.01$).

Conclusions: The present study showed the presence of topographical disorientation in mild stages of

AD. By contrast SD do not show TD. The present data should encourage to explore in detail skills linked to driving in the different forms of dementia because there is evidence of a differential profile.

Numerical knowledge in Semantic Dementia and Alzheimer's Disease

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Background: Numerical abilities play an important role in day-to-day life and recent evidences show alterations of this competence since the early stages of Semantic Dementia (SD) and Alzheimer's Disease (AD).

Objectives: To explore numerical knowledge in Semantic Dementia (SD) and Alzheimer's Disease (AD).

Methods: Twelve patients with Semantic Dementia (SD) and 20 patients with Alzheimer's Disease (AD) were enrolled in the study. A group of 22 healthy subjects, served as reference group.

All patients underwent an extensive neuropsychological battery exploring numerical knowledge (Capasso and Miceli battery) which included magnitude judgement tasks and transcoding tasks involving numerals (repetition of numbers, reading of Arabic numbers, reading of number words, writing Arabic numbers to dictation, transformation of written number words in Arabic numbers).

Results: Both groups performed flawlessly in magnitude judgment tasks while transcoding tasks were significantly worse ($p < 0.01$) in the two diseases group than controls' performance. The qualitative pattern of error revealed to be different in the two diseases group. AD profile was almost composed by intrusions and perseverations, while SD profile was characterized by "syntactical errors".

Conclusions: The present data are in favour of an early impairment of numerical knowledge in AD and SD, although the neurocognitive profile seems to be different. Assessment of everyday numerical skills may be crucial in planning adequate support for these patients and may offer new insights on the cognitive changes underlying these neurodegenerative diseases.

To what extent is language impaired in the Corticobasal Syndrome?

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Background: It is generally assumed that semantic knowledge is relatively preserved in Corticobasal Syndrome. Recently, some case reports have showed semantic breakdown in CBS.

Objective: To explore semantic knowledge in Corticobasal Syndrome (CBS).

Methods: Twenty-three patients with CBS were enrolled in the study. Twenty patients with AD served as disease reference group. All patients underwent a background neuropsychological evaluation exploring the main cognitive domains. Language was explored in deep with test of letter and category fluency, picture naming, picture reading, word-picture matching, writing, repetition, semantic association tasks.

Results: Both disease groups showed reduced fluencies with mild naming impairment in absence of comprehension, writing and repetition errors. Semantic association tasks were almost preserved. In background neuropsychology the AD group showed significantly worse performance in long term memory tasks while CBS patients were impaired in the visuospatial, executive and praxis domains.

Conclusions: The present study shows absence of semantic breakdown in a consecutive unselected group of CBS reinforcing the concept that semantic breakdown is not a frequent finding in this syndrome.

A singular pattern of magnetic resonance in a rare subtype of sporadic Creutzfeldt-Jacob disease

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Background: Prion diseases, also called transmissible spongiform encephalopathies (TSEs), are a heterogeneous group of infectious diseases caused by the accumulation of abnormal prion protein (PrPsc), encoded by a gene (PRNP) located on the short arm of chromosome 20. The classic form of Creutzfeld-Jacob sporadic (sCJD) affects patients between 45 and 75 years old. The most frequent clinical presentation is characterized by myoclonus and severe cognitive

impairment with a rapid progressive course. The clinical heterogeneity of sCJD has been related to genetic differences (polymorphisms of codon 129 of the PRNP gene and of " banding pattern" of PrPsc). Six molecular subtypes have been described (MM1, MM2, MV1, MV2, VV1 and VV2) and each may have different aspects of magnetic resonance (MR) imaging.

Case report: A 68 year old man came to our attention for a subacute Korsakoff-like syndrome in the absence of other clinical manifestations. In the diagnostic work-up EEG was normal and brain MRI showed diffuse bi-hemispherical hyperintensity on DWI and FLAIR (temporal, frontal, parietal and occipital lobes), similar to a pattern of hypoxic-ischemic cerebral damage. No alterations in the signal level in the basal ganglia, cerebellar cortex or thalamus were found. CSF examination showed normal routine analysis, presence of 14-3-3 protein (immunoblot) and increased levels of tau protein (ELISA). The neuropsychological pattern demonstrated a widespread cognitive impairment, mainly of the long-term memory and in the spatial and verbal component and of the executive functions. The Genetic analysis showed a VV1 molecular subtype.

Conclusions: In patients with VV1 molecular subtype of Creutzfeldt-Jacob is possible to find a pattern of cortical lesions only at the MRI, compared with a clinical expression characterized by a widespread cognitive impairment in the absence of myoclonus or EEG abnormalities.

Preclinical MRI alterations in a sporadic case of Creutzfeldt-Jakob disease

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Background: Creutzfeldt-Jakob disease (CJD) is a neurodegenerative prion disorder with a fatal outcome. Typical MRI findings consist of hyperintense signal abnormalities in DWI and FLAIR sequences in deep grey matter nuclei (caudate, putamen and thalamus), cerebral cortex or both.

Objectives: We describe a case of sporadic CJD (sCJD) with MRI cortical alterations pattern preceding the clinical disease onset.

Case report: A 74 year-old woman affected by a carotid body tumour underwent a follow up brain MRI study that showed a DWI hyperintensity of the parieto-temporal-occipital cortex bilaterally, with no basal ganglia involvement. Although she denied neurological symptoms, she was urgently admitted to the internal medicine ward suspecting a probable subacute cerebral ischemia. Neurological examination was normal (except for a known deficit of the XII left cranial nerve due to the tumour). In particular, visual disturbances, including visual agnosia, or impairment of other cortical functions were not detected. Screening for metabolic and vascular risk factors turned out negative. Two weeks later she started to complain complex visual disturbances (visual agnosia, hemianopsia) associated with a rapidly progressive global cognitive decline. A second MRI (two months later) showed diffuse cortical DWI hyperintensity involving also the frontal cortex but sparing the basal ganglia. EEG revealed periodic sharp wave complexes. CSF analysis showed a positive 14-3-3 protein and total TAU protein level >2400 ng/ml. Three months later the patient was in akinetic mutism state and died a month later. Brain pathological examination confirmed the diagnosis of sCJD (MM1 PrP pattern).

Conclusions: This is the first case reporting preclinical MRI evidence of autopsy proven sCJD, suggesting that PrP-related brain changes might be detectable by MRI in a pre-clinical phase. Our observation confirms the role of MRI-DWI as an early/preclinical diagnostic marker for CJD.

Phenotyping familial Alzheimer's disease caused by presenilin 2 mutations

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Background: Familial Alzheimer's disease (FAD) represents a rare autosomal dominantly inherited condition sustained by highly penetrant mutations involving the genes encoding for the amyloid precursor protein, presenilin 1, and presenilin 2 (PSEN2). Despite representing a rare condition, FAD is attracting a growing interest in the scientific community. To date, available evidences have been mainly focused on the novelty of the mutations and on their potential molecular and functional consequences. Relatively few reports have provided extensive documentation of their clinical characteristics, making difficult operating genotype-phenotype correlations.

Objective: This study aimed at performing a systematic review of studies describing the phenotypic features of FAD cases sustained by PSEN2 mutations, the less common cause of monogenic AD. Methods. Particular focus was given to the clinical aspects as well as to the main findings coming from the most commonly and widely adopted diagnostic procedures. The study quality was evaluated by adopting an ad-hoc score combining both genetic and clinical criteria. The collected data were then used to conduct a genotype-phenotype correlation analysis.

Results: Overall, the mutations involving the PSEN2 gene represent an extremely rare cause of FAD, having been reported to date in less than 200 cases. They are mainly associated, despite some peculiar and heterogeneous features, to a typical AD phenotype. Nevertheless, the frequent occurrence of psychotic symptoms may represent a potential distinctive element.

Conclusions: The paucity of available phenotypic descriptions strongly limits the implementation of genotype-phenotype correlations as well genetic counseling procedures.

The effect of age of onset on the brain functional connectivity in Alzheimer's disease: a graph analysis study

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Objective: To examine the relation between the topological organization of functional brain networks and the age of onset in patients with Alzheimer's disease (AD) using a network-based approach.

Background: Brain connectomics opened new horizons to the understanding of brain organization and could add significant advances to the understanding of AD at different age of onset.

Methods: Graph theoretical analysis was applied to resting state functional MRI data from 36 late onset AD (LOAD) patients (age: 75±5,CDR-SB: 6±2), 23 early onset (EOAD) patients (age: 60±5,CDR-SB: 5±2) and two groups of old (N: 16,age: 73±4) and young (N: 22, age: 59±3) healthy individuals. Functional connectivity between 90 cortical and subcortical brain regions was estimated using bivariate correlation analysis and thresholded to construct a

set of undirected graphs. Measures of global and local network organization were obtained.

Results: Small-worldness was verified in controls and patients. Globally, the functional brain networks of LOAD patients were characterized by a significantly lower local and global efficiency, lower clustering coefficient and higher assortativity compared with age-matched controls. In contrast, functional brain networks of EOAD patients were characterized by a significantly higher hierarchy and lower assortativity compared with age-matched controls. Locally, lower nodal degree and local efficiency, and higher betweeness centrality were observed in both AD groups compared to the age-matched controls. However, while LOAD showed local alterations (in terms of decreased nodal degree and increased betweeness centrality) in the medial temporal, parietal and occipital lobes, EOAD patients showed a widespread pattern of damage involving also the frontal regions.

Conclusions: Graph analysis showed that global functional network organization was abnormal in AD patients. Compared to LOAD, the EOAD patients showed a widespread pattern of local network alterations involving also the frontal regions. The topological differences between patient groups may represent the effect of age of onset on functional connections.

Mapping alexithymia: How the brain identifies, processes and talks about emotions

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Objective: To provide a brain model of identification, processing and communication of emotions, and to investigate the association between alexithymia and brain functionality in these three conditions.

Background: Alexithymia is a personality construct characterized by a continuum spectrum of difficulties in identifying, interpreting and communicating feelings.

Methods: Twenty-three healthy young subjects underwent the TAS-20 scale and a functional MRI (fMRI) scan. The 2x3 fMRI design included 2 conditions (neutral-N and negative emotional-NE) and 3

tasks: physiological activation/identification (film watching), processing (judgment of felt emotion pleasantness/intensity), and preparation for emotion communication (felt emotion report). In each task, one-sample t-tests and multiple regressions were performed to investigate differences between N and NE conditions and the relationships between the NE fMRI signal and TAS-20 scores.

Results: Three subjects were alexithymic according to the TAS-20. Compared to N, NE condition showed: a greater recruitment of the anterior and middle cingulum, superior frontal cortex and retrosplenial cortex during the identification task; a massive recruitment of the frontal cortex during processing; and the involvement of the inferior orbitofrontal cortex, supplementary motor cortex, insula, thalamus and occipital associative cortices during preparation for communication. In the activation and preparation for communication tasks, all the regions were less activated with increasing values of TAS-20; in the processing task the frontal regions were highly activated with increasing TAS-20 scores.

Conclusions: The brain emotional system includes cognitive regions responsible for emotional awareness during the identification, frontal regions for processing emotional memories, and subcortical and cortical associative regions for organizing emotional material for communication. Alexhitymia is associated with an altered recruitment of each part of this complex system.

Diffusion tensor imaging of the parietal lobe differentiates Posterior cortical atrophy from Alzheimer disease

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Background: In PCA the most important radiological feature is the focal atrophy of grey matter (GM) in posterior lobes.

Objective: The aim of this study was to compare patterns of cerebral atrophy on MRI using diffusion tensor imaging (DTI) in patients with posterior cortical atrophy (PCA) and typical Alzheimer's disease (AD).

Methods: We studied the brain macroscopic appearance and the possible damage of GM microstructure in 3 patients with PCA and in 3 patients with AD. At the time of DTI acquisition, the disease duration was

2.5 years. The study was performed with equipment high-field MR (1.5 T, GE HDX). Scans were performed with conventional techniques and technology diffusion tensor imaging (DTI) (b-value: 1500, direction: 25). In post-processing Fractional Anisotropy (FA) and Mean Diffusivity (MD) values were acquired of at the level of GM as well as white matter (WM), through the use of ROI localized at the level of the parietal lobes and occipital lobes.

Results: The study with conventional techniques showed an evidence of brain atrophy in particular of GM of posterior lobes in all patients. FA values of almost all ROIs were substantially reduced in occipital and parietal region in both the AD and the PCA patients compared to age-matched healthy controls. Also MD values were increased in both AD and PCA patients compared to age-matched healthy controls. In addiction PCA patients exhibits a significant FA reduction and MD increase only in correspondence of the parietal lobe if compared with AD patients.

Conclusions: Our results confirm a WM and GM damage in AD and PCA patients, but FA and MD values in parietal lobes can differentiate, at least in early stage of disease, this two conditions.

CSF ß-amyloid1-42, 181p-tau and htauAg, and Brain 18FDG-PET in the differential diagnosis between Alzheimer's Disease and Vascular Dementia

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Objectives: To evaluate the role of CSF ß-amyloid1-42, 181p-tau, and htauAg concentrations, and brain 18FDG-PET in the differential diagnosis between Alzheimer's Disease (AD) and Vascular Dementia (VaD).

Methods: Sixteen patients with probable AD (NINDS-ADRDA criteria), 12 with probable VaD (DSM-IV-R and Hachinski scale), and 8 neurologically normal subjects, matched for age, were studied. CSF ß-amyloid1-42, 181p-tau and htauAg concentrations were measured in all subjects by Innotest ELISA. Brain 18FDG-PET was performed in AD and VaD patients. Statistical analysis was performed using one-way ANOVA followed by multiple comparisons tests with Tukey's HSD test, Innotest Amyloid Tau Index (IATI), and Linear discriminant analysis (LDA).

Results: HtauAg concentration was significantly higher in AD compared to VaD patients ($p < 0.05$). 181p-tau concentration was significantly higher in AD compared to VaD ($p < 0.001$) and to normal subjects ($p < 0.001$). Differently, in AD patients the ß-amyloid1-42 levels were lower and their distribution pattern less dispersed compared to VaD patients and normal subjects, even if not significant. The IATI chart put in evidence that CSF pattern of VaD patients overlapped with normal subjects pattern, while they were both very different to AD cluster. The combined evaluation of the three CSF biomarkers by LDA allowed to identify the three different clusters of subjects with an accuracy of 61.1%, In AD patients, brain 18FDG-PET showed a marked reduction of glucose metabolism in temporo-mesial regions, precuneus, and cingulate gyrus. Differently, in VaD patients there was a slight global reduction of brain glucose metabolism.

Conclusions: This study confirms that CSF biomarkers and brain 18FDG-PET may support the differential diagnosis between AD and VaD. Moreover, the CSF biomarker pattern of VaD patients is not different from that of normal subjects.

Pre-stroke and follow up neuropsychiatric profile in patient affected by Post-Stroke Dementia

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Background: As the population ages, patients are increasingly likely to present with stroke and pre-existing dementia, which may lead to greater disability and death. Stroke is an important risk factor for dementia, but the exact mechanisms involved in cognitive decline remain unclear.

The term post-stroke dementia (PSD) is used to define any dementia occurring after stroke irrespective if the leading cause is vascular, degenerative or mixed.

Methods: Premorbid clinical and cognitive features of 145 consecutively recruited patients with a diagnosis of acute cerebrovascular pathology were assessed by interviewing the caregivers and using multidimensional assessment at the patients bedside. Patients were divided into two groups (Post Stroke Dementia group, PSD, and Post Stroke Non Dementia Group, PSND). Baseline cognitive, functional and behavioral variables, clinical variables at onset of symptoms and

neuroradiological hallmarks (medial temporal lobe atrophy, MTLA) were compared between these two groups.

Results: Forty-three patients (29.7%) were diagnosed as affected by dementia (MMSE<24; IADL lost>1; PSD group) at the 3 month follow-up after the acute stroke, while 102 patients (70.3%) were not classified as demented (MMSE>24; IADL<1 lost, PSND group) at the same time of follow up. In a logistic regression model, older age (OR 1.09, 95% CI 1.0–1.2; $p = 0.008$), pre-stroke apathy after a stroke (OR 1.51, 95% CI 1.1– 2.1; $p = 0.02$), and MTLA (OR 0.83, 95% CI 0.7–0.9; $p = 0.04$), were the variables independently associated with PSD.

Conclusions: These findings support the hypothesis that cognitive impairment in patients with stroke may not only be a direct consequence of acute cerebrovascular event but also a consequence of underlying neurodegenerative pathology.

Mapping regional grey and white matter damage in patients with progressive supranuclear palsy syndrome

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Background: The progressive supranuclear palsy syndrome falls under the umbrella of frontotemporal lobar degeneration (FTLD) clinical spectrum. Pathological and neuroimaging studies suggested that in syndromes with an underlying FTLD-tau pathology, such as PSPs, white matter damage is prominent compared to grey matter loss.

Objectives: To investigate the pattern of grey matter (GM) atrophy and white matter (WM) microstructural damage in a patients with probable progressive supranuclear palsy syndrome (PSPs) using advanced magnetic resonance imaging (MRI) techniques.

Methods: We enrolled 21 patients with probable PSPs and 21 healthy controls. Patients underwent clinical and neuropsychological evaluation, and brain structural and diffusion tensor (DT) MRI. The regional patterns of brain GM atrophy and WM microstructural damage were assessed using voxel-based morphometry and tract-based spatial statistics, respectively ($p < 0.05$ FWE).

Results: PSPs patients were in a moderate stage of disease (mean Hoehn and Yahr score: 3.3) and showed mild to moderate cognitive impairment involving especially attentive-executive functions. PSPs patients did not show significant GM atrophy relative to controls. On the contrary, they showed a significant reduction of fractional anisotropy and a significant increase of mean, axial and radial diffusivities in the main WM tracts bilaterally, including body and splenium of corpus callosum, cingulum, inferior fronto-occipital, superior longitudinal and uncinate fasciculi, anterior and superior corona radiata, corticospinal tract, and thalamic radiations. Superior cerebellar peduncles and internal capsules showed a significant increase of diffusivity values, but no FA changes.

Conclusions: In PSPs patients, WM microstructural damage is prominent compared to GM atrophy even in the moderate stage of the disease, suggesting that diffuse WM damage in tauopathies is not merely a function of disease severity. Regional differences in DT MRI metrics might reflect a different vulnerability of WM tracts.

Cortico-striatal-thalamic network functional connectivity in hemiparkinsonism

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Background: In hemiparkinsonian patients, the cerebral hemisphere ipsilateral to the affected limbs can be considered "presymptomatic". Resting state (RS) fMRI in mild/moderate stage of PD revealed an altered connectivity of the cortico-striatal-thalamic network, which is likely to be modulated by L-DOPA in both chronically treated (t-PD) and drug-naïve (n-PD) patients.

Objective: To investigate functional connectivity (Fc) of the cortico-striatal-thalamic networks in patients with early lateralized Parkinson's disease (PD) (hemiparkinsonism), and the effects of levodopa (L-dopa) on the brain networks at the earliest stage of PD.

Methods: RS fMRI was obtained from 69 hemiparkinsonian patients (25 n-PD+44 t-PD) and 27 healthy

subjects. Fc analysis was performed using caudate, putamen, pallidus nucleus and thalamus bilaterally as seed regions of interest. The images of patients whose symptoms were on the left (L) side were left-right (R) flipped so that the hemisphere contralateral to the affected limbs was the L for all patients.

Results: Relative to controls, n-PD patients showed an increased basal ganglia reciprocal Fc bilaterally, and a decreased connectivity of the affected caudate nucleus and thalamus with the ispilateral prefrontal, frontomedial, orbitofrontal and insular cortices. Compared with both controls and n-PD patients, t-PD patients showed a decreased Fc among the striatal and thalamic regions, and an increased Fc between the striatum and the temporal cortex and between the thalamus and several cortical regions involving the sensorimotor areas. In both n-PD and t-PD groups, patients with more severe motor disability had an increased striatal/thalamic Fc with temporo-parietal-occipital regions.

Conclusions: Cortico-striatal-thalamic functional abnormalities occur in hemiparkinsonism, antecede the onset of motor symptoms on the opposite body side, and are modulated by L-dopa. L-dopa is likely to facilitate a compensation of PD functional abnormalities possibly through an increased thalamic outflow.

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

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Background: [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.

Conclusions: 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.

Different Patterns of Serial Position Effects: Evaluation of the "Cortical" Hypothesis in Older HIV Positive Patients

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Background: Older HIV+ patients (OHIV+) might show a qualitatively different expression of the cognitive decay compared to younger adult patients (YHIV+), who typically display a "subcortical" cognitive profile.

Objective: The aim of our study was to explore the hypothesis of the extension of the cognitive deficit to "cortical" functions in OHIV+ by observing a reduced primacy effect as indicator of defective learning ability as in typical "cortical" dementia like Alzheimer's disease (AD).

Methods: We retrospectively investigated the Recency (R) (total number of words recalled over the first two trails in the last five positions), Primacy (P) (total number of words recalled over the first two trails in the first five positions) and R-P difference, in Immediate Rey's Words Learning Test (RWLT) in 304 subjects: 58 Parkinson Disease patients (PD), 63 AD,

44 Frontotemporal Dementia (FD) patients, 53 YHIV+ (=50 years old), 24 OHIV+ (=60 years old) and 62 healthy controls (C). Groups were not comparable for age ($p < 0.001$), MMSE performance ($p < 0.001$), and for education ($p = 0.031$).

Results: The ANOVAs showed a significant effect of "group" (F (5, 294) = 2.37; $p = 0.040$) after adjusting for age, education, MMSE and Immediate Recall of RWLT. Post hoc analyses (LSD test) revealed that AD had the more severe reduction of P with the higher value of R-P (X = 2.25; DS = 2.74), while in the other patient groups both effects were slightly reduced (with P-R close to 0).

In C the normal pattern of P and R was confirmed (mild prevalence of R).

Conclusions: Results did not confirm the hypothesis: while AD patients showed the expected reduction of Primacy Effect, OHIV+ patients were not different from YHIV+ and showed the same pattern of P and R observed in "subcortical" damage like PD.

Assessment of cerebral vaso-reactivity in Alzheimer's Disease using ultrasound techniques

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Background: There are growing evidences that cerebral hemodynamic changes play a role on cognitive decline in the old age.

Objectives. The aims of this study were to assess in subjects affected by Azheimer's Disease (AD) the cerebral vasomotor reactivity and to evaluate the possible correlation between this reactivity and the cognitive deficit.

Methods: Thirty-six subjects (mean age±SD, 68,58±6,16 years) were consecutively enrolled. We recruited twenty-five AD subjects, matched for age and education to eleven healthy control. Subjects with a Mini Mental State Evaluation (MMSE) score less than 15, cerebrovascular disease history, severe leucoencephalopathy and carotid stenoses major than 40% were excluded. All the subjects underwent MRI imaging, Neuropsychological evaluation and Carotid Duplex Utrasonography. Cerebral vasomotor reactivity was assessed using the transcranial Doppler based breath-holding index test (BHI).

Results: Both Cerebral blood flow velocity at the steady-state (CBFV) and BHI values were significant-

ly lower in AD subject than in healthy control ($46,34\pm7,61$ cm/s vs $55,1\pm8,09$ cm/s, $p=0,007$; $0,99\pm0,26$ vs $1,21\pm0,24$, $p=0,031$). We found a correlation between CBFV value and MMSE score ($p=0,003$, $r=0,654$; Spearman's correlation). AD subjects with carotid stenoses had a lower CBFV and BHI values than those without carotid stenoses ($43,12\pm7,56$ cm/s vs $48,68\pm7,07$ cm/s, $p=0,008$; $0,9\pm0,23$ vs $1,06\pm0,27$, $p=0,04$; respectively). Considering the correlation between each neuropsychological test and the cerebrovascular reactivity indices, we found a significant correlation with the Digit Span test score (CBFV: $r=0,542$, $p=0,046$; BHI: $r=0,525$, $p=0,05$; Spearman's correlation).

Conclusions: Our study suggests that AD subjects have changes in both dynamics and structure of their cerebral blood flow circulation. In particular, the CBFV reduction is correlated with the severity of the cognitive decline, suggesting that it can influence the cognitive decline in AD subjects.

Sleep disturbances in demented patients

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Background: Sleep is a complex behavioral state whose ultimate functions remain poorly understood. Disturbed sleep can mean different things to different people. Nearly half of older adults report difficulty initiating and maintaining sleep. Comorbid insomnia and other sleep disturbances are common in patients with neurodegenerative disorders, such Alzheimer's disease (AD) and other dementing disorders.

Objective: To descibe sleep disturbances observed in patients suffering from dementia.

Methods: Medline and Google Scholar searches were conducted for relevant articles, chapters, and books published since 1975. Search terms used included sleep disturbances, dementia, Alzheimer's disease, frontotemporal dementia. Publications found through this indexed search were reviewed for further relevant references.

Results: Not all dementia patients develop sleep problems. Individuals suffering from Dementia with Lewy bodies (LDB) and Parkinson' disease with dementia (PDD) patients have the highest frequency of occurrence of any sleep disturbances that are present in 90% of the patients. Insomnia frequency is identical in AD and frontotemporal dementia (FTD) patients, but it is about 2.5 and 1.5 times more frequent in vascular dementia (VaD) and LBD/PDD patients, respectively. Nocturnal and daytime sleep disturbances are common in persons with AD, affecting up to 44% of patients in clinic and community-based samples.

Conclusions: The magnitude and significance of the issue of disordered sleep among elderly individuals in general and particularly widespread among individuals affected by dementia is clearly demonstrated. Their etiology is complex, involving multiple factors, such as neurodegenerative changes in the brain, the patient's environment, medical or psychiatric morbidity, and medications used to treat chronic illnesses and dementia-related behavioral symptoms.

Homicide or attempted homicide in demented patients

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Background: Brain disease may contribute towards criminal behavior. Although the elderly have been studied as victims of violence, geriatric patients can display violent behavior. Some dementia patients have profound behavioral and psychological symptoms which might cause homicide.

Objective: To investigate homicidal behaviors in demented patients.

Methods: The authors searched electronic databases and key journals for original research and review articles on homicide in demented patients using PubMed to search the MEDLINE database, combining the terms homicide, dementia.

Results: There are few reports of homicide or attempted homicide in the elderly population, but Alzheimer's disease (AD), vascular dementia, dementia due to hydrocephalus, and alcoholic dementia have been implicated in aggression, violence, and homicide. It was described a case of a patient with dementia due to B-12 deficiency and syphilis who killed his ex-wife. It was explored the association of delusional misidentification syndrome and attempted homicide in an individual suffering from AD, a 71-year-old man who was admitted to a psychiatric hospital after threatening to shoot his wife. He was essentially unable to link the correct visual experience of his wife to her correct biography. It was suggested that the following antecedent factors increase the risk for homicidal behavior in persons with dementia: history

of previous violence or "other-directed" behaviors; history of alcohol abuse; active paranoia and other psychotic symptoms; psychotic depression; vascular dementia; history of catastrophic reaction; traits such as low frustration tolerance and aggressiveness; military/law enforcement/firefighter history.

Conclusions: Clinical experience suggests that serious assaults by patients suffering from dementia represent an area of increasing interest, but research on elderly offenders has been limited. This is probably linked to the fact that the elderly commit far fewer crimes of every type than do their younger counterparts.

Behavioural variant Fronto-Temporal Dementia: a novel mutation in progranulin gene

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Background: Behavioural variant Fronto-Temporal Dementia (bvFTD) is primarily characterised by behavioural changes and progressive deterioration of personality, with behavioural alterations and impairment of cognitive functions, with relative sparing of memory. Mutations in progranulin gene (GRN) are the most common cause of autosomal dominant familial FTD. We describe a novel mutation in GRN found in two bvFTD patients.

Case reports: a) Male, 69-years-old, disease onset 67-years-old, 18-years education, presented disinhibition, hypersexuality, loss of judge capacity, hypercriticism, episodes of hallucination and sporadic delusions of theft, with spared memory. Familiar history for Alzheimer's disease and FTD. Mild frontal bilateral anterior atrophy and bilateral fronto-temporal hypometabolism, more marked on the right, were evidenced by cerebral CT and FDG-PET. Cerebrospinal fluid (CSF) biomarkers were normal.

b) Male, 68-years-old, disease onset 66-years-old, 10-years education, developed apathy, depression, mood fluctuations, impulsiveness, disinhibition and loss of control, and mild to moderate deficits in praxis and attention. Family history was positive for FTD and behavioral variant FTD. Patients presented fronto-temporal atrophy, ventricular dilatation and extensive right fronto-temporal and thalamus

hypometabolism, less evident in left frontal and insular areas. He refused CSF exam.

Results: Genetic analysis in both patients revealed progranulin plasma levels below the detection threshold (<15ng/ml). We sequenced GRN finding a novel mutation in exon 5: g.1159_1960delGT, leading to a frameshift, which in turn creates a stop codon (p.G148GfsX11). The mutation was not observed in the cDNA isolated from peripheral blood cells, confirming that the aberrant mRNA is degraded through nonsense mediated decay.

Conclusions: FTD patients had a novel mutation in GRN. Although further studies on other family members will be needed to demonstrate the segregation of the genetic defect with the disease, the evidence of very low plasma progranulin levels together with the mRNA nonsense mediated decay strongly support the hypothesis that the variant is pathogenic and cause haploinsufficiency.

Detection of high levels of 14.3.3 brain protein in the cerebrospinal fluid (CSF) of patient with paraneoplastic dementia

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Background: Finding of the 14.3.3 protein in CSF shows a high predictive value for the in vivo diagnosis of Creutzfeldt-Jakob disease (CJD). False-positive results of the 14.3.3 protein assay are found in patients with extensive damage of the nervous system, however.

Case Report: M.R. male 75 years-old. He was recovered in our hospital for subacute cognitive impairment, personality change, agitation and cerebellar ataxia. There was progressive clinical aggravation with also falls. In his past medical history was: 1) severe vascular pathology and cardiopathy; 2) bladder cancer. He has been smoking 20 or more cigarettes every days for a lot of years. We carried out a massive investigation. The most important date were: a) in MRI there was condition like to carcinomatosis; b) in CSF there was the positivity for protein 14,3,3 and the high levels of TAU protein (>1300 pg/ml), inflammatory findings and neoplastic cells like to lung adenocarcinoma. There are in course: neoplastic antibodies in CSF.

Results: Diagnosis was dementia with paraneoplastic encephalomyelitis in lung cancer. The paraneoplastic encephalomyelitis (PEM) is often associated with malignancy, most frequently lung cancer (80%) and can involve multiple areas of the nervous system. Common clinical features are subacute cognitive impairment, in addition to various neurological findings including personality change, depression, anxiety etc, depending on affected brain areas.

Conclusions: CSF examination is useful to differentiate sCJD from PEM. Although protein 14.3.3 in CSF can be detected in both PEM and sCJD, inflammatory findings in the CSF are typically seen only in PEM but not in sCJD. Anti-Hu antibodies are frequently seen in PEM. We expect to find them.

Weight loss predicts progression of Mild Cognitive Impairment to dementia

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Objective: To assess the 1-year weight change (WC) as a predictor of progression from mild cognitive impairment (MCI) to dementia.

Methods: Ninety-three subjects with MCI underwent dual detection of body weight after one year from each other and thereafter they were followed-up for dementia surveillance. The 1-year WC was categorized as weight loss, weight gain and no change.

Results: Out of 93 subjects (mean age 74.1 ± 7.1 years; female 60%), 35 lost weight (median 3 Kg; range 1-6), 27 gained weight (median 2 Kg; range 1-4) and 31 had a body weight unchanged. Over a mean follow-up of 46.7 ± 20.1 months, dementia occurred in 23 subjects, including 13 cases of Alzheimer's disease. Cumulative incidence (CuI) of dementia was significantly higher among MCI subjects who lost weight (CuI = 37.8%) as compared to those whose weight has increased (1 CuI = 1.5%) or didn't change (CuI = 20.0%) (Pearson's Chi-Square Test $p = 0.045$). In multivariate Cox proportional hazard regression models (adjusted for age, sex, education, Mini-Mental State Examination, MCI subtype, APOE genotype, Geriatric Depression Scale, hypertension, diabetes, hypercolesterolemia, smoke, atrial fibrillation, cerebrovascular disease, cardiovascular disease, Age Related White Matter Change

score) weight loss was associated to a 5.6 (95% CI 1.41-22.68) increased risk of dementia.

Conclusions: To our knowledge, this is the first prospective clinical study that demonstrates that weight loss increases the risk of progression to dementia in subjects with MCI.

Reason for weight loss in cognitive decline remain unclear. A variety of social, medical and environmental factors could lead to healthy eating behaviours withdrawal during cognitive decline. Disruption of energy-regulating mechanisms has been proposed as a biological mechanism for weight loss in AD. The surveillance of weight change may help improving prognostic accuracy of MCI in clinical practice.

Identification of heterozygous mutations in the NPC1 and NPC2 genes associated to early onset degenerative dementia in adults

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Background: Niemann-Pick type C disease is a lipid storage disorder caused by mutations in NPC1 and NPC2 genes. The broad clinical presentation mimicking other neurodegenerative diseases makes hard the diagnosis in adults. Although NPC is an autosomal recessive disorder, clinical reports and studies on animal models suggest that heterozygous mutations could be pathogenic.

Methods: We carried out a retrospective study on 50 unrelated subjects affected by early onset degenerative dementia to estimate the NPC1 and NPC2 genes mutations frequency. We excluded mutations in causative genes for FTLD and AD by preliminary genetic screening. Sequencing of NPC1 and NPC2 genes were performed and heterozygous mutations in NPC1 and NPC2 genes were found in 4 out of 50 patients.

Results: Two known NPC1 gene heterozygous mutations in exon six of two different patients were

detected. Patient 1 carried a heterozygous deletion with a premature stop codon (F284LfsX26) and the clinical diagnosis was progressive supranuclear palsy. Patient 2 beared a missense heterozygous mutation (N222S) associated to the known variant rs66620415 in intron 12 and she showed a corticobasal syndrome. Filipin staining on skin fibroblasts revealed a pattern of the variant biochemical subtype in patient carrying the deletion. For both patients, MLPA and analysis of total cellular RNA excluded deletion, duplication and possible discrepancy between cDNA and genomic DNA. One known NPC2 gene heterozygous mutation in exon 2 (V30M) was detected in patient 3. One known NPC2 gene heterozygous variant in intron 4 (rs 140130028) with high probability of being pathogenic, since it is a splice donor variant, was detected in patient 4.

Conclusions: Both latters patients were clinically diagnosed as affected by corticobasal syndrome. We speculated that the heterozygous mutations in NPC1 and NPC2 gene could be pathogenic or alternatively a risk factor in our cohort, explaining the late onset and the slow progression of disease.

Pain and dementia: beyond the cognitive syndrome

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Background: Pain in person with dementia it's a topic of great interest in human clinical studies and in focus of significant research. It 's an event difficult to understand in a "difficult disease" that raises many questions.

Objective: To answer three questions about the relationship between pain and dementia. Is in dementia pain? Are persons affected by the disease preserved from this experience? Do persons with dementia suffer from the loss of the mind?

Methods: We performed a literature review and at the same time we made a careful reflection on our clinical experience on the topic.

Results: We found that somatosensory cortex is relatively preserved in dementia and therefore the threshold of pain does not seem to be significantly different compared to elderly subjects without cognitive impairment. The involvement of the hippocampus and amygdala can impair cognitive and affective-emotional component of the event painful. The person with dementia does not remember the pain and it is able to draw on previous experience to give the right meaning. The person with dementia lives alone in this pain and than each event painful becomes a threatening and distressing. The pain of the loss of patient's mind and of his identity, perceived, but not always cognitively identified, produce sadness and despair. Anxiety and depresssione with the progression of the disease often become behavioral disorders.

Conclusions: Pain in affected person with dementia is a complex event difficult to understand. It 's a feeling without history and without memory; it 's despair and fear, it 's an experience that the patient is no longer able to communicate adequately. This evidence has enabled us to create in our clinical practice a new and interesting approach in the management of the patient aimed at improving his quality of life.

Network-Based Cognitive Stimulation can Regulate Functional Connectivity in Mild Cognitive Impairment

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Background: Limited evidence supports the efficacy of cognitive interventions in Alzheimer's disease (AD). The main reason behind this global insuccess lies in the lack of a theoretical rationale by which engaging in behavioural tasks would trigger specific changes in cerebral parameters. Here we propose a candidate mechanism whose conceptualisation is based on the ingravescent loss of functional connectivity (FC) observed in AD within the brain Default-Mode Network (DMN), a circuit activated in the absence of explicit cognitive tasks.

Objective: We hypothesised that tasks with multiple cognitive requests would trigger the concurrent activity of distant areas and would, if administered repeatedly, regulate area-to-area FC. This hypothesis was tailored on the DMN, and was tested in samples of healthy ageing participants (with attenuated, yet similar down-regulations in DMN activity) and patients with mild cognitive impairment (MCI) probably due to AD-neurodegeneration.

Methods: DMN-based computerised exercises were designed, tapping lexical-semantic, mnestic and

prefrontal function. Participants enrolled in the experimental groups (19 healthy elderly adults and 15 MCI patients) completed 20 intensive sessions in the laboratory. Fourteen healthy elderly and 10 MCI participants were additionally recruited in the control condition based on routine everyday activities. Resting-state fMRI recordings were acquired at baseline and after the completion of the study. FC of a posterior-cingulate seed was used as DMN proxy. One-sample t tests were run to identify baseline-to-retest FC changes.

Results: Up-regulation of seed-based FC emerged in the experimental groups. This was seen in parietal and pericentral regions in the healthy subgroup, and in midline prefrontal-anterolimbic areas in the MCI subgroup. No major change was observed in control participants.

Both patterns of increased FC featured up-regulation of important DMN computational pathways.

Conclusions: Cognitive stimulation operationalised as a function of a paradigm of DMN-based FC is beneficial in suspected early-stage AD and in healthy ageing.

The Impact of the Apolipoprotein E e4 Allele on the Default-Mode Network in Mild Cognitive Impairment

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Background: The Apolipoprotein E (ApoE) e4 allele is a well-established risk factor for sporadic Alzheimer's disease (AD). In healthy adulthood the presence of this isoform influences functional connectivity within the brain Default-Mode Netowrk (DMN), a circuit normally active when individuals are not engaging in any overt cognitive task. Since the DMN is gradually disrupted by AD, it is not known whether the e4 allele still influences this network after the onset of early symptoms of neurodegeneration or, alternatively, its effect is overwhelmed by the detrimental impact of the pathology.

Objective: We compared the DMN of e4 carriers and non-carriers showing early signs of AD-associated degeneration and being diagnosed with Mild Cognitive Impairment (MCI).

Methods: All MCI patients with a known e4e3 genotype (12 individuals) were recruited from a large cohort together with 12 e3e3 MCI patients matched

for age, years of education, intracranial volume, global proportion of grey and white matter, cognitive abilities, and profile of cognitive decline. Resting-state fMRI recordings were obtained from all participants. A spherical region of interest was drawn in the posterior cingulate cortex, and seed-based functional connectivity was calculated to estimate individual DMN maps. Two-sample t tests were run to compare the two genetic profiles.

Results: E4 carriers had reduced connectivity between the seeds and mediotemporal areas, and increased connectivity between the seeds and frontal and temporo-insular clusters.

E4-dependent down-regulation was observed in mediotemporal-to-limbic connectivity, a computational pathway which is extremely susceptible to AD. The frontal up-regulation can be interpreted as a compensatory network reorganisation, while the the temporo-insular involvement might represent a pathological interpolation with the salience network, which is normally anticorrelated with the DMN.

Conclusions: The presence of the ApoE e4 isoform is associated with disruption of circuital architecture even after the onset of suspected AD-type neurodegeneration.

Can the baseline CSF-AD biomarkers predict the future clinical changes?

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Background: Low amyloid ß42 (Aß42) and high total tau and phosphorylated tau (p-tau) concentrations in the cerebrospinal fluid (CSF) are biomarkers of Alzheimer's disease (AD), reflecting brain deposition of amyloid plaques and tangles. The baseline CSF biomarkers, particularly the Aß42 /p-tau181 ratio, are related to brain atrophy and may predict the progression of the disease.

Objective: To characterize the shape of the trajectories of MMSE in AD and MCI patients as a function of cerebrospinal fluid biomarkers over a follow-up period.

Methods: At baseline, CSF biomarkers were evaluated in 30 AD pts (18F and 12M, mean age 71,2 yrs) and 6 MCI pts (4F and 2M, mean age 72,0 yrs) meeting the new NIAA criteria (Albert,2011) for probable AD and MCI. Each patient had a planned clinical

interview, neuropsychological assessment, laboratory exams, MRI and PET-FDG scan. The longitudinal MMSE changes were considered for each pts in the clinical follow-up (from 0 to 36 months). Considering a cut-off of 6.7 for Aß42/p-tau181 ratio, we identified two groups of patients: group 1 (9AD and 4MCI) with>6.7 and group 2 (11AD,1MCI) with<6.7 of ratio.

Results: CSF biomarker concentrations in AD and MCI pts were: Aß1-42 317.3 ± 149.4 and $638,5 \pm 223,5$; Tau $547,7 \pm 217.4$ and $330,5 \pm 189,4$; p-Tau 181 69.0 ± 52.5 and $55,1 \pm 30,9$, respectively. Considering the follow-up period of 36 months, we found a different worsening progression of the MMSE between group 1 (T0 mean MMSE=23,2; T1 mean MMSE=23; T2 mean MMSE=22,2; T3 mean MMSE=20.8; T4 mean MMSE=24; T5 mean MMSE=21,3; T6 mean MMSE=23) and group 2 (T0 mean MMSE=18.3; T1 mean MMSE=18,3; T2 mean MMSE=18,5; T3 mean MMSE=18,6; T4 mean MMSE=15,1; T5 mean MMSE=10,1; T6 mean MMSE=8,6).

Conclusions: The evaluation of CSF-AD biomarkers can help to make a correct diagnosis and to predict clinical progression over time.

Targeting ß-amyloid by the A2V Aß variant: a novel disease-modifying strategy for the treatment of Alzheimer's disease

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Background: A variant of amyloid ß (Aß) carrying an A-to-V substitution at position 2 (A2V) has a dominant-negative effect on Aß amyloidogenesis (Di Fede G, 2009).

Objective: The aim of the study is to test the efficacy of A2V-mutant peptides in preventing amyloidogenesis in nematode models expressing human Aß and in a mouse model of Alzheimer's disease (AD) (APPswe/PS1dE9 line). Distinct from previous approaches based on theoretical grounds, our strategy stems from the clinical finding that a natural Aß variant protects human heterozygous carriers from AD.

Methods: To translate these findings into therapeutic purposes, we designed a short peptide, homologous to residues 1-6 of A2V Aß (Aß6A2V), which retains in vitro the anti-amyloidogenic properties of the parent full-length mutated Aß. The D-isomer [Aß6A2V(D)], predicted to be more resistant to degradation by endogenous proteases, resulted even more effective than the L-isomer in preventing the aggregation of wt full-length Aß. To improve its translocation across the blood brain barrier and cell membranes, the D-isomer of the six-mer peptide [Aß6A2V(D)] was linked to all-D-retroinverso TAT sequence [Aß6A2VTAT(D)].

Results: Preliminary results by in vitro and in vivo studies showed that Aß6A2VTAT(D) hinders: assembly of wt Aß into amyloid fibrils in vitro; Aß-induced toxicity on cultured SHSY-5Y cells; synaptopathy caused by wt Aß in hippocampal neurons; occurrence of paralysis and Aß oligomerization in a C. elegans model expressing wt Aß in muscles; cognitive deterioration, Aß aggregation and amyloid deposition in the brain of the APPswe/PS1dE9 model.

Conclusions: These results indicate that the "A2V Aß-based strategy" is a promising approach to the prevention and treatment of AD.

D2 agonist administration restores altered cortical plasticity in Alzheimer's disease patients

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Background: In animal models of Alzheimer's disease (AD), amyloid beta fragments interfere with cortical plasticity mechanisms such as long-term potentiation (LTP) and long-term depression (LTD). Recent evidence showed that in AD patients LTP-like cortical plasticity is impaired, while LTD is preserved. Despite its major role in synaptic plasticity mechanisms, the dopamine (DA) involvement in controlling cortical plasticity mechanisms in AD is still debated.

Objective: Here we aimed at investigating whether a D2 agonist administration could modulate cortical plasticity in AD patients, as measured by standard theta burst stimulation (TBS) protocols applied over the primary motor cortex (M1).

Methods: Three groups of mild AD patients were tested before and after four weeks of treatment with

rotigotine, rivastigmine or placebo. Each patient was evaluated for plasticity induction of LTP/LTD-like effects using respectively intermittent TBS (iTBS) or continuous TBS (cTBS). Central cholinergic activity was also evaluated by means of the short latency afferent inhibition (SLAI) protocol. Neuropsychological evaluations were performed to assess memory, executive functions and visuo-spatial abilities.

Results: At baseline AD patients showed the previously described pattern of impaired LTP-like cortical plasticity. After two weeks of D2 agonist administration we observed a remarkable change in the iTBS protocol effects, revealing that LTP-like plasticity was strikingly enhanced. No effects were seen in the rivastigmine and in the placebo group. LTD-like cortical plasticity was not modulated in any condition. Cholinergic activity was slightly increased by both rotigotine and rivastigmine groups. Neuropsychological testing showed that increased levels of LTP-like cortical plasticity in the rotigotine groups were paralleled by an improvement in the MMSE and in the executive functions.

Conclusions: Our findings highlight a role for dopamine in the pathophysiology of AD suggesting that a dysfunction of D2-like receptors is involved in mechanisms of altered cortical plasticity and providing novel implications for new therapies based on dopaminergic stimulation.

Synaptic plasticity in Sporadic Early-Onset and Late-Onset Alzheimer's Disease Patients. A TMS study

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Background: Early Onset Alzheimer's disease (EOAD) accounts for less than 10% of all AD cases. EOAD and Late-Onset ALzheimer's disease (LOAD) share the same pathological features as neurofibrillary tangles and amyolid plaques, and are considered the same disorder affecting people at different ages, before or under 65 years. Early pathological finding showed that sporadic EOAD have greater pathological burden, due to the great synapse loss that in turn would lead to a faster cognitive decline. Whetehr the different pathological burden could influence also the mechanism of cortical plasticity is still unknown.

Objective: To verify this hypothesis we tested 12 EOAD patients for plasticity induction of LTP-LTD

like effects by means of theta burst stimulation. Central cholinergic function was also evaluated. A control group of 45 LOAD patients was enrolled.

Results: Both EOAD andf LOAD groups showed impaired LTP-like cortical plasticity, although EOAD patients showed greater impairment. Cholinergic activity was impaired in both groups, but LOAD showed more impairment.

Conclusions: These data indicate that the different pathological burden could be the result of greatly impaired mechanisms of sinaptic plasticity, leading to pathological neuronal remodeling and for rapidly progressive evolution of cognitive decline.

CSF levels of tau protein are related to detrimental SLAI and LTP-like cortical plasticity in AD patients

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Background: In animal models of Alzheimer's disease (AD), Beta-amyloid and tau proteins interfere with synaptic transmission. Recently, we showed that AD patients are characterized by an impairment of Long Term Potentiation (LTP)-like cortical plasticity. Furthermore AD patients have a weakened Short Latency Afferent Inhibition (SLAI) that is a neurophysiological measure known to be under cholinergic control, reflecting the cholinergic dysfunction occurring in the pathology. Cerebrospinal Fluid (CSF) sampling is an useful tool in clinical practice in detecting AD biological markers and predicting disease progression.

Objective: Aim of this study is to investigate the relation between CSF values of Beta-amyloid, T- tau and p-tau and cortical plasticity in a sample of AD patients. All patients underwent lumbar puncture for CSF sampling for clinical testing. By means of repetitive transcranial magnetic stimulation we tested in 55 AD patients the LTP/LTD-like effects induced by the intermittent TBS (iTBS) and continuous TBS (cTBS) protocols applied over the primary motor cortex, and the efficacy of SLAI circuits. Each patient was evaluated for iTBS and cTBS plasticity induction in two different sessions. K-means cluster analysis including the 3 CSF biomarkers was carried out.

Results: The three resulting clusters differed by the value of T-tau: cluster 1 (low levels of T-tau = 250); cluster 2 (intermediate levels of T-tau = 750); cluster 3 (high levels of T-tau = 1150). There was no difference between clusters regarding age, gender, years of education, or APOE genotype. We found that cluster 2 showed more impaired LTP-like cortical plasticity and SLAI efficiency, while cluster 1 and cluster 3 have surprisingly the same pathological trend for both measures. Moreover cluster 2 showed more preserved frontal functions related to the other clusters.

Conclusions: Our results shed light on tau protein role in the physiopathology of AD, showing a similar U shaped-curve related to the level of LTP impairment and SLAI deficiency.

Robust MRI Multimodal Investigation and Whole Brain Statistics on a cohort of patients affected by Amnestic Mild Cognitive Impairment

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Background: Translational research necessitates shared definitions, especially in multidimensional fields like neurodegenerative diseases. While magnetic resonance imaging (MRI) should provide valid biomarkers, the heterogeneity of patient's inclusion criteria, acquisition, processing and statistical methods, and the lack of methodological details, don't comply with the prescriptions of reproducible research.

Objective: In our study, we compared a cohort of 20 patients affected by amnestic mild cognitive impairment (MCI) with a group of 20 healthy volunteers through whole-brain neuroimaging approach, focusing on robustness and reproducibility.

Methods: Robustness and reproducibility where assessed by: a) age and sex matching; b) a robust intra-subject inter-modality and inter-subjects registration method; c) a last generation 3T Scanner (GE MR750); d) a multimodal approach, including deformation fields morphometry (DFM) of gray matter (GM) and white matter (WM), relaxometry based abnormal iron content measurement GM and WM, diffusion tensor based WM investigation; e) the use of a study population template; f) a whole brain statistical analysis performed by nonparametric permutation tests and threshold free cluster analysis; g) results reported at $p < 0.05$ family wise error corrected level.

Results: The DFM investigation revealed atrophic GM regions in MCI patients in the left mediotemporal lobe (especially amygdala) and in the left posterior insula. Diffusion tensor investigation revealed whole brain WM distributed areas of increased mean diffusivity and radial diffusivity in the MCI group, especially in the dorsal stream regions and in longitudinal inferior and superior fasciculus tracts. No significant differences were found in fractional anisotropy or relaxometry data.

Conclusions: We collected in a single study the complementary information allowed by the MRI state of art through a multimodal approach, whose reliability was granted by the use of robust registration procedures, accurate enrollment and non-parametrical statistical analysis. Our results confirmed previous findings with a statistical significance stated at the family wise error corrected level.

Cognitive frontal dysfunction and mood disorder are early clinical manifestations of idiopathic basal ganglia calcification

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Background: Basal ganglia calcification is an heterogeneous condition characterised by mineral deposits in the basal ganglia, dentate nuclei, talami and white matter. It can be caused by phosphocalcic methabolic diseases (eg hypoparathyroidism, pseudo-hypoparathyroidism, hyperparathyroidism), mitochondrial diseases, connective tissue disorders, numerous hereditary and non hereditary congenital syndromes. Idiopathic basal ganglia calcification (IBGC) is a rare genetically-determined condition which should be suspected in presence of diffuse and widespread brain calcifications, when all secondary causes have been ruled out. The genetic substrate is heterogeneous, sometimes an autosomic-dominant pattern of transmission has been identified.

Case Report: A 61 year-old woman came to our attention with a four year history of depressed and anxious mood. Her past medical history was significant for arterial hypertension, diabetes and high cholesterol serum levels. Her family history was unremarkable. She started antidepressive therapy

without clinical benefit. She also showed difficulty performing everyday household tasks for lack of pianification and organisation. A neuropsychological evaluation showed marked cognitive deficits involving attention, executive functions and working memory, visual-spatial and perception deficits, and ideo-motor and constructive apraxia. In the following 4 years the patient progressively developed a mildly unstable gait and slurred speech. Neurological examination revealed a slight wide-based gait and dysarthric speech, dishinibition and perseveration; verbal fluency was also reduced; no sensory-motor deficits or extrapiramidal signs were detected. MMSE: 23/30.

A CT scan showed marked and symmetrical calcifications involving the basal ganglia and dentate nuclei. Extensive biochemical screening ruled out abnormalities of phosphocalcic methabolism.

A diagnosis of probable idiopathic basal ganglia calcification was made.

Conclusions: Our clinical case underlines how precocious signs and symptoms of basal ganglia calcification can be subtle and aspecific, solely involving cognitive and psychiatric functions. In the early stage diagnosis can be therefore challenging in the absenceof motor or cerebellar signs and of a positive family history.

Neurosyphilis in differential diagnosis of subacute dementia: report of a case

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Background: Neurosyphilis is any involvement of the central nervous system (CNS) by syphilitic infection, resulting from invasion of T. pallidum. Rates of primary and secondary syphilis plummeted with advent of penicillin, becoming again to climb from 2000. We describe here the case of a 48-year-old Romanian man, with a remote history unremarkable, which was admitted to our Emergency Room because of an episode of spatial disorientation, occurred while he was at work as a lorry driver. About 6 months before he had started to present apathy, loss of appetite and memory impairment. The neurological examination appeared normal except for slowed thinking, dysphoria and frontal release signs. In relation to subacute nature of cognitive impairment, degenerative, inflammatory-dysimmune, infectious, neoplastic-paraneoplastic and toxic-metabolic hypotheses could

have been formulated. During hospitalization our patient presented delirious ideation, treated with antipsychotic therapy. Blood tests were normal except for TPHA>1: 5120 and RPR 1: 512. The lumbar puncture showed increased total protein (104 mg/dL) and blood cells (16/?L), a VDRL test suggestive of intrathecal synthesis. Gadolinium-enhanced brain MRI revealed some focal T2-hyperintense lesions in periventricular and bilateral subcortical white matter, without enhancement, mass effect or peripheral oedema, compatible with vasculitic parenchymal abnormalities of syphilitic origin. Neuropsychological assessment pointed out a MMSE score of 26/30, with deficits in executive, visuo-spatial and mnesic functions. Penicillin G 24,000,000 iu per day by continuous infusion for 14 days was administered, preceded by 2-days twice-daily Amoxicillin 1 g, in order to avoid Jarish-Herxheimer reaction. At the following hospital admission, performed 6 months later, a normalization of cerebrospinal fluid (CSF) chemical examination and optimization in cognitive profile (MMSE 29/30) were found.

Conclusions: We would like to emphasize the importance of considering neurosyphilis in differential diagnosis of subacute dementia, being a disease which, as long as recognized early, can be treated with good prognosis.

A case of atypical dementia carrying the PSEN2 Arg62Hys mutation

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Background: The Presenilin 2 (PSEN2) missense mutation Arg62His has been described in sporadic Alzheimer's disease (AD) cases, but also in healthy controls, and in a fronto-temporal dementia patient. Thus, pathogenetic nature of this mutation is unclear.

Case report: We describe the case of two sisters examined at our Neurology Unit with Subjective Memory Impairment. Both sisters ,60 and 56 years old at the time of first visit, underwent a complete clinical assessment including medical history, neurological examination, detailed neuropsychological battery, morphological and functional neuroimaging (MRI and FDG-PET). The oldest sister presented normal neurological examination and normal MRI.

Neuropsychological tests showed a slight constructive apraxia and mild impairment of executive function (MMSE 28/30). Moderate depression was also present. Bilateral parietal and right temporo-mesial hypometabolism were evidenced at FDG-PET. The 56 years-old sister presented normal cognitive performance on neuropsychological tests, however euphoric behaviour and slight disinihibition were higlighted. FDG-PET showed abnormal pattern typical for prodromal AD, with hypometabolism in bilateral parietal lobes, posterior cinguli, hyppocampi, and slight in frontal lobes. Genetic testing was performed and showed that the oldest sister carried the PSEN2 Arg62His mutation, while the other sister was negative for mutation on AD genes. Both resulted apolipoprotein E e3/e3 carriers. Clinical follow-up of both sisters were performed. After 4 years the sister carrying PSEN2 mutation presented amelioration of cognitive performance but began to present mild behavioural alteration, as anxiety, sleep difficulties and social disinhibition. The other showed a worsening of executive function, (Frontal Battery 13/18, v.*n* > 14,11) and persistence of behavioral disturbances.

Conclusions: The pathogenetic role of PSEN2 Arg62His mutation has not been demonstrated in our case. The mutation is probably combined with other unknown genetic factors thus contributing to neurodegeneration, and specifically in our case, with predominant frontal structures involvement.

Genetic analysis suggests lysosomal and immune system involvement in frontotemporal dementia

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Background: Frontotemporal dementia (FTD) is a rare and complex neurodegenerative disease characterized by heterogeneous clinical and pathological signatures, and by considerable genetic variability. Currently, three genes – MAPT, GRN, and C9orf72 – are mainly associated with FTD.

Objectives: In this study we aimed to identify novel risk loci associated with the disease by performing a 2-stage GWAS on clinical FTD analyzing a total of 3,526 FTD cases and 12,538 controls with European ancestry.

Methods: We performed separate association analyses for each FTD subtype (bvFTD, SD, PNFA, and FTD-MND) and a final meta-analysis of the entire cohort during the discovery phase. We then assessed the significant loci (*p*-value < 10-5) in an independent sample series during the replication phase and ultimately performed joint and brain e/mQTL (expression/methylation quantitative trait loci) analyses.

Results: We identified two novel loci strongly suggestive of association with FTD. Combined analyses of discovery and replication phases showed genome-wide significant association for rs9268877 (p-value=1.05x10-8, OR=1.204, effect allele A), rs9268856 (p-value=5.51x10-9, OR=0.809, effect allele A) and rs1980493 (p-value=1.57x10-8, OR=1.290, effect allele T) at 6p21.3, whilst joint p-values showed suggestive association for rs302668 (p-value=2.44X10-7, OR=1.229, effect allele T) at 11q14. Expression and methylation quantitative trait loci (e/mQTL) data suggested that risk at these loci may be associated with in-cis changes of expression and methylation levels.

Conclusions: Our current study implies that FTD pathogenesis involves lysosomal and autophagy pathways (link to 11q14, encompassing RAB38/CTSC), and immune system processes (link to 6p21.3, encompassing the HLA locus).

Diffusion tensor MRI contributes to the multimodal diagnosis of primary progressive aphasia

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Objectives: To test the ability of a multiparametric MRI-based approach, including cortical thickness and white matter (WM) tract damage measures, to discriminate in vivo the two major variants of primary progressive aphasia (PPA).

Methods: T1-weighted and diffusion tensor (DT) MRI scans were obtained from 13 patients with the nonfluent PPA variant (nfvPPA), 13 patients with the semantic PPA variant (svPPA), and 23 healthy controls. Cortical thickness and DT-MRI measures from the long-associative and interhemispheric WM tracts were obtained. A Random Forest approach was used to identify the restricted set of image features correlated with each clinical syndrome at an individual patient level.

Results: NfvPPA patients showed cortical thinning of the left frontal lobe, particularly inferior and middle frontal gyri, precentral gyrus, and insula. A similar but less extensive pattern of loss was seen in the right hemisphere. NfvPPA patients had altered DT-MRI measures of the superior longitudinal fasciculus (SLF) and cingulum bilaterally, left inferior longitudinal fasciculus (ILF), and corpus callosum (CC). Patients with svPPA had cortical thinning of the left temporal lobe, particularly temporal pole, entorhinal cortex, and parahippocampal, fusiform, and temporal gyri, right temporal gyri, and insula bilaterally. SvPPA patients showed altered DT-MRI measures of the ILF and uncinate fasciculus bilaterally, left SLF, left cingulum, and CC. RF analysis showed that the best diagnostic markers to differentiate the two PPA variants at individual patient level were the thickness of the left temporal pole and DT-MRI measures of the left uncinate, followed by the thickness of the left inferior frontal gyrus and DT-MRI measures of the left ILF.

Conclusions: A combination of structural and DT-MRI provides a quantitative method to distinguish PPA patients. These findings emphasize the additional role of WM neuroimaging for in vivo discrimination between PPA variants at an individual patient level.

Implementation of an Integrated Care Pathway for dementia in the clinical practice: rationale, design and methodology. The REMIND Study

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Background: An Integrated Care Pathway (ICP) for dementia was approved by Milan Health Authority (HA) in Italy.

Objectives: The REMIND study aims: (i) to implement the ICP shared with GPs, memory clinics (HMCs), and community-based specialist services (CSSs); (ii) to evaluate the ICP effectiveness in improving diagnostic skills of GPs in early identification of dementia cases and appropriateness of patients' referral to specialists.

Methods: A 3-year population-based prospective cohort study in the districts of Milan HA. Expected population: 3000-4000 patients with suspected dementia syndrome. Intervention: implementation of the ICP including education of GPs, administration of the MMSE by GPs and development of a web based

database to enhance information exchange between GPs and specialists. Outcomes: proportion of patients receiving = 2 GP visits/year and a consistent review of interventions, adhering to the ICP recommendations.

Results: 336 GPs, 13 HMCs, and 18 CSSs are involved. The network agreed a consensus process in the application of the ICP along with timetables. The educational prescriptions appeared acceptable to GPs. From May 2013 through January 2014, 4,218 patients (2,796 women and 1,422 men, 31 to 96 years old) were included in the study and followed up. 77% of all patients had one or more morbidities, and 91% assumed one or more drugs. Memory impairment was reported in 62% of all patients, and multiple cognitive impairment including memory in 32%. Agreement between GPs and specialists on MMSE score was observed in more than 60% of the cases. 992 (24%) of 4,218 patients were referred to specialists and 90% of them are now cared by specialists.

Conclusions: Preliminary results show that GPs carefully applied the ICP, properly administered the MMSE and improved the appropriateness of patients' referral to specialists. Updated results will be presented at the conference.

Parkinson Dementia and Dementia with Lewy Bodies: overlapping or distinct pathologies?

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Background: Parkinson disease (PD) and Dementia with Lewy Bodies (DLB) are neurodegenerative synucleinopathies with clinical overlapping features. Dementia is increasingly recognized as a common feature of Parkinson disease itself (Parkinson Dementia, PDD). Whether PDD and DLB are distinct disorders, or whether they represent different presentations of the same disease, is an area of debate.

Objective: To examine distinctive functionally affected brain structures in PD, DLB and PDD by advanced neuroimaging MRI techniques.

Methods: Ten patients with PD, 10 patients with DLB, 4 patients with PDD and 10 age-matched healthy controls (HC) were studied to evaluate changes in resting-state functional MRI, considering amplitude fractional flow frequency fluctuations (fALFF)

and Regional Homogeneity (ReHo) (four-groups ANOVA, $p < 0.01$ uncorrected, FWE 0.05 cluster level).

Results: When compared to HC and when considering fALFF, PD patients showed greater involvement of frontal regions (left superior and right medial/middle frontal gyrus) as well as right angular gyrus; a decreased connectivity in posterior cingulate gyrus was evident in DLB group; PDD patients exhibited significantly reduced connectivity in left medial frontal gyrus and in right parietal lobe (precuneus). The direct comparison between PD and DLB patients demonstrated a functional impairment of frontal lobe (right superior frontal gyrus) in the first group and of occipital lobe (cuneus) in the latter. PDD patients showed the same pattern of PD patients, but with a greater involvement of both frontal and parietal areas. ReHo confirmed a similar pattern of abnormalities between groups.

Conclusions: Different brain areas are specifically involved in DLB and PDD. More anterior involvement characterized PD, and PDD showed the same pattern of damage of PD, even more pronounced. Conversely, predominant functional involvement of posterior areas is the signature of DLB. These preliminary results seem to suggest that the overlapping clinical spectrum in DLB and PDD is determined by specific and different pathogenic pathways.

Cortical M1 Activation In Alien Hand of Corticobasal Syndrome

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Background: Alien hand movement (AHM) indicates unintentional hand movements interfering with normal tasks. It appears, in different forms, following lesions of frontal or parietal cortex or corpus callosum and in 30% of Corticobasal Syndrome (CBS) patients.

Objectives: Our aim was to highlight possible neural correlates of AHM in CBS with cortical atrophy.

Methods: Whole brain functional Magnetic Resonance Imaging (fMRI) activity was studied in one CBS patient during right AHM vs. absence of movements, in three CBS patients during left AHM vs. absence of movement and vs. willed movements. In a further comparison fMRI activity was studied in one patient affected by a psycogenic (distractible/factitous) right hand tremor.

Results: During AHM, fMRI showed a statistically significant ($p<0.01$) activation of the contralateral primary motor area (M1), no reliable changes in other cortical or subcortical areas in all four CBS patients. Voluntary movements of the AHM affected arm elicited activity also in the premotor cortex, primary sensory cortex, supplementary motor area and cerebellum, same as voluntary movements of unaffected side. The same pattern of activities was also observed during the psychogenic 'pseudo-involuntary' tremor, which could be induced in response to a stimulus. A secondary finding was that, in the four patients, willed movements induced higher and wider activation of M1 area, suggesting disinhibition or hyperactivity of the area. The intensity of M1 activation during AHM was lower than during willed movement.

Conclusions: Our findings evidence that AHM is characterised by isolated activation of contralateral M1, thus showing that activation of a cortical area may be independent of conscious will. The findings show also that AHM is a disconnection symptom, characterized by the involvement of an isolated cortical area and no involvement of a network. The finding suggests that consciousness of willed action, or consciousness of a stimulus which drives an action, requires the recruitment of a network, while the recruitment of isolated cortical areas can be independent of volition, thus probably independent of consciousness.

Analysis of angiogenin gene in patients with Alzheimer's Disease

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Background: Despite enormous investigative efforts, the pathological basis for Alzheimer's disease (AD) remains unclear. It has been suggested that Alzheimer's disease (AD) is mediated by pathological angiogenesis. Angiogenin is a angiogenic ribonuclease whose activity is related to its ability in regulating ribosomal RNA (rRNA) transcription [Cronin et al., 2006]. The human ANG gene (Entrez Gene ID 283) is located on chromosome 14q11.1-q11.2, and it codes for a protein of 147 amino acids. Mutations in the coding region of ANG have been detected in Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease (PD) [Van Es et al., 2011]. A decreased level of ANG protein was found in AD patients serum [Kim et al., 2012].

Objectives: to investigate the role of the ANG gene in AD.

Methods: Genetic analysis of ANG gene was done in a cohort of 509 AD patients and 417 healthy volunteers over 65 years of age using Sanger sequencing of the coding regions of ANG gene.

Results: Genetic analysis showed the presence of a nonsynonymous mutation in heterozygosis in position g.2162012 causing the change of a lysine to a Stop codon (K73X). This new mutation was found in two AD patients (0.48% of the whole AD cohort): patient 1 is a man, 69 years old, with family history of dementia; patient 2 is a woman, 74 years old, with no familiarity for AD or dementia. No mutations were found in control subjects.

Conclusions: This study suggests that ANG gene mutations may be associated with rare cases of Alzheimer's disease. Interestingly, the K73X mutation may be specific for AD, since it has not been found in the numerous genetic studies on ALS and PD so far reported.

Brain functional connectomics in early Parkinson's disease

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Background: The study of connectomics in Parkinson's disease (PD) may shade light on the pathophysiology of the disease.

Objective: To explore the integrity of the functional brain connectome in patients at different stages of PD.

Methods: Graph theoretical analysis was applied to resting state fMRI data from 212 PD patients (100 with Hoehn and Yahr score [HY]=1-1.5, 54 with HY=2-2.5, 44 with HY=3-3.5, 14 with HY=4-5) and 46 matched healthy controls (HC). Functional

connectivity between 90 cortical and subcortical brain regions was estimated using bivariate correlation analysis and thresholded to construct a set of undirected graphs. Measures of global (mean degree, clustering coefficient, global efficiency, characteristic path length) and regional (nodal degree, betweeness centrality) network properties were obtained. Correlations between UPDRS III score and network metrics were tested.

Results: Functional brain networks in PD and HC showed the same hub organization, with differences only in the right cingulum, left postcentral gyrus, precuneus bilaterally (hubs only in patients), and right fusiform gyrus (hub only in HC). However, all global network metrics were altered in PD patients. At a regional level, PD patients showed nodal degree reduction and betweeness centrality increase. Such local abnormalities were relatively focal in patients with HY=1-1.5, involving globus pallidus, putamen, supplementary motor area, cingulum, and gyrus rectus bilaterally, spreading to the frontal, temporal, parietal and occipital cortical regions in the more advanced disease stages. In PD, network metrics showed significant correlations with UPDRS III.

Conclusions: In PD, functional brain networks are characterized by an imbalanced structure, with a loss of efficiency in information exchange between both close and distant brain areas. Abnormal functional network connectivity occurs early in the disease and is an important factor contributing to PD motor deficits.

Corpus callosum damage and motor function in Parkinson's disease

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Background: In Parkinson's disease (PD), corpus callosum (CC) diffusion tensor (DT) MRI metrics may be valuable markers to asses disease evolution and motor function worsening.

Objectives: To investigate CC microstructural damage and its relationship with motor impairment in patients with PD at different disease stages.

Methods: We enrolled 173 PD patients (98 with Hoehn and Yahr score [HY]=1-1.5, 37 with HY=2-2.5, 29 with HY=3-3.5, 9 with HY=4-5) and 39 matched healthy controls (HC). Diffusion tensor (DT) MRI tractography was performed to obtain the CC and its main three partitions: CC-genu, CC-body, and CC-splenium. Mean tract fractional anisotropy (FA) and mean diffusivity (MD) values were measured. Between group comparisons adjusting for age were assessed. Pearson's correlations were used to explore the relationship between CC DT MRI metrics and UPDRS III score.

Results: All PD patients relative to HC showed decreased FA and increased MD of CC and its partitions. Such a microstructural damage to the CC is more marked with increasing PD severity, being only mild in PD patients with HY=1-1.5 (showing the greatest damage in CC-body) and severe (same degree of damage in all CC partitions) in patients at the later stages of the disease. UPDRS III score correlated significantly ($p<0.001$) with FA values of the whole CC ($r=-0.399$), CC-genu ($r=-0.199$), CC-body ($r=-0.481$), and CC-splenium ($r=0.270$) and MD values of CC ($r=0.367$), CC-body ($r=0.438$), and CC-splenium ($r=0.257$).

Conclusions: PD is associated with microstructural damage of CC that becomes more significant with disease worsening. In PD patients, the best predictor of motor function deterioration is the involvement of CC-body, which includes the transcallosal motor tracts. Assessing CC microstructural alterations may improve the understanding of the pathogenetic mechanisms associated with motor impairment in PD.

The Default Mode Network functional connectivity is involved in semantic memory performance in Mild Cognitive Impairment

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Background: Semantic memory deficits and alterations of the Default Mode Network (DMN) connectivity have been described in Mild Cognitive Impairment (MCI). Nonetheless, the role of DMN changes in semantic memory impairments associated with this clinical condition is still unknown.

Objectives: The present study aimed at investigating the relationship between semantic memory performance and brain intrinsic connectivity within the DMN in MCI patients.

Methods: Twenty-one MCI patients and twenty-one healthy elderly controls took part in this study. All participants underwent a multi-tasking semantic battery involving tasks of category fluency, visual naming and naming from definition for objects, actions and famous people, a word-association task for early and late acquired words and a reading task. A subgroup of the original sample (sixteen patients and twenty controls) had a functional magnetic resonance imaging (fMRI) scan at rest. DMN functional connectivity of the medial prefrontal cortex (mPFC) and posterior cingulate (PCC) was estimated using a seed-based approach. Two sample t-tests were used to compare connectivity across diagnostic groups for each seed. The brain-behaviour relationship with indexes derived from the semantic battery was assessed using simple correlations.

Results: Patients showed decreased performance in category fluency, visual naming, naming from definition, words-association and reading. Compared to healthy elderly, patients showed increased DMN connectivity between the mPFC and the PCC, and between the PCC and the parahippocampus and anterior hippocampus. Patients showed also a significant negative correlation of mPFC connectivity with parahippocampus and posterior hippocampus and total scores on the visual naming task.

Conclusions: Our findings suggest that DMN connectivity alterations may contribute to semantic memory deficits in MCI, specifically in visual naming. An increased DMN connectivity between the mPFC and the PCC, and between the PCC and the parahippocampus and anterior hippocampus, appears to cause relevant disadvantageous reorganization of brain functions in MCI.

Does free and cued selective reminding test (FCSRT) works better than other psychometric test in identifying MCI subjects who will progress to dementia?

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Background: The Free and Cued Selective Reminding Test (FCSRT) is considered a sensitive marker of early Alzheimer's Disease (AD)1, but it is still unknown whether its diagnostic performance exceed that of other psychometric tests.

Objectives: In order to answer this question, we compared in a cohort of MCI subjects the diagnostic accuracy of the FCSRT2 to that of the following tests: MMSE, Rey Auditory Verbal Learning Test (RAVLT), Story recall, Rey's figure, clock drawing, words fluencies, Frontal Assessment Battery, Trail Making test, Stroop test.

Methods: From April 2009 to August 2012, 150 MCI consecutive subjects underwent the baseline neuropsychological battery and the follow-up for dementia surveillance. For each test 2X2 contingency tables were constructed in which cases were classified as converters to dementia or non-converters, and tests were classified as under-threshold or normal according to the Italian normative values. Test indicators were calculated, including positive likelihood ratio (LR+), negative likelihood ratio (LR), diagnostic odds ratio (DOR).

Results: Over a median follow-up of 22.6 ± 10.6 months, 55 (36.7%) MCI subjects progressed to dementia, including 43 AD cases. The FCSRT delayed total recall (TR) showed the highest LR+ value (3.17), whereas the FCSRT delayed free recall (FR) provided the lowest LR- value (0.36). The FCSRT has proved superior to the other tests with respect to the DOR values: FCSRT-delayed FR 6.22; FCSRT-delayed TR 6.10; FCSRT-immediate FR 6.03, FCSRT-intrusion 5.63; FCSRT- immediate TR 5.53; FCSRT-index of sensitivity to cueing 4.96; RAVLT delayed recall 4.09; RAVLT immediate recall 3.34; MMSE 3.28; Story recall 3.14; semantic fluency 3.01; Frontal Assessment Battery 2.74; Stroop errors 2.67; clock 1.84; Rey's figure recall 1.76; Stroop time 1.52; Rey's figure copy 1.39; Trail Making 1.39 (A) and 1.21 (B); phonemic fluency 0.62.

Conclusions: The FCSRT works more efficiently than other psychometric tests in identifying those MCI subjects who will progress to dementia.

CSF and neuropsychological profile in a case of Dementia pugilistica

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Objective: Single or recurrent traumatic brain injuries are associated with increased risk of cognitive

decline. The clinical entity known as "dementia pugilistica" has no diagnostic criteria available. We present a single case of suspected dementia pugilistica: an entity for which there are no neuropsychological and cerebrospinal fluid (CSF) data in literature.

Case report: C.Q., 52 years old man, ex professional boxer, came to our memory clinic of "Luigi Sacco" Hospital in Milan in winter 2013 for the insidious appearance of memory impairment, spatial disorientation and affective disturbances. We evaluated the patient with clinical examination, blood test, brain MRI, EEG, neuropsychological evaluation, APOE genotype and C9ORF72 hexanucleotide expansion analysis. In addition, the patient underwent lumbar puncture. Neurological examination and blood tests were unremarkable. Brain MRI showed a severe cortical and sub- cortical atrophy. APOE genotype was 3/3 and C9ORF72 expansion was negative. The Mini-Mental State Examination score was 20/30 and the functional scale shown the first stage of a compromised self-sufficiency (Clinical Dementia Rating score=1). The neuropsychological profile showed multi domain deficit, including episodic memory impairment. CSF examination was unremarkable with normal Aß protein and borderline value of fosfoTAU.

Despite the symptoms onset and the neuropsychological profile could evoke Alzheimer's disease, the history of repeated traumatic brain injuries together with the negativity of CSF biomarkers, led us to diagnose dementia pugilistica.

Conclusions: To our knowledge, this is the first study that report detailed neuropsychological profile and CSF examination in a suspected dementia pugilistica case. Neuropsychological multi domain deficits confirm the unselective damage from recurrent traumatic brain injury, without configuring a specific neurodegenerative pattern. Normal CSF Aß protein suggests the hypothesis of the independence of this clinical form of dementia from amyloid cascade, configuring a specific clinical entity.

The methylated compounds affect the aggregation of amyloid peptide (25-35)

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Background: Neuritic plaques, the hallmark of Alzheimer's disease (AD), are primarily composed of ß-amyloid peptides Aß(1-40) and Aß(1-42). Aß(25-35) represents the biologically active region of Aß, as it includes the shortest fragment capable of forming large ß-sheet aggregates.

Objectives: Aim of our research is to provide a better understanding of the critical structural requirements to stabilize the interaction of N-methylated compounds with Aß(25-35) peptide and the subsequent Aß(25-35) conformational preferences.

Methods: The ability of N-methylated compounds to interact with the Aß(25-35) peptide is evaluated using a combined approach based on circular dichroism, nuclear magnetic resonance and thioflavin fluorescence spectroscopy.

Results: Our data show that N-methylated compounds favor the prevalence of soluble random coil and turn- helical structure in solution, while limit the presence of Aß aggregates. This effect is emphasized in presence of micellar aggregates due to the modification of micelle surface.

Depending on conditions, Aß(25-35) undergoes a conformational transition from random coil or alpha-helical monomers to the highly toxic ß-sheet oligomers, which form the mature fibrils.

A widely employed approach in the research of anti-Alzheimer agents involves the identification of substances able to prevent amyloid aggregation, or to disaggregate the amyloid fibrils. A selective mode of interaction of these compounds with soluble oligomers or amyloid aggregates has not been clearly established yet. The development of small molecules able to interact with amyloid peptides is considered strategic in view of identifying the structural parameters responsible for Aß stabilization and/or aggregation.

Conclusions: In the present contribution, we show that a panel of N-methylated compounds are able to slow the aggregation of Aß(25-35). This effect is emphasized in presence of micellar aggregates employed as bio-membrane mimicking, suggesting that the stabilization of soluble form may be related to the modification of electrostatic potential of the environment surrounding the peptide.

The aggregation of Aß (25-35) blunts the phosphorylation of cPLA2 in LAN-2 cholinergic cell line

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Background: The major protein component of the neuritic plaques, the hystopathological hallmark of Alzheimer's disease (AD), is the 40-42 aminoacid residues amyloid ß-protein (Aß). In the brain, Aß exhibits a variety of biophysical states. In neuritic plaques Aß occurs principally in a fibrillar form as a peptide of 42 residues (Aß42), although the form ending at amino acid 40 (Aß40) usually colocalizes with the longer form. Aß40 is the major product of APP processing while Aß42, more hydrophobic and with a greater tendency to aggregate spontaneously into amyloid fibrils is the predominant form in neuritic plaque core in both demented and non-demented individuals. Aß(25-35) represents the biologically active region of Aß, as it includes the shortest fragment capable to form large ß-sheet aggregates.

Depending on the conditions, amyloid peptides undergo a conformational transition from random coil or alpha-helical monomers to the highly toxic ß-sheet oligomers, which form the mature fibrils. Our previous work shows that N-methylated compounds favour the prevalence of soluble random coil and turn- helical structure in solution, while limit the presence of Aß aggregates.

Objectives: In order to test the possible biological consequence of Aß aggregation, we evaluated the effect of Aß in different states of aggregation with or without N-methylated compounds on phospholipase A2 (cPLA2) phosphorylation in a cholinergic cell line (LAN-2).

Results: Our results show that the activation of phosphorilated form of cPLA is dependent on the Aß aggregation state. In particular, cPLA2 phosphorylation decreases when Aß aggregates. We also observed that when the cells were treated with a specific N-methylated compound at different time points, cPLA2 phosphorylation was lost.

Blood pressure variability in Alzheimer's Disease

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Background: The relationship between vascular disease and cognitive impairment has been a matter of an ongoing debate. In particular, hypotheses suggesting an additive or synergistic effect between cerebrovascular impairment and neuro-degeneration have been developed. The increase in arterial blood pressure (BP) is one of the most important modifiable vascular risk factor implicated in the promotion of cognitive decline and the concept that BP variability (BPV) may be even more harmful than hypertension is a relatively recent notion.

Objectives: The aim of our study was to evaluate whether BPV influences the rate of cognitive decline in Alzheimer's Disease (AD).

Methods: One hundred AD patients were periodically evaluated for a 12-month period. Progression of cognitive decline was investigated using the Mini Mental State Examination (MMSE) administered at entry and at the end of follow-up.

Among the considered BP indices, only variability in systolic BP explained the decrease in the MMSE score after adjustment for confounding variables ($p < 0.001$).

Results: Our results suggest that fluctuations in SBP may play a role in determining the rate of neuropsychological decline in AD patients and that BP variability may be added to the list of the potential vascular risk factors and included in the evaluation of AD patients to better define their risk profile.

Is Limbic Encephalitis a potential risk factor for dementia?

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Case report: A 70 years old man with 5 month history of episodic memory loss was admitted to our Clinic. Neurological examination was normal, neuropsychological tests showed encoding and retrieval memory deficits (MMSE29).Blood thyroid hormones, folate and B12 vitamin were in range, plasmatic iron was low. Since brain MRI showed signal increase in bilateral temporo-mesial and perinsular areas in T2 weighted imaging, Limbic Encephalitis (LE) was diagnosed. FDG-PET scan showed left hippocampal hypermetabolism. Anti-nuclear and anti-thyroid antibodies were in range.. Electroencephalography was normal. Tumor markers were normal. A neuron surface antibody serum positivity was identified by indirect immunofluorescent assay. 5 months later the patient referred melena and a colonoscopy revealed a colonic polyp that was removed. A diagnosis of microscopic adenocarcinoma was done and the patient became asymptomatic. 3 years later, because of

behavioral changes, an examination was planned. Neuropsychological tests revealed executive functions and memory deficits and significative behavioral symptoms, especially sexual disinhibition (MMSE 22). FDG-PET scan showed prefrontal, anterior cingulate and mesial frontal hypometabolism, normal metabolism on left hippocampus, compatible to a behavioral variant of Frontotemporal Dementia (FTD).

Conclusions: Colorectal cancer rarely occurs with neurological paraneoplastic disorder(Sio e al,2012). In isolated cases LE and Alzheimer's Disease are described concurrently (Klimkovicz et al, 2011) but no cases of concomitant LE and FTD or FTD subsequent to LE are reported. Since immunological processes in FTD are described as a pathophysiological con-cause of disease (Sjogren, 2011), autoimmunity may be suspected as the underlying shared mechanism between LE and FTD. However, autommune encephalitis may occur with a clinical picture indistinguishable from FTD (McKeon, 2007).

Severe and reversible Presynaptic Ligand SPECT captation reduction in Akinetic Crisis of parkinsonism and neuroleptic malignant syndrome

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Background: Akinetic Crisis (AC) is akin to Neuroleptic Malignant Syndrome (NMS) and is the most severe and possibly lethal complication of parkinsonism. Diagnosis is clinically based, but often is marred by concomitant precipitating factors. Instrumental evidence of diagnosis has never been presented.

Methods: Four parkinsonian patients underwent presynaptic dopamine trasporter ligands FP/Cit Single Photon Emission Computerized Tomography (SPECT) in the acute phase and after follow-up of AC (three patients, two survivors) and of possible NMS (one patient with residual parkinsonism)

Results: Absent ligand captation was observed with semiquantitative analysis, during the AC, and recovery of captation was observed in surviving patients.

Conclusions: This finding might be helpful for instrumental diagnosis of these disorders.

Multidisciplinary approach for diagnosis of frontotemporal dementia patient

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Background: Frontotemporal Dementia is characterized by a varying combination of cognitive impairmant and behavioural deseases. It can present like neurodegenerative or psychiatric disorders.

Objectives: to describe a case of behavioural-variant Frontotemporal Dementia-like syndrome presented with disregulation impulse disorders diagnosed through a multidisciplinary approach.

Methods: Diabetic, dyslipidaemic and high-blood pressure sufferer 73-years old man, admitted to hospital because of a seizure and examination of cerebrospinal fluid positive for encephalitis.

Results: At neurological examination epilepsy, apathy, slowness executive and diurnal somnolence were observed. Cerebral MRI showed a chronic vascular suffering. Neuropsychological battery assessment revealed small deficits in executive function and long-term memory. The patient presented an awareness desease. Just later a psychological examination with relatives, has emerged from two years decline in social manner, impairment in regulation of food and sexual conduct, nervousness. A clinical diagnosis of behavioural-variant Frontotemporal Dementia was done.

Conclusions: For diagnosis of Frontotemporal Dementia the clinicians should keep in mind it can display like a pure behavioural and neuropsychiatric syndrome. In such cases, the neurological examination and neuroimaging alone are not sufficient to put diagnosis. Neuropsychological assessment and examination psychological according to the "bio-psycho-social approach" are essential for an accurate diagnosis and to avoid a late diagnosis.

Connectivity-Based Cognitive Stimulation Improves Cognitive Performance in Mild Cognitive Impairment

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Background: There is no hard evidence that Cognitive Stimulation (CS) is effective at improving neuropsychological functions in Alzheimer's disease (AD). Multiple factors contribute to the degree of success of CS; a major variable is indoubtedly represented by the nature of the mechanism supporting potential benefits.

Objectives: We hypothesised that a programme of CS based on the hypothesis of neural disconnection seen in AD would improve neurophsychological abilities in older adults at the mild cognitive impairment (MCI) stage of AD. We also tested this hypothesis in healthy older adults.

Methods: Seventy-eight participants were recruited and administered a battery of neuropsychological tests as baseline measures of cognition and as one of the clinical elements for determining group membership, following Petersen's criteria for MCI. The same battery was repeated at the end of the study. Nineteen MCI patients and twenty-six healthy older adults were assigned to an experimental condition consisting of twenty intensive sessions of connectivity-based computerised exercises, to be completed in the lab within one month. CS tasks were based on lexical-semantic abilities, logical reasoning, prefrontal function, memory, and processing speed. The remaining participants were allocated to a control condition consisting of everyday activities and neurological monitoring. Raw scores were analysed separately within each diagnostic group. Time-by-condition interactions were tested, controlling for age, years of education, and test-retest interval.

Results: A significant interaction emerged for Stroop accuracy scores in MCI patients, indicating significant improvement in the experimental group. Two significant interactions were found in the group of healthy participants but these did not survive statistical correction.

Far-transfer was found in the MCI experimental group following stimulation of multi-componential cognitive skills based on the architecture of functional connectivity to inhibitory skills, a high-order function not directly trained by the programme.

Conclusions: Connectivity-based CS may be an effective therapeutical avenue in patients at the MCI stage prodromal to AD.

Route learning training in older adults: specific and transfer gains

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Background: Route learning is a complex skill that requires the integration of information on distance, direction, and place. It is a crucial function in daily living that declines with aging, limiting older adults' autonomy and also affecting their social activities. It is therefore important to develop procedures that will help to maintain and improve their ability to navigate in their environment, and hence sustain their independence.

Objectives: The main aim of this study is to examine the gains derivable from a route learning training and the related transfer and maintenance effects.

Methods: Twenty 70- to 90-year-olds participated in the present study and ten were randomly assigned to the 14 route learning training sessions. We focused on the specific training-related gains in route learning tasks –the criterion measures– and on the transfer effects on visuospatial short-term memory (Corsi Blocks Task [CBT], forward version; Visual Pattern Test), visuospatial working memory (CBT, backward version; Puzzle Task), and spatial self-assessment measures. Maintenance of training benefits was also assessed at a follow-up after 3 months.

Results: The older adults who received training did better than controls in the criterion measures, and retained this benefit 3 months later. Immediate transfer effects were seen in most of the visual short-term memory and visuospatial working memory tasks considered, and were substantially maintained at the 3-month follow-up. As for the spatial self-assessments, an immediate gain was reported only by the trained group for Sense of Direction and Spatial Representation.

Conclusions: These findings suggest that providing training on route learning is a promising approach for preserving environment learning abilities in older adults.

Spatial cognition and aging: preliminary data from three new environmental spatial tests

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Background: Spatial cognition is a crucial function in daily living that declines with aging, limiting older adults' autonomy and spatial orientation, and also affecting their social activities.

Objectives: The main goal of this study was to develop a battery of three new and more ecologically valid spatial tests to improve the characterisation of the real spatial ability of older adults in daily living. The study also investigated the role that these new tests could play in understanding the relationship between basic spatial abilities and perceived self-efficacy.

Methods: A total of ninety healthy older adults (forty-one males; mean age 70.46; mean education 8.53) were enrolled in this study. They were assessed with a cognitive battery including basic spatial abilities tests (such as Minnesota Paper Form Board, Embedded Figure Test, Corsi's Blocks Test and Visual Pattern Test) and the new environmental spatial tests, such as an object and location recognition test, and map and route learning tests. We also administered self-rating spatial questionnaires, including scales assessing sense of direction, self-efficacy and spatial anxiety.

Results: There were significant correlations across the three environmental spatial tests. The environmental spatial tasks correlated partially differently with the self-rating spatial questionnaires. Confirmatory factor analysis showed that all the environmental spatial tests could be grouped in three factors that represent different components of spatial abilities: objects memory, sequential spatial memory and simultaneous spatial memory. Path models showed that environmental spatial tests mediate the relationship between basic spatial abilities and the self-rating spatial dimensions.

Conclusions: This study tested the reliability of three new environmental spatial tests in measuring different components of spatial abilities and their mediating role between basic spatial abilities and self-rating spatial dimensions. Further studies with a larger sample need to be carried out to standardize these new spatial tests facilitating their use in research and clinical settings.

Amyloid cytotoxicity depends on membrane lipid composition in Alzheimer's disease

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Background: Lipid rafts microdomains act as critical pathological platforms for the toxic signaling pathways that underlie synaptic dysfunction and neuropathology in Alzheimer's disease (AD). In particular, it has been demonstrated that lipid rafts are key sites of Aß production, aggregation and interaction at the cell membrane. Different cell susceptibility to toxic amyloid aggregates of familial AD (FAD) fibroblasts depends on their ability to accumulate the amyloid assemblies onto the plasma membrane.

Objectives: Here we analysed the ability of lipid rafts to bind Aß42 prefibrillar aggregates in relation to membrane cholesterol content in primary cultures of skin fibroblasts from FAD patients bearing APPVal-717Ile, PS-1Leu392Val or PS-1Met146Leu gene mutations, as well as age-matched healthy subjects.

Results: We found that a moderate enrichment in membrane cholesterol reduces amyloid binding to lipid rafts, preventing the increase in cytosolic free Ca2+ and membrane permeabilisation triggered by Aß42 in FAD fibroblasts. Moreover, the recruitment of amyloid assemblies to lipid raft domains of cholesterol-depleted fibroblasts was significantly increased, thus triggering an earlier and sharper increase in intracellular Ca2+ levels and plasma membrane permeabilisation. In primary rat cortical neurons and human SH-SY5Y neuroblastoma cells, mild cholesterol enrichment also prevented Aß42-induced membrane permeabilisation, while cholesterol depletion enhanced this permeabilising effect, corroborating our hypothesis in a neuronal system.

Conclusions: Overall, this data suggests that plasma membrane injury depends on lipid raft composition in Alzheimer's disease.

The organization of the neuropsychiatric 'macro'-UVA at IRCCS AOU 'San Martino-IST', Genova

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One of the major problems in the organization of UVA is the heterogeneity in diagnostic and therapeutic tools among UVA from different cultural backgrounds. Beginning in January 2011, four of the UVA IRCCS AOU San Martino -IST of Genoa, including 2 Neurological University UVA, 1 Neurological Hospital UVA and 1 Psychiatric University UVA, are functionally merged to create a single 'macro' UVA with the purpose to share diagnostic and therapeutic routes and foster inter- disciplinary consultancy and scientific research.

The main objectives achieved after 3 years are the common use of: i) a computerized medical record built on 'Access' (Windows) and IRCCS-server-based with the ease of 'queries' for the selection of case studies in clinical and scientific purposes; ii) a diagnostic instrumental and clinical flow chart; iii) a standardized neuropsychological battery for the evaluation of memory, language, visuoconstruttive function, executive function, and cognitive flexibility. Moreover, it is currently undergoing the Italian validation of the memory test with printed words of Grober - Buschke 16 items and a new legislation for the Stroop test, full version. For both, data collection in 200 normal subjects has just ended, the preliminary data have been presented at SIN 2013.

There are regular monthly courses of information/ training for caregivers as well as the monthly discussion of clinical cases, presented in rotation. Finally, it is now customary a day conference in November, with different themes each year, to present the activities to GPs, allied specialties, civil society and the institutions, now in its third edition in 2013 ('The Brain that Changes'). The conference is accredited ECM and constitutes Teaching Elective for students in Medicine and Psychology. Future prospectives include, in addition to the consolidation of the achievements, the strengthening of research and design of a single physical location where we can achieve more immediate diagnostic and therapeutic integrated approach for patients with cognitive disorders.

Epilepsy in Alzheimer's disease: Clinical experience in outpatient neurology of Alzheimer's disease (UVIA)

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Numerous studies have shown a greater risk of seizures in Alzheimer's disease patients. On the other hand, studies on prevalence, prognosis, progression of both diseases have reported contradictory data. The prevalence of epilepsy in Alzheimer's disease varies from 1.5 to 64%. Some data do not correlate the onset of seizure with the severity of Alzheimer's disease. The cause of onset of epilepsy has not yet been identified. Some authors have hypothesized that syntesis of A-beta amyloid can involve many proteases that produce neuronal hyperexcitability. It is possible that seizures are generated by a reduced regulation of sodium channel Nav1.1. Another mechanism involved is Tau protein that leads to neuronal hyperexcitability.

Generalized and complex partial seizures are the most common clinical forms of epilepsy in Alzheimer's disease although it is difficult to differentiate other clinical seizures from numerous behavioral and cognitive symptoms of Alzheimer's disease. Some authors have identified the mesial temporal sites as the epileptic focus in Alzheimer patients, although EEG abnormalities are not always in that region as well as EEG seizures discharges are recorded in few patients and also EEG abnormalities are registered in Alzheimer patients without epilepsy.

Studies on animals have shown that anticholinesterases inhibitors drugs documented an increase of seizures but a randomized trial of donepezil did not reveal an increased risk of seizures and Alzheimer patients. Discordant data are reported also with memantine and its risk of triggering seizures. The use of neuroleptics and antidepressants drugs showed risk of seizures from 0.1 to 9% in Alzheimer's disease with BPSD. There are no randomized controlled studies on treatment of epilepsy in Alzheimer patients.

The use of antiepileptics is similar to that in elderly people suffering from epilepsy. We report our data on clinical experience about patients with Alzheimer's disease and seizures.

The Cognitive Reserve: Perspectives In Parkinson's Disease-Mild Cognitive Impairment

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Background: Cognitive reserve (CR) is an exciting construct that provides an explanation for individual differences in susceptibility to age-related brain changes or neurodegenerative disorders like Alzheimer's disease. Knowledge about cognitive reserve in Parkinson's Disease (PD) is still limited. Preliminary empirical evidence shows that education might exert a protective effect on cognitive decline in PD.

Objectives: The aim of this study was to evaluate the relation between CR and PD-MCI.

Methods: 23 non-demented, drug-naïve, PD patients (mean age 66 years) were assessed by a neuropsychological battery together with the Cognitive Reserve Index questionnaire (CRIq3), that comprehensively assessed CR. The CRIq includes demographic data and items grouped into three part: education, working activity and leisure time, each of which returns a subscore. CRIq score was divided in medium-low (up to 100) and medium-high (>101). MCI diagnosis was made according to MDS criteria. Assessment was performed at baseline and after 1 year.

Results: A chi-square test was performed to examine the relation between MCI and CRIq subscore. The relation between MCI and CRIq education, working and leisure activity was not significant at baseline; while at follow-up patients with higher CRIq education score were less likely to present MCI ($X2=9.16$, $p<.005$). In particular, none of the MCI subjects had a medium-high CRIq education value.

Conclusions: Our findings confirm that CR may provide an exploratory approach on cognitive dysfunction in PD. Education appeared the factor affecting cognitive evolution, while working and leisure activity did not seem to play a role. We might speculate that cognitive impairment due to dopaminergic dysfunction in de novo PD patients is not modulated by CR and could be restored by therapy. Differently CR may modulate cognitive impairment during the course of the disease, by providing a buffer for cognitive compensation probably through mechanism of cortical reorganization.

MoCA is more strongly associated with white matter ultrastructural damage than MMSE in patients with vascular mild cognitive impairment (VMCI). The VMCI-Tuscany Study

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Background: Diffusion tensor imaging (DTI) is sensitive to white matter (WM) ultrastructural damage. MoCA is a brief cognitive test proposed as a valid tool in vascular cognitive impairment because it includes items reflecting mental speed and executive functions. Our aim was to investigate if MoCA was more sensitive than MMSE to WM ultrastructural damage caused by small vessel disease.

Methods: In the multicentre observational VMCI Tuscany study, patients were enrolled according to the following criteria: 1) MCI (Winblad criteria); 2) moderate to severe degrees of WM hyperintensities on MRI (modified Fazekas scale). On MRI also lacunar and non-lacunar infarcts, cortical atrophy (Pasquier scale), and DTI parameters (mean diffusivity, MD and fractional anisotropy, FA) were evaluated. All patients were assessed with MoCA and MMSE.

Results: One hundred and fifty-four patients (mean age 74.8 ± 6.9, females 45.5%, mean years of education 7.9 ± 4.2, mean MoCA score 19.9 ± 4.9, mean MMSE score 26.4 ± 2.9) were evaluated. In univariate analyses, we found no significant association between either cognitive test and WM hyperintensities, lacunar and non-lacunar infarcts. In a multivariate linear regression model including MoCA, MMSE, age, and education as independent variables, only MoCA score resulted significantly associated with DTI parameters (MD, ß: -0.370, $p<0.001$; FA, ß: 0.221, $p=0.032$). In an analogous regression model, MMSE score, together with age, was instead significantly associated with cortical atrophy (ß: -0.224, $p=0.007$; ß: 0.163, $p=0.048$, respectively).

Conclusions: In this comparison between two widely used cognitive screening tests, MoCA is associated with WM ultrastructural damage, while MMSE has a

stronger association with cortical atrophy. Our data suggest that MoCA could be indeed considered a better instrument than MMSE in the evaluation of patients with damage of WM related to small vessel disease.

The VMCI-Tuscany is funded by Tuscany region.

Novel Presenilin 1 Mutations in Italian familial Alzheimer's Disease patients

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Familial form of Alzheimer's disease (FAD) is due to mutations in three major genes [amyloid precursor protein (APP) gene, presenilin1(PSEN1) gene and presenilin 2 (PSEN2) gene].

To date, 185 pathogenic PSEN1 mutations in 405 different families have been reported in the AD and FTD mutation database, making PSEN1 mutations the most common known genetic cause of Early onset FAD.

A genetic screening of DNA samples belonging to FAD families present in the DNA bank at the Department of Neuroscience, Psychology, Drug Research and Child Health (University of Florence, Italy) was conducted by PCR and HRM techniques to identified nucleotide variants in the APP, PSEN1 and PSEN2 genes. An eventually DNA alteration was sequenced by ABI PRISM 310 sequencer.

The effect of the identified missense variants on the function of the protein was estimated using different software (SIFT, Polyphen2, Mutation taster, PMut, MUpro and I-Mutant2.0). Homologene and ClustalW were used to evaluate the protein sequence conservation creating alignments of multiple targets sequences (human gene was aligned with protein sequence of ten different mammalian species).

We identified two previously undescribed PSEN1 missense mutations in three Italian patients belonging to three different families.

The Ile408Thr at the transmembrane domain VIII of the PSEN1 protein was identified in two unrelated and clinically heterogeneous patients.

A Ser438Ala mutation at the transmembrane domain IX of PSEN1 was described in a patient with a severe cognitive decline with a very early-onset (49 ys). In silico analysis based on evolutionary conservation and protein modeling evidences that all the three mutations are most likely pathogenic.

Anti-Aß autoantibody in CAA-ri and AD: different singers for the same ARIA? Report from the iCAß International Network

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Background: The data emerged from the two phase 3 bapineuzumab trials provided valuable insights into its mechanism of action and the need of biomarkers in trial safety, highlighting the APOEe4 and dose-related development of Amyloid-Related Imaging Abnormalities (ARIA) as the most notable adverse event. Similar MRI abnormalities have been recently shown both in a human spontaneous model of ARIA, represented by Cerebral Amyloid Angiopathy-related inflammation (CAA-ri) and in immunized PDAPP mice, confirming the hypothesis that anti-Aß antibody and vasogenic edema are linked to a transient vascular leakage at the sites of major vascular Aß clearance. Since new AD clinical trials have been launched, the opportunity to better explore autoantibody dosage as biomarkers for patient enrichment and ARIA safety would be highly desirable.

Methods: World-wide case-control study in 120 patients from the iCAß International Network. By a novel ultra-sensitive technique, we evaluated the anti-Aß autoantibody concentration in the CSF of CAA-ri, CAA, AD, MS and healthy-controls. All patients undertaken T2*/SWI and FLAIR MRI analyses. 15/45 CAA-ri underwent brain biopsy for histopathologic confirmation. Aß40, Aß42, tau, P-181 tau and APOE4 were investigated.

Results: In CAA-ri, a higher amount of anti-Aß autoantibodies is accompanied by massive drainage of Aß from the brain and vascular deposits into the soluble forms, followed by a reduction of both autoantibodies and neurodegenerative markers after remission. An increased concentration of autoantibodies in AD carrying the APOE4 allele has been also observed. Diagnostic cut-off for CSF anti-Aß autoantibodies, by ROC curve analyses, has been determined.

Conclusions: Increased CSF anti-Aß antibodies are linked to a shift in CAA accumulation and increased vascular permeability, eventually leading to ARIA.

CSF anti-Aß autoantibody test as biomarkers for the CAA-related consequences of treatment could mark an important advance for the current ongoing AD clinical trials, opening also new scenarios for CAA therapy and diagnosis.

Episodic Memory Quotient (EMQ): a new neuropsychological prognostic indicator in amnesic Mild Cognitive Impairment (aMCI)

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Background: Episodic memory tests have been repeatedly reported as predictors of conversion of aMCI to Alzheimer's disease (AD). Test battery are generally indicated as the best approach to identify converters, but there is scanty evidence of the superiority of a memory test among others. Furthermore no specific indices or cut-off have been shown to be effective predictors of conversion to AD. This study propose a new synthetic index of memory impairment in aMCI.

Methods: 198 aMCI subjects were consecutively enrolled at the Policlinico Gemelli and Santa Lucia Foundation in Rome. Patients were followed for two years by means of a battery of neuropsychological tests that explore various cognitive domains. Score obtained on RAVLT-immediate recall, RAVLT-delayed recall, RAVLT-accuracy of and Rey-Osterrieth Figure-delayed recall were subdivided in tertiles. EMQ was obtained summing the tertile score obtained on each of the memory test; the total score ranged 4 (worst performance) to 12 (best performance).

Results: 55 subjects (28% of the sample) converted to AD. The relative frequencies of converters stratified by EMQ score were: EMQ=4, converters=53%; EMQ=5, converters=48%; EMQ=6, converters=48%; EMQ=7, converters=26%; EMQ=8, converters=21%; EMQ=9, converters=11%. None of the converters reported an EMQ score above 9. Converters performed worse than non-converters on most of the neuropsychological tests (MMSE, Copy of figures, Digit span forward and backward, semantic and phonological verbal fluency, Modified Card Sorting Test, Stroop's test – all $p < 0.05$ on t-test). These variables, along with EMQ, age and education were entered into a logistic regression model; the only variable to predict conversion to AD was EMQ ($OR = 0.59$; 95% CI = 0.460-0.773; $p = < 0.001$).

Conclusions: The EMQ score may be useful as a specific marker of conversion to AD. Its ability to identify subjects at low risk to convert may allow to save resources by preventing subjects to undergo invasive or expansive exams.

Performance of [18F]FDG-PET in 142 MCI pazients with at least 2 years clinical follow up: a multicentric study of the European Alzheimer Disease Consortium (EADC)

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The [18F] FDG-PET is a biomarker of neurodegeneration indicated by the research criteria for the early diagnosis of Alzheimer's disease (AD), potentially more sensitive than MRI because it detects the synaptic dysfunction before atrophy appears. The indications of the 'research' criteria require clinical validation in large series.

One hundred and forty patients with amnestic MCI were assessed by clinical-neuropsychological examination and [18F] FDG-PET and were followed until conversion to dementia or for at least 2 years (mean follow-up : 33.4±19.5 months).

Seventy-seven (54.2%) patients developed AD-dementia after 28.6±19.3 months, 10 patients fronto-temporal dementia after 29.9±22.5 months, 2 patients dementia with Lewy bodies, 3 patients returned to normal conditions, and 50 patients remained MCI after 42.3 months±17: 18.

The [18F] FDG-PET has been evaluated i) by two moderately-skilled readers (modEXP), ii) by two experienced (EXP), iii) with automatic calculation of the T-sum score and the PALZ probability of suffering from AD (software PMOD). Among them, the two modEXP readers and the two EXP readers were forced to reach an agreement.

We present only the results of the Group of 77 'MCI due to AD'. The sensitivity of modEXP is of 85.7%, EXP of 89.6 % and PALZ of 90%. The correlation between EXP and PALZ is 84.4%, and between mod-EXP and PALZ is 81.8%, between modEXP and EXP is 70.1%. In 2.6% of cases both EXP and PALZ give reading of non-AD (possible error of clinical diagnosis).

It is confirmed in a large series that the [18F] FDG-PET is a sensitive tool for the diagnosis of MCI due to AD. The sensitivity between 85% and 90% increases from modEXP to PALZ, which emphasizes both the need for adequate training in the reading of the images and the relevance of automatic analysis in assisting reading, especially for less experienced readers.

The Default Mode Network and the Working Memory Network are not anti-correlated during all phases of a working memory task

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The default mode network (DMN) and the working memory network (WMN) are known to be anti-correlated during sustained cognitive processing, in a load-dependent manner. To address the dynamic links between DMN and WMN, we used a delayed visuo-spatial working memory paradigm, which allowed us to separate three different phases of working memory (encoding, maintenance, and retrieval), and analysed the functional connectivity during each phase within and between the DMN and WMN networks. We hypothesized that functional connectivity among nodes of the two networks could be dynamically modulated by task phases across time. This would allow to specifically interfering with the cognitive process by means of non-invasive brain stimulation techniques (i.e. transcranial magnetic stimulation, TMS), opening new opportunities for deeper insights in the WM understanding.

We found that the two networks are anti-correlated only during the maintenance phase of working memory, i. e. when attention is focused on a memorized stimulus in the absence of external input. Conversely, during the encoding and retrieval phases, when the external stimulation is present, the DMN is positively coupled with the WMN, suggesting the existence of a dynamically switching functional connectivity between "task-positive" and "task-negative" brain networks.

Our results reinforce the hypothesis of a direct involvement of DMN in cognitive functions, via a dynamic interaction with specific networks like the WMN in this case, but also demonstrate that the well-established dichotomous organization of human brain (anti-correlated networks during rest and balanced activation-deactivation during cognition) is dynamically suspended during specific sub-phases of a cognitive task.

Prolonged unconscious state in rapidly progressive DLB: clinical and neurophysiological findings

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Objectives: To describe a case of rapidly progressive dementia with Lewy bodies (DLB) that presented with prolonged fluctuations of alertness with generalize slow-wave activity and periodic discharges on EEG. Case report: A 78 year-old woman was admitted to the

Neurology ward for a 10-day history of unsteady gait, cognitive decline with loss of functional activities and complex visual hallucinations. Her medical history was positive for arterial hypertension, heart arrhythmia, and chronic HCV hepatitis. At first examination she was awake and alert, space-time disoriented with impaired memory, confabulations and verbal perseverations. At neurological examination she had a mild gait apraxia with retropulsion and no focal motor-sensitive deficit or abnormalities of the cranial nerves were found. On the third day the patient became comatose, without any drug therapy intervention, and this condition lasted for almost 36 hours. Thereafter, she shifted between phases of reduced attention, drowsiness even to stupor and phases of motor agitation with vivid visual hallucinations. EEG performed in the state of stupor, showed generalized polymorphic delta activity with periodic spikes and sharp-waves on both hemispheres. When arousal spontaneously improved, follow-up EEG proved the almost compete disappearance of the periodic discharges. Routine biochemical tests were normal. Brain MRI with gadolinium showed cerebral atrophy without other alterations of signal intensities (no DWI hyperintensity was detected). CFS analysis was normal, including negative testing for neurotropic viruses and 14.3.3 protein (Tau protein level 163 pg/ml). Whole body CT scan was negative for malignancy. A diagnosis of probable DLB was made and confirmed at follow-up visit. Conclusion: Rapid progressive DLB represents a disease variant in which fluctuating cognitive symptoms and visual hallucinations could be preeminent. Periodic shifts in the level of arousal with reversible generalized theta-delta activity and periodic sharp waves transients on EEG could represent the onset of a rapid progressive DLB.

Functional genetic variation in the serotonin 5-HTTLPR gene modulates brain damage in Frontotemporal Dementia

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Background: Frontotemporal Dementia (FTD) is a progressive neurodegenerative disorder with unpredictable progression. Serotonin neurotransmission has been proved to be impaired in FTD. Up to now, no modulators, but cognitive reserve (CR) as measured by educational levels, have been related to brain damage in FTD.

Objective: To evaluate the impact of functional serotonin transporter 5-HTTLPR polymorphism on regional cerebral blood flow (rCBF) in FTD patients, and its interaction with CR.

Methods: Seventy-six FTD, patients genotyped for 5-HTTLPR polymorphism (i.e. LL, LS, SS) and with SPECT scan available, were recruited and underwent clinical, neuropsychological, behavioral assessment. The effect of the 5-HTTLPR polymorphism and CR on has been analyzed separately, and then the addictive effect computed.

Results: No differences in neuropsychological and behavioural scores have been detected according to 5-HTTLPR (14 SS, 24 LL, 38 SL). At the same disease stage, LL carriers, which have higher transcriptional activity, showed greater bilateral frontal rCBF decrease ($p < 0.001$ uncorrected) as compared to SS carriers. As previously demonstrated, higher CR was associated with greater damage in right frontal region ($p < 0.001$ uncorrected). The additive effect of CR and 5-HTTLPR polymorphism was characterized by greater rCBF deficit in the same regions as compared by each variable considered alone ($p < 0.05$ FWE cluster level).

Conclusions: Serotonin neurotransmission affects brain damage in FTD, and functional genetic serotonin trait confers greater brain reserve. This study further confirms the role of serotonin in the pathogenesis of FTD and may suggest a role of serotonin-based treatment in modulating disease progression in these patients.

Is there a link between modifiable risk factors and the inverse occurrence of cancer and neurodegenerative diseases?

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Many different factors related to genetics and environment could be responsible for decreased co-occurrence of neurodegenerative diseases (ND) and

cancer. Aim of this study was to evaluate the role of dietary habits, life-style and clinical factors in determining the risk of cancer in persons with ND and vice-versa.

This is a prospective cohort study on a population of residents in a district of Northern Italy aged 40-74 during the period from 1991 to 1995. For 1693 subjects, socio-demographic, anthropometric, clinical, dietary and life-style variables were collected at baseline. Incident cancer cases and incident ND cases, including Alzheimer's disease and Parkinson's disease, were ascertained using a passive case-finding procedure. Cox proportional hazards regression was used to evaluate associations between exposure and incident cancer in persons with ND and vice-versa. The multivariate model included gender, baseline age, educational level, body mass index (BMI), fasting glucose, HDL-cholesterol, blood pressure, smoking status, alcohol intake, physical activity, Mediterranean Diet (MeDi) score adherence and energy intake.

In total, 54 incident ND cases and 347 cancer cases had occurred (9 co-occurrence). People with incident cancer were younger, more likely to be male, more educated, more smokers, less active physically, reported slightly less adherence to MeDi and were more deceased during follow-up than those with ND. The two groups did not differ by BMI, glucose, HDL, blood pressure, alcohol intake. The risk of cancer was 64% reduced in persons with ND (95% Confidence Intervals 0,15-0,87) and in subjects with cancer the ND risk reduction was similar. These results were independent of socio-demographic, anthropometric, clinical, dietary and life-style factors.

This study confirms that subjects with cancer have a reduced risk to develop neurodegenerative diseases compared with individuals without cancer and vice-versa independently of environmental exposure, supporting the hypothesis of a role of genetics in determining this inverse relationship.

The Network of dementia: opportunities and tools

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Dementia is cause for alarm in the world due to disability and high related social costs. To ensure effective treatments, it is necessary to organize an integrated network of health services and welfare helping families to counteract patients institutionalization. Primary Care Physicians (PCP) have to play a crucial role in the disease management but in our region, patients come late to specialist observation and about 50% cases of dementia are unidentified.

Methods: Training seminars for 35 PCP were performed to improve their capability to detect early symptoms of dementia and to use a 13 items list (0 = normal; 1 = observation by PCP; from 2 to 13 patients driven to dementia unit). PCP were also trained to use a web platform shared with a dementia research center.

Results: All 35 PCP administered the items list and 851 subjects (570 females, 281 males, age at examination 74 and 75 yrs, respectively) were screened in six months. 26% resulted cognitively normal ; 20% reported a score of 1 and have to be rechecked after 30-60 days); 54% resulted cognitively impaired scoring 2 to 13, of whom 71% were driven to a dementia unit; 25% were visited and received diagnosis of Alzheimer's dementia (50 %-unidentified dementia the others). Patients scoring 2-13 had onset 24-36 months before examination.

Conclusion: Specific training for PCP is mandatory in order to detect patients with early symptoms of dementia. Web platform is useful to 1) allow interaction among different professionals, 2) perform statistical analyses and epidemiology thus improving dementia care. Moreover, it is fundamental to reorganize the network of dementia units in Calabria and to improve people knowledge about disease.

Homozygous and heterozygous patients carrying APP A713T mutation in the same family

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To date the APP A713T mutation has been reported as dominant and in heterozygous state associated to Familial early onset Alzheimer's Disease and cerebro-vascular lesions (CVLs) mostly in Calabria, probably

due to a founder effect. A new large consanguineous FAD family segregating the A714T mutation has been identified and clinical phenotype of homozygous and heterozygous patients were here reported.

Living patients have been genealogically inquired, clinically studied with also neuropsychology, morphological and functional imaging (when possible). Molecular screening of FAD genes and APOE genotype was performed.

The family has been reconstructed over six generations; 13 affected persons, eight affected by history and five alive, were identified on two consecutive generations. A713T mutation (GCGtoACG) was found in five affected persons (three homozygous; two heterozygous). APOE was 33 in four patients and 23 in one homozygote. Homozygous patients: onset at 70 in two; one at 76 yrs and died at 84. Clinical picture was in agreement with classical Alzheimer's disease although slow: one patient after 5 yrs from the onset still able to drive, 18.3 at MMSE; the other is in a moderate state after 13 yrs (15.5 MMSE). CT scan, MRI showed frontoparietotemporal atrophy with CVLs; PET examination reduced blood flow in left temporal- parietal region.

Heterozygotes: one patient had onset at 62 showing classical AD, he is currently 88, MMSE 20.4; CTscan: cortical atrophy and CVLs. The other patient at 73 presented with amnestic MCI (MMSE 26.7, 25.7 after 1 yr, CDR0.5, neuropsychology: visuo-contructional abilities and Rey's figure copy impaired. Imaging in progress.

Our findings confirm the pathogenic role of the APP A713T mutation and the large span of onset not influenced by APOE genotype. No substantial differences concerning clinical phenotype and course were evidenced between hetero and homozygous patients. Of note the very long course in both genotypes.

The effectiveness of music and music therapy on behavioral disturbances in dementia

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Background: Music therapy is a significant non-pharmacological intervention in dementia [1-2]. In this context, the music is used in ways that relate to specific music therapeutic technics but also to listen to music according to criteria that make individualized intervention [1, 3-4].

Objectives: Identify the most recent scientific findings related to an "evidence-based" music therapeutic approach in the context of dementia [5].

Methods: We consulted the following databases: PubMed, PsychInfo and Cochrane register of randomized controlled trials In the review we included studies in the English language, randomized controlled trials (RCTs) and controlled clinical trials (CCTs), published in peer reviewed journals in the period 2000-2013.

Results: The analysis of the results showed a prevalence of studies that evaluate the effectiveness of music and music therapy on BPSD (Behavioral and Psychological Symptoms of Dementia) through active approaches. These studies reveal some methodological and statistical shortcomings as well as a not always satisfactory definition of the techniques used.

Conclusions: Despite the need for further studies, the use of music and music therapy in the context of dementia is a significant resource and allows a better pharmacological management of BPSD, in addition to standard of care, even in advanced stages of the disease.

Voxel-based morphometry reveals gray matter loss in patients with Paget's disease of the bone carrying SQSTM1 gene mutations

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Objective: To search for brain abnormalities in patients with Paget's disease of the bone (PBD) carrying mutations in SQSTM1 gene using voxel-based morphometry.

Background: Recently, mutations in the sequestosome 1 (SQSTM1) gene, which encodes the autophagic p62 protein, have been described in patients with Frontotemporal Lobar Degeneration (FTLD) and/or Amyotrophic Lateral Sclerosis (ALS). SQSTM1 mutations have been described in approximately 25% of patients with familial PBD. Neurologic involvement in these patients have not yet been investigated.

Methods: 12 newly diagnosed patients with familial PBD (5 males, 7 females, mean age±SD: 59±8 yrs)

carrying SQSTM1 gene mutations (E396X, M404V, G425R), and 12 healthy controls were recruited for the study. On examination, PDB patients show no signs of any neurological diseases and neuropsychological screening was normal. Structural MRI scans of all participants were acquired on a 1.0 T Impact Magnetom Imager scanner. Whole brain scans were obtained as high-resolution T1-weighted 3D MP-RAGE. Images were analyzed with FASL-VBM 4.1. All patients underwent clinical and neuropsychological assessment (MMSE, Semantic Fluency, Phonemic Fluency, Attentional Matrices, Corsi Span, Short Story Recall, Token test). Anxiety and depression were also evaluated with self-administered questionnaires (STAI-X1, STAI-X2, BDI).

Results: PDB patients carrying SQSTM1 gene mutations had significantly lesser ($p < 0.01$) regional gray matter density in right middle temporal gyrus, right parahippocampal gyrus and left lingual gyrus, in comparison with controls. Age-related reduction in gray matter density was significantly ($p < 0.001$) increased in PDB patients than in controls within a large brain network (including precuneus, cingulum and frontotemporal lobes, especially on the left side).

Conclusions: Our study shows that, in patients with PDB carrying SQSTM1 gene mutations, there is a significant gray matter decrease even in absence of neurologic symptoms. The clinical relevance our findings requires additional investigations.

M233V PSEN1 mutation presenting as very early-onset dementia and spastic paraparesis

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The phenotype of PSEN1 Alzheimer Disease (AD) often includes behavioral and psychiatric symptoms, parkinsonism, seizures, features suggestive of frontotemporal dementia, aphasia, cerebellar ataxia and spastic paraparesis. Over 190 different mutations have been described in PSEN1 gene, but there is not yet a clear genotype-phenotype correlation except for the so called "variant AD" (familial AD with spastic paraparesis), that seems most often to be associated with mutations in exons 8 and 9. Here we describe a PSEN1 mutation in exon 7 (M233V)

presenting as very early-onset dementia with spastic paraparesis.

The proband was affected by spasticity and cognitive deterioration starting from 27 years. She presented a very rapid disease course. At 32 years of age, brain MRI showed diffuse and symmetric mild brain atrophy with major involvement of the temporomesial lobes. Her mother had died at 34; she was also affected by spastic paraparesis and progressive dementia. Both had been experiencing learning disabilities from childhood.

DNA sequencing of the proband revealed an ATG to GTG mutation leading to a methionine to valine change at the codon 233 of PSEN1 exon 7. No other relatives were available in the family. The mother's brain pathology showed diffuse neurofibrillary tangles and amyloid plaques.

Only two mutations in PSEN1 exon 7 were previously reported in "variant AD" (G217D, F237I).

One family with autosomal dominant AD carrying the M233V mutation was described. Affected family members presented with dementia, parkinsonism and epileptic seizures starting between 28 and 34 years. Age of death was between 34 and 37 years.

Our report expands the clinical phenotype associated with M233V mutation and confirms that this mutation is associated with very-early-onset and rapidly progressive AD.

Neuropsychological assessment and clinical description of a patient carrying two GBA gene in cis mutations affected by atypical early-onset parkinsonism and dementia

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Heterozygous glucocerebrosidase (GBA) gene mutations are a common risk factor for Parkinson Disease (PD). GBA mutation carriers display cognitive and neuropsychiatric disorders more frequently than PD patients without GBA mutations. Early visual memory deficits have been proposed as possible neuropsychological markers of GBA mutations in PD.

We describe a male patient carrying two GBA in cis mutations and affected by a severe early-onset parkin-

sonism, poorly responsive to levodopa, associated with behaviour disorders and cognitive decline.

The patient had been presenting aggressive behaviors, apathy, depression and memory loss since the age of 33. One year later he developed a bradykinetic parkinsonism partially responsive to levodopa therapy. SPECT study showed mild striatal presynaptic dopaminergic dysfunction. The neuropsychological assessment performed at 34 years of age showed deficits in all tested skills with worse performances in tasks assessing executive function and attention and relative sparing of visuospatial abilities; Mini Mental State Examination (MMSE) score was 26/30.

At 37 years of age MMSE score was 22/30; the neuropsychological evaluation showed worsening of verbal fluency with relative sparing of visuospatial skills.

Brain MRI showed diffuse and symmetric brain atrophy with major involvement of the temporomesial lobes and the cerebellar vermis.

Testing of PARK2, LRRK2, DJ1 and IT15 genes was normal. GBA molecular analysis detected two in cis mutations in exon 10 (L444P and A456P) inherited from the father. These mutations are probably due to a recombination event between GBA gene and its pseudogene.

Clinical and neuropsychological examination of the father and family history were unremarkable.

Reports on neuropsychological assessments in GBA mutation carriers with parkinsonism may contribute to defining the cognitive phenotype of these patients, the possible genotype-phenotype correlations and the clinical markers that may be useful in identifying candidate subjects for GBA genetic testing.

Magnetoencephalography as a tool to investigate neurodegenerative disorders

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Magnetoencephalography (MEG) may represent a valuable tool to integrate classical approaches to study neurodegenerative diseases.

MEG is a noninvasive functional imaging technique that measures magnetic fields generated by neuronal activity of the brain with an excellent spatial resolution (<1 cm) and an outstanding time resolution (few msec). MEG is currently used in clinical conditions such as in preoperative assessment of brain tumors and intractable epilepsy.

Sporns (2005) has introduced the concept of "connectome", based on graph theory. In this framework neural networks consist of nodes, and links between them. The highly connected regions are called "hubs".

fMRI has been used to evaluate connectomics assuming the BOLD response to be linearly and time-invariantly dependent on the underlying neuronal activity. However this assumption holds true only when a stimulus with durations less than four seconds is used to predict a response of more than six seconds, thereby excluding most neurological processes.

MEG, with its excellent time resolution, can integrate fMRI casting light on how modification in the BOLD signals are generated by modifications of neuronal activity.

The pathogenesis of neurodegenerative disorders, such as Alzheimer's disease (AD) or frontotemporal degeneration (FTD), is still poorly understood and the exact correlation between pathological findings and the neurodegenerative process is unclear. One can speculate that greater or lesser activation of the hubs influences the neurodegeneration patterns and partially accounts for the clinical heterogeneity. For instance, AD could be seen as a "disconnection syndrome", and the evidence of a correspondence between hubs and regions most susceptible to amyloid deposition suggests a lesser resistance to AD by the most active areas, with a higher basal metabolism(Buckner 2009).

Concluding, the integration between fMRI and MEG will be a powerful approach in studying the impairment of connectivity which possibly underlies neurodegenerative disorders.

Kinematics study in patients with Frontotemporal Dementia and Alzheimer's Disease through a motion analysis system

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In the last decade, the relationship between cognition and motor function has received increasing attention. Gait is no longer considered as a merely automated mechanic activity but rather one requiring involvement of complex cognitive functions such as executive functions, attention, motivation and judgment of external and internal cues.

The aim of our study was to evaluate the relationship between cognitive functions and gait.

Subjects with an early stage of the behavioral variant of Frontotemporal Dementia (16 bvFTD) and Alzheimer's Disease (14 AD) were evaluated through a motion analysis system, during both normal gait or dual-task (motor and cognitive). The values were compared with 22 normal subjects. All patients underwent a clinical examination including UPDRS-III and an extensive neuropsychological battery exploring memory, executive and visuospatial domains. Mean value and coefficients of variation (CoV) of the following variables were calculated: speed, stride width, stride length, cycle time, step length, step time, double limb support time (DLS), cadence, stance time, swing time, double/single limb support time (DLS/SLS).

The bvFTD patients, when compared to the control group, showed significant differences in speed, stride length, cycle time, cadence and DLS, during normal walking. Moreover, in the same groups both dual-tasks (motor and cognitive) were able to determine differences in cycle time CoV, whereas in AD group, with respect to healthy subject, the same parameter was significantly different only in the cognitive dual-task.

Significant differences between motor and cognitive dual-task were found in cycle time CoV and cadence CoV, both in bvFTD and in AD groups. Finally, in healthy subjects only cognitive dual-task was able to affect speed, stride length and stance time when compared to normal walking.

Our study shows a close link between executive functions and variability of gait that could represent an important factor for a major risk of fall.

Agraphia in Alzheimer's Disease: cognitive basis and clinical-diagnostic correlations

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Writing requires "central" cognitive (semantic and phonological) and "peripheral" processes devoted to motor actions which are needed to produce written word in a variety of formats/shapes. Agraphia (i.e. a disorder of the writing output) is referred to an impairment of one or both these processes resulting in "central agraphia" or "peripheral agraphia", respectively. Agraphia is actually regarded as a common feature of Alzheimer's disease (AD).

We collected data in order to determine which spelling and grammatical-syntactical elements may be regarded as "predictors" of cognitive impairment progression in patients with AD at an early stage. The "writing item" of the Mini Mental State Examination (MMSE) has been used as a task for testing writing abilities. Furthermore, we assessed the ratio between the number of errors and the numerosity of syntactical elements in MMSE writing task. We indicated this ratio as RAI (Relative Agraphia Index).

We enrolled 177 patients with a diagnosis of mild AD (MMSE score > 20 at baseline) who were followed-up for 3 years. Overall, we found that RAI tends to grow in parallel with the progression of the disease, and displays a significant correlation with MMSE score at baseline. Finally, initial RAI predicts cognitive decline over time.

Dynamic assessment of drawing: spatial and temporal indicators of neuropsychological disorders

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In clinical setting, copy of drawings is usually administred to investigate visuo-constructive abilities, because of its convenience and immediacy. However the alterations in drawing tasks might reflect a primary visuo-constructive deficit or it might be a secondary effect arising from other cognitive and/or motor problems. Aim of the present study is to investigate visuo-constructive abilities bringing a new approach combining spatial, temporal and speed indexes, to better investigate visuo-constructive abilities in different neurological condition (i.e. subjects with Parkinson's Disease -PD; $N=12$- and subjects with right focal brain damage -FD; $N=13$-) in comparison to a control group (HC; $N=25$). For this purpose, we administer copy of Rey's complex figure (Rey, 1941, 1959; Caffarra, 2002), because of its validity and sensitivity in detecting constructive difficulties (Gasparini et al, 2008). We collected drawing tracks by using a graphic tablet. Kinematic, planning and programming executive-motor indexes for each stroke were extracted using homemade MatLab script. ANOVA with LSD post-hoc correction was performed to

compare the performance of these three groups. Statistical results (pcorrected < 0.05) show that: 1) PD e FD total score lower than HC; 2) FD group showed a worse performance than both CT and PD groups in indices of Spatial Dimension (i.e. completeness); 3) PD group showed a worse performance than both CT and FD groups in Temporal Dimension (i.e. "interval mean duration" and "mean speed"). Our data suggest that a dynamic assessment of visuo-constructive abilities might help in the discrimination between a primary visual-constructive deficit and a secondary effect arising from other impairments (i.e. motor dysfunction, executive functions, ...).

Development and psychometric properties of a neuropsychological battery for Vascular Mild Cognitive Impairment. The VMCI-Tuscany Study

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Objectives: Vascular cognitive impairment caused by small vessel disease (SVD) is thought to be characterized by a disexecutive profile. However, few attempts have been made to validate a neuropsychological battery for SVD patients. We aimed at developing a neuropsychological battery for VMCI (vascular mild cognitive impairment) caused by SVD, and verifying its psychometric properties in the VMCI-Tuscany Study baseline cohort.

Methods: Tests were selected among those most widely used, sensitive to vascular cognitive decline, and for which norms based on healthy Italian samples and equivalent scores methodology were available. Confirmatory factor analysis was applied to verify the fit of the theoretically assumed dimensions to empirical data and derive each cognitive dimension compound measures. Descriptive statistics were performed to analyze the quality and distribution of the neuropsychological data.

Results: The battery (11 tests, 4 cognitive domains) was applied to 201 patients with VMCI and SVD. Most cognitive tests showed good applicability. MMSE resulted largely normal, while Rey–Osterrieth Complex Figure, Symbol digit modalities test and Trail Making Test B resulted the most frequently abnormal tests. Confirmatory factor analysis showed a good fit of the 4-factor theoretical model to empirical data. Praxis domain resulted in the highest percentage of abnormal performance (65%), followed by Memory and Attention/EF domains (19% and 15%), and Language (8%).

Conclusions: The VMCI-Tuscany neuropsychological battery is a comprehensive, valid, robust and applicable instrument. We confirmed that attention-executive dysfunction is a prominent feature of VMCI profile that however includes also impairments in memory and high level visuo-constructional abilities.

Progression of cognitive impairment in parkinsonian patients

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Background: Parkinsonisms at onset can be associated to cognitive impairment.

Objective: To describe the progression of cognitive deficits in patients with parkinsonism at onset.

Material and methods: We consecutively selected patients with parkinsonism and disease duration up to three years to take part in the Bologna-motor and non motor Prospective study on Parkinsonisms at onset (Bo-ProPark).

All patients underwent, at baseline (T0) and after sixteen months (T1), neuropsychological assessment (Brief Mental Deterioration Battery, Stroop Test, Semantic Fluency Task, Beck Depression Inventory). Progression of cognitive impairment (CI) was defined as a drop of 1,5 SD in the corrected score for age sex and education. For all test, except Barrage and Stroop, a positive score indicates CI progression.

Results: 35 patients were recruited. 27 patients were diagnosed as Parkinson Disease (PD), 2 as Progressive Supranuclear Palsy (PSP), 1 as Multiple System Atrophy (MSA), 1 as Cortico Basal Degeneration (CBD) and 4 as Parkinsonian Syndromes not otherwise specified (PS). At T0 13 patients (8 PD, 1 MSA, 1 CBD, 2 PSP and 1 PS) presented CI. The degree of CI was stable at T1. Global CI was detected in 2 PSP and 1 PD patients; executive function impairment in 5 PD, 1 DCB, 1 MSA, 1 PS and memory impairment in 2 PD patients. Progression of cognitive deficits at T1 was observed in 5 PD patients, only executive functions.

Conclusions: CI can be observed in patients with parkinsonism at disease onset, independently from the clinical diagnosis. Progression of CI should be further evaluated as predictors of the diagnosis and prognosis.

The distribution of gray and white matter damages in Posterior Cortical Atrophy, Alzheimer Disease and Logopenic Variant of Primary Progressive Aphasia: a Diffusion Tensor Imaging study

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Introduction: Posterior cortical atrophy (PCA), Alzheimer disease (AD) and logopenic variant of Primary Progressive Aphasia (PPA-L) are degenerative disorders where it is observed the typical framework of AD. In this study we compared gray matter (GM) and white matter (WM) of cerebral lobes in these patients, by using Diffusion Tensor Imaging (DTI) technique.

Material and Methods: We have studied the possible damage of GM and WM microstructure of cerebral cortex in 3 patients with PCA, 3 with AD and 2 with PPA-L. We compared the observed images with those detected in 3 healthy controls. The study was performed with equipment high-field MR (1.5 T, GE HDX). Scans were performed with conventional techniques and technology diffusion tensor imaging (DTI) (b-value: 1500, direction: 25).

Results: The study showed an evidence of GM atrophy and WM damage within the parietal and temporal lobes in all patients showing a different distribution pattern in these three forms of neurodegenerative dementias. In fact, while AD compromised the parietal lobe only marginally from both sides, PCA significantly damaged the entire lobe bilaterally and PPA-L the most ventral part of the lobe, exclusively on the left side. On the other hand, while in AD the whole temporal lobe of both sides was involved, in PCA the damage mainly involved bilaterally the more posterior region and PPA-L the supero-posterior part of the lobe, almost exclusively on the left side.

Conclusions: Our results confirm the presence in PCA, AD and PPA-L of GM atrophy and WM damage within parietal and temporal lobes with different alteration patterns in these three forms of dementia. Our findings suggest that a DTI analysis of GM and WM of parietal and temporal lobes could be an useful

differential criteria between these three neurodegenerative forms, at least in the earliest stages of the disease.

ERPs and SPECT as early markers of cognitive decline in MCI patients

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Objectives: This study aims at evaluating whether functional investigations such as ERPs and SPECT could be considered as early markers of cognitive decline in patients affected by MCI and especially by subjective (SCI), amnestic (aMCI) and multidomain (mMCI) subtypes.

Methods: Forty-three patients (age 66.4 ± 7.6; 12 men; MMSE 27.1 ± 2.3; education 10.7 ± 4.1) performed a selective neuropsychological (NP) battery to assess general cognitive status, short- and long-term verbal memory, general intelligence, constructional praxia and verbal fluency. All patients underwent ERPs recordings (N400 and P300) and 99mTc-HMPAO SPECT. The distribution of MCI subtypes resulted as follows: 8 SCI, 17 aMCI and 18 mMCI.

Results: Pathological performances were recorded in the following neurological tests: Rey Auditory Verbal Learning Test (45.0%), FAB (42.9%), Verbal Span (39.5%), Prose Recall (37.2%). The P300 and N400 were altered in 44.0% and 86.0% of the patients tested, respectively.

Overall, a significantly higher regional hypoperfusion incidence was detected in all patients with a special interest in the limbic lobe bilaterally, the left frontal lobe (BA6,8,9,10,44,45,46,47) and the left temporal lobe (BA20,22,37).

Conclusions: In spite of a normal NP profile, SCI patients show alterations of ERPs and SPECT patterns compared to other MCIs. Functional exams state the involvement of prefrontal, frontal and temporoparietal areas. The functional networks seem to involve the declarative memory and executive functions: particularly the Working Memory (WM) system seems to be early affected by a possible neuronal dysfunction.

The functional impairment is likely to precede detectable structural changes and cognitive deficit. The use of ERPs and SPECT might be considered as a valuable tool for clinicians to longitudinally screen and monitor subjects with memory disorders, so an

early diagnosis of MCI might be able to predict the conversion from MCI to dementia.

Visual short-term memory deficits in Mild Cognitive Impairment

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Background: Binding is a cognitive function responsible for integrating features within complex stimuli (e.g., shape- colour conjunctions).

Short Term Memory (STM) binding is sensitive to the effects of sporadic and familial Alzheimer's disease (AD).

By contrast it is not affected by healthy ageing, chronic depression or non-AD dementias. Whether STM binding is also impaired in Mild Cognitive Impairment (MCI) is an issue yet to be investigated.

Methods: Sixty-seven subjects with MCI, 27 AD patients and 46 healthy controls were assessed with a computerized visual short-term memory task and a neuropsychological battery. The STM task assessed the recognition of shapes or shape-colour bindings.

Results: MCI subjects performed similarly to controls but significantly better than AD patients in the condition assessing memory for shape only (STM shape accuracy: controls 0.92 ± 0.09, MCI 0.83 ± 0.14, AD 0.72 ± 0.16. Post-hoc analysis: controls vs. MCI non significant; controls vs. AD $p = 0.003$; MCI vs. AD $p = 0.045$). By contrast, MCI subjects performed similarly to AD patients but significantly worse than controls in the condition assessing the shape-colour binding in memory (STM binding accuracy: controls 0.83 ± 0.15, MCI 0.65 ± 0.16, AD 0.58 ± 0.12. Post-hoc analysis: controls vs. MCI $p = 0,006$; controls vs. AD $p = 0,011$; MCI vs. AD non significant).

Conclusions: MCI subjects could not remember the temporary binding of shapes and colours to the same extent as the controls. Indeed in the condition assessing shape-colour binding they performed similarly to AD patients. This evidence does not warrant

a future diagnosis of AD for the impaired MCI patients, nevertheless it does motivate future longitudinal research towards a better characterization of MCI due to AD.

STM binding is impaired in MCI. This raise the question as to whether STM binding deficits, which have been demonstrated to be a preclinical marker of familial AD, might also be an early marker of sporadic AD.

Hearing genes: genotypes prevalence in the elderly population of Southern Italy

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Age-related hearing loss (ARHL) is the most common hearing disorder in older subjects. Genetic factors may worsen ARHL as well as cognitive status and depression in the elderly. The main aim of this population-based study is the identification of these genetic risk factors and their possible interaction with cognitive decline and ARHL in the elderly population of Southern Italy. To this aim we have investigated 523 subjects (310 males and 213 females) aged $= 60$ years selected from "Great Age" population based study of aging. All subjects underwent multidisciplinary (neurological, neuropsycological, otorinolaringoiatry, geriatric and psychiatric) assessment. After informed consent from each patient a blood sample was collected for the genetic investigation with real-time methodology. By means of real-time technologies we have investigated 21 markers single nucleotide polymorphisms (SNPs) selected from the 1000 genome projects in 11 genes potentially involved in the pathogenesis of ARHL. At baseline 124 (23.71%) out of 523 subjects ()were diagnosed as neurodegenerative diseases (AD, PD), whereas 61 (11.66%) were diagnosed as ARHL. Comparison of the genotype

frequencies with those observed in Caucasian revealed that 6 SNPs (genes IL8/TH/TPH2/HTR2A and SLC6A4) showed a significant inversion ($p < 0.001$) of the allele frequencies, whereas nine SNPs (genes DFNA5/SLC26A5/TH/TPH2/GJB2/GJB6/LDLR) showed a significant higher/lower ($p < 0.001$) allele frequency. Genotype frequencies of one SNP (rs7994748 in GJB2A) did not match the expected Hardy-Weinberg frequencies ($p = 0.008$). A different genetic background was observed in our population sample from Southern Italy in respect to those observed in Caucasian. Further analysis will investigate if these differences might be synonymous of relationships between ARHL and mild/moderate/severe cognitive impairment and the possible impact of hearing genes and ARHL on the risk of onset of several grade of cognitive impairment.

Circulating miRNAs as potential biomarkers in Alzheimer's disease

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Background: Circulating (mi)RNAs have been reported as promising biomarkers with great accuracy for neurodegenerative disorders and processes affecting the central nervous system (CNS), especially in aging, Parkinson's disease and multiple sclerosis.

Up to now, some studies demonstrated that a number of circulating miRNAs were dysregulated in AD with promising results.

Objectives: This study was conducted to identify specific circulating miRNAs in serum as possible biomarkers for Alzheimer's disease (AD).

Methods: A specific PCR array containing 84 most common miRNAs was used to screen miRNA serum levels in a discovery population composed of 7 patients with Alzheimer's disease (AD) and 6 non-inflammatory neurological controls (NINDCs). Best hits were validated in serum and cerebrospinal fluid (CSF) samples by real time PCR in an independent cohort consisting of 15 AD patients and 12 NINDCs, comparing them also to 10 subjects affected by sporadic Frontotemporal Lobar Degeneration (FTLD) and 8 inflammatory neurological controls (INDCs).

Results: Statistically significant decreased levels of miR-125b, miR-223, miR-23a and miR-26b were observed in AD patients compared to NINDCs (–5.5, –4.5, –5.0 and –6.3 fold regulation over NINDCs respectively, $p < 0.050$). MiR-125b, miR-223 and miR-26b were then validated both in serum and CSF ($p < 0.050$), while miR-23a failed to be replicated in CSF. Moreover, miR-223 was also found down-regulated both in serum and CSF from FTLD patients ($p < 0.050$).

Conclusions: Our findings suggested a potential use of circulating miRNAs, along with other markers, as non-invasive, relatively inexpensive and peripheral biomarkers for AD.

Accumulation of gray matter atrophy in frontal lobes accounts for conversion to Alzheimer's disease in patients with amnestic Mild Cognitive Impairment

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Background: Previously, it has been demonstrated that different patterns of gray matter (GM) density distribution in patients with amnestic Mild Cognitive Impairment (a-MCI) may be associated to different rates of conversion to AD since in the early stage. Aims of the present study were investigate longitudinally the cognitive profile and the pattern of GM atrophy in a-MCI patients.

Methods: we enrolled 31 patients with a-MCI (single domain or multiple domain). On the basis of their clinical follow-up after 2-years from baseline, we reclassified the a-MCI patients as converter to AD ($N = 14$, Converter) and nonconverter ($N = 17$, No-Converter). At any time-point all subjects underwent neuropsychological battery and a MRI examination at 3T and T1-weighted images were pre-processed using the VBM protocol. We used a flexible-factorial design on GM, to model the groups differences and interactions.

Results: There was no difference in the number of patients with single or multiple deficits between Converter and No-Converter groups. At baseline patients in the Converter group performed worse than with those No-Converter just in a test assessing executive functions and showed higher scores in the sum of

boxes of CDR. During time memory was the only domain worsened in the Converter group. VBM-Group comparison: At baseline patients Converter respect to No-Converter showed atrophy in the temporal lobes and cerebellum. When passing from baseline to follow-up patients in the Converter group showed significant atrophy respect to No-Converter in the frontal medial cortex and in the anterior cingulum bilaterally, in the right orbito-frontal cortex and in the middle temporal gyrus.

Conclusions: This study confirms that patients at different stage of AD show different pattern of GM loss since at earlier stage of disease and that both groups accumulate severe GM atrophy during time, mainly in the frontal areas.

Altered brain diffusivity in Mild Cognitive Impairment: relationship with linguistic and semantic memory processes

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Background: Microstructural abnormalities on diffusion tensor imaging (DTI) are promising in vivo biomarkers of brain changes associated with the progression of Alzheimer's Dementia pathology. Recent studies indicate that a decrease of white matter integrity has been found in Mild Cognitive Impairment (MCI) defined as a prodromal condition for AD.

Objectives: The present study aimed to investigate the brain diffusivity changes in MCI quantified as fractional anisotropy (FA) and mean diffusivity (MD), and to evaluate if the changes in white matter diffusivity are related to linguistic and semantic memory processes.

Methods: Eighteen healthy elderly and 22 MCI patients were enrolled in this study. All participants underwent 3T MRI exam for diffusion tensor based white matter investigation and cognitive tests of visual naming, naming from definition, categorical fluency and reading for objects, actions and famous people, and words-association. The comparison of FA and MD between groups and correlations between them and cognitive performance in MCI were carried out.

Results: There were no group differences in FA, but there was a hemispheric lateralization effect, such as a decreased FA on the right hemisphere compared to the left one. Compared to healthy elderly, MCI patients showed a reduced mean FA in the right inferior longitudinal fasciculus (ILF) and elevated MD in the uncinate fasciculus (UNC), suggestive of a neuronal loss in these tracts. Moreover, the FA of the ILF correlated with the reading of action performance, confirming the role of ILF in language and visual identification processes.

Conclusions: Our findings evidenced that MCI presents white matter diffusivity alterations in ILF and UNC, which might underling cognitive impairment. Across the linguistic and semantic variables, reading of action appeared to be related to ILF FA, forthcoming studies will encompass also other cognitive abilities.

Grey matter changes in different brain areas account for retrograde memory deficits in patients with Mild Cognitive Impairment

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Background: Retrograde memory (RM) decline in Mild Cognitive Impairment (MCI) has been shown to affect both or either public events and/or autobiographical memories. However, the relationship between RM and regional brain atrophy still remains unclear.

Objectives: The present study, using voxel-based morphometry (VBM), aimed at assessing the potential association between RM and grey matter (GM) loss in patients with MCI.

Methods: 18 amnestic MCI patients (either single or multiple domain) and 33 healthy controls (HS) were recruited. All patients and part of HS underwent an assessment of RM by using the Public events questionnaire (PeQ) and the Autobiographical Memory Interview (AMI), while all subjects underwent MRI at 3T. VBM data were processed according to a standard protocol and used for cross sectional comparison and correlation analyses with RM measures.

Results: A-MCI patients compared to HS reported lower performances at both episodic and semantic AMI, showing the expected temporal gradient. Conversely, they did not show any significant impairment

in PeQ. VBM revealed the expected pattern of regional GM loss in patients compared to HS (i.e., bilateral temporal-frontal atrophy). In the patient group, positive correlations were found between the episodic part of AMI and GM volumes in the left frontal and temporal areas, and in the left caudate nucleus. In addition, direct associations were found between PeQ scores and GM volumes in the right hippocampus/parahippocampus and caudate nucleus, and in the prefrontal cortex bilaterally.

Conclusions: This study indicates a selective impairment of autobiographical memory (but not public events' memory) in patients at early stages of Alzheimer's disease. The underlying pathophysiological substrate of this peculiar cognitive feature (personal episodic memory deficits) is likely due to GM loss in the left prefrontal cortex and in the caudate nucleus. Conversely, the hippocampus seems to be more crucial for the retrieval of public memories.

Regional White Matter disruption within the Corpus Callosum in patients with Mild Cognitive Impairment Single and Multiple domain

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Background and Objectives: The investigation of the microstructural abnormalities of white matter (WM) among different subtypes of Amnestic Mild Cognitive Impairment (aMCI) and their relationships with cognitive performances can help to understand the variability among aMCI patients. This study examined the corpus callosum (CC) by applying DTI-based tractography in order to delineate the specific WM damage in aMCI-single-domain (SDamci) and aMCI-multiple-domain (MDamci, having a higher risk of converting to Alzheimer's disease, AD, and more severe gray matter atrophy) when compared to both healthy subjects (HS) and AD patients.

Methods: We investigated 54 patients with AD, 42 with aMCI (23 SDamci and 19 MDamci) and 25 matched HS. All subjects underwent extensive neuropsychological assessments and 3T-MRI, including diffusion-weighted scans. Probabilistic tractography was used to reconstruct the CC in each subject. Age and gender were set as nuisance variables and T-con-

trasts evaluated with significance set at $p < 0.05$ (FEW-cluster-level-corrected).

Results: Compared to HS, SDamci reported signs of damage in the Splenium of the CC when considering FA and RD, and in the body when considering ADif. Conversely, no signitificant differences were obtained using MD. MDamci showed significantly greater damage to the Genu of the CC when compared to both HS and SDamci, in all considered matrixes. Conversely, AD patients showed an overall damage in the Splenium, body and Genu of the CC when compared to both SDamci and MDamci in all diffusivity measures.

Conclusions: This study indicates a specific pattern of WM damage in the CC in MDamci and SDamci that precedes the conversion to AD. Our results are consistent with the evidence that aMCI is a heterogeneous condition, including patients at different clinical stages between normal aging and dementia. More importantly, this study delineates a precise direction of WM damage that, in MCI patients, parallels the accumulation of cognitive disability.

A score of impairment in different linguistic domains allow to improve diagnosis of the three variants of Primary Progressive Aphasia

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Background and Objectives: Primary progressive aphasia (PPA) criteria (Gorno Tempini et al. 2011) collect three different variants of degenerative linguistic disorders (agrammatic, semantic and logopenic variants). Actually not all PPA cases conform to these distinctive patterns and not exhibit a clear neuroimaging profile. We suppose that it could be useful identify a critical number of impaired linguistic subtest to improve diagnosis of uncertain cases.

Methods: Fifthteen PPA patients (6 semantic, 5 agrammatic, 4 logopenic) were submitted to an extensive linguistic assessment by means of the Battery for the Analysis of Aphasic Deficits, investigating several linguistic abilities. After that, these patients underwent a 3T MRI, on which data was applied a VBM procedure with a group of matched healty subjects.

Results: Agrammatic-variant patients showed poorer performances on visual sentences comprehension ($p > 0.01$), grammatical judgement ($p > 0.01$) and phonological fluency ($p < 0.003$) than other PPA groups; semantic-variant patients showed lower scores on nouns comprehension ($p < 0.002$) and on object naming ($p > 0.05$); logopenic-variant patients were characterized by impaired words repetition ($p < 0.003$), sentences repetition ($p < 0.001$), words and pseudowords writing ($p > 0.02$). In every described subtest, patients were operatively segregated as 'not impaired' (90-100% of corrected responses), 'slight impaired' (75-90% of corrected responses), 'moderately impaired' (50-75% of corrected responses), 'severely impaired' ($< 50\%$ of corrected responses). Afterwards we extracted three specific scores (ranging 0-12) calculated on the linguistic tasks previously identified as able to distinguish the three linguistic pattern (agrammatic, semantic or logopenic). The three scores are all significantly able ($p < 0.001$) to discriminate the three variants. As for the MRI findings, VBM data show a pattern of reduction of GM concentration (PPA compared to HS, $p < 0.001$) placed in left temporo-ventral regions, but not specific for the clinical diagnosis.

Conclusions: Fine grained analyses of linguistic performances seems a reliable method to distinguish between the three variants of PPA.

Cognitive changes and white matter tract damage in the motor neuron disease spectrum

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Objective: To assess the relationship between white matter (WM) tract abnormalities and cognitive changes in patients within the motor neuron disease (MND) spectrum using diffusion tensor (DT) MRI tractography.

Background: A detectable degree of cognitive involvement, which can vary in magnitude, appears in many patients with MND. DT MRI has the potential to provide an objective in vivo assessment of the extramotor brain damage in amyotrophic lateral sclerosis (ALS) and other MND.

Methods: Eighty-two MND patients (including 41 ALS, 31 primary lateral sclerosis/pure upper motor neuron, and 10 progressive muscular atrophy [PMA]) and 35 healthy subjects were studied. All patients underwent clinical evaluation, neuropsychological assessment, and DT MRI. To fulfill criteria for cognitive impairment, patients had to demonstrate impairment in at least 2 validated executive tasks. Using the same approach, The presence of non-executive cognitive impairment was also taken into account. DT MRI metrics were obtained from corpus callosum (CC), corticospinal tract and extra-motor tracts. Groups comparisons were assessed using age-adjusted linear regression models. WM tract damage contribution to cognitive deficits was assessed using Spearman correlation coefficients adjusted for age and ALSFRS-r.

Results: No PMA patients had cognitive impairment. In the remaining group, seven patients (9.7%) had frontotemporal dementia, six patients (8.6%) had an executive cognitive impairment, and non-executive deficits were found in two patients (2.8%). Relative to controls, ALS patients showed damage to motor and extra-motor tracts. PMA patients did not show tract damage. In the whole MND group, performances at tests assessing verbal fluency, attention and executive functions correlated with DT MRI measures of the CC, cingulum, inferior and superior longitudinal fasciculi, and uncinate bilaterally. Correlations remained significant adjusting for ALSFRS-r.

Conclusions: Interhemispheric, limbic and major associative WM tract degeneration is associated with neuropsychological deficits in patients with MND.

Early onset Alzheimer's dementia and spastic paraparesis bearing a PSEN1 V261I mutation: the first Italian report

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Background: Presenilin-1 (PSEN1) mutations account for most of autosomal dominant Alzheimer's disease cases, often with an early age of onset (< 50). Additional features are sometimes present.

Case report: Here we describe a 41 year-old patient with a two-year progressive history of cognitive impairment involving episodic memory with apraxic features and spastic paraparesis involving lower limbs. Past medical history was significant for migraine since the age of 20. Family history was negative. A brain MR scan was significant for white matter disease, particularly marked in the left fronto-temporal area. Clinical examination evidenced diffusely increased deep tendon reflexes with sustained bilateral ankle clonus and spastic gait. A lumbar puncture was performed demonstrating a pattern compatible with amyloidopathy. Genetic tests were run: NOTCH3 was negative, but the PSEN1 test disclosed a V261I heterozygous mutation.

Conclusions: This is the first Italian report of V261I mutation within the exon 8 of the PSEN1 gene and the second case worldwide. However, other two mutations affecting the codon 261 of the PSEN1 gene are known (V261F and V261L); in most of these cases the disease course presents with features of early onset dementia associated to spastic paraparesis; peculiar cotton-wool plaques have been demonstrated at the pathological examination. This case draws further attention to importance of considering PSEN1 mutation in early onset dementias associated to spastic paraparesis even in absence of a positive family history.

Environmental factors affecting the aggregation state of Aß 25-35: role of Omega3 dependent membrane fluidity

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ß-amiloid plaques composed of ß-sheet-rich fibrillar aggregates of peptides - Aß(1-40) and Aß(1-42), are the hallmark of the brain of Alzheimer disease patients. Aß peptides are produced in the form of soluble molecule, but in response to environmental factors they form low–molecular weight soluble oligomers and higher-molecular weight protofibrillar oligomers that give rise to insoluble fibrils forming amyloid plaques. Soluble oligomers are recognized as the primary toxic species in Alzheimer disease and in many other degenerative diseases, while the accumulation of large fibrillar deposits are considered either inert, protective, or pathological by different mechanisms.

The toxicity of amyloidogenic Aß protein is correlated to its ability to interact with cell membrane.

The composition and the physiochemical state of cell membrane can regulate the size and shape of Aß?aggregates as well as their kinetic of formation. The highly unsaturated Omega-3 fatty acid DHA and EPA that contribute to the hyperfluidizing properties of the membrane and enhance crucial membrane processes are found to be decreased in brain tissue of people with AD, suggesting DHA/EPA neuroprotective role.

Aß?25-35) is the shortest fragment that exhibits large ß-sheet aggregated structures and retains the toxicity of the full-length peptide. It is an important research tool for investigating the molecular recognition and self-assembly mechanisms that promote the formation of ?brillar amyloid deposits.

In order to have insights on the role played by the chemical environment on the aggregation of Aß-(25–35), here we present an AFM investigation of Aß(25-35) aggregation in phosphate buffer solution and in lipid DOPC and DOPC/DHA bilayers.

Our study shows that Aß(25-35) forms modular, round shaped aggregates, both in hydrophilic and hydrophobic environments. The presence of Omega-3 as membrane fluidizing agent is a key factor to antagonize the destabilizing, potentially toxic action of Aß peptide.

The callosal angle best differentiates idiopathic normal-pressure hydrocephalus from neurodegenerative dementia

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Objectives: To explore the accuracy of the callosal angle measured on standard brain MRI images in the differential diagnosis of idiopathic normal-pressure hydrocephalus (iNPH) from dementia with Lewy bodies (DLB) and Alzheimer's disease (AD).

Methods: 76 patients with cognitive decline (24 iNPH, 30 DLB, 22 AD) and 40 elderly healthy controls underwent standard brain MRI. The measure of the callosal angle was obtained on the coronal image crossing the corpus callosum midpoint. A set of other conventional MRI markers of iNPH reported in the literature was evaluated for comparison.

Results: The iNPH group showed a significant decrease of the mean callosal angle value compared to

both disease groups and controls (iNPH$=109\pm9$; DLB$=136.9\pm8.2$; AD$=135.4\pm11.3$; Controls$=138.5\pm5.2$; $p<0,00001$). Using a cut-off angle of 123, derived by the mean -3SD of the control group, an accuracy of 96%, sensitivity of 100% and specificity of 95,4% were observed in the discrimination of iNPH from DLB and AD. By ROC analysis, the area under the curve was 0.99 (95% CI: 0.97–1). The measure was consistent and reproducible (inter and intra-rater reliability of $r=0,94$ and $r=0,89$; respectively).

None of the conventional MRI signs reached the same diagnostic accuracy and all, except the Evan's index, had a lower reliability. The result of ROC analysis for Evan's index was 0.94 (95% CI: 0.91–0.99).

Conclusions: A callosal angle measure$=123$ on coronal MRI represents an accurate, easy and reproducible marker of iNPH, that may be valuable in the differential diagnosis with neurodegenerative dementia.

Functional Amnesia: memory and cognitive recovering after SSRI and selegiline therapy

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Background: Functional (or psychogenic) Amnesia (FA) can be defined as a forgetfulness of autobiographical memory, often accompanied by loss of personal identity without or minimal problems in learning new information and in general intelligence. It usually occurs under an acute emotional stress, and in absence of brain damages. We describe a case of FA, successfully treated with SSRI and selegiline according to Kopelman's cognitive framework about the role of executive control processes.

Case-report: Our patient is a right-handed, 51-year-old woman with 8 years of education. Her psychiatric history was irrelevant until April 2013, when she started suffering from a depressive-anxious state referred to a psychological reaction to her mother's diagnosis of Alzheimer's disease. In July, the patient had a heated phone conversation with her sister, after which she appeared confused and inattentive for about two hours, and then displayed an autobiographical memory loss. During the examination, the patient complained of muscle spasms on four limbs expecially during sleep and being afraid to go out or stay alone

at home. Neurological examination was normal except for the presence of a frightened face and astonished gaze. Both brain MRI and EEG studies were normal. A 99mTc-HMPAO SPECT study showed a slight reduced perfusion in right fronto-parietal and left temporal areas.

A neuropsychological assessment showed a deficit in executive functions, short-term recall and shifting abilities. A second assessment, performed after 6 months therapy with citalopram (20mg/daily) and selegiline (10mg/daily), showed an improvement in the amnesic state whereas emotions were still "flat". A good improvement was also present in both short-term recall and shifting abilities.

Conclusions: Functional amnesia is an extremely rare disorder with variable clinical picture and prevalence still undetectable. Description of all FA cases might help in determining further comprehension of this condition.

Aß1-42 monomers or oligomers have different effect on autophagy and apoptosis

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The role of autophagy and its relationship with apoptosis in Alzheimer's Disease (AD) pathogenesis is poorly understood. Disruption of autophagy leads to buildup of incompletely digested substrates, amyloid-ß (Aß) peptide accumulation in vacuoles and cell death. Aß, in turn, has been found to affect autophagy. Thus, Aß might be part of a loop in which it is both the substrate of altered autophagy and its cause. Given the relevance of different soluble forms of Aß1-42 in AD, we have investigated whether monomers and oligomers of the peptide have a differential role in causing altered autophagy and cell death. Using differentiated SK-N-BE neuroblastoma cells, we found that monomers hamper the formation of the autophagic Bcl-2/beclin I complex and activate the JNK pathway phosphorylating Bcl-2. Monomers also inhibit apoptosis and allow autophagy with intracellular accumulation of autophagosomes and elevation of levels of beclin 1 and LC3-II, resulting in an inhibition of substrate degradation due to an inhibitory action on lysosomal activity. Oligomers, in turn, favor the

formation of the Bcl-2/beclin I complex favoring apoptosis. They also cause a less profound increase in beclin 1 and LC3-II levels than monomers without affecting the autophagic flux. Thus, data presented in this work show a link for autophagy and apoptosis with monomers and oligomers, respectively. These studies are likely to help the design of novel disease modifying therapies.

Emotions and caregivers psychological distress in patient's with Alzhiemer's disease: the effect of support group

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Introduction. Patients with Alzheimer Disease need assistance and supervision in their daily activities. In literature, the term "burden" has been used to indicate the overload of work experienced by the caregiver.

Objectives. The aim of this study was to investigate the behavioural disorders perceived by caregivers in patients with AD and evaluate the effectiveness of psycho-educational and support groups to improves the quality of life of family caregivers.

Methods: We enrolled 50 patients with an MMSE of > 15 and probable AD according to the NINCDS – ADRDA criteria who consecutively attended the UVA Centre of our Department in Messina. The cognitive levels were investigated by MDB, ADL, IADL, NPY. Caregivers were assessed by HDRS, CBI. Caregivers were randomly assigned to the treatment or to the control group. The treatment group for 25 caregivers was conducted by a trained psychologist. The results were compared by a control group who did not participate in group meetings. All caregivers signed an Informed Consent for Clinical Trials.

Results: In Baseline testing, more than 89% of caregivers suffered clinically significant levels of depressive symptomatology. In particular, 79% showed an average score of 23.9 CBI. At the conclusion of the psycho-educational group and support programme which lasted seven month, the control group became increasingly more depressed ($P < 0.001$). Only those who participated in the group reduced their burden.

Conclusions: Alzheimer's Disease causes a distressing preview in the mourning context. The psycho-educational consultancy group provides relevant information regarding the illness, allowing the caregiver to interpret the behaviour of the patient as non-intentional. If it is true that without our memories we lose our identity, he who is not recognized after spending a lifetime together risks the feeling of being deprived of the present and past emotional bond. A specific intervention (support group) was aimed at reducing psychological distress and anxious-depressive symptoms.

Functional Correlates Of Implicit Awareness In Alzheimer's Disease And Mild Cognitive Impairment

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Introduction. Studies using functional magnetic resonance imaging (fMRI) to explore neural correlates of anosognosia in AD and MCI patients have adopted functional tasks explicitly eliciting patients' self-reflection about themselves. The purpose of this study was to investigate the presence of an implicit processing of self-referential information in cognitive impaired subjects using an emotional Stroop paradigm.

Methods: Fifteen patients (10 MCI and 5 AD) took part in an fMRI study, in which they were presented with an emotional Stroop task composed by 3 conditions: neutral words, generally negative words, and disease-related words. For each patient, a caregiver was asked to participate in order to have information about patients' activities of daily living and cognitive performance. The presence of anosognosia was assessed by means of Clinical Insight Rating Scale (CIRS) and Anosognosia Questionnaire Dementia (AQ-D). Reaction time and neural correlates during the three fMRI conditions were investigated.

Results: Behavioural results showed that aware patients took the longest time to process disease-related words, whereas unaware patients demonstrated comparable reaction time for neutral and disease-related words. Imaging results showed specific activation in posterior cingulate in aware vs unaware subjects for the disease-related words condition compared to neutral and negative words condition.

Conclusions: The presence of an emotional Stroop effect indicates that awareness may be processed even at an implicit level and activity in posterior cingulate seems to play an important role in implicit self knowledge.

Neural Correlates Of Unawareness In Alzheimer's Disease And Mild Cognitive Impairment: Multidimensional Assessment And Domain-Specificity

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Background: Patients with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) may present lack of awareness of their cognitive deficits, a symptom known as "Anosognosia". It can be measured in different ways, i.e. by the examiner clinical judgments, or by measuring the discrepancy between the patient's and an informant's judgment, or between the patient's judgment and their actual performance on cognitive testing. We investigated if anosognosia is associated with grey matter loss in specific brain regions in patients with MCI and AD, and tested whether different measures of anosognosia reveal similar brain correlates.

Methods: Anosognosia was evaluated in 27 patients with cognitive decline (15 MCI and 12 AD) trough three different measures of awareness: clinical rating (Clinical Insight Rating Scale, CIRS), discrepancy between patient-informant judgments (Anosognosia Questionnaire Dementia, AQ-D) and discrepancy between patient's judgment and performance on cognitive testing (self-appraisal discrepancies, SAD). Patients undervent hig-resolution MRI imaging. Correlational Voxel-based morphometry analises were performed to indentify associations between the above scores and regional grey matter loss.

Results: All measures of anosognosia (CIRS, AQ-D, SAD) were correlated with grey matter loss in the right hippocampus.

Conclusions: Right hippocampus emerged as a key structure in awareness mechanisms, irrespective of the assessment methods used; this is in accordance with recent findings suggesting that anosognosia is primarily caused by a decline in specific mnemonic processes leading to a loss of personal knowledge. In addition, our results suggested that "on-line monitoring" required by the self-discrepancy task was dependent on the specific neural networks elicited by the task itself, accordingly with the theory that the presence of locally and central modules may explain domain-specific unawareness.

Early Onset Dementia in Italy: a multicenter preliminary study

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Background: Early Onset Dementia (EOD) represents an increasing health emergency in developed countries (Rossor et al.'10) with an estimated prevalence of 54 cases/100,000 inhabitants (Harvey et al., '03) and incidence rate of 13.4 cases /100,000 person-year in people between 30 and 64 year-old (Garre-Olmo et al.,'10). In Italy, we estimated 18,000 prevalent and 4,800 incident cases.

Objectives: To evaluate clinical and epidemiological aspects of EOD.

Methods: A cross-sectional study in seven regions on patients with EOD in 10 Italian dementia care units for 2012.

Results: The study identified 426 EOD patients (3.2%) followed by the selected dementia care units in 2012. The average age of onset observed was 57 years and M/F ratio of 0.8. Most represented diagnoses were AD (49.3%) and FTLD (33.3%). Family history of dementia was reported in 43.9% of EOD patients. Most patients (78.8%) had other neuropsychological tests besides MMSE, 12.2% had CSF tests, while 53.6% were genetically screened. Treatment with cholinesterase inhibitors or memantine was reported in 61.9% of patients.

Conclusions: This preliminary study highlights the potential clinical, diagnostic, and therapeutic aspects of EOD in Italy that would require further collaborative work.

The role of microscopic damage in the inferior-frontal occipital fasciculus in determining cognitive dysfunctions in different forms of dementia

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Background: The inferior-frontal-occipital fasciculus (IFOF) is one of the major brain connections, although its functions still remain poorly understood. It has been claimed to be implicated in visual-attention and memory abilities and in language. Only a few previous studies have reported IFOF reduced integrity in Alzheimer disease (AD).

Objectives: To clarify the potential pathophysiological role of IFOF damage in determining some peculiar cognitive dysfunctions in AD and dementia with Lewy bodies (DLB) the diffusion MRI and probabilistic-tractography was used.

Methods: Thirty-seven patients with AD, twelve with DLB and twenty-two healthy controls (HC) underwent diffusion MRI at 3T. We reconstructed individual IFOFs and assessed their mean fractional anisotropy (FA) values (i.e., a measure of microscopic tract integrity/damage). Then, we used these values for cross-sectional comparisons (i.e., employing a 3 (group) x 2 (side) ANOVA) and correlations with cognitive measures (i.e., using the Pearson's correlation analysis).

Results: Cross-sectional comparisons revealed a bilateral reduction of FA values in the IFOF of AD patients, and a unilateral (right) reduction in that of DLB patients. Moreover, when considering AD and DLB patients altogether, a significant positive correlation was found between patients' FA in the right IFOF and correspondent Mini-Mental State Examination (MMSE) scores. A bilateral association was also found between patients' IFOF FA and Wisconsin Card Sorting Test (WCST) scores.

Conclusions: This study suggests that IFOF damage plays a pathophysiological role in dementias, with a bilateral pattern of abnormalities in AD and a unilateral pattern in DLB. This is consistent with a previous report that, based on functional brain connectivity (FC), demonstrated an asymmetric disconnection in DLB patients. The current microstructural abnormalities might represent the anatomical substrate for those FC changes. Moreover, as demonstrated by correlation analyses, they might account for some cognitive disabilities in both forms of dementia.

New brain reperfusion rehabilitation therapy improves cognitive impairment in mild Alzheimer's disease: a prospective, controlled, open-label 12-month study with NIRS correlates

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Objectives: The aim of our study was to evaluate whether the brain reperfusion rehabilitation therapy (BRRT) would improve verbal memory and learning and/or global cognitive impairment in mild Alzheimer's disease (AD).

Methods: using a prospective, controlled, open-label 12-month study, we enrolled 15 patients with mild AD, who underwent BRRT program (BRRT group), and 10 age - sex matched mild AD patients, who received no treatment (control group). At baseline (T0), and at the end of the 3 month (T3), 6 month (T6) and 12 month (T12) participants from both groups were given an evaluation, using Mini Mental State Examination (MMSE) and Rey Auditory Verbal Learning Test (RAVLT). In both groups by means of near-infrared spectroscopy, at T0 and T12, we measured tissue oxygen saturation (TOI) on temporal-parietal and frontal cortex of both sides. BRRT were administered to 15 patients twice a day, for 30 minutes (BRRT group). The BRRT, by means of a custom device, increases the blood flow of cerebral microcirculation.

Results: Ten patients from the BRRT group and 10 from the control group completed the 12-month follow-up. At the end of rehabilitation protocol a significant improvement of MMSE and RAVLT was observed in the BRRT group as compared to control group, $F > 78$, $p < 0.001$, with large effect size, Cohen $d > 0.88$. At T12 compared to T0, a significant improvement of TOI on frontal cortex of both sides was observed in the BRRT group as compared to control group, $F > 10$, $p < 0.003$.

Conclusions: In our pilot study, BRRT improves verbal memory-learning and global cognitive impairment which are associated with increased TOI values on frontal cortex of both sides. Additionally, BRRT seems to be well tolerated and, thus, might have a reliable application in the clinical management in mild AD patients.

When FDG-PET puzzles the diagnosis: description of three cases with Subjective Memory Impairment

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Background: Subjective cognitive impairment (SCI) is a widespread complaint in the elderly community. Cerebral glucose metabolism reductions have been observed on FDG-PET before the onset of AD symptoms and a growing list of observations has highlighted the importance of PET as a tool for the detection of early disease and for estimating an increased risk for future dementia. However, what is the predictive value of FDG-PET abnormalities at the very early stages of cognitive decline?

Methods: We describe three patients with SCI that presented an impaired FDG-PET pattern. The cases, longitudinally studied, were recruited from our Memory Clinic and were re-examined periodically for a period ranging from two to fourteen years.

Results: All subjects performed periodically a complete neuropsychological evaluation, always confirming a normal profile. No past or present psychiatric disorders were diagnosed according to DSM-IV criteria. FDG-PET showed a temporo-parietal hypometabolism in all patients; one patient exhibited a moderate hippocampal atrophy at structural MRI, while all subjects had a high cognitive reserve index. One subject completed the diagnostic procedure performing also a genetic study and CSF Aß42 and tau dosage.

Conclusions: The risk in SCI of converting to MCI is 10% over 3 years, about 3 times higher than subjects without SCI. Some studies (1-2) suggested that patients with SCI had significant cerebral metabolic rate of glucose reductions in several brain regions, including the parahippocampal gyri, parieto-temporal and inferior frontal cortices, fusiform gyrus, and thalamus, as compared to controls, with a 75% accuracy, even though none of the subjects investigated converted to MCI after a 35 months of follow-up. Therefore, other factors, including CR, together with FDG-PET have to be taken into account in the selection of patients at risk of developing dementia.

Alterations of white matter integrity in patients with dementia with Lewy bodies and visual hallucinations

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Background: Presence of recurrent complex visual hallucinations (VH) is a core feature of dementia with Lewy bodies (DLB). The pathophysiology and neuronal correlates of VH are still controversial.

Objectives: The aim of this study was to investigate whether the presence of VHs in DLB was associated with microstructural changes of the white matter tracts studied with Diffusion Tensor Imaging (DTI) MRI sequences.

Methods: Thirty DLB patients, 12 with VHs (VH+) and 18 without (VH-), and 19 patients with Alzheimer's disease (AD) were enrolled. Patients were matched for age and severity of cognitive impairment. All participants underwent extensive neuropsychological testing. Fluctuations in attention, REM sleep behaviour disorder (RBD) symptoms, extrapyramidal signs and behavioural disturbances were studied with dedicated clinical scales. DTI was performed at 1.5T. Mean diffusivity (MD), axial and radial diffusivity, and fractional anisotropy (FA) maps were obtained using whole brain tract-based spatial statistics (TBSS).

Results: The DLB VH+ group had significantly increased FA and radial diffusivity values in bilateral inferior fronto-occipital fasciculus, inferior longitudinal fasciculus (p corrected=0.05) and widespread in the corpus callosum, compared to VH- group. An increased MD was significant in the superior longitudinal fasciculus and the body of the corpus callosum only in the right hemisphere in VH+ patients. The increased MD in this tract correlated with poor performances on test assessing visual attention. No differences in diffusivity and FA values have been found between DLB and AD patients.

Conclusions: This study was the first to explore diffusivity and FA values in whole brain white matter in DLB patients with VH. The findings of diffuse microstructural alterations of white matter in VH+ patients may be the key to the understanding of underlying neurobiological mechanism of VH in DLB.

Author Index

Adorni, F.	S41	Bernardi, L.	S5, S6, S18, S25, S42
Adrian, E.	S36		
Agosta, F.	S1, S11, S13, S14, S26, S28, S29, S53	Bernini, S.	S44
		Berti, V.	S32
Agosti, V.	S45	Bertola, F.	S53
Alberici, A.	S27	Bessi, V.	S5
Alberoni, M.	S2	Bianchi, M.	S28, S44
Albertini, S.	S49	Bianchi, V.	S15
Alexopoulos, P.	S25	Binda, D.	S53
Alonso, E.	S25	Binetti, G.	S5, S25
Amidei, S.	S17	Bini, P.	S28, S44
Amore, M.	S36	Blandini, F.	S44
Anfossi, M.	S6, S18, S25, S42	Blasimme, A.	S10
Appollonio, I.	S53	Blesa, R.	S25
Arancio, O.	S55	Boada, M.	S25
Archetti, S.	S4, S41	Bobba, F.	S54
Ariano, S.	S55	Bocchetta, M.	S5
Arighi, A.	S50	Bocchicchio, S.	S17
Arnaldi, D.	S39	Boeve, B.F.	S25
Attems, J.	S25	Bonanni, L.	S27, S33
Ausili – Cefaro, G.	S33	Boncoraglio, G.	S38
Avolio, C.	S12	Bonfiglio, C.	S4
Babiloni, C.	S5	Bongianni, M.	S6
Baborie, A.	S25	Bonnì, S.	S21, S22
Baglio, F.	S2	Bonsi, R.	S50
Bagnoli, S.	S5, S24, S25, S35, S38	Bonuccelli, U.	S37
		Borella, E.	S34
Baker, M.	S25	Borroni, B.	S4, S5, S25, S27, S41, S57
Baldinelli, S.	S3, S8, S9		
Baldonero, E.	S15	Borsello, T.	S21
Baratti, M.	S17	Bosia, M.L.	S36
Barbarulo, A.	S57	Bossert, I.	S39
Barbieri, M.P.	S36	Bottoni, G.	S39
Barocco, F.	S17	Bove, R.	S33
Baroni, M.	S6	Bozzali, M.	S39, S50, S51, S52, S57
Bartley, L.	S25		
Bartolini, V.	S8	Bracco, L.	S5, S38
Barulli, M.R.	S4, S49	Brandimarti, A.	S36
Bechi Gabrielli, G.	S51	Brice, A.	S25
Bellandi, D.	S43	Brooks, W.S.	S25
Bellodi, L.	S11	Brugnolo, A.	S36, S39
Benussi, A.	S4	Bruni, A. C.	S5–S7, S18, S19, S25, S42, S57
Benussi, L.	S5, S25, S28		
Benuzzi, F.	S56	Bruni, A.C.	S42
Bergui, M.	S43	Bruno, G.	S10, S46, S55, S57
Bernardi, G.	S20	Buongarzone, M.P.	S58