Functional connectivity in the Default Mode Network relates to the severity of depression in autosomal recessive Parkinson's disease

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Background: mutations in the Parkin and PINK1 genes are frequent causes of early onset, autosomal recessive Parkinson's disease (ARPD). Affected individuals usually carry biallelic mutations, even though carriers of single heterozygous mutations may manifest subclinical or subtle signs related to the disease. The phenotype of ARPD is characterized by slow progression and good response to dopaminergic therapy, but psychiatric features including depression are a frequent occurrence. Resting state fMRI has already been used to investigate the pathophysiology of depression. **Methods:** we enrolled eight PD patients homozygous for Parkin or PINK1 mutations (HOM), and nine heterozygous healthy relatives (HET). All subjects underwent neuropsychological and behavioral assessments including Hamilton Depression scale (Ham-d) and Hamilton Anxiety scale (Ham-a). An MRI assessment at 3T, including EPI images for resting state fMRI, was obtained in each patient. Independent component analysis (ICA) was used to identify the Default Mode Network (DMN). The second level analysis was performed in SPM8 using a two sample T test, with group (HOM or HET) as factor, Ham-d or Ham-a scores as covariates of interest, and total grey matter volume and the Unified Parkinson's Disease Rating score as covariate of no interest. **Results:** HOM patients presented significantly higher scores than HET subjects at all behavioral measures. In resting-state fMRI analyses, HAM-d scores were negatively correlated with functional connectivity within the DMN across the whole population in the BA 23/31 and in the BA 9/46. A significant "group by score" interaction was also observed, within DMN connectivity, in the precuneus of HOM *vs* HET subjects. **Conclusions:** our data indicate that, in ARPD caused by PINK1 and Parkin mutations, depression is pathophysiologically associated with brain tissue abnormalities by the disconnection mechanism. As expected, depression and brain disconnection are both more severe in HOM than in HET mutation carriers.

Anti-Aβ autoantibodies in cerebral amyloid angiopathy-related inflammation: a human spontaneous model of amyloid-related imaging abnormalities (ARIA) in Alzheimer's disease

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Objective: cerebral Amyloid Angiopathy-related inflammation (CAA-ri) is characterized by vasogenic edema and multiple cortical/subcortical microbleeds, sharing several aspects with the recently defined Amyloid-Related Imaging Abnormalities (ARIA) reported in Alzheimer's disease (AD) passive immunization therapies. Herein, we investigated the role of anti-amyloid beta (Aβ) autoantibodies in the acute and remission phases of CAA-ri. **Methods:** we used a novel ultra-sensitive technique on patients from a retrospective multicenter case-control study, and evaluated the anti-Aβ autoantibodies concentration in the cerebrospinal fluid (CSF) of 10 CAA-ri, 8 CAA, 14 multiple sclerosis and 25 control subjects. Levels of soluble Aβ40, Aβ42, tau, P-181 tau and APOE4 genotype were also investigated. **Results:** during the acute phase of CAA-ri, anti-Aβ autoantibodies were specifically increased and directly correlated with Aβ mobilization, together with augmented tau and P-181 tau. Following clinical and radiological remission, autoantibodies progressively returned to control levels, and both soluble Aβ and axonal degeneration markers decreased in parallel. **Interpretation:** our data support the hypothesis that the pathogenesis of CAA-ri may be mediated by a selective autoimmune reaction against cerebro-vascular Aβ, directly related to autoantibodies concentration and soluble Aβ. The CSF dosage of anti-Aβ autoantibodies with

the technique here described can thus be proposed as a valid alternative tool for the diagnosis of CAA-ri. Moreover, given the similarities between ARIA developing spontaneously and those observed during immunization trials, anti-Aβ autoantibodies can be considered as novel potential biomarkers in future amyloid-modifying therapies for the treatment of AD and CAA.

Cerebrospinal fluid Alzheimer's disease like pattern in the diagnosis of atypical dementias

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Background: differential diagnosis between Frontotemporal Dementia (FTD), Corticobasal Syndrome (CBS), Progressive Supranuclear Palsy Syndrome (PSP), FTD with motor neuron disease (FTD-MND) is often challenging, because of the occurrence of atypical cases. Autopsy series have identified Alzheimer Disease (AD) pathology in a consistent percentage of patients with atypical dementias. It has been demonstrated that Cerebrospinal Fluid (CSF) tau/Aβ42 dosage is a reliable marker for AD. **Objective:** to evaluate the presence and percentage of CSF AD-like patterns (high CSF tau/Aβ42 ratio) in patients with atypical dementias in order to identify an ongoing AD neurodegenerative process. **Methods:** one hundred seventy two consecutive patients fulfilling current clinical criteria for behavioural variant FTD (bvFTD, n=73), agrammatic variant of Primary Progressive Aphasia (avPPA, n=19), semantic variant of PPA (svPPA, n=12), FTD-MND (n=5), CBS (n=42), PSP (n=21) were recruited and underwent CSF analysis. CSF AD-like and non AD-like (nAD-like) patterns were identified. **Results:** CSF AD-like pattern was reported in 6 out of 73 cases (8.2%) in the bvFTD group, in 3 out of 19 (15.8%) in the avPPA group, and in 7 out of 42 (16.7%) in the CBS group. One out of 12 (8.3%) in the svPPA group had CSF AD-like pattern. None of the FTD-MND and PSP patients had CSF AD-like pattern. No differences in demographic characteristics were detected between subgroups in each phenotype. **Conclusions:** our findings convey that the CSF tau/Aβ42 ratio could be found in a proportion of cases with clinical bvFTD, avPPA and CBS. Detecting an on-going AD pathological process in atypical dementias has several implications for defining distinctive therapeutic approaches, guiding genetic screening and helping in patients' selection in future clinical trials.

Resting functional connectivity reveals residual functional activity in Alzheimer's disease

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Objective: functional MRI (fMRI) has great potential for unravelling mechanisms of functional decline in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), but task-fMRI studies have produced conflicting results, partly due to failure to account for underlying morphological changes, and to variations in ability to perform the tasks. Resting-fMRI is promising because it does not require a task. We aimed to improve the understanding of how resting-fMRI relates to brain function. **Methods**: 80 elderly (25 controls, 25 MCI, 30 AD) underwent a combined multimodal MRI protocol including task- and resting-fMRI. Task-fMRI data were acquired during the execution of a memory paradigm designed to account for differences in task performance. Structural and physiological confounds were modelled for both fMRI modalities. **Results**: successful recognition was associated with increased task-fMRI activation in lateral prefrontal regions in AD relative to controls; this overlapped with increased resting-fMRI functional connectivity in the same regions. **Conclusions**: our results show that task- and resting-fMRI can reveal residual ability over the known changes in brain morphology and cognition occurring in AD, and suggest that resting-fMRI has a potential to measure the effect of new treatments.

Presenilin gene mutations in Alzheimer's disease and Idiopathic Dilated Cardiomyopathy (iDCM): a multisystemic disorder

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Alzheimer's disease (AD) is defined as a neurodegenerative disease, which lacks the ischemic lesions typical of vascular dementia. However, it is widely accepted that cardiovascular risk factors and diseases favor the onset and progression of the cognitive decline in patients affected by AD. The finding that presenilin (PSEN), one of the major proteins involved in the pathogenesis of AD, is expressed in the heart imposes a reconsideration of cardiac biology and pathology in AD patients. We advanced the possibility that mutations in PSEN1 and PSEN2 dictate alterations in cardiac anatomy and function, by inducing maladaptive responses of cardiomyocytes and cardiac stem cells (CSCs). Twelve donor human hearts and 23 explanted hearts affected by idiopathic dilated cardiomyopathy (iDCM) were studied microscopically. Unexpectedly, iDCM hearts contained intracellular and extracellular amyloid deposits indistinguishable from the senile plaques and tangles typically present in AD brain. Cardiomyocytes exposed to oligomers showed defects in contractility and calcium transients. Importantly, genetic screening led to the identification of 2 known and 2 previously unknown mutations of PSEN1 and PSEN2 in iDCM patients. Based on these observations, mice were treated with γ-secretase inhibitors to test the effects of this compound on the evolution of the post-infarcted heart and the development of DCM. By echocardiography and invasive hemodynamics, inhibition of γ-secretase led to severe impairment in cardiac function, ventricular dilation and wall thinning. These defects were induced by blockade of the regenerative response of the myocardium. The proliferation of CSCs and myocytes was significantly reduced resulting in a decrease in cell number. Our results suggest that presenilin is involved in diseases affecting organs other than the brain. Presenilin mutations may induce the onset of iDCM characterized by amyloid deposits similar to AD senile plaques. Additionally, γ-secretase inhibition is coupled with defects in cardiac regeneration.

Frontotemporal Lobar Degeneration due to the C9ORF72 hexanucleotide repeat expansion: psychotic clinical presentation

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Background: a hexanucleotide repeat expansions in the first intron of C9ORF72 has been shown to be responsible for a high number of familial cases of Amyotrophic Lateral Sclerosis (ALS) or Frontotemporal Lobar Degeneration (FTLD). However, atypical presentations have been described, particularly psychosis. **Methods:** we determined the frequency of the hexanucleotide repeat expansions in a population of 651 FTLD patients, and compared the clinical characteristics of carriers and non-carriers. In addition, we genotyped 21 patients with Corticobasal Syndrome (CBS), 31 patients with Progressive Supranuclear Palsy (PSP) and 222 controls. **Results:** the pathogenic repeat expansion was detected in 39 (6%) patients with FTLD (17 males and 22 females), however not in any CBD and PSP patients or controls. Twenty-four out of 39 carriers had positive family history for dementia and/or ALS (61.5%), whereas only 145 out of 612 non-carriers had positive family history (23.7%; P<0.000001). Clinical phenotypes of carriers included: 29 patients with the behavioural variant Frontotemporal dementia (bvFTD; 5.2% of all cases diagnosed with bvFTD), 8 with bvFTD/Motor Neuron Disease (MND; 32% of cases with bvFTD/MND), 2 with SD (5.9% of patients with SD), and none with Progressive Non-Fluent Aphasia. The presentation with psychosis was more frequent in carriers than non-carriers (10/33 versus 3/37, P=0.029) as well as the presence of cognitive impairment at onset (15/33 versus 5/37; P=0.0039). **Conclusions:** the repeat

expansion in the C9ORF72 gene is a common cause of FTLD, and often presents with late onset psychosis or memory impairment.

C9ORF72 gene locus in frontotemporal dementia and primary progressive aphasia

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Background: a pathogenic expansion of a hexanucleotide (G4C2) repeats in the regulatory region of C9ORF72 was recently identified as a major cause of ALS/FTD pathogenesis. Less clear is the role of this repeat expansion, and in particular of the C9ORF72 gene locus as a whole in non ALS forms bvFTD and PPA. **Methods:** a total of 285 patients with a clinical diagnosis of FTLD and 298 cognitively healthy subjects (MMSE >= 28, CDR = 0) were consecutive recruited at Neuropsychology Unit (Department of Neurology) of the Catholic University School of Medicine in Rome (Italy) and to the Centre for Ageing Brain and Neurodegenerative Disorders (Neurology Unit) at the University of Brescia (Italy). The three single nucleotide polymorphisms rs10122902, rs1565948 and rs2282241, spanning about 15.5 kb at the C9ORF72 locus (9p21.1), were chosen to be suitable for mapping the locus. Genetic analysis was made in blinded fashion by means of the allele discrimination assay using an ABI PRISM 7700 Sequence Detector system. **Results:** a significant difference in the distribution of rs2282241-A/G between PPA and controls (42.31% vs 29.19%; p=0.039) or bvFTD (42.31% *vs* 26.64%; p=0.005) was observed. Thus, the rs2282241-A/G genotypes appeared at risk for PPA as compared with Controls (OR=1.782, 95%CI 1.027-3.090) or with bvFTD (OR=2.250, 95% CI 1.244-4.064). No significant differences were observed in the distribution of the estimated haplotypes among the study groups. **Conclusion:** whereas more studies on highly selected samples of patients are needed to confirm our results and to clarify the role of C9ORF72 gene locus in FTLD, our results confirm a minor role, if any, of the C9orf72 locus, independently from the causative hexanucleotide expansion in PPA.

A 12 years clinical follow-up of two PINK1 families: motor, cognitive and psychiatric features

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The PINK1 gene (PARK6) is the second most frequent cause of autosomal recessive Parkinson disease (ARPD) 1. Currently, no studies have systematically assessed non-motor symptoms (NMS) in PINK1 carriers, including cognitive and psychiatric profiles, nor long-term follow up studies are present in literature. Aim was to evaluate homozygous and heterozygous PINK1 mutation carriers from two large Italian families previously described 2 over a follow up period of twelve years. All subjects underwent a complete neurological examination with Unified Parkinson's Disease Rating Scale motor scale (UPDRS-III), Hoehn and Yahr staging. Motor complications and NMS were investigated. Cognitive status was assessed with UPDRS section I, mini-mental state examination, Montreal Cognitive Assessment (MoCA) and an extensive neuropsychological battery. Depression, apathy, anxiety and impulsiveness were also assessed. We evaluated 5 homozygotes and 13 heterozygotes (follow-up 12.1+1.0 years). In all homozygotes, motor evaluation revealed a slight progression of motor symptoms and a persistent excellent response to levodopa, with slight motor complications. Sleep impairment was presented in all patients, and NMS in four. Three presented impulse control disorders and two slight anxiety and apathy symptoms.Three heterozygotes showed motor signs and were diagnosed as possibly affected. They all had NMS and sleep disorders. In neuropsicological testing, both groups had abnormal values at MOCA and low performances in a test of oral confrontation naming of nouns and verbs. All homozygotes showed some deficits in specific cognitive domains especially in test sensitive to frontal functions, one of them presented a general cognitive decline. Among heterozygoted, 3 over 13 showed an impairment of long and short-term memory, 3 over 8 reported im-

paired verbal fluency. None presented hallucinations or psychosis. We confirm slow progression and good levodopa response in PINK1-related ARPD and expand the phenotypic profile including psychiatric and cognitive features as part of the core clinical presentation of this disease.

Visual hallucinations and white matter integrity in dementia with Lewy bodies: a whole brain tract-based spatial statistic study

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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. **Aim:** 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:** 30 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 MD and radial diffusivity values (p corrected=0.05) in the bilateral superior and inferior longitudinal fasciculus and widespread in the corpus callosum, compared to the VH- group. An increased axial diffusivity was significant in the superior longitudinal fasciculus and the body of the corpus callosum only in the right hemisphere in VH+ patients. A non significant trend towards reduced FA values was found in the occipital white matter in the DLB VH+ group. No differences in diffusivity and FA values have been found between DLB and AD patients. **Discussion:** 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.

White matter lesions and BPSD in mild cognitive impairment

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Background: behavioral disorders and psychological symptoms (BPSD) are frequently observed in patients with dementia but, at a lesser extent, also in patients with mild cognitive impairment (MCI). **Aim:** to investigate whether a relationship exists between White Matter Hyperintensity (WMHs) and BPSD in patients with amnesic (a-) MCI. **Methods:** fifteen patients with a-MCI single (-sd) and seventeen with a-MCI multiple domain (-md) were enrolled for this study. All patients underwent the Neuropsychiatric Inventory-12 and MRI scanning 3T. MRI acquisitions included T2-weighted and FLAIR scans to assess identify White Matter Hyperintensities (WMHs) and to assess the total lesion volumes (WHM-vol). Moreover, WMH anatomical localization were evaluated by quantitative scales. **Results:** there were no significant differences between groups in the presence and severity of BPSD. However, a significant association was found between the presence and severity of apathy and WMHs in the basal ganglia (BG) across all groups. Individual group correlations revealed that this relationship is stronger, in the a-MCI-sd group, for white matter lesions anatomically located in parieto-occipital areas (inferior frontal-occipital fasciculus-IFO). Conversely, a-MCI-md patients revealed a relationship between their apathy scores and total WMH-vol, and WMHs distribution in the Caudate nucleus and Putamen. These results were confirmed by regression analyses. **Conclusion:** this study suggests that, in patients with a-MCI-sd, apathy is, at

least partially, due to a disconnection syndrome. In contrast, in the patients with a-MCI-md, apathy is more strictly associated with strategic infarcts involving the fronto-striatal circuits.

Validation and comparison of NIA-AA and IWG diagnostic criteria for Alzheimer's Disease in MCI patients coming from three european memory clinics

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Objectives: the availability of *in vivo* biomarkers of Alzheimer's Disease (AD) neuropathology has led to the development of new diagnostic criteria that reconceptualize AD as a disease featuring the combination of brain amyloidosis and neurodegeneration beyond a core of clinical symptoms. **Aim**: to validate new diagnostic criteria, assessing and comparing diagnostic performance of individual criteria in patients with Mild Cognitive Impairment (MCI) coming from 3 European memory clinics. **Methods:** markers of amyloidosis (abnormal CSF Aβ42) and neurodegeneration [hippocampal atrophy, temporoparietal (TP) hypometabolism on FDG PET, and abnormal CSF tau] were measured in 73 MCI patients clinically followed for at least 1 year (mean of 28±17 months) to ascertain progression to AD. Positive (LR+) and negative likelihood ratios (LR-) of individual items of IWG and NIA-AA criteria were compared. **Results:** 29 MCI patients progressed to AD (pMCI) and 44 remained stable (sMCI). Among IWG criteria, positivity to any biomarker had lowest LR- (0.00), while positivity to FDG-PET had highest LR+ (5.82) and low LR- (0.24). Among NIA-AA criteria, positivity to neurodegeneration (FDG-PET, MRI or CSF tau markers, irrespective of amyloidosis status) had lowest LR- (0.06), while positivity to Aβ42 and FDG-PET or Aβ42 and hippocampal volume atrophy had highest LR+ (6.45 and 5.56). **Conclusions:** markers of neurodegeneration are the strongest positive and negative predictors of short term incident dementia in MCI, irrespective of amyloidosis status. FDG-PET is the strongest individual positive predictive biomarker.

TMEM106B polymorphism modulates functional brain connectivity in asymptomatic Granulin mutation carriers

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Background: Granulin (GRN) mutations represent one of the most frequent genetic causes of inherited Frontotemporal Dementia (FTD). The study of asymptomatic carriers of GRN Thr272fs mutation (aGRN+) gives the unique opportunity to study the natural history of the disease and the role of modulating factors on disease onset. It has been demonstrated that TMEM106B polymorphism affects age at onset in GRN mutation carriers.
Objective: to evaluate the impact of TMEM106B genetic status on resting state functional connectivity in aGRN+. **Methods:** 17 aGRN+ and 14 healthy controls (HC) were studied to evaluate changes in resting-state functional connectivity, focusing on Default Mode Network (DMN), Ventral and Dorsal Salience Networks (SN), Executive Network (EN), Frontoparietal Networks (FPNs) and Attentive Network (AN). Differences of slope analyses were used to evaluate the effect of TMEM106B polymorphism in aGRN+ compared to HC ($P<0.05$ FDR-corrected). **Results:** the direct comparison between aGRN+ and HC revealed an increased connectivity within the EN, mainly involving the right precentral gyrus and a reduction of connectivity within left FPN (i.e. right caudate and left superior parietal lobule) in the former group. TMEM106B polymorphism (T/T) was associated with a decreased connectivity within the ventral SN (i.e. medial frontal gyrus), left FPN (precuneus) and AN (right medial frontal gyrus); furthermore we found an increased connectivity within EN in right medial frontal gyrus.

Discussion: this study suggested that different networks are specifically involved in disease onset in GRN-related FTD, and that the natural history may be modulated by additional genetic factors. Reduced connectivity within FPNs represented the target of GRN-disease itself, but an extra damage of ventral SN and AN was observed in aGRN+ subjects carrying at-risk TMEM106B polymorphism. Genotyping TMEM106B is of importance in aGRN+ subjects to assess earlier brain damage.

The genetics of cognitive impairment in ALS

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Background: an overlap between amyotrophic lateral sclerosis and frontotemporal dementia (FTD) has been described for over a century, and the recent identification of C9ORF72 mutations has confirmed the strict relationship between the two diseases. **Aim:** to assess the frequency and the clinical pattern of cognitive impairment in a population-based series of ALS patients identified through the Piemonte and Valle d'Aosta register for ALS, fully characterized from the genetic point of view. **Methods:** DNA samples were screened in a series of 183 incident subjects for the presence of major ALS-related genes (C9ORF72, SOD1, TARDBP, FUS, OPTN and ANG) and for PGRN. All patients underwent an extensive neuropsychological battery. Cognitive diagnosis was made according to the international consensus criteria (Neary, 1998; Strong, 2008). A control group of age- and gender-matched controls was tested with the same battery. **Results**: in 161 cases (87.9%) no mutations were identified. Out of 22 (11.9%) mutated patients, 9 (4.9%) had mutations in the C9ORF72 gene, 5 (2.7%) in SOD1, 5 (2.7%) in TARDBP, 1 (0.5%) in FUS and 1 (0.5%) in OPTN. No mutations in ANG or PGRN were found. Of the 9 cases with C9ORF72 mutations, 6 had ALS-FTD, 2 had ALS with executive impairment and only one was cognitively normal. One of the 5 patients with SOD1 mutations and one of the 5 patients with TARBDP mutation had ALS with behavioural impairment, while all the other patients were cognitively normal. Both patients with FUS and OPTN mutations were cognitively normal. **Conclusions:** patients with SOD1, TARDBP, FUS, and OPTN mutations were mostly cognitively normal, while almost all patients with C9ORF72 mutations had FTD or executive impairment. Compared to the control group, C9ORF72 patients had a reduction of overall cognitive efficiency, mental flexibility and reasoning.

Estimating the inheritance of Frontotemporal Lobar Degeneration

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Background: Frontotemporal Lobar Degeneration (FTLD) has a strong genetic basis, familial forms occurring in 30-50%. Causative genes have been identified, with an autosomal dominant pattern of inheritance. Notwithstanding, in a number of cases with positive family history no pathogenetic mutation has been reported, and the role of genetics in sporadic cases is still unclear. **Objectives:** to estimate the genetic contribution to FTLD using concordance among parent-offspring pairs. **Methods:** a liability threshold model of disease was used to estimate heritability of early (EO, <65 years) and late-onset (LO, >=65 years) FTLD, by examining the concordance between parents and offspring. Probands with at least one parent whose dementia status was known were recruited from 15 Italian centres, and the presence or absence of dementia was considered in siblings. Different prevalence estimates, as available by literature data, were tested. **Results:** a total of 260 probands, and 1619 family members were considered in this study. We found that parent-offspring concordance in FTLD was 6.25%, resulting in hereditability of 98.5% (95% confidence interval, CI 85.0%-100.0%). Equal heritability for both sexes regardless of parental gender was reported. EO-FTLD showed hereditability of 86.3% (95% CI: 77.0%-95.0%), and LO-FTLD of 75.7% (95% CI: 65.0%-86.0%). **Conclusions:** estimating the contribution of genetics in FTLD may help in driving future genetic studies to identify new pathogenetic determinants. We suggest that FTLD is a ge-

netic-based disease in the most of cases, even in the elderly. Different inheritance modality might be considered in future work, beyond autosomal dominant disease.

Understanding phenotype variability in Frontotemporal Lobar Degeneration due to Granulin mutations

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Background: phenotype in patients with Granulin (GRN) mutations is unpredictable, ranging from behavioural variant Frontotemporal Dementia (bvFTD) to agrammatic variant of Primary Progressive Aphasia (avPPA). **Objective:** to identify genetic pathways differentiating phenotypic expression in patients carrying GRN mutations. **Methods:** patients carrying the same GRN T272SfsX10 mutation and sharing a common ancestor were consecutively enrolled. A careful clinical assessment was carried out, and the diagnosis of either bvFTD (n=8, age=69.5±6.4) or avPPA (n=6, age=59.1±4.5) was done. A group of healthy controls was considered as well (n=9). Microarray gene expression analysis on leukocytes was performed in the two groups. **Results:** several transcripts have been identified as differentially expressed in bvFTD and avPPA patients carrying GRN T272SfsX10 mutation. In particular, genes encoding for neurotrophic factors, genes involved in ubiquitin degradation system and encoding for transmembrane proteins were mainly involved. **Discussion:** genotype-phenotype association is heterogeneous in GRN-mutation carriers, even within the same mutation and in the same family. However, this study suggests that specific molecular pathways drive the clinical picture, and thus the selective focal brain damage. Future work are warranted to elucidate these molecular mechanisms.

Clinical characteristics and neuroimaging features of frontotemporal dementia associated with C9ORF72 mutations in a cohort of Sardinian patients

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Recently a hexanucleotide repeat expansion in noncoding region of C9ORF72 has been found to be a major cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Several studies has suggested that clinical, behavioural and neuroimaging characteristics of FTD patients with C9ORF72 mutations are qualitatively distinct from the others FTD patients. We describe the clinical phenotypes of our Sardinian cohort of patients with FTD carriers of C9ORF72 mutations. We screened 49 patients with Bv-FTD, progressive non fluent aphasia (PNFA) and semantic dementia (SD) for mutations in C9ORF72 gene. We identified 7 patients with C9ORF72 mutations representing the 14,3% of the cohort. The mean age at onset was 58 years. The clinical presentation varied: 6 had Bv-FTD alone, 1 had mixed PFNA-Bv-FTD. 2 patients during the disease course developed also motor neuron disease. In the cohort 5 cases were familial (71%) and 2 sporadic. 6 patient (86%) presented with psychosis; of these 2 had delusions and hallucinations, 4 delusions only. 1 patient presented with apathy. Mutation carriers showed more than other FTD patients, the presence of complex repetitive behaviours and fixed ideas. 6 of the 7 patients showed extrapyramidal signs. All the patients showed apathy. Structural neuroimaging was performed in all the patients and showed frontal and temporal atrophy but, in most of cases, also parietal and other posterior areas involvement. 4 of the 7 patients underwent a perfusion SPECT that found fronto-temporal areas dysfunction and, in 2/3 of patients, also the involvement of the parietal lobes. Our clinical and

neuroimaging findings, in accord with others previous reports, suggest that the patients carriers of C9ORF72 mutations have a distinct phenotypes. We highlight that C9ORF72 mutations have a strong association with the presence of psychotic symptoms, usually not common in FTD; moreover neuroimaging findings show frequently the involvement of fronto-temporal but also posterior areas.

Network analysis of intrinsic functional connectivity in the semantic variant of primary progressive aphasia

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Objective: the semantic variant (SV) of primary progressive aphasia is associated with focal, typically asymmetric, temporal lobe degeneration. However, language abilities must arise from the activity of distributed neural networks. Graph theoretical analysis allows examining the topology of complex network systems. This study examines the integrity of the functional brain connectome in patients with SV. **Methods:** Graph theoretical analysis was applied to resting state (RS) functional magnetic resonance imaging (fMRI) data from 13 SV patients and 25 age- and sex-matched healthy subjects. Functional connectivity between 90 cortical and subcortical brain regions was estimated using bivariate correlation analysis and thresholded to construct a set of undirected graphs. **Results:** Functional brain networks in SV patients showed loss of small world properties, characterized by a significantly lower clustering coefficient, lower global efficiency and longer characteristic path length compared with healthy elderly subjects. Compared with controls, SV patients did not show hub regions in the left temporal pole, anterior cingulate cortex (ACC), basal ganglia, occipital cortices, and bilateral parietal cortices. Nodal degree and local efficiency were globally reduced in patients relative to controls. SV patients showed the greatest decrease in nodal centrality in the bilateral temporal pole and gyri, amygdala, basal ganglia, orbitofrontal, middle frontal, inferior parietal gyri, occipital cortices, and left fusiform, hippocampus, ACC, postcentral gyrus. **Conclusions:** Graph analysis showed that SV functional networks are characterized by an imbalanced structure, with a loss of efficiency in information exchange between both close and distant brain areas. Our study showed that local functional network organization is also altered in SV patients. Focal degeneration of “classic” (temporal) language regions in SV patients may ultimately manifest in widespread connectivity disturbances elsewhere in the brain. **Funding:** this study was partially supported by a grant from the Italian Ministry of Health (Grant #GR-2010-2303035).

Diagnosis disclosure and advance care planning in Alzheimer disease: opinions of a sample of Italian citizens

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Background: in current Alzheimer disease (AD) research there is a growing asymmetry between the modest benefits of the currently available treatments and prevention options, in contrast to the possibility to diagnose AD early in its natural history. This complex situation brings along a number of important ethical issues about diagnosis disclosure and end-of-life decisions that need to be addressed. **Aims:** to investigate the influence of sociodemographic factors and the experience of being a caregiver on opinions about ethical issues of AD, in a sample of Italian citizens. **Methods:** a sample of 1111 Italian citizens residing in Brescia were interviewed using a structured questionnaire. **Results:** the majority of the sample (83%) wanted disclosure for themselves. Women and caregivers were significantly less likely to agree that their hypothetically afflicted relative should be informed of a diagnosis of AD. The majority of the sample (81%) was in favor of advance care planning completion, most of all

younger participants and non-caregivers, whereas caregivers and the less educated subjects were more inclined to accept relatives' decisions in this situation. Less than a third of the sample (24%) was aware of the existence a judicially appointed guardian for patients affected by dementia. **Conclusions:** the majority of participants wanted a potential diagnosis of AD to be disclosed to them and to their relatives if they were to be afflicted. The utility of completion of advance care planning and designation of a judicially appointed guardian is frequently endorsed by the sample, but there is still poor knowledge about laws that protects patients affected by AD.

Repetitive deep transcranial magnetic stimulation improves verbal fluency and written language in a patient with primary progressive aphasia-logopenic variant (LPPA)

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Background: to date, no therapies are available for the logopenic variant of primary progressive aphasia (LPPA). Even though deep repetitive transcranial magnetic stimulation (rTMS) may improve cognitive functions in some neurodegenerative disorders, no previous studies investigated its effects in patients with LPPA. **Objective:** our aim was to investigate the effects on cognitive function of high frequency rTMS (hf-rTMS) delivered over the left dorso-lateral prefrontal cortex (DLPFC) through a coil designed for deep rTMS, compared to a SHAM stimulation, in a right-handed patient with LPPA. **Methods:** the patient presented a progressive language impairment (phonological errors in speech and naming, impaired single word retrieval and sentences repetition) and predominant left perisylvian atrophy and hypoperfusion. He received four stimulation cycles (two REAL and two SHAM) each of whom lasted 20 minutes for 5 consecutive days. Patient's performances in frontal, visuo-spatial and linguistic tasks were evaluated before and after each stimulation session. Test scores after REAL were compared with those obtained at baseline and after SHAM. **Results:** we found a temporary and highly significant improvement in the linguistic skills (both oral and written tasks) but not in the other cognitive domains tested, after REAL, but not SHAM stimulations. **Discussion:** Hf-rTMS delivered over the DLPFC could improve language in LPPA by enhancing long-term potentiation and synaptic plasticity within the stimulated and interconnected areas involved in language network. Our findings might prompt future researches into the feasibility and efficacy of deep hf-rTMS as a therapeutic tool in progressive aphasia syndromes and other neurodegenerative disorders.

Cognitive Reserve modulates the default mode network in patients with MCI and AD

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Aim: the aim of this study was to assess the impact of some proxy measures of "cognitive reserve" (CR), estimated using individual data on formal education and occupation, on functional connectivity of the default model network (DMN) in patients with AD or amnesic mild cognitive impairment (a-MCI). **Methods:** we investigated 11 patients with AD and 18 with a-MCI. All patients underwent an extensive neuropsychological battery and received: 1) a CR assessment (a questionnaire to assess the activities performed during life which are likely to impact on CR) obtaining 3 different indices; 2) MRI scanning at 3.0T, including MDEFT scan and T2*-weighted-EPI sensitized to BOLD contrast for resting state functional MRI (RS-fMRI). RS-fMRI data were processed for Independent Component Analysis (ICA) to identify the DMN. The second level analysis was then performed using a factorial model for each CR index separately. The factor was the group (a-MCI and AD), with a covariate of interest (the CR index). Age, total grey matter volume, and MMSE scores were entered as covariates of no interest to adjust the analysis for these potential confounds. Results: were accepted as significant at $p<0.05$ FWE-corrected at cluster level. **Results**: neither score (education and occupation) was significantly different between AD and a-MCI patients. The Education score was positive-

ly correlated with functional connectivity within the DMN (p=0.003) across the whole population in the precuneus. **Discussion:** our data confirm that CR, specifically that accumulated in youth, has an impact on brain connectivity in mitigating the effects of AD pathology. Modulation of connectivity occurs in one of the most critical nodes of the DMN, i.e. the posterior cingulate, for which disconnection with the medial temporal lobes through the cingulum has been hypothesized to play a critical role in the conversion from MCI to AD.

Cognitive predictors of good functional outcome in normal pressure hydrocephalus after ventriculoperitoneal shunting

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Background and Objectives: hydrocephalus is a condition of altered cerebrospinal fluid (CSF) dynamics idiopathic or secondary to cerebral injuries. Among patients with communicating hydrocephalus, 60% have a normal CSF pressure (NPH). NPH clinical presentation is characterized by Hakim-Adams' classic triad of clinical symptoms, namely: gait disturbances, urinary incontinence and cognitive impairment. Ventriculoperitoneal shunting (VS) represents the elective treatment of this syndrome. Several studies attempted to find predictors of good response to VS. Our study aims to identify neuropsychological predictors of good functional outcome after VS in patients with NPH. **Methods:** variation in the cognitive performances was evaluated three months after VS in 28 patients with NPH. Functional outcome one year after surgery established on functional scales (scoring other NPH symptoms such as ataxia and urinary incontinency) was assessed. The neuropsychological examination was composed by MMSE and subtests exploring short and long term memory, attention, praxis, language, executive functions and conceptual reasoning. **Results:** a One Way Manova showed no significant interaction between the variation of cognitive performance at follow-up and functional outcome ($p > 0.381$). On the contrary, the improvement in some tasks was good predictor of good functional outcome after one year. Specifically, an improvement in Mini Mental State Examination (MMSE, $p < 0.001$), Multiple Features Target Cancellation (MFTC: number of false alarms, $p < 0.05$), Semantic verbal fluency ($p < 0.03$) and in a subtest of cognitive flexibility (Stroop test Interference Time, $p < 0.05$ and Stroop test Interference Errors, $p < 0.02$) was significant among patients with good functional outcome. **Discussion and Conclusion:** neuropsychological pattern of NPH at presentation is mainly related to the damage of subcortical and frontal-subcortical circuits with greater impairment of executive functions. Our findings show that rapid improvement in executive tasks after VS is predictive of better long-term functional outcome.

Apathy evaluation scale: role of apathy symptoms in the evolution of subjects affected by Mild Cognitive Impairment

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Background and aims: apathy has been demonstrated an important symptom in the characterization of Mild Cognitive Impairment evolution, being associated to an increased risk of progression towards dementia. The Aim of this study was to describe the clinical evolution of MCI subjects with and without apathetic symptoms, evaluated by the Apathy Evaluation Scale (AES). **Methods:** one hundred-fifty five subjects meeting revised diagnostic criteria for MCI were enrolled and underwent a clinical, neurological and neuropsychological assessment at baseline and after 12 months. Patients were classified on the basis of the AES and the Geriatric Depression Scale (GDS) scores into three groups: MCI subjects scoring > 38 in AES and < 6 in the GDS were defined apathetic MCI (20%), subjects with a

GDS > 6 were defined depressed MCI (21%), subjects without apathy nor depression were defined normal MCI (59%). **Results:** after one year follow-up, 52% of apathetic MCI showed a worsening in global cognitive and functional assessment measured with the Clinical Dementia Rating Scale (CDR sum of boxes) in comparison with 15% of Depressed MCI (p= .000) and 24% of normal MCI (p= .000). **Conclusion:** apathy is hardly distinguishable from depression, thus it is necessary to use a specific instrument as the AES to detect apathetic symptoms in clinical practice. Apathetic MCI subjects identified with the AES seem to have an higher risk to develop Alzheimer's Disease.

High levels of participation in physical leisure activities protects MCI subjects against the risk of dementia

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Aim: to study the influence of life style on the risk of progression of mild cognitive impairment (MCI) to dementia. **Methods:** from January 2007, 176 MCI subjects from the "Luigi Sacco" Hospital underwent a standardized life-style questionnaire. Social, cognitive and physical scores were derived based on the assiduity of interpersonal contacts and on the frequency of participation in individual leisure activities. Subjects were requested to return every 12 months. The follow-up ended at the diagnosis of dementia (DSM IV criteria) or death. May 2011 was chosen as the end date for dementia surveillance. Cox regression was used to estimate the risk of dementia in relation to baseline social, cognitive and physical scores. In multiadjusted models, age, gender, education, MCI subtype, APOE genotype, Mini Mental State Examination (MMSE) and Geriatric Depression Scale (GDS) scores were controlled. **Results:** over a median follow-up of 2.59 year, 92 (52.2%) MCI subjects developed dementia. These subjects were older (75.7±6.1 vs. 72.2±8.2 years; p= 0.001) and more educated (8.5±4.6 vs. 7.1±3.6; p=0.03) as compared to non-converters. They had lower MMSE score (24.8±2.6 vs. 26.0±2.5; p=0.002) and lower GDS score (8.4±5.9 vs. 10.6±6.3; p=0.02) as to non-converters. Among patients who developed dementia APOE e4 genotype was more frequent compared to non converters (64% vs. 36%; p= 0.045). Subjects with physical score in the highest third had a lower risk (HR 0.44 95%CI 0.23-0.85) of progression toward dementia compared with those in the lowest third. No association was found between either cognitive or social scores and the risk of dementia. **Discussion:** to our knowledge, this is the first prospective clinical study which demonstrates that high levels of participation in physical leisure activities is associated with reduced risk of dementia in subjects with MCI attending a memory clinic. **Conclusion:** clinicians should encourage MCI subjects to perform physical activity.

Ventral visual stream is more impaired than dorsal stream in prodromal DLB: a cognitive study

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Background: the pattern of cognitive decline in dementia with Lewy bodies (DLB) is typically characterized by attentive, executive and visual-spatial deficits. **Aim:** to investigate the presence and type of deficit in visual abilities (spatial-perceptual-constructive) in the prodromal phase of DLB. **Materials and methods:** 25 patients with non-amnestic Mild Cognitive Impairment (MCI) (MMSE >27/30) diagnosed as prodromal DLB were enrolled (mean age: 75.5±6.1 years; mean MMSE score: 28.5±1). The diagnosis of DLB was confirmed at 3-year follow-up visit according to established criteria. A group of 60 patients with mild to moderate DLB dementia (MMSE < 27/30) served as control group (mean age: 75±6.4 years; mean MMSE score: 22.4±2.6; p<0.001). Visual-spatial and perceptual abilities were evaluated with the Visual and Object Space Perception (VOSP) battery. **Results:** visual perceptual deficits were detectable in 83% of the DLB-MCI patients: the performance in the subtest 2 (silhouettes task) was pathological in 71% and borderline in 12% of MCI patients. This frequency was similar to that of the DLB-dementia group (p=0.14). In the subtests exploring visual-spatial abilities (subtests 5-8) the DLB-MCI patients scored differently from the DLB-de-

mentia cases being within the normal range in more than 50% of cases. The scores at VOSP subtests did not correlate with disease duration, while they correlated with the disease severity (MMSE score) except for VOSP subtest 2 (p=0.14). **Discussion:** although visual-spatial deficits are claimed to be an hallmark of DLB since the early stages, a specific battery for visual-spatial and perceptual abilities showed that early deficits in visual perceptual abilities are more frequent than those in the visual-spatial and constructive spectrum. This findings suggest a progression of the cognitive deficits from the ventral to the dorsal visual pathway during the disease course, while specific perceptual deficits are detectable with dedicated tools in the very early stage of DLB.

Fast and slow conversion to Alzheimer's disease in Mild Cognitive Impairment: role of cerebrospinal fluid biomarkers

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Introduction: it is well known that cerebrospinal fluid (CSF) levels assessment of Aβ1-42 and Tau protein helps discriminating preclinical Alzheimer's disease (AD) from age-associated memory impairment, depression and other forms of dementia. Little is known about the ability of these biomarkers to predict speed of progression to AD in MCI patients. **Objective:** to examine whether demographic, neuropsychological and CSF parameters at the preclinical stage of AD can be used to discriminate between slow and rapid converters to AD in patients with MCI. **Materials and methods**: a group of 71 MCI patients were recruited from our Memory Clinic according to clinical criteria. At baseline, all patients underwent neurological assessment, complete neuropsychological evaluation, routine blood tests, ApoE determination, and lumbar puncture to dose t-Tau, p-Tau, Aβ1-42. We investigated baseline CSF and neuropsychological biomarkers patterns between groups of MCI patients stratified by later diagnoses of conversion to AD or other dementia. In addition, MCI patients who converted to AD (cMCI) where classified in slow and rapid converters (< or > 18 months). **Results:** MCI patients who went on to convert to AD show at baseline lower Aβ1-42 as compared to patients who remained stable MCI or who developed other dementia. The subgroup analysis between slow and rapid converters confirmed the role of Aβ1-42 to discriminate between the 2 groups: rapid converters showed already at baseline lower Aβ1-42 levels as compared to slow converters. No neuropsychological or demographic measures showed significant results in the analyses. Survival analysis performed in the cMCI patients subgroup confirmed that cMCI patients with lower value of CSF Aβ1-42 at baseline had significantly shortest median dementia-free survival. **Conclusion:** our results suggest that Aβ1-42 may be related to speed of conversion to AD in MCI patients and it could be useful in the stratification of cMCI population to support patients work-up in clinical setting.

ADAM10 at the synapses: new perspectives on Alzheimer disease pathogenesis

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Generation of Amyloid beta peptide is at the beginning of a cascade that leads to Alzheimer's disease (AD). Amyloid precursor protein, as well as beta- and gamma-secretases, are the principal players involved in Amyloid beta production, while alpha-secretase cleavage on APP prevents Abeta deposition. A disintegrin and metalloproteinase 10 (ADAM10) has been recently demonstrated to be alpha-secretase in neurons. Moreover, ADAM10 is a sheddase for many neuronal proteins and is located at the glutamatergic postsynaptic density. Although localization of ADAM10 in the synaptic membrane is key for its shedding activity, currently very little is known about the mechanisms that control the synaptic abundance of ADAM10. Here we show that two established form of long-term activity-dependent plasticity, i.e. long-term potentiation (LTP) and long-term depression (LTD) differentially regulate the synaptic availability and activity of ADAM10. LTP decreases ADAM10 surface levels and activity by promoting its endocytosis. This

process is mediated by activity-regulated association of ADAM10 with the clathrin adaptor AP2 complex, interaction which requires the distal 15 aminoacids of ADAM10. Conversely, LTD fosters ADAM10 insertion in the membrane and stimulates its activity. Furthermore, ADAM10 interaction with SAP97 is necessary for LTD-induced ADAM10 trafficking and required for LTD maintenance and LTD-induced spine morphology changes. Regulated interaction of ADAM10 with SAP97 and AP2 discloses a novel physiological mechanism of ADAM10 activity regulation at the synapses. This phenomenon produces a situation whereby synaptically regulated ADAM10 activity is positioned to modulate synaptic functioning. Moreover, the characterization of SAP97 and AP2 interaction and function in activity-dependent synaptic plasticity gives new insights on possible therapeutic targets of AD.

CSF biomarkers in the differential diagnosis of primary progressive aphasia

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Introduction: Primary Progressive Aphasia (PPA) is a neurodegenerative disorder involving primarily language. Three PPA variants have been currently characterized: non fluent/agrammatic variant (nfvPPA), semantic variant (svPPA) and logopenic variant (lvPPA). Recent evidences suggest that lvPPA is most commonly associated with Alzheimer's Disease (AD) pathology, while nfvPPA and svPPA with Fronto-temporal lobar degeneration (FTLD) pathology. Therefore cerebro-spinal fluid (CSF) beta-amyloid1-42 (Aβ42), total tau protein (t-tau), and tau phosphorylated at position threonine 181 (p-tau), frequently abnormal in AD patients, could be useful tools in differential diagnosis of PPA. **Objective:** to compare Aβ42, t-tau and p-tau CSF levels in lvPPA and sv/nfv PPA groups and evaluate their reliability in differential diagnosis of PPA. **Methods:** we measured CSF biomarker levels in a group of fourteen patients, seven with a clinical diagnosis of lvPPA, six with nfvPPA, one with svPPA. Measurements were performed using ELISA kits (Innogenetics, Ghent). **Results:** Aβ42 and p-tau CSF levels were significantly different in lvPPA *vs* nfv/sv PPA patients (mean value [± SE]): Aβ42 (377,14 [±53,87]) *vs* (842,43 [±114,6]) pg/mL, P=0,007 and p-tau (109 [±16,01]) *vs* (50,57 [±5,28]) pg/mL, P =0,007, whist no significant differences was found for t-tau (623,43 [±110,31]) *vs* (302,43 [±69,75]) pg/mL, P= 0,073. Six out of seven lvPPA and only one out of seven sv/nfv PPA patients had at least two abnormal CSF biomarker values. Finally, in lvPPA patients, CSF biomarker levels were very similar to those found in a sample of 72 AD patients admitted to our Department. **Conclusions:** PPA was previously considered a variant of FTD with few or no therapeutic option. Evidence that lv PPA is associated with AD pathology opened new diagnostic and therapeutic horizons. Our data, although the small sample size, show that CSF biomarkers can be useful in differential diagnosis of PPA, thus offering the possibility of targeted therapeutic interventions.

Early onset dementia associated with M239I Presenilin 2 mutation: executive dysfunction and frontal atrophy

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Background: Presenilin 2 gene (PSEN2) mutations are responsible for rare cases of Alzheimer Disease (AD), although atypical disease presentation and clinical features have been described. We previously identified the M239I pathogenic mutation in PSEN2, which was associated with a remarkable clinical intrafamilial phenotypic variability. **Subject and Methods:** we describe an additional family member with a presenile dementing condition. Extensive clinical and cognitive evaluation was assessed, along with genetic and Cerebrospinal Fluid determinations. Brain MRI scan was performed and analyzed by Voxel Based Morphometry with SPM. **Results:** the cognitive and behavioural profile, along with neuroimaging features with a selective atrophy in the left superior frontal gyrus and in the inferior temporal gyrus ($p<0.001$) demonstrated a peculiar involvement of the frontal

lobes, mimicking a Frontotemporal Lobar Degeneration (FTLD). Indeed, the pattern of CSF determinations (Abeta1-42 =430 pg/ml, Tau protein=792 pg/ml, and phospho-TAU =81 pg/ml) was comparable to those commonly found in AD patients. **Discussion:** this case description further endorse the evidence that presenile dementia, frequently overlapping AD with FTLD, constitutes a clinical conundrum, in which CSF tau and A-beta1-42 biomarkers offer a clear cut point of reference, also for the therapeutical implications of the diagnosis.

Detecting cognitive changes in ALS: a population-based study

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Background: cognitive changes in amyotrophic lateral sclerosis (ALS) range from mild forms of cognitive and behavioural impairment up to an overt frontotemporal dementia (FTD) and have been detected in 10 to 50% of patients. **Aim:** to assess the frequency and features of cognitive impairment in a population-based series of ALS patients compared to a gender-, age- and education-matched control group. **Methods:** a series of 183 incident ALS patients from the Torino and Cuneo provinces (72% of all incident patients) diagnosed between January 1st 2009 and December 31st 2011 underwent an extensive battery of neuropsychological tests encompassing executive function, memory, visuo-spatial function and language. The Frontal Systems Behaviour Scale was administered to caregivers (FrSBe-CG) to assess patients' behavioural abnormalities. A group of 86 matched controls underwent the same neuropsychological battery. Diagnosis of frontotemporal cognitive and behavioural syndromes was based on international consensus criteria (Neary et al., 1998; Strong et al., 2009). Patients were classified in six groups according to similarities in performances at the neuropsychological evaluation. **Results:** according to cut-off scores, clinical impressions and the international clinical criteria 92 (50.3%) patients were cognitively normal, 23 (12.6%) had ALS-FTD, 36 (19.7%) executive cognitive impairment (ALS-ECI), 10 (5.5%) non-executive cognitive impairment (ALS-NECI); 11 (6%) behavioural impairment (ALS-Bi); 11 (6%) non-classifiable cognitive deficits (ALS-NCCI). The comparison with the control group revealed the presence of impairment in multiple areas of cognition, with significantly lower MMSE scores and more evident neuropsychological deficits in the executive function domain. Patients with ALS-FTD and ALS-ECI had a significantly shorted survival than patients with normal cognition and other cognitive impairments. **Conclusions**: about half of the total series of ALS patients had some degree of cognitive impairment, but only 12.6% of them had a full-blown ALS-FTD. The presence of FTD or executive dysfunction significantly reduced patients survival.

Analysis of the diagnostic performance of short amyloid-beta peptide fragments in CSF of AD and MCI patients: data from two european centres

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Background: a striking pathological feature of Alzheimer's disease (AD) is the deposition of neuritic plaques, consisting mainly of amyloid beta peptides. One of the most abundant peptides in the plaques is the 42 aminoacid-form of Aβ (Aβ1-42). This fragment is generated by sequential cleavage steps of the amyloid precursor protein (APP), then it can be further degraded by a range of endogenous proteases. Recent studies have shown that a number of Aβ fragments measured using immunoprecipitation and mass spectrometry (MS) are increased in AD patients. **Aim:** we tested the hypothesis that Aβ fragments profile can be monitored in CSF using MS and may be useful to detect AD-related changes in Aβ processing. **Methods:** four groups of patients from two different cohorts (Perugia and Amsterdam) were included in the study (overall, 54 AD, 35 MCI-AD, 45 MCI-MCI and 41 controls). Short Aβ fragments

(Aβ 1-13 to Aβ 1-19) were quantified using immunoprecipitation and MALDI-TOF-MS. **Results:** seven peptides were reproducibly detectable and quantifiable using 200 μL of CSF. Only in Perugia's cohort, Aβ1-15 and Aβ1-16 were significantly increased in AD patients when compared to controls (p= 0.032 for Aβ1-15 and p = 0.014 for Aβ1-16). No significant changes were noticed for the other peptides. Aβ1-15 and Aβ1-16 peptides did not show any change in the MCI groups. **Discussions and conclusions:** using immunoprecipitation and MS, we were able to quantify seven short Aβ fragments in CSF of AD patients, showing a different expression profile in the four groups considered. This may underline a different processing of Aβ short fragments in AD, not related to progression, that needs to be further evaluated. Detection and quantification of short Aβ fragments might be useful for high-throughput screening in secretase inhibitors clinical trials. The observed differences in the two cohorts need further analysis for assessing possible sources of variability.

Longitudinal observation of MMSE Pentagon Test in autopsy-verified dementia with Lewy bodies and Alzheimer's disease patients: an application of the new Qualitative Scoring MMSE Pentagon Test (QSPT)

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Visual-constructional apraxia is a prominent feature of dementia with Lewy bodies (DLB) that may help to distinguish it from Alzheimer's disease (AD). The main goal of this study was to assess the pentagons copy performance of Mini-Mental State Examination (MMSE) with a new Qualitative Scoring MMSE Pentagon Test (QSPT) (Caffarra et al., in press) in order to determine which aspects of the drawings differentiate DLB from AD. QSPT is based on the assessment of different parameters of the pentagons drawing, such as number of angles, distance/intersection, closure/opening, rotation and closing-in. The QSPT scores were compared between demographically-similar DLB (n=16) and AD (n=15) patients at four different time points: the first year in which they received a diagnosis of dementia or any other cognitive deficit, and then three years, two years, and one year prior to death. Patient groups did not differ in dementia severity at baseline (MMSE: DLB = 24.5; AD = 24.81) and at any other point. All of them were autopsy-confirmed. During the first evaluation, number of angles was the only parameter that showed a significant decline in DLB compared to AD. Three years before death no differences were found in any parameters. Two years before death the total pentagons score and closure/opening parameter was significantly worse in DLB group. Finally one year before death only rotation parameter was worse in DLB than AD. The number of angles is the first parameter to differently decline in patients with autopsy-confirmed DLB compared with AD, and it may be an early marker of DLB. A gradual decline in other parameters and total pentagons score occurs in both groups during the following years, with greater severity for the DLB group. This study highlights the sensibility of adopting a qualitative scoring method for pentagon construction in differentiating DLB and AD dementia.

Alzheimer' s disease progression: hunting for predictors of the speed of cognitive decline

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Background: persons affected by Alzheimer's disease (AD) deteriorate progressively over several years until death showing a great variability. Although many studies have investigated factors that can influence the speed of cognitive decline, results are inconsistent. **Aims:** to describe natural history of AD and to explore the role of genetic and non genetic factors on disease progression. **Methods:** 53 subjects affected by mild AD were enrolled in 2009 at the Neurological Department of the University of Florence and were followed until July 2012. Information on demographics and medical history were taken at baseline and updated at each follow-up. APOE genotype was obtained from blood samples. **Results:** of the 53 subjects, 36 were female and 28 ε4 carriers,

mean MMSE score at baseline was 22.3, subjects were followed for a mean of 2.7 years. Cognitive decline was not linear (-1.1 point on MMSE the first year, -3.3 points the second year) and presented a great variability. Multi-adjusted regression analyses showed that cardiovascular diseases (CVD) increased the risk of rapid progression with an OR of 5.31 (95% CI 1.15-24.9). Gender, age at onset, education and APOE genotype didn't influence AD progression. Stratifiyng the population by APOE genotype, the effect of CVD was present only among ε4-carriers, while female gender and early age at onset increased the risk of rapid decline in the non-ε4 population. **Conclusion:** the interaction of ε4 allele and CVD determined a faster rate of AD decline, as previous reported in the literature. Disease progression among no-ε4 carriers was influenced by gender and age at onset in our sample. Different genotypes present different risk factors for AD progression.

Brain Computer Interface and Eye-Tracking for neuropsychological assessment of cognitive functions in Amyotrophic Lateral Sclerosis: the eBrain Project

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Background: many patients affected by Amyotrophic Lateral Sclerosis (ALS) show cognitive alterations, especially regarding frontal executive functions. Cognitive assessment is problematic in moderate-severe stages of ALS, due to the presence of motor-verbal impairment. Recently, Eye-tracking (ET) and Brain Computer Interface (BCI) have been preliminarily used in ALS to administrate cognitive testing. However, an extended motor-verbal free neuropsychological (NP) battery is not available for ALS longitudinal assessment. **Objective:** a recently funded project, "eBrain: BCI-ET for ALS", aimed to evaluate the use of P300-based BCI and ET technologies to administrate cognitive tests in ALS. **Methods:** 28 ALS patients (mean age: 62.6±11,8; mean education: 9.6±3.6) and 30 healthy subjects (mean age: 56.2±11.9; mean education: 13.7±4.2) underwent a traditional cognitive and psychological screening. Then, adapted versions of NP tests assessing verbal comprehension, frontal functioning, attentive and theory of mind abilities were administered with both BCI and ET. Moreover, clinical data were collected and usability of both devices was evaluated with an *ad hoc* questionnaire. **Results:** data showed significant differences between healthy subjects and ALS patients performances in BCI and ET adapted measures of frontal abilities ($p<.05$); furthermore, a correlation between traditional NP assessment and BCI-ET one was found ($p<.05$), supporting the concurrent validity of the adapted measures. Finally, even if a better perceived usability was overall observed for ET, compared to BCI ($p<.05$), patients evaluated BCI as a positive and useful tool in order to compensate the verbal limitation, more than controls did. **Discussion:** this results offer a promising insight on the use of BCI and ET for cognitive assessment in ALS. Besides, the high perceived usability not only of ET, but also of BCI system seems relevant, since BCI represents the only mean to bypass verbal-motor deficit for patients in advanced stages of the disease, in which also ocular motility can be damaged.

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

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Alzheimer's disease (AD) is a neurodegenerative process characterized by progressive neuronal degeneration and altered synaptic plasticity. In animal models, β-amyloid (Aβ)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. Cerebrospinal Fluid (CSF) sampling is an useful tool in clinical practice in detecting AD biological markers and predicting disease progression. Low levels of Aβ are typically found in AD patients. Moreover, it has been proposed that high levels of t-tau in AD patients CSF are related to a faster cognitive decline and more malignant form of dementia. Aim of this study was to investigate the relation between the CSF values of β-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 (rTMS) we tested in 22 AD patients the LTP/LTD-like effects induced by intermittent TBS (iTBS) and continuous TBS (cTBS) protocols applied over primary motor cortex. Each patient was evaluated for iTBS and cTBS plasticity induction in two different sessions. In each session twenty motor evoked potentials (MEPs) were collected at baseline and then, over the same hot-spot, at 1-5, 6-10, 11-15, 16-20 and 21-25 minutes after TBS protocols. We found that patients with high CSF value of t-Tau (>700 pg/mL) had a more impaired LTP compared with patients with lower t-tau values ($p<0.05$). Conversely patients with low levels of Aβ (<250 pg/mL) had less LTP-impairment than patients with higher values ($p<0.05$). These results show that high CSF t-tau levels are associated to a weakened LTP-plasticity. Follow-up studies are needed to evaluate the clinical impact of CSF sampling and TMS combination as predictor of disease outcome.

Identification of the novel PRNP gene mutation PRO39LEU in patients affected by frontotemporal dementia

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Prion diseases have a high phenotypical variability related to the type of mutation and to PRNP polymorphic codon Met129Val. Beside to Creutzfeldt-Jakob Disease and Gerstmann Straussler Schenker, a few cases resembling other neurodegenerative diseases such as Frontotemporal Dementia (FTD) have been reported. Here we described two patients affected by FTD carrying a novel PRNP gene mutation. Sequence analysis revealed the P39L variation in both patients, negative for GRN, MAPT and C9ORF72 gene mutations. Polymorphism at 129 codon was Met/Met in the first carrier and Met/Val in the second one. The first carrier was a 67 year-old male with a familial history for dementia: onset was at 60 years with progressive non-fluent aphasia and after 3 years he developed FTD with behavioral disturbances. The second carrier was a 78 year-old male affected by behavioral variant-FTD, with onset at 75 years. In both patients brain MRI showed marked frontal and temporal atrophy but no hyperintense alterations of cortical and subcortical structures in diffusion-weighted scans were reported. EEG did not show typical periodic complexes of prion diseases. Pathogenicity of the PRNP substitution is suggested by its exclusion as common polymorphism in 200 cognitively healthy aged controls and by functional in silico analysis that predicted the variation as deleterious. Moreover, it has been reported that a proline mutation within the PRNP N-terminal region (23-50 residues) might produce deleterious effects. The phenotype of our patients, not classifiable as prion disease, might depend to the location of mutation in a region outside to the amyloid core of disease-related form of PrP. The difference of onset and clinical picture between the two patients could be ascribed to the PRNP Met129Val polymorphism. Genetic screening of PRNP gene becomes of major importance in familial degenerative dementia, mainly in geographical areas known for high prevalence of inherited prion diseases.

Altered brain connectome in the behavioral variant of frontotemporal dementia

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Objective: to investigate whether functional organization of the human brain connectome is disrupted in patients with the behavioral variant of frontotemporal dementia (bvFTD). **Methods:** graph theoretical analysis was applied to resting state functional MRI data from 18 bvFTD patients and 50 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. Correlations between network properties and cognitive variables were tested. **Results:** global topological organization of the functional brain network in bvFTD was significantly disrupted as indicated by reduced small-world properties, reduced global efficiency and increased assortativity relative to normal sub-

jects. Compared to controls, bvFTD data showed retention of major "hub" regions in the medial parietal, temporal and occipital lobes, but cortical hubs were not noted in the frontal lobes. The left caudate nucleus, left insular cortices and some regions of the temporal lobes bilaterally showed decreased nodal centrality. BvFTD patients showed the greatest decrease in inter-regional connectivity between the insular cortices and subcortical, temporal and frontal regions. In bvFTD, altered global network properties correlated with executive dysfunction. **Conclusions:** global and local functional networks are altered in bvFTD, suggesting a loss of efficiency in information exchange between both distant and close brain areas. Altered brain regions are mainly located in structures that are closely associated with neuropathological changes in bvFTD. Aberrant topology of the functional brain networks in bvFTD appears to underlie cognitive deficits in these patients. **Funding:** this study was partially supported by a grant from the Italian Ministry of Health (Grant #GR-2010-2303035).

Frailty among Alzheimer's disease patients

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Frailty is a transitional state through which total physiological reserves progressively decline leading to inability to repair the ageing body. Central to the clinical concept of frailty is the multiple involvement of systems in the progressive decline of body. Clinically frail status is largely accepted to be represented by muscle wasting, reduced nutritional status, loss of endurance, gait disturbances, relative inactivity, apathy and even cognitive decline. Also persistent changes of several biological markers like serum CRP, fibrinogen, IL-6, or IGF-1, suggestive of pro-inflammatory status, may predict the transition to frail status. Alzheimer's disease (AD) is strictly connected with aging and as a consequence with frailty. At the same time, it is not known whether among AD patients, which represent certainly an heterogeneous group of patients, it is possible to identify a subgroup of frail individuals. In this work we sought for clinical features as well as biochemical indices of frailty among AD. To do this we evaluated clinical presentation (disease progression rate and response to pharmacological treatment), presence of risk factors (diabetes, hypertension, heart disease, etc.), CSF biomarkers (Aβ42, t-tau and p-tau) levels, presence of ApoE4 genotype, inflammatory indices (serum CRP, fibrinogen, D-Dimers) in a group of patients with a diagnosis of probable AD. Results of this study confirm the great heterogeneity of AD patients. Our work contribute to identify a subgroup of AD patients with peculiar features (rapid cognitive decline progression, reduced or absent response to therapy with acetylcholinesterase inhibitors, very high levels of CSF t-Tau, negative ApoE4 genotype) that fatally develop inability and vulnerability and thus could well be considered frail among AD patients. Further studies are however needed to deepen our understanding of the pathophysiological mechanisms responsible for such rapid and particular evolution of AD.

Overlap between Frontotemporal Dementia and Alzheimer Disease: CSF pattern and neuroimaging study

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Background: differential diagnosis between Frontotemporal Lobar Degeneration (FTLD) and Alzheimer Disease (AD) is often challenging, because of the occurrence of atypical cases. Autopsy series have identified AD pathology in a consistent percentage of patients clinically diagnosed as Frontotemporal Dementia (FTD). It has been demonstrated that Cerebrospinal Fluid (CSF) Tau/Abeta42 dosage is a reliable marker for AD. **Objective:** to evaluate the presence of CSF AD-like pattern in patients with FTD, and the related brain changes, to assess whether these patients had features resembling AD pattern of hypoperfusion. **Methods:** clinically diagnosed FTD patients underwent an extensive neuropsychological assessment, 99mTc-ECD single photon emission computed tomography (SPECT) and CSF analysis (Tau and Abeta42 dosage). A single-subject analysis of SPECT scan was performed, to ensure frontotemporal hypoperfusion in all included cases (Statistical Parametric Mapping, SPM8). FTD AD-like pattern and FTD nAD-like were identified, and neuropsychological and neuroimaging features compared. **Results:** CSF AD-like

pattern was reported in 9 cases out of 43 (21%). FTD AD-like and nAD-like patients did not differ for demographic characteristics, cognitive deficits and behavioural changes. Both groups had greater hypoperfusion in frontotemporal lobes as compared to age-matched controls. When FTD AD-like patients were compared to FTLD with non AD-like group, the former had greater hypoperfusion in the brain areas typically affected by AD, namely precuneus and parietal areas (P<0.001). **Conclusions:** CSF AD-like profile in sporadic FTD is associated with brain abnormalities typically found in classical AD, confirming the usefulness of CSF testing. Detecting an on-going AD pathological process in FTD has several implications for defining distinctive treatment approaches, guiding genetic screening and helping in patients' selection in future clinical trials in both FTLD and AD therapeutics.

Does Free and Cued Selective Reminding Test (FCSRT) predict the progression of MCI to dementia in clinical practice?

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Background: the Free and Cued Selective Reminding Test (FCSRT), an episodic memory task which controls for encoding and measures the sensitivity to cueing, has been proposed as a sensitive marker of early Alzheimer's Disease (AD). We have developed a new version of the FCSRT and standardized Italian normative data. **Aim:** to evaluate if FCSRT Italian normative data predict the progression of MCI to dementia. **Methods:** from April 2009 to December 2011, 119 MCI consecutive subjects from the "L. Sacco" hospital underwent FCSRT. Subjects were requested to return every 12 months. The follow-up ended at the diagnosis of dementia (DSM IV criteria) or death. Cox regression was used to estimate the risk of dementia in relation to the following baseline FCSRT sub-scores: Immediate Free recall (IFR), Immediate Total Recall (ITR), Delayed Free Recall (DFR), Delayed Total Recall (DTR), Index of Sensitivity to Cueing (ISC). **Results:** over a median follow-up of 17 months, 40 (34%) MCI subjects progressed to dementia. These subjects had lower Minimental State Examination score (24.5±2.6 vs. 26.1±2.3; p=0.001) compared to non-converters. Subjects who developed dementia had significantly (p<0.001) lower baseline FCSRT sub-scores (IFR, ITR, DFR, DTR, ISC) compared to stable MCI subjects. The multivariate analysis, showed that the risk of progression from MCI to dementia was associated with under-threshold DFR score (OR 5.64; 95% CI 2.57-12.35), loss of Instrumental Activities of Daily Living (OR 1.75; 95% CI 1.18-2.60) and increasing age (OR 1.05; 95% CI 1.00-1.10). **Discussion:** under-threshold DFR score was the best predictor of progression from MCI to dementia. FCSRT is a useful tool in identifying subjects with MCI at increased risk of dementia who should undergo further diagnostic more invasive and expensive procedures.

Cohort study of prevalence and phenomenology of tremor in Dementia with Lewy bodies

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Objective: to study prevalence, specific patterns and response to treatment of tremor in Dementia with Lewy bodies (DLB), in comparison with other tremulous disorders. **Methods:** prevalence, qualitative and quantitative features of tremor were studied in an incident cohort of 67 dopaminergic treatment naive DLB, 111 Parkinson's Disease (PD) and 34 Essential Tremor (ET) patients. Tremulous DLB patients (tDLB) were compared with tremulous PD (tPD) and ET patients and followed for two years. Double blind placebo-controlled acute drug challenge with L-dopa and alcohol was performed in all ET, 24 tDLB and 27 tPD. Effects of dopaminergic chronic treatment in all tDLB and tPD patients and primidone in 8 tDLB were also assessed. **Results:** tremor occurred in 44.76% of DLB patients. tDLB patients presented a complex pattern of mixed tremors, characterized by rest and postural/action tremor, including walking tremor and standing overflow in 50% tDLB. Standing tremor with overflow was

characteristic of tDLB (p<.001). Head tremor was more frequent in tDLB than tPD and ET (p=.001). tDLB tremors were reduced by acute and chronic dopaminergic treatments (p<.01) but not by alcohol or primidone. **Conclusions:** tremor occurs commonly in DLB patients with a complex mixed tremor pattern which shows a significant response to acute and chronic dopaminergic treatments. Recognizing that there is a clinical category of tremulous DLB may help the differential diagnosis of tremors.

Semantic-corticobasal dementia: a further variant of frontotemporal lobe degeneration

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We report the first two documented cases of association of corticobasal degeneration and semantic dementia.The first lady described is a woman presenting with semantic dementia who developed after a 2 year follow-up the features of corticobasal syndrome. At the first examination she showed at the general neuropsychological examination exclusively a semantic memory impairment (impaired word comprehension and naming, semantic paraphasias). RMN scan showed an asymmetrical bilateral temporal atrophy (right>left). The PET study showed bitemporal (right>left) hypomethabolism. A detailed praxis battery was performed and showed exclusively errors pertaining to semantic sphere in absence of alteration of gesture execution. After 2 years she developed the features of corticobasal syndrome with right upper limb apraxia associated with cortical sensory loss and mild extrapyramidal syndrome. Repeated neuropsychology showed together with a mild worsening of the semantic impairment the presence of ideomotor apraxia in the upper right limb, which was confirmed by a detailed study of praxis. Repeated PET showed a new area of hypoperfusion in the left parietal region. CFS examination excluded CJD, revealed high tau and phosfotau in absence of altered B-amyloid. The second patient previously described in 2011 showed the reverse pattern; she presented with a prominent corticobasal syndrome. A semantic breakdown was documented at the first examination. We describe a four years follow-up. The two patients come from the same Italian region. An accurate review of literature fail to find other objective and documented reports of this unusual phenotypic association. We argue the present cases should be added as a new variant of the frontotemporal lobar degeneration. A possible genetic basis can be supposed for the present cases as the two patients described come from the same Italian region.

Cognitive and brain metabolism improvement after cognitive stimulation therapy

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The effects of the cognitive stimulation on memory, attention, language, every-day living and social activities of patients with Alzheimer's dementia (AD) are still debated. Guidelines about non pharmacological treatment in AD are still lacking. The present preliminary study aimed at investigating the effects of a double-blind cognitive treatment protocol on brain metabolism in AD subjects. 18 AD patients were randomly assigned to a three-months double-blind cognitive stimulation treatment or placebo (3 out 8 were discarded for motion artifacts during baseline PET scanning) and 18F-FDG PET brain scanning before and after the training. Patients and controls did not differ at the baseline cognitive evaluation. MMSE, ADAS-Cog total score, phonemic and semantic fluencies, mood state (GDS), functional daily activities (DAFS) and quality of life (QoL) significantly improved after treatment. No differences were found in cognitive and functional measures in control group after three months. A significant improvement in the metabolism was observed in the bilateral posterior cingulate gyri (bilateral BA 23; left BA 30), involved in memory and attention processes, in the right anterior cingulate gyrus (BA 33), parahippocampus (BA 30), inferior parietal lobule (BA 40) and in the left thalamus in the treated group. The brain metabolism remained unchanged in the control group after three months. Even in presence of the limitation due to a small sample of subjects, this study was able to demon-

strate the efficacy of the cognitive stimulation in AD in terms of cognitive measures and neurophysiological changes of brain areas critical for memory processes.

Nonfluent variant of familial primary progressive aphasia associated with progranulin (GRN) exon 6 mutation g101349_101355delCTGCTGT

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Frontotemporal Lobar Degeneration (FTLD), a common cause of dementia characterized by behavioural alterations, and/or language disturbances, relative preservation of memory with frontal and temporal lobes degeneration. Familial cases of FTLD with autosomal dominant mode of inheritance are reported in 25-50% of cases indicating the existence of strong genetic component. Several association studies identified mutations in microtubule-associated protein tau (MAPT) gene and Progranulin (GRN) both on chromosome 17, accounting for about 5-20% of FTLD cases. Additionally a large hexanucleotide (GGGGCC) repeat expansion on C9ORF72 chromosome 9p21, was identified as responsible for familial form of FTLD associated with Amyotrophic Lateral Sclerosis (ALS-FTLD). Our study identified a four-generation Southern Italian family segregating FTLD, with four affected family members showing a dominant inheritance pattern and a strong clinical heterogeneity. Under approved ethical protocols we collected and analyzed 3 out of the five siblings on generation III: one unaffected and two affected once. These FTLD siblings showing different clinical phenotypes characterized by behavioral variant (bvFTLD) in one case, and Primary Progressive Aphasia (PPA) in the other case. We screened the genome of the three members for MAPT and PGRN genes in particular we sequenced all exons, exon-intron boundaries and the 5' and 3' regulatory regions in search for mutations. We found that the two affected members carry chromosome 17 g101349_101355delCTGCTGT deletion on exon-6 PGRN gene thus causing a premature stop codon with frameshift error and mRNA non-sense mediated decay. This might result in a reduction of progranulin synthesis by at least 50% (haploinsufficiency) and suggests that PGRN may be a possible modifier of the course of the disease in FTLD patients.

Novel missense progranulin gene mutation associated with semantic variant of primary progressive aphasia

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In the last few years, it has become clear that multiple genetic autosomal dominant mutations are associated with frontotemporal lobar degeneration (FTLD). Microtubule-associated protein tau, progranulin (GRN) and chromosome 9 open reading frame 72 genes are widely involved in the disease pathogenesis. GRN mutations show highly heterogeneous phenotypic presentations mostly associated with behavioral variant of frontotemporal dementia and non fluent variant of primary progressive aphasia. Many of these cases are apparently sporadic, given the incomplete inheritance penetrance. In this study, we described the case of a patient affected by semantic variant of primary progressive aphasia (svPPA) and carrying a novel GRN missense mutation (g.2897 C>T in exon 11_p.thr409met) with a strong family history of dementia (i.e. maternal grandmother, mother and mother's stepsister). Our description contributes to confirm that GRN mutations represent one of the most relevant genetic cause of FTLD and aims to encourage clinicians to screen for GRN mutation all suspected subjects, also in case of svPPA presentation.

The relationship between microglial microvesicles and MRI metrics in probable Alzheimer's disease patients

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Objectives: astrocytosis and microgliosis are known contributors to neurodegeneration in Alzheimer's disease (AD). Microglial microvesicles (MMVs) represent a novel marker of microglial activation. Aim of this study was to investigate whether the number of MMVs in the cerebrospinal fluid (CSF) correlates with measures of structural gray matter and microstructural white matter (WM) damage in patients with probable AD. **Methods:** CSF, and T1-weighted and DT MRI scans were obtained from 31 probable AD patients (mean age at the MRI 69±7 years; mean disease duration 4±2 years; mean Clinical Dementia Rating scale-Sum of Boxes 5±2). CSF was analyzed by flow cytometry to detect MMVs. Hippocampal volumes were obtained using an automatic approach (FIRST in FSL). The association between hippocampal volume and the MMV level was estimated using the Pearson's coefficient. Tract-based spatial statistic (TBSS) was used to perform a voxel-wise regression analysis investigating the relationship between WM fractional anisotropy (FA) and the number of MMVs. **Results:** in probable AD patients, the level of MMVs significantly correlated with the hippocampal volumes (r=-0.51, p=0.005, for both right and left hippocampal volumes). In addition, TBSS showed a negative correlation between the number of MMVs and the FA values of the hippocampal part of the cingulum bundle, bilaterally. **Conclusions:** this study shows that the level of MMVs in the CSF of probable AD patients is associated with damage to the gray matter and WM structures of the medial temporal lobe. These findings suggest a greater vulnerability to microglial activation in those regions typically hit by AD.

Presence and gender differences of behavioural and psychological symptoms in the early phase of Alzheimer's disease

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Background: behavioural and psychological symptoms of dementia (BPSD) are typical characteristics of cognitive impairment, present in every phases of illness. They represent a very relevant aspect of patients' management and produce a significant stress for caregivers. In Alzheimer disease (AD), the most common form of dementia, BPSD are frequent. There are several studies about different characteristics of BPSD, but unexpectedly we do not have data about gender differences. Aim of this study was to evaluate possible differences of typology and frequency of BPSD between genders. **Methods:** we enrolled 200 consecutive patients (M/F: 100/100) referring to our Neurologic Clinic for suspected cognitive impairment and whom we performed a first diagnosis of AD according to NINCDS-ADRDA criteria. Each patient's caregiver was submitted to a Neuropsychiatric Inventory scale (NPI) to assess the presence of BPSD in the AD affected subject. Chi-squared test was used first to evaluate differences in frequency distribution of each BPSD. We applied a multivariate balanced model analyzing all NPIs variables. Statistical analysis was performed with SPSS13.0 for Windows systems. **Results:** in this sample, 185 (92,5%) subjects showed BPSD at disease onset. The most prevalent symptom in the whole sample was apathy (40%), followed by depression (26,3%), irritability (20,6%) and anxiety (17,5%). When we divided our sample between the two genders, we observed that aggressiveness and irritability were significantly more present among men (p=0.042;p=0.040), while depression was more relevant in women (p=0.036). **Conclusions:** BPSD are a very problematic aspect in the management of AD patients. Every item is useful for a better comprehension of this problem: for example, a more specific BPSD differentiation between genders could help the neurologists to manage specific situations and to reduce caregivers' stress.

Late onset semantic dementia with progranulin Cys139Arg mutation

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A 81 year-old right handed woman attended our Memory Clinic for speech comprehension and production difficulties since she was 79, followed by behavioral and memory disturbances. She has a significant history of depression and irritability since she was 76, treated with SSRI with poor response. There was a family history of late-onset dementia; her mother, suffering of dementia with personality changes as onset, died at 84; her maternal uncle died at 92, demented, suffering of Parkinsonism in his late years. Her past medical history was unremarkable except for hypertension on medical control. Neurological examination showed poor comprehension, low insight, echolalia, perseverative behavior, disinhibition and blink reflex. MMSE was 17 and neuropsycology showed low performances in executive functions, attention and a fluent aphasic syndrome. Brain MRI showed atrophy in the left temporo-polar and temporo-parietal areas, FDG-PET revealed hypometabolism in these areas. Following the current criteria, a diagnosis of semantic dementia was done. A genetic analysis on MAPT, progranulin (PGRN) and C9ORF genes was performed and a Cys139Arg mutation on exone 5 of PGRN was found. Cys139Arg was previously described in literature in two early onset (EO) fronto-temporal dementia (FTD) (age 61 and 53) and a senile onset Alzheimer's Disease. While most PGRN pathogenetic mutations are predicted to create null alleles leading to a 50% loss of PGRN transcript and a decrease in PGRN plasmatic levels5, Cys139Arg is supposed to cause a missense mutation causing a reduction in plasmatic PGRN compared to controls, but not as great as null mutations, due to a possible reduction in function of PGRN produced by this gene. Our patient is the first described senile onset FTD patient with Cys139Arg mutation. The causes for these pleomorphic phenotype and onset and the pathological nature of the mutation are still debated.

Psychic akinesia and Korsakoff syndrome following anterior cingulated circuit disconnection

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Background: psychic akinesia is a subtype of apathy described after lesions of the prefrontal cortex (PFC), the basal ganglia and in neurodenegerative diseases. Psychic akinesia is a consequence of the PFC-basal ganglia disconnection, a functional system involved in the generation and control of self-generated purposeful behaviour. Previously, apathy was related to cognitive impairment and was described in association with other behavioural and neuropsychological features in patients with thalamic lesions. Furthermore, the anterior thalamic nuclei and PFC are involved in the Korsakoff syndrome. **Case report:** a 77 year-old right handed woman suddenly presented spontaneous confabulation and anterograde amnesia. Confabulations concerned the idea of being pregnant; she said to be in hospital and to give birth. Brain CT showed a chronic left anterior thalamic lesion and an acute ischemic lesion of the anterior right thalamus. Confabulations lasted for 1 mounth, while she had persistent cognitive impairment with global amnesia and executive dysfunction. In the following months she developed psychic akinesia. In the DTI study the average FA values of the right anterior cingulate circuit of the patient resulted significantly reduced compared to healthy controls (0.264 vs. 0.351 ± 0.024; 0.026 SD; 95% CI), whereas differences were not significant on the left circuit. **Discussion and conclusions:** in the present report we describe a patient with isolated ischemic lesions of bilateral anterior thalamic nuclei occurring in two times. She presented acutely a Korsakoff syndrome and after some months psychic akinesia. We hypothesized that the disconnection of the anterior thalamic nuclei from the cingulated cortex was the cause of this cognitive and behavioural syndrome and we investigated this hypothesis with DTI. DTI results confirm the disconnection of the right anterior cingulate circuit which may contribute to the onset of behavioral and cognitive changes.

A case of Alzheimer's disease presenting as Limbic Encephalitis

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A 69 years old man presented with a 6 month history of episodic memory loss. He had a family history of late-onset dementia and he was a long time strong smoker. Neurological examination was normal, neuropsychological tests showed memory impairment with encoding and retrieval deficits; MMSE score was 25/30. Amnestic-MCI was suspected. Concentrations of thyroid hormones, folate and B12 vitamin were in range. Since brain MRI showed symmetrical signal increase associated with atrophy in bilateral hippocampus and amygdala in T2 weighted imaging (WI), Limbic Encephalitis (LE) was suspected. Syphilis and HIV serology and interferon-gamma release assay were negative. Anti-nuclear and anti-thyroid antibodies were in range. Electroencephalography (EEG) was normal. Examination of cerebrospinal fluid (CSF) was normal. PCR for neurotropic virus was negative. Tumor markers, antineuronal antibodies, Thoracoabdominal CT and total body PET scan were negative for tumor and paraneoplastic process. Patient was invited to regularly perform medical checks in order to exclude an appearance of tumor. 6 months later he repeated the same investigations that were again negative for the presence of tumor and paraneoplastic process. PET scan showed parietal-temporomedial hypometabolism. Brain MRI showed no alterations in signals, slight enlargement of subarachnoid spaces of convessity. Neuropsychological tests revealed memory impairment associated with slight temporal disorientation. MMSE score was 25/30. CSF biomarkers of dementia were also evaluated: total-TAU and p-TAU concentration were slight increased (380 pg/ml and 74 pg/ml), instead β-amyloid was normal. A diagnosis of Alzheimer's disease (AD) was done. **Conclusions:** T2 WI showing symmetrical signal increase in bilateral hippocampus may be found in different clinical pathological conditions as LE, infectious encephalitis, autoimmune encaphalopathy, glioma, lymphomatous infiltration. Isolated cases have been described of AD and LE occurring together-CSF analysis, EEG and PET scan may improve the accuracy in the diagnosis of LE and AD.

Diagnostic accuracy of Creutzfeldt-Jacob disease among rapidly progressive dementia

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Background: rapidly progressive dementia (RPD) is a rare presentation of different neurological disorders characterized by cognitive impairment leading to loss of functional independence within 24 months or less. The increasing recognition of treatable non-prion causes of RPD has made the differential diagnosis with sporadic Creutzfeldt-Jakob disease (sCJD) of crucial importance. **Aim:** to assess the accuracy of newly proposed diagnostic criteria for sCJD and to evaluate the diagnostic value of additional CSF biomarkers in a tertiary dementia care setting. **Methods:** clinical records of patients with RPD referred to Memory Clinic between 2007 and 2012 were retrospectively analyzed. The accuracy of diagnostic criteria for sCJD was evaluated by: a) MRI images in DWI and FLAIR sequences; and (b) CSF 14-3-3 protein. In addition, CSF total tau protein level determination and detection of protein 14-3-3 isoforms were performed. Final diagnosis was obtained after a 1-year follow-up or after autopsy. **Results:** among 37 patients with RPD, the most frequent causes were non-prion diseases, either untreatable (38%) or potentially treatable (32%), thus leaving sCJD as a less frequent cause (30%). DWI images had a sensitivity of 73% and specificity of 96%, while FLAIR yielded a very low sensitivity (40%). CSF 14-3-3 protein had a sensitivity of 100%, but a very low specificity (43%). The strongest independent predictor of sCJD diagnosis was the CSF total tau level ($p = 0.002$). Presence of 14-3-3 protein isoform γ or ε and was specific of sCJD cases (70% sensitivity, 100% specificity) and demonstrated a better accuracy than presence of total 14-3-3. **Discussion:** DWI images and CSF analysis combining 14-3-3 and total tau protein determination hold the best informative diagnostic value. In non-prion cases with high CSF level of total tau and positive 14-3-3 protein, determination of 14-3-3 protein isoforms may be of added value.

Progression of Alzheimer's disease: are fast decliners really fast? Update on a four-years follow-up

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The cognitive and functional decline in Alzheimer's disease (AD) is variable among subjects and at present no predictive model has been validated yet. The aim of this study was to assess whether "fast decliners", defined by a loss of at least 5 pts at MMSE within the first 12 months, might be defined true fast decliners after a 4-year-time interval in order to help clinicians and caregivers in making decision on assistance strategies. We retrospectively studied 324 AD patients, followed for 4 years and divided into three clusters: "fast-progressive" (a loss =5 points on MMSE score within the first year from baseline), "intermediate-progressive" (a loss = 5 points in the time interval between the first year and the 18th month from the baseline); "slow-progressive" (remaining subjects). 225 patients were slow decliners, 62 patients fast decliners and 37 patients were intermediate decliners. Data entry: MMSE, IADL, ADL performed at baseline and every six months. The three groups were homogeneous at baseline on demographic and clinical variables. No differences were evidenced in cognitive performance between groups at baseline nor at the end of the follow-up. The analysis of the patients lost during the 4-year-time interval showed a correlation between drop-out and worse cognitive performances and no significant difference in the percentage of lost patients was observed among the three groups.The lack of differences in the evolution of the disease progression of the different clusters could suggest the inconsistency of the so called «fast decline» category. In conclusion a twelve months follow-up seems to be a too short period of time to define the rate of progression of the disease, leading to a high probability to misclassify subjects, thus leaving open the need to define further reliable predictors of decline.

The effect of treatment on grey and white matter in Alzheimer's disease patients

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Introduction: despite the numerous quantity of studies into structural MRI changes in Alzheimer's disease, there has been relatively little information related to multimodal structural imaging modifications following treatment (Likitjaroen et al., 2012; Goveas et al., 2011). We examined longitudinal changes in both cerebral volume and microstructure abnormalities in patients with Alzheimer's Disease (AD) before and after treatment with cholinesterase inhibitor Donepezil. Voxel-based morphometry (VBM) was used to measure grey-matter volume while diffusion tensor imaging (DTI) was used to measure microstructural white-matter integrity. Longitudinal results were interpreted according to changes observed cross-sectionally between controls, patients with Mild Cognitive Impairment (MCI) and patients with AD. **Methods:** 70 participants (27 with probable AD, 20 MCI, 23 controls), each accompanied by a study partner, were recruited for the cross-sectional study and underwent multimodal MRI including T1-weighted and diffusion sequences. A subgroup of 18 AD patients, for whom there was clinical indication to commence treatment with Donepezil, were also included in the longitudinal study. They repeated the scan 12 weeks after starting the treatment (5 mg for the first 4 weeks, then 10 mg). All participants undertook neurological examinations and extended neuropsychological assessments prior to the MRI scan. **Results:** significant effect of treatment was found on both grey-matter volume and white-matter integrity of the cholinergic system. More precisely, treatment increased volume of fronto-insular and basal ganglia regions. **Conclusions:** this study suggests that cholinesterase inhibitors may potentiate compensatory structural and microstructural changes in patients with AD. Further placebo-controlled longer studies should be undertaken to confirm our results and to test if the treatment effects on structural MRI persist over a longer term.

VBM-DTI MRI morphologic and voxel-based [18F] FDG-PET metabolic imaging in Posterior Cortical Atrophy: beyond the posterior involvement

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Objective: to evaluate in Posterior Cortical Atrophy (PCA) subjects the gray- (GM) and white-matter (GM) damage using voxel-based morphometry (VBM) and Diffusion Tensor Imaging (DTI) studies, and the regional hypometabolism at the single-subject level using voxel-based statistical parametrical mapping (SPM) [18F] FDG-PET imaging. **Background:** PCA is characterized by progressive decline of higher order visuo-spatial processing. VBM provided evidence for a selective posterior brain damage (Migliaccio et al., 2009). DTI showed alteration of long white-matter tracts. Consistently, [18F] FDG-PET showed a broader functional damage, involving not only the occipital cortex, but also the frontal lobes (Nestor et al., 2003; Schmidtke et al., 2005). The latter findings support disconnection mechanisms. **Methods:** 9 PCA patients (mean time from symptom's onset = 3 years) were enrolled for the study. Brain glucose metabolism was measured in 6 subjects. A large population (112 PET scans) of normal subjects represented the database for single-subjects SPM [18F] FDG-PET analysis. Six out of 9 patients were also investigated using VBM and DTI, and compared with 20 controls. **Results:** in PCA patients, VBM results showed atrophy involving the inferior occipital (fusiform gyrus), lateral temporal and posterior parietal regions. DTI analysis was consistent with previous findings of microstructural changes in long connecting tracts, namely ILF, SLF, IFOF and CC, suggesting a wide fibre degeneration. In each PCA case, SPM [18F] FDG-PET analysis showed hypometabolism in the whole occipital regions, and in lateral temporal and parietal lobes. In some cases, dorsolateral and/or medial frontal hypometabolism was present. **Conclusions:** these anatomo-functional data suggest an extensive brain involvement in PCA patients, due to a degeneration of occipital, temporal and parietal regions and of the connecting main fibre tracts. SPM [18F] FDG-PET imaging at single subject level can detect a specific functional pattern that also reflects deafferentation processes from the posterior occipital lobes to more anterior frontal regions.

Neuropsychiatric subsyndromes in Alzheimer's disease: identification and evaluation of predictive value

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Behavioral and psychological symptoms of dementia (BPSD) represent common clinical features of the dementia syndrome. BPSD are extremely burdening for patients, families, caregivers, and public health. They represent extremely dynamic conditions. Their clinical manifestation may be influenced by different factors such as the patient's age at the onset of dementia, gender, and concomitant pharmacological treatments. Moreover, each BPSD symptom is characterized by different biological, neuropathological, and psychosocial correlates. Some reports have recently classified BPSD in specific clusters/subsyndromes exploring the internal structure of the Neuropsychiatric Inventory (NPI), the most widely adopted clinical tool for the screening of these symptoms. First, we performed a systematic review of available studies adopting a factor analysis to explore the NPI and describe neuropsychiatric phenotypes in the context of Alzheimer's disease (AD). Overall, our analysis showed a relatively low concordance among available evidence for what concerns the definition and composition of NPI clusters, possibly due (at least in part) to the heterogeneity of the sampled populations. However, we also observed some consistent associations of specific symptoms across studies, defining potential phenotypes in AD. Second, we evaluated, in the cohort of the Impact of Cholinergic Treatment USe (ICTUS) study, whether specific behavioral subsyndromes are associated with worsening cognitive function. 1375 mild to moderate AD patients were recruited. Neuropsychiatric symptoms were classified in three subsyndromes, identified at baseline, grouping different combinations of NPI items: 1) "psychotic"; 2) "affective"; 3) "behavioral". All analyses were stratified according to AD severity as defined by the Clinical

Dementia Rating (CDR). No NPI cluster was found to significantly ($p<0.05$) affect the rate of cognitive decline (measured as changes in the ADAS-Cog score) across the 3 CDR classes for a 2-years follow-up. Our results suggest that the cognitive course of AD is not substantially influenced by the presence of specific neuropsychiatric phenotypes.

Comparison of clinical, functional and cognitive features between two groups of patients with mild cognitive impairment (MCI) of degenerative or vascular origin. Preliminary data from the "Investigation on MCI Study".

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Background: Mild Cognitive Impairment (MCI) is a transitional status between the cognitive decline of normal aging and dementia, and can be supported by different types of brain lesions (vascular or atrophic). Clinical and neuropsychological markers differentiating between the two conditions are still incompletely elucidated. **Objective**: we aimed to study demographic, clinical and cognitive factors selectively differentiating degenerative (deg-MCI) from vascular MCI (vas-MCI). **Methods**: to be included, patients have to be classified as affected by MCI (Winblad criteria) with evidence on MRI of white matter changes of moderate to severe degrees (modified Fazekas scale) for the vas-MCI, or cortical atrophy of moderate to severe degrees (Pasquier scale) for the deg-MCI. Two groups of MCI patients, matched by age and gender, underwent an extensive clinical, functional, mood, and neuropsychological assessment. **Results**: we enrolled 60 patients: 30 deg-MCI (mean age 71.1±5.9 years) and 30 vas-MCI (mean age 71.8±5.5 years). Family history of dementia was significantly more prevalent in the deg-MCI group (67% *vs* 33%, p=.019), while hypercholesterolemia (13% *vs* 67%, p<.001), heart disease (3% *vs* 27%, p=.026), stroke (3% *vs* 37%, p=.002), migraine (23% *vs* 53%, p=.033), psychiatric disorders (40% *vs* 73%, p=.018), gait disorders (10% *vs* 70%, p<.001), and urinary disturbances (20% *vs* 50%, p=.029) were more common in the vas-MCI group. Controlling for education, functional status, cognitive performance and depression, the logistic regression model showed that story recall test resulted independently associated with deg-MCI (OR=1.9; 95% CI=1.3-3.0, p=.003), while depression severity with vas-MCI (OR=9.5; 95% CI=1.1-85.8, p=.045). **Conclusion**: family history for dementia, vascular risk factors, and gait and urinary disturbances are confirmed to be distinctive features of deg-MCI and vas-MCI. The strongest differential markers are a deficit of episodic memory and depressive disturbance. This information may be useful to the setting of clinical-functional screening of patients with different MCI types.

Use of rTMS in the treatment of Primary Progressive Aphasia (PPA): two case-reports taken from open study protocol

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Repetitive transcranial magnetic stimulation (rTMS) has been identified as a potentially valuable tool for the rehabilitation of chronic aphasia after left hemisphere stroke. Moreover rTMS improved action naming in subjects with aphasia in neurodegenerative disorders. Only a few cases have been reported in the literature about the rehabilitation of this disorder and in this debate engages our cases report.

As part of ongoing study protocol we present data of first two consecutive patients affected by Progressive Primary Aphasia (PPA)-nonfluent type, that have completed treatment at this time. The patients' performance was evaluated on a battery of language (Italian version of AAT), before and after a cycle of 3 weeks of integrate high frequency rTMS and logopedic treatments.
For the first case (OG) with mild disease (correct MMSE=25,2) after treatment we observed a significant improvement of patient's performance in subtest "denomination", the more compromised at the baseline evaluation, a slight increase in "written language" and fewer number of error in "Token Test". 6 months follow-up after treatment should be performed next month. The second case (PG) with severe disease (correct MMSE=4,9) discontinued treatment after 8 days for the occurrence of adverse events (aggression and agitation).
According to our experience, the rTMS may not be indicated, for the safety of patient, in advanced and severe stages of disease, when, in addition to the language, the other domains are heavily involved. The finding in mild disease patient, in accordance with others previous investigations, suggests that rTMS of dorsolateral prefrontal cortex (DLPFC) may strengthen the neural connections within an area of metabolic dysfunction with a facilitation effect on lexical retrieval processes. Case-control studies are needed to confirm the utility of rTMS as an alternative therapeutic tool for neurodegenerative forms of aphasia in mild-moderate stage of PPA.

Counterfactual Thinking deficit in patients with Huntington's disease

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Background: Counterfactual Thinking (CFT) is the mental simulation of alternatives to past events. Previous evidences showed that CFT is impaired in patients with frontal dysfunctions, i.e. schizophrenia, Parkinson's disease and prefrontal cortex lesions. Our aim was to analyze CFT in patients with Huntington's disease (HD), an autosomal dominant inherited neurodegenerative disorder characterized by frontal impairment. **Methods:** 24 symptomatic patients with HD (12 males, 12 females, mean age: 52.3±13.8 years; mean education: 11.4±3.2 years) and 24 healthy subject (12 males, 12 females, mean age: 52.5±14.0 years; mean education: 11.3±2.8 years) underwent an extensive neuropsychological battery, assessing global cognitive functioning, attentional and frontal abilities, memory, language and reasoning. CFT was evaluated using measures of spontaneous generation, counterfactual-derived inferences (CIT) and anticipation of regret. **Results:** our data show quantitative differences in cognitive performances between HD patients and controls, mainly in attentional and frontal abilities. Moreover, HD patients performed significantly worse than controls in two measures of CFT, i.e. spontaneous generation test (Median: HD=1.5; Controls=3; $p<0.000001$) and the counterfactual inference test (CIT) (Median: HD=1; Controls=3; $p=0.000013$). Furthermore, the spontaneous counterfactual generation test significantly correlated with several cognitive tests assessing frontal and executive functioning, i.e. Phonemic Verbal Fluency Test ($r=.540$, $p=0.006$), Trail Making Test – A ($r=.456$, $p=0.020$) and Frontal Assessment Battery ($r=.430$, $p=0.030$). **Discussion:** results suggested that HD patients are unable to spontaneously generate counterfactual thoughts and this deficit is related to poor frontal lobe functioning. Moreover, they showed difficulties in deriving inferences about hypothetical events, as confirmed by the poor performance at CIT. Finally, the correlations between frontal abilities measures and CFT showed that CFT requires an unimpaired functioning of frontal lobes. **Conclusions:** spontaneous counterfactual thinking and the use of this kind of reasoning are impaired in HD and this deficit may be strictly related to frontal lobe dysfunction.

Influence of lexical variables on semantic fluency in subjects affected by amnesic Mild Cognitive Impairment (a-MCI)

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Impairment of semantic memory assessed by categorical word generation tasks is common among subjects with a-MCI, affecting about 30% of the subjects. This study was aimed at investigating the effect of lexical variables (word frequency [WF] and protipicality [Prt]) on semantic (SVF) and phonological (PVF) verbal fluency tasks performed by a-MCI subjects. We enrolled 60 a-MCI subjects and 20 age - and education-matched healthy controls (HC). Each subject underwent PVF (F, A, S) and SVF (birds and furniture). WF was determined following the LIP corpus for spoken Italian (http://badip.uni-graz.at); Prt was determined (only for SVF) according to norms proposed by Van Overschelde et al. (2004). Mean WF and Prt were computed for each subject. Mean values were compared by means of t-test and ANOVA controlled for age, education and gender. We analyzed 1972 entries (a-MCI= 1424; HC=548) for PVF, and 1171 entries (a-MCI=813; HC=358) for SVF. Mean PVF was comparable between a-MCI and HC (23.72±10.23 vs 27.40±8.19; t=1.631; p=0.111); SVF was significantly lower in a-MCI subjects (respectively, 13.55±3.62 vs 17.90±4.38; t=4.012; p=0.0004). Mean WF in PVF was similar between a-MCI and HC (82.49±167.97 vs 69.39±80.39; t=0.465; p=0.643). On SVF, a-MCI showed higher WF than HC (9.89±3.32 vs 8.49±2.35; t=2.056; p=0.045); on multivariate ANOVA there was a trend toward the effect of group (a-MCI vs HC) on WF in SVF (p=0.088). Furthermore, a-MCI showed higher Prt than HC (0.26±.062 vs 0.22±0.033; t=4.139; p=0.0001); this difference remained significant after multivariate ANOVA (p=0.005). Our results support the hypothesis that lower semantic fluency in a-MCI may represent the index that a progressive breakdown of semantic knowledge could be detect also in the initial stage of a-MCI condition and that it starts from less frequent and prototypical items. Longitudinal studies are needed to investigate if a successive diffusion of semantic deficit is observable.

Role of combination of CSF AD biomarkers and a synuclein for predicting cognitive impairment in Parkinson's disease

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Background: Parkinson's disease (PD) is a common neurodegenerative disorder. In approx. one third of cases, development of dementia (PDD) is observed. The mechanisms involved in PDD pathogenesis are not completely understood yet; Alzheimer's (AD) and Lewy bodies pathologies may play a significant role. **Objective:** in this prospective study we wanted to verify if classical CSF AD biomarkers – Aβ42, t-tau, p-tau- and a-syn may predict cognitive decline in PD. **Methods:** a total of 56 consecutive PD patients and 45 controls were enrolled. CSF analysis and neuropsychological evaluation was carried out at baseline. The follow-up duration ranged from 1 to 10 years. MMSE score has been used for monitoring cognitive changes. **Results:** according to our internal reference values for CSF Aβ42 (cut-off: 800 pg/mL), we obtained two PD subgroups:-Group I "low Aβ42" (<800pg/mL):n=36; M/F=24/12; mean age= 66.97 years; mean baseline MMSE score= 25.83; mean MMSE score at follow-up= 23.86; mean CSF Aβ42=554 pg/mL; -Group II "normal Aβ42" (>800pg/mL):n=20, M/F=11/9, mean age= 59.90 years; mean H&Y score=1.6; mean baseline MMSE score= 27.85; mean MMSE score at follow-up= 27.25; mean CSF Aβ42=1049 pg/mL. Using a linear regression model we found that lower CSF Aβ42 levels at baseline are associated with a higher risk of cognitive deterioration, measured as rate of change in MMSE scores (p=0.0014). Furthermore, low Aβ42 (<800 pg/mL) is associated with a MMSE score decline (p=0.008; sensitivity = 80%, specificity = 54%). Combination of Aβ42, t-tau, p-tau- and a-syn does not improve the capacity to predict cognitive deterioration, while they better differentiate PD from OND. **Conclusions:** reduced CSF Aβ42 is a predictor of cognitive impairment in PD patients. This observation shows the usefulness of applying the CSF biomarkers model as prognostic factor in PD.

Altered LTP-like cortical plasticity in AD patients is restored by dopaminergic administration

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In animal models of Alzheimer's disease (AD), amyloid beta fragments interfere with mechanisms of cortical plasticity such as long-term potentiation (LTP) and long-term depression (LTD) and with cholinergic transmission. In a recent study with theta burst stimulation (TBS) we showed that LTP-like cortical plasticity is impaired in AD patients, while LTD seems to be preserved. We aimed at investigating whether administration of a D2 agonist could modulate cortical plasticity induced with TBS over primary motor cortex (M1) in AD patients. We tested the impact of two weeks administration of D2 agonist (rotigotine) on LTP/LTD-like effects induced respectively by means of intermittent (i-) and continuous (c-) TBS delivered over M1 in eight mild AD patients. Each patient was separately evaluated for iTBS and cTBS plasticity induction before and after the two weeks treatment. In each session twenty MEPs were collected at the baseline and then, over the same hot-spot, at 1-5, 6-10, 11-15, 16-20 and 21-25 minutes after TBS protocols. We also investigated SLAI circuits before and after rotigotine administration. We found that at baseline AD patients showed an impaired LTP-like and a normal LTD-like cortical plasticity as assessed by iTBS and cTBS respectively. The efficacy of SLAI circuits was also reduced. After two weeks of D2 agonist administration we observed a marked change in the iTBS protocol effects, revealing that LTP-like plasticity was strikingly enhanced ($p<0.05$), while the cTBS protocol did not show similar remarkable modifications. SLAI was partially restored by D2 agonist therapy, confirming our recent findings. These preliminary results increasingly highlight the role of dopamine in the pathophysiology of AD and in particular suggest that a dysfunction of D2-like receptors is involved in abnormal cortical plasticity in AD. Clinical studies are needed to better understand and identify the potential place of this class of drugs in AD treatment.

Lower concentrations of β-amyloid in CSF correlates with higher apathetic symptoms in patients affected by amnestic MCI

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Background: apathy is considered the most frequent neuropsychiatric disturbance in dementia and its outcome is generally deleterious. Apathetic Alzheimer patients have faster functional and cognitive decline; apathy seems to be more prevalent as dementia progresses and is also a relatively permanent behavior once following onset, in contrast to depression whose prevalence appears to be reduced in advanced stages. **Objective:** to evaluate the relation between apathy and amyloid concentration in patients with amnestic mild cognitive impairment (aMCI). **Methods:** sixteen outpatients fulfilling the criteria of amnestic MCI were enrolled. Patients were evaluated by medical screening, behavioural observation, magnetic resonance scans, neurocognitive profiling, and lumbar puncture to obtain cerebrospinal fluid measuring the concentrations of β-amyloid1-42 (Aβ42), total tau protein (T-tau) and tau phosphorylated, that are associated to the Alzheimer Disease (AD). Apathy was assessed with the Apathy evaluation scale (Marin, 1991). **Results:** aMCI patients with lower CSF concentration of Aβ42 were more apathetic than MCI patients with higher level of Aβ42 (mean Apathy 25,7 + 7,8 *vs* 13,3 + 5,1; p= ,002). Contrary the mean score of Geriatric Depression Scale (GDS) was significant lower in MCI patients with the Aβ42 lower level (mean GDS 4,6 + 2,7 *vs* 2 + 0,9; p= ,04). **Conclusion:** preliminary data confirmed a division of apathy and depression into separate behavioural dimensions. Apathetic symptoms are associated with cerebrospinal fluid biomarker changes significantly associated with incipient AD. High apathy Marin scores seems to be predictors of worse clinical outcomes in patients affected by aMCI due to Alzheimer disease.

The modulating effect of cognitive reserve at the onset of cognitive decline

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Objectives: among the factors that may influence the speed of progression toward the clinical manifestations of Alzheimer's disease, cognitive reserve (CR) is probably the most intriguing one, considering its dynamic features as

a possible target for potential intervention with disease-modifying therapy. The aims of our study were to evaluate the contribution of CR to performance on executive and memory task and to investigate the correlation between CR and pattern of brain response in subjects with Mild Cognitive Impairment (MCI) and Subjective Cognitive Impairment (SCI). **Matherials and methods:** the Cognitive Reserve Index questionnaire (CRIq), was administered to 51 individuals with MCI (mean age 75.6) and 53 with SCI (mean age 71.9), diagnosed on the basis of extensive neuropsychological assessment; a subgroup of 31 MCI (mean age 74) and 24 SCI (mean age 72) subjects underwent a fMRI experimental protocol (GE 1.5 T, GRE-EPI) with a visual spatial attention task. **Results:** the ANCOVAs revealed that better performances on attentive measures (TMT B,A and attentive matrices) were associated with high CR ($F= 8.327$, $p<.05$; $F= 5.438$, $p<.005$ respectively) in both groups; this effect was more evident in SCI subjects as they showed higher CRIq scores. Regarding fMRI analysis, either in SCI and MCI subjects, CRIq and education showed a negative correlation ($p<0.05$) with neural responses in the task-related bilateral parietal and dorsal occipital areas, in the superior frontal cortex and in the posterior cingulate cortex; age positively correlated ($p<0.05$) with anterior cingulate, medial prefrontal and orbital cortex. **Conclusions:** our results suggest that at the early stages of cognitive impairment CR may modulate the attentional but not memory processes, increasing the performance on selective and divided attention tasks. Moreover these findings point out that subjects display different patterns of neural activation during attention tasks depending on cognitive reserve, according to the hypothesis of neural efficiency.

Verbal fluency: different dementias, different mistakes

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Background: it's acknowledged that both patients with Alzheimer Disease (AD) and Frontotemporal Dementia (FTD) show a poorer verbal fluency than normal subjects. Nevertheless studies on AD and FTD fail to show a differential qualitative pattern in these disease. Up to now, a qualitative error analisys has not performed. This study is aimed to analyze the different pattern of errors in verbal fluency tasks committed by patients with AD and FTD. **Methods:** a verbal fluency task (composed of both category and letter fluency tasks) was administered to 142 AD patients, 36 FTD patients (behavioural variant) and 114 healthy controls. Errors were classified in three groups: perseverations, breaking-rules and intrusions. **Results:** perseveration were more frequent in FTD patients than in healthy controls and AD. In particular, FTD patients repeated the same word at least twice (by contrast AD patients only once); furthermore they made more intra-task and inter-task perseverations than healthy controls and AD. On the contrary, breaking rules were more frequent in AD patients than in healthy controls and FTD. Ultimately, intrusion were more frequent both in AD and FTD patients than in healthy controls. **Discussion and conclusions:** this study shows that a differential qualitative pattern of error can be detected in AD and FTD and can have value to improve the differential diagnosis between the two diseases. According with the disesecutive syndrome the FTD patients usually show, they displayed perseverations (intra and inter-task). By contrast, AD patients tended to break rules likely consequent to the memory problem. In summary, a qualitative error analisys in verbal fluency task can be of value to improve differential diagnosis in dementia.

qMT imaging to assess brain tissue modifications in patients Myotonic Dystrophy type-1

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Background: several MRI studies have demonstrated that both focal white matter (WM) lesions and diffuse grey matter (GM) atrophy can be detected in the brain of patients with Myotonic Dystrophy type-1 (DM1). In these subjects, the importance of a diffuse pathology that significantly involves the GM has been stressed by several neuropathological studies, showing the presence of neurofibrillary tangles and tau proteins in the cerebral cortex. **Aim:** to evaluate the sensitivity of the voxel-wise quantitative magnetisation transfer (qMT) imaging in de-

tecting subtle GM and WM abnormalities in DM1 patients. **Methods:** twenty-one DM1 patients, with no or minimal macroscopic lesions detectable on conventional MRI, and 21 healthy controls had MRI at 3T, including volumetric, MT-weighted, T1 and B1 scans. MRI data were analyzed to obtain normalized qMT maps. Voxel-wise statistics was carried out using SPM8 to assess between-group differences in GM and WM qMT parameters. **Results:** GM-RM0B (sensitive to changes in intracellular pH) was the only qMT parameter showing significant ($p<0.05$, FWE-cluster-level-corrected) between-group differences, distributed in the cingulum, in the thalami, in the right postcentral cortex and in the right temporo-parietal cortex. No other significant differences were observed. **Discussion:** our results show that, among qMT parameters, RM0B is the most sensitive to DM1 pathology. Moreover, this study indicates that microscopic damage to the GM largely exceeds that detectable in the WM tissue. This supports the idea that neurodegeneration dominates the pathophysiological processes occurring to DM1 brains, and that GM and WM involvement may represent two pathophysiologically independent processes.

Neuroanatomical correlates of constructional apraxia in Alzheimer's disease

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Background: constructional apraxia (CA) is a deficit in the ability to reproduce spatial relations which is often observed in Alzheimer Disease (AD). Aims of this study were: 1) to evaluate in AD patients whether CA is due to a specific deficit of planning or to a more large visuo-spatial dysfunction; 2) to investigate, using a voxel-based morphometry (VBM), the presence of different patterns of gray matter (GM) damage in AD patients with or without CA. **Methods:** 24 patients with AD and CA (ADca), 24 patients with AD without CA (ADnoca) and 20 healthy subjects (HS) were recruited. They all underwent an extensive neuropsychological assessment and MRI at 3T including T1-weighted volumes. T1-weighted volumes were processed by an optimized VBM protocol. **Results:** there were no differences between the 2 patient groups for the level of dementia, while ADca patients showed lower performances at visuo-spatial tests. VBM analysis: when comparing patients with ADca to HS the former showed more GM atrophy in the precuneus, in the posterior cingulate cortex, in the lateral occipital cortex bilaterally, and in the right cerebellum. Conversely, patients with ADnoca compared to HS showed a more prominent GM atrophy in the medial temporal and in the prefrontal lobes. Patients with ADca compared to those with AD revealed a GM density loss bilaterally in the angular gyrus, in the precuneus, in the posterior cingulate, in the right fusiform and middle temporal gyri and finally in the lateral occipital cortex. **Discussion:** this study reinforces the idea that the occurrence of CA in patients with AD requires an impairment of a wide visuo-spatial network, involving, particularly, the spatial logical and the working memory functions. The neuropsychological results are supported by evidence of GM atrophy in ADca, but not in ADnoca patients, in brain regions traditionally involved in the visuo-spatial processing.

Interlink among ERK phosphorylation, APP metabolism and EAAT1 processing in fibroblasts from Alzheimer patients

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Amyloid-beta leads to neurodegeneration and memory impairment via critical signal transduction processes, including ERK that is phosphorylated in the CNS of AD patients. Moreover, ERK-pathway is involved in non-amy-

loidogenic APP metabolism, anti-inflammatory processes and, by specific transcriptional factors (CREB), might modulate the expression of glutamate transporter (EAAT1) mRNA, previously demonstrated correlating with disease-severity in AD fibroblasts (r=0.8306). By western blot and phospho-Elisa, fibroblasts from AD patients, MCI, PD, as pathological control, and age-related subjects were tested to investigate ERK-pathway alterations associated to the different stages of disease. APP-alpha isoforms were detected in cell lysates by Elisa kit (Biosource). EZ-ChIP assay (Millipore) was used to test ERK-CREB association with EAAT1-promoter. ERK phosphorylation status was reduced by 60% in fibroblasts from MCI and mild-to-moderate AD, compared to severe patients and controls. An inverse correlation was observed between phospho-ERK and disease-severity (r=-0.584). No significant ERK modulation was observed in PD fibroblasts. A 50% reduction of APP-alpha was shown in AD compared to control subjects. MCI APP-alpha distribution was heterogeneous. Moreover, phospho-ERK and APP-alpha correlation in control subject was very significant (r=0.935) while in MCI subjects and AD patients this correlation was lost. A 2,5 fold increase association between EAAT1-DNA and pCREB was observed in AD fibroblasts, justifying a specific ERK involvement in EAAT1 mRNA processing. ERK pathway plays a key role also in the ex-vivo peripheral AD model, showing a tight link to EAAT1-processing, and it is useful to investigate the molecular mechanisms underlying disease progression.

Investigating extracellular vesicles in cerebrospinal fluid of patients with Alzheimer's disease and Frontotemporal dementia: preliminary findings

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Extracellular vesicles (EVs) are nanometer sized vesicles released by most cell types in physiological conditions. EVs, that include exosomes and microvesicles, are specifically equipped to mediate intercellular communication via the transfer of mRNAs, microRNAs, proteins, and lipids. EVs detection may represent a very promising strategy to gain pathogenic information, select specific biomarkers and identify therapeutic targets for neurological disorders. At present, however, very few experimental evidences are available for EVs alterations in dementia. The purpose of this study was to evaluate the presence of EVs in the cerebrospinal fluid (CSF) of patients with Alzheimer's disease (AD), Frontotemporal dementia (FTD) and healthy controls. At present, 25 subjects (10 AD, 10 FTD and 5 controls) were involved in the study. EVs were collected by filtration through a 0.22 mm filter, centrifugal concentration, and pelleting at 100,000 x g. Using a NanoSight device, we observed that the mean particle size was of 263 nm and we found dilution-adjusted concentration of 0.61 x 108 particles/ml. EVs in CSF of AD and FTD patients showed a significant heterogeneity both in size and concentration. The exosome fractions of the samples have been analyzed by Western blotting, and the electrophoresed samples were incubated with antibodies against β-amyloid, total tau, tau phophorylated. A significant amount of both total tau and phosphorylated tau was found. Our preliminary data suggest that CSF extracellular vesicles may be investigate as novel biomarker in neurodegeneration.

Muscle ultrasonography as an additional tool for differential diagnosis in dementia?

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Introduction: the differential diagnosis between frontotemporal dementia (FTD) and Alzheimer's disease (AD) is not infrequently challenging. Mild motor signs in FTD patients are still often overlooked, possibly because the instrumental gold standard for lower motor neuron (LMN) involvement is EMG, a quite invasive technique for such poorly collaborative patients. The ultrasound detection of fasciculations has been recently proposed for assess-

ing LMN dysfunction in ALS patients. **Aim:** to examine muscle ultrasound in FTD and AD, both for feasibility and for comparison regarding the prevalence of fasciculations in these two types of dementias. **Methods:** FTD patients and AD patients were examined (5 muscles bilaterally) with a 7 MHz linear transducer. Each muscle was observed and video-recorded for at least 30 seconds. A rating from 0 to 3 was assigned to each muscle for the eventual presence/amount of fasciculations. Accuracy was subsequently checked on records by a second rater blind to diagnosis. Two groups of healthy subjects and ALS patients were included as well. **Results:** FTD patients displayed fasciculations in about 50% of the cases, albeit values for about 40% of those who were positive might still be considered compatible with benign fasciculations (<6). The average fasciculation score in the remaining positive patients was 17.7 (range 6-30). AD patients displayed a fasciculation score always <6 (average 2.8, range 1-5). No healthy control displayed fasciculations, while the score for ALS patients was always =22. Ultrasounds can be easily applied defining LMN involvement and, possibly, a subset of FTD patients. **Conclusions:** with a more aggressive disease. Conversely, AD patients display a minimal involvement of LMN, possibly suggesting that muscle ultrasonography might aid in the diagnosis when in doubt between these two types of dementias. Extension of this study protocol at CBS and LBD patients might help in better understanding the potentialities of this approach.

Numerical and arithmetical knowledge in early Alzheimer's disease

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Background: numerical abilities play an important role in day-to-day life and there is growing evidence in literature showing alterations of this competence since the early stages of Alzheimer's Disease (AD). However, the issue if and to what extent numerical and arithmetical knowledge are impaired in this disease, is still under debate. **Purpose:** to explore numerical and arithmetical knowledge in a group of 20 patients affected by Alzheimer's Disease (AD). **Materials and methods:** 20 patients affected by mild Alzheimer's Disease (AD) were enrolled in the study. A group of 22 healthy subjects, matched with the patients for demographical characteristics, served as reference group. All patients underwent an extensive neuropsychological battery exploring numerical and arithmetical knowledge (Miceli and Capasso battery, 1991), which included: numerical tasks, which comprehend both tasks exploring the capacity of a subject to understand the magnitude of a number in three different conditions (written Arabic numbers, written number words and spoken numbers) 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); calculation tasks (recognition of arithmetical signs; written and mental calculation). **Results:** the AD group performed flawlessly in magnitude judgment tasks. Both transcoding tasks and calculation were significantly worse ($p<0.01$) than controls' performance. The analysis of the single patient performance did not reveal an entirely consistent pattern. Also the qualitative pattern of error was not homogeneous across the entire AD group. **Discussion:** the present data are in favour of an early impairment of numerical and arithmetical knowledge in AD. Assessment of everyday numerical skills may be crucial in planning adequate support for these patients and may offer new insights on the cognitive changes underpinning this disease.

Longitudinal effects on plasma Abeta levels of Imatinib, a gamma-secretase activating protein inhibitor

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Imatinib Mesylate is a competitive tyrosine-kinase inhibitor used in the treatment of multiple types of leukaemia, including Ph+ chronic myelogenous leukaemia (CML). The recent report that Imatinib inhibits gamma-secretase activating protein (gSAP), reducing beta-amyloid- (Abeta) production without affecting Notch-1 cleavage has led to

the proposal of a possible application of this drug in AD therapeutics. In fact, one major drawback of Semagacestat, a direct inhibitor of gamma-secretase, was identified in the low Abeta/Notch therapeutic index, with the consequent failure of the phase III trial. Imatinib peripheral administration (20 mg/kg/day) was able to reduce Abeta content in mouse brain. Usually, leukaemia patients receive an average oral dose of 400 mg/day (~5-6 mg/kg/day). In this longitudinal study we investigated if Imatinib administration in 10 leukemic patients could reduce plasma Abeta1-40 levels. Patients' blood was sampled prior to treatment (time T0) and after 15, 30, and 60-to-90 days of treatment. Abeta1-40 plasma levels were assessed by ELISA as previously described. No significant reduction in plasma Abeta1-40 was observed at any time point. In fact, ratios to T0 of Abeta1-40 T15-, T30- and T90 were: 1.07 ± 0.39, 1.37 ± 0.59, and 1.48 ± 0.61, respectively, indicating no decrease with Imatinib. While these results are negative at standard dosing of Imatinib for CML, they do not exclude the possibility that Abeta lowering effects might be present at higher doses of this drug or with second generation tyrosine-kinase inhibitors, such as Dasatinib or Nilotinib, which can cross the blood brain barrier more easily. Further exploration of this issue might lead to advances in AD therapeutics.

Donepezil modulates the endogenous immune response in Alzheimer's disease, an *ex vivo* and *in vitro* study

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Donepezil (DNPZ), an acetyl-cholinesterase inhibitor (AChEI), is widely used as a symptomatic drug in AD, given the involvement of cholinergic damage in the onset of memory loss. DNPZ, besides being able to improve acetylcholine (ACh) transmission, might have a neuroprotective effect reducing toxic Abeta fibrils and regulating the immune response. Considering that we previously showed a specific increase of plasma anti-Abeta1-42 antibodies in AD patients treated with AChEI, we evaluated in this study the role of DNPZ in favouring a Th2 phenotype, involved in modulating the immune humoral response. Moreover we hypothesized that this mechanism might be mediated by the a7-nicotinic ACh receptor expressed in lymphocytes. 60 patients with mild or moderate AD, either treated (n=22) or not (n=38) with DNPZ, and 30 controls were enrolled. AD DNPZ+ showed significantly higher plasma levels of anti-Abeta antibodies than DNPZ- (+40%) and lower levels of Abeta 1-42 than controls (-50%). In a subgroup of subjects, GATA-3, a transcription factor involved in Th2 differentiation, and a7nAChR expression was evaluated. No differences were found in GATA-3 mRNA in AD DNPZ+ when compared to DNPZ- and controls. On the opposite, we found by chromatine immunoprecipitation a significant three-fold increase of the association of GATA-3 with the IL-5-promoter in DNPZ+ patients, which also showed a significant twofold increase in a7-nAChR mRNA, with respect to DNPZ- ones. *In vitro* analyses demonstrated that the capacity of DNPZ to modulate GATA-3 expression is mediated by a7nAChR, since MLA, a specific antagonist, prevents it. Further studies are needed to better understand the role of DNPZ in modulating the immune response against Abeta, possibly ameliorating therapeutic strategies for AD.

Long-lasting cognitive stimulation temporary improves cognitive impairment in patients with Alzheimer's disease: the results from a 6-months follow-up controlled clinical study

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Introduction: several data suggest that non-pharmacological interventions, such as cognitive stimulation, may temporary slow cognitive decline due to Alzheimer's disease (AD). Our objective was to assess the impact of a long-term cognitive rehabilitation on cognitive functions in a cohort of patients with mild-to-moderate AD compared to a control

group. **Methods:** 80 AD patients (18=MMSE=24) were randomly divided into two groups of 40 subjects matching for age, sex and education. The active treatment group participated in a program of cognitive rehabilitation over a period of 6 months. The intervention was administered in-group sessions offered twice a week for 24 consecutive weeks. Sessions lasted 60 minutes each time. The program consisted of several cognitively stimulating activities (memory training, speech therapy, occupational therapy, reading and logic games). The control group did not receive any rehabilitative treatment. All the participants underwent a complete neuropsychological evaluation at the baseline and at the end of the study period (T1). 25 subjects among treatment group also received a third neuropsychological evaluation after further 6 months from the end of the intervention (T2) as follow-up. **Results:** at T1, measurements of global cognitive function and performances on the activities of daily living remained stable whereas several cognitive functions (orientation, memory, verbal fluency and naming) significantly improved in the experimental group. The mean scores obtained by the controls, instead, displayed mild but significant worsening at T1. The 25 subjects that received the follow-up examination at T2 showed a cognitive decline similar to that observed in the control group. **Conclusions:** this study provides evidence that prolonged cognitive stimulation improves cognition in AD patients keeping their autonomy levels stable. As the beneficial effects due to this kind of cognitive rehabilitation seems to be temporary, highly standardized, non-pharmacological group interventions could be useful to postpone decline in cognitive function when repeated over time.

Melanopsin retinal ganglion cells and circadian dysfunction in Alzheimer's disease

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Objectives: to characterize optic nerve involvement and in particular melanopsin retinal ganglion cells (mRGCs) in relation to rest-activity rhythm dysfunction in Alzheimer disease (AD). **Methods:** ophthalmologic evaluation and retinal nerve fiber layer (RNFL) thickness measurements by optical coherence tomography were performed 21 AD and 74 age-matched controls. Actigraphic monitoring was performed in 16 AD patients and 10 age-matched controls. Non-parametric methods were applied to assess interdaily stability (IS), intradaily variability (IV) and relative amplitude (RA) of rest-activity rhythm. We also performed immunohistochemical analysis of mRGCs and axonal count on optic nerve cross-sections in 14 neuropathologically confirmed AD and 11 control postmortem retinas. **Results:** OCT evaluation demonstrated reduced average (p=0.03) and superior (p=0.005) RNFL thickness in AD patients. Actigraphic monitoring demonstrated a tendency towards an increased IV (p=0.09) and significantly reduced RA (p=0.04). Furthermore, AD patients were significantly less active during the day (p=0.03). Considering the patients with at least one circadian parameter outside the 2SD from the mean of controls, a significant correlation between IV, average (p=0.035), superior (p=0.045) and inferior (p=0.017) RNFL thickness was found. Melanopsin RGCs density was significantly reduced in AD post-mortem retinas compared to controls (p=0.008) and axonal count also showed an almost significant reduction in AD optic nerves (p=0.067). **Conclusions:** we demonstrated a subclinical optic nerve involvement in AD patients, both by OCT and histopathology. We also documented rest-activity circadian dysfunction in AD patients. Postmortem investigation revealed loss of mRGCs and RGCs. The reduction of mRGCs may contribute to circadian rhythm dysfunction in AD.

Clinical salience of visuospatial memory and structural brain deficits in Mild Cognitive Impairment

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Spatial abilities decline in normal aging and decrease faster and earlier in Alzheimer's disease (AD), but these deficits are under investigated specially in the preclinical Mild Cognitive Impairment (MCI) stage. The main goal

of this study was to assess visuospatial memory functions in the predementia stage of AD, such as MCI, in order to verify whether visuospatial memory evaluation might increase the diagnostic power of MCI compared with other standard clinical tests. We also aimed to investigate the level of atrophy in MCI compared with controls in order to establish if these structural deficits might underpin visuospatial decline. Twenty MCI patients (ten females and ten males) and fourteen healthy controls (ten females and four males) were included in this study. All participants underwent to an extensive standard neuropsychological assessment, experimental visuospatial memory testing (objects location, route learning and map learning) and MRI brain scanning. Compared to healthy elderly controls, MCI patients scored significantly worse in almost all visuospatial tasks. ROC analysis showed that visuospatial tasks had an elevated discriminant power between groups (AUC superior to .90) comparable to some standard cognitive tests and superior to several standard tests. Voxel-based morphometry analysis showed that, compared to controls, patients had a higher level of atrophy in middle and superior frontal gyrus and uncus, the anterior extremity of the parahippocampal gyrus. This study supports that visuospatial memory is a valid diagnostic tool of MCI and visuospatial decline is underpinned by brain deficits in regions involved in spatial abilities, such as parahippocampal cortex.

Definition of EADC-ADNI Harmonized Protocol for hippocampal segmentation

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Heterogeneity of protocols leads to different volume estimates, hampering comparison of studies and clinical use for Alzheimer's disease (AD). A Harmonized Protocol for manual hippocampal segmentation from magnetic resonance images (MRIs) is urgently needed. Differences among the 12 most commonly used segmentation protocols were extracted, operationalized, and quantitatively investigated. Results were used to run an evidence-based Delphi panel (iterative anonymous voting sessions with feedback from previous rounds) with sixteen experts on hippocampus, to converge on a consensual definition of landmarks and segmentation modalities. Panelists voted the most inclusive among the proposed landmarks, defining a model of hippocampus that covers 100% of hippocampal tissue, captures 100% of AD-related atrophy, and has good intra-rater (0.99) and inter-rater (0.94) reliability. Based on these data, the Harmonized Protocol (HP) has been written. Five expert tracers from independent centres manually segmented 40 benchmark hippocampi (selected from ADNI dataset and balanced for diagnosis, atrophy and magnet field strength) as the reference gold standard. Inter-rater agreement among the 5 tracers was over 0.94 (absolute method, 5 level ANOVA) for ICC, and over 0.73 for similarity coefficient (intersection among all 5 tracers). The Qualification of human tracers according to the HP has been started through a web-platform. The platform provides statistical and point by point feedback informing the tracer about how far his/her segmentation is from the benchmark segmentation. The HP is currently being validated versus the most frequently used "local protocols" in twenty EADC-ADNI centres for dementia, and with neuropathological data. Updated information on this ongoing project is available at www.hippocampal-protocol.net.

Colour processing in dementias: evidence from Alzheimer's disease and semantic dementia

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Introduction: up to now, there are many studies dealing about how our brain organizes semantic knowledge, but only few of them deals about colours. Our aim is to investigate colour processing in two different dementias, i.e. semantic dementia (SD) and Alzheimer's Disease (AD). **Materials and methods:** we created an ex-

perimental neuropsychological test battery exploring perceptual, linguistic and semantic features linked to colours. The experimental battery was administered to 9 patients with Semantic Dementia (SD), to 10 patients with Alzheimer Disease (AD) and to a reference group (21 normal subjects). **Results:** SD, AD and normal subjects did not differ in tasks of colour perception. AD did not differ from normal subjects in tasks exploring both linguistic and semantic features of colours. By contrast, SD patients showed a significant lower performance than in other two groups in linguistic and semantic tasks. **Discussion:** the present study allows to explore the colour processing in two dementias. AD patients did not show problems in colour processing. By contrast, according to the general neuropsychological profile, SD patients displayed problems in processing colours from linguistic and semantic point of view. The study supports the hypothesis of a multimodal organization of the semantic knowledge in the brain.

Effect of choline alphoscerate on cognition in patients with mild-to-moderate Alzheimer's disease treated with a cholinesterase inhibitor therapy

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Objective: to evaluate efficacy and tolerability of the acetylcholine precursor choline-alphoscerate (GPC) as add-on therapy to cholinesterase inhibitors (ChEIs) in patients with mild-to-moderate Alzheimer's disease (AD). **Materials and methods:** this was a prospective, randomized, 12 month, parallel-group study comparing ChEIs vs ChEIs+GPC (1200 mg/die). Drug effects on cognition were evaluated cross-sectionally at baseline, 6 and 12 months using two rating scales: MMSE and ADAS-Cog. **Results:** 217 patients were randomized to ChEIs or ChEIs+GPC groups. Mean age was 75.6 years (range 54-89years). Of these 184 (84.7%) completed the study. The MMSE score for ChEIs+GPC group showed a mean improvement versus baseline of +1.46 points compared with ChEIs group that showed a mean improvement of +0.17 points. MMSE score for the combination therapy group reached statistical significance vs baseline (p= 0.05). The between-group difference in MMSE change showed a trend for superiority of combination therapy and reached statistical significance (p= 0.05). The ADAS-Cog score for ChEIs+GPC group showed a mean improvement versus baseline of -1.34 points compared with ChEIs group that showed a mean improvement of -0.41 points.The ADAS-Cog scores for both groups did not differ significantly from baseline. The between-group difference in ADAS-Cog change showed a trend for superiority of combination therapy, but did not reach statistical significance (p <0.1). Adverse events occurred in 36.2% and in 42.5% of patients on ChEIs+GPC and ChEIs groups respectively. The most common was nausea, followed by vomiting and anorexia. **Discussion:** the use of GPC as add-on therapy to ChEIs resulted in significantly better outcomes than ChEIs monotherapy on measures of cognition without major side effects. Both treatments were well tolerated; most adverse events were transient and of mild-to-moderate intensity. **Conclusions:** the addition of a cholinergic precursor like GPC to the current standard treatments for AD may represent a way to prolong on time the beneficial effects of cholinergic therapies.

Occurrence of cancer and Alzheimer's disease are inversely associated in elderly persons: a population-based incidence study

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Objectives: to evaluate the incidence of cancer in persons with Alzheimer's disease (AD) and the incidence of AD in persons with cancer in a large general population. **Methods:** this was a prospective cohort study on

an Italian population, of about one million, living in an area North-West of Milan served by a single Local Health Authority (ASL-Mi1). Cancer incidence in the whole population was derived from the ASL-Mi1 tumor registry and AD incidences from registries of drug prescriptions, hospitalizations and payment exemptions. The risk of AD in persons with cancer and vice versa, relative to general population was estimated as observed timed expected cases for from 2004 to 2009. Expected cases of AD were calculated applying the age-, sex-, and calendar year-specific incidence rates observed in the whole population of ASL-Mi1 to the subgroup constituted of person with newly-diagnosed cancers during the period of observation. The same calculations were carried-out for cancers in AD persons. To control for potential confounding separate analyses were carried-out for the time period preceding or following the index diagnosis, for survivors and non-survivors until the end of 2009 and for different types and sites of cancer. **Results:** the risk of cancer in person with AD was halved and the risk of AD in persons with cancer was 35% reduced. This inverse relationship of occurrence was observed in almost all the subgroup analyses suggesting that some anticipated potential confounding factors did not influenced in a relevant manner the results. **Conclusions:** the occurrence of both cancer and AD increases exponentially with age, but with an inverse relationship; older person with cancer have a reduced risk of having AD and vice versa. Since AD and cancer are negative hallmarks of aging and senescence we suggest that AD, cancer and senescence could be manifestation of a unique phenomenon related to human aging.

Morphological and metabolic changes in the nigro-striatal pathway of Synthetic Proteasome Inhibitor (PSI)-treated rats: a MRI and MRS study

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Systemic administration of a Synthetic Proteasome Inhibitor (PSI) in rats has been described as able to provide a model of Parkinson's disease (PD), characterized by behavioral and biochemical modifications, including loss of dopaminergic neurons in the substantia nigra (SN), as assessed by post-mortem studies. With the present study we aimed to assess *in vivo* by Magnetic Resonance (MR) possible morphological and metabolic changes in the nigro-striatal pathway of PSI-treated rats. 10 animals were subcutaneously injected with PSI 6.0 mg/kg dissolved in DMSO 100%. Injections were made thrice weekly over the course of two weeks. 5 more animals injected with DMSO 100% with the same protocol served as controls. The animals underwent MR sessions before and at four weeks after the end of treatment with either PSI or vehicle. MR Imaging was performed to measure SN volume and Proton MR Spectroscopy (1H-MRS) was performed to measure metabolites changes at the striatum. Animals were also assessed for motor function at baseline and at 4 and 6 weeks after treatment. Dopamine and dopamine metabolite levels were measured in the striata at 6 weeks after treatment. PSI-treated animals showed volumetric reduction of the SN ($p<0.02$) at 4 weeks after treatment as compared to baseline. Immunofluorescence analysis confirmed MRI changes in SN showing a reduction of tyrosine hydroxylase expression as compared to neuron-specific enolase expression. A reduction of N-acetyl-aspartate/total creatine ratio ($p=0.05$) and an increase of glutamate-glutamine-γ amminobutirrate/total creatine were found at spectroscopy ($p=0.03$). At 6 weeks after treatment, PSI-treated rats also showed motor dysfunction compared to baseline ($p=0.02$), accompanied by dopamine level reduction in the striatum ($p=0.02$). Treatment with PSI produced morphological and metabolic modifications of the nigro-striatal pathway, accompanied by motor dysfunction. MR demonstrated to be a powerful mean to assess *in vivo* the nigro-striatal pathway morphology and metabolism in the PSI-based PD animal model.

An open-label, prospective, controlled study on the efficacy of innovative rehabilitation therapy in mild Alzheimer's disease

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Introduction: a large body of evidence indicates that sporadic Alzheimer's disease (AD) is a vascular disorder with neurodegenerative consequences and cerebral hypoperfusion is one of the earliest pathological signs in the development of cognitive failure. **Aim:** the aim of this study is to evaluate if brain reperfusion rehabilitation therapy (BRRT) may improve the cognitive impairment in mild Alzheimer's disease (AD). **Methods:** by an open-label, prospective, controlled, randomized study, we studied 25 patients, 14 M and 11 F, mean age: 72.7 (SD 6.6) years with mild AD [Mini Mental State Examination (MMSE) range 21- 26], at baseline (T0), and 3 (T3), 6 (T6) and 12 (T12) months by means of MMSE and Rey Memory Test (RMT). 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. Ten patients received no treatment (control group). **Results:** in the BRRT group 10 of 15 patients completed the study: we found a significant improvement of MMSE and RMT scores at T3, T6 and T12 compared to T0, and a significantly greater improvement of MMSE at T3: + 2.3 (SD 1.6), $p < 0.001$, at T6: + 4.3 (SD 1.8), $p < 0.0001$, and T12: + 5.3 (SD 2.5), $p < 0.0001$, compared to the control group. No significant side effects were reported. **Conclusions:** in our pilot study, BRRT seems able to achieve a significant improvement of cognitive impairment and might be a promising innovative therapy for mild AD.

EEG characteristics of MCI-A longitudinal study

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Objectives: to evaluate the hypothesis that abnormalities of electrocortical arousal found in DLB patients could be already present at the stage of MCI. **Methods:** a total of 47 subjects referred to our centers, underwent a composite battery of tests for cognition, including the Mini Mental State Examination, the Clinical Dementia Rating the Global Deterioration Scale and the Dementia Rating Scale, fulfilled the criteria for MCI and were followed for three years. The patients underwent EEG recordings according to previously published methods, Clinical and neuropsychological assessments were repeated every 6 months. All the subjects admitted to the study underwent a standardised neurological examination, a Magnetic Resonance Imaging (MRI) scan, and a dopaminergic presynaptic ligand ioflupane Single Photon Emission Computer Tomography (SPECT)- Dopamine transporter (DAT) scan. **Results:** at the end of the three year follow-up study 29 subjects were affected by overt dementia (MCI-converter). 15 patients fulfilled the criteria for DLB and were designed as MCI-DLB converter; 14 patients were diagnosed as AD; A 11 patients still fulfilled diagnostic criteria for MCI and were defined as MCI non converters. 60.9% of MCI subjects presenting with abnormal EEGs (a QEEG pattern different than 1 with either a DF <8.0 or DFV >1.5), converted in the three-year follow-up to DLB. 8 subjects (34.8%) with abnormal EEG were MCI non converters. The 14 MCI-AD presented with the same EEG patterns observed at admission to the study. This suggests that, even if AD patients after 2 years of disease show EEG pattern disruption, as suggested by follow-up data in the 50 AD patients included in the study for comparison, these changes are modest as compared to DLB patients even at the stage of MCI. This implies that instability of electrocortical arousal is a prominent and early feature of DLB.

Vestibular rehabilitation in patients with Parkinson's disease and lateral axial dystonia

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Lateral axial dystonia (LAD) is frequently observed in patients with Parkinson's disease (PD). LAD is often associated with peripheral vestibular impairment and asymmetric tone of paravertebral muscles.
The aim of this study was to identify a non-pharmacological treatment based on a physiotherapy approach through adaptation, habituation and compensation, to improve posture in patients with PD and LAD associated to vestibular imbalance.
We have screened 4 patients with PD and LAD among local cohort of 100 patients with PD (H/Y 1-2,5 e lateral flexion of the trunk 10° measured on a wall goniometer).
All patients were treated with optimal dose of dopaminomimetic (L-DOPA EQ mg 700±163,3) and they underwent to vestibular exams: Dix-Hallpike, Pagnini-McClure, Head-Shaking test, video Head Impulse Test, Static Stabilometry, Audio-impedance Exam and to tests: PDQ-8, Dizziness Handicap Inventory (DHI), VAS-QoL and Tinetti balance and gait scale.
Two patients showed deficit of right labyrinth, one patient had left peripheral impairment, one patient showed benign paroxysmal positional vertigo of the left posterior semicircular canal.
Patients performed an Integrated Program including vestibular rehabilitation exercises: Cawthorne-Cooksey, point de mire, static and dynamic boite, vestibular-proprioceptive exercises on different surfaces, exercises of fixation, active and passive exercises of muscle elongation and rehabilitation of respiratory dynamic.
At the final visit all patients had an improvement in static and dynamic posture with an increase of the Tinetti balance and gait Scale and with a reduction of DHI. All patients showed gain in quality of life highlighted by an increase in VAS-QoL and a reduction in PDQ-8.
This pilot study will be extend to a larger number of patients in order to validate this alternative treatment, based on a physiotherapy approach, to improve balance in patients with PD and LAD associated to vestibular hypofunction.

A case of apraxic agraphia in a patient with Progressive Supranuclear Palsy

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Introduction: apraxic agraphia is an acquired writing disorder following disruption of skilled movement plans of writing that cannot be attributed to sensorimotor dysfunction. Thus, patients are unable to execute the sequence of strokes necessary to produce the letter form specified by the allographic code. The neural network responsible for writing includes the superior parietal region, dorsolateral and medial premotor cortex and cerebellum. We report a case of a patient with Progressive Supranuclear Palsy (PSP) who developed a disorder of handwriting. **Case report:** a 56 year old right handed man with an educational level of 5 years was admitted to our clinic because of frequent falls since 4 years. Neurological examination on admission showed hypomimic face, hypophonic and festinated speech, down gaze palsy, diffuse bradykinesia and rigidity, postural instability. According to Litvan criteria (1996) a diagnosis of PSP was made (clinical phenotype: Richardson's syndrome). A morphometric MRI study was performed, revealing a Magnetic Resonance Parkinsonism Index of 19 compatible with a diagnosis of PSP. Neuropsychological examination revealed an important executive dysfunction. Spontaneous speech was characterized by palilalia, echolalia, but a good amount of information was produced. There was good comprehension, normal reading and repetition but reduced verbal fluency. Both numbers and words writing to dictation was impossible because the patient produced illegible scrawls. Grapheme formation improved during copy. There was no change in quality when the patient wrote with the non-dominant left hand. However, legibility got better when the patient wrote uppercase letters. **Conclusion:** apraxic agraphia can be associated or not with ideomotor apraxia. Our patient had not this kind of apraxia. Progressive agraphia often accompanies progressive aphasia and it can be an early symptom

of degenerative dementia as in Alzheimer's disease. Among parkinsonism it has been reported in corticobasal degeneration. To our knowledge this is the first description in PSP.

Rey-Osterrieth Complex Figure performance in patients with degenerative dementia using Boston Qualitative Scoring System

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Objectives: to investigate the Rey-Osterrieth Complex Figure (ROCF) performance in three type of neurodegenerative dementias using the Boston Qualitative Scoring System (BQSS). **Patients and methods:** we examined consecutive outpatients met current diagnostic research criteria for Alzheimer's disease (AD), frontotemporal dementia (FTD) and dementia with Lewy Bodies (DLB). General exclusion criteria were mixed and vascular dementia, Mini Mental State Examination <15/30, history of other disorders that may have caused the cognitive deficits. We included sixty-four patients (39 AD, 18 FTD and 7 DLB). Patients underwent standardized neuropsychological battery and ROCF. We used both quantitative (36-point scores) and qualitative (BQSS) scoring system for evaluating copy condition of Rey figure. ANOVA, Bonferroni correction and Chi-square test were used to analyze group differences. **Results:** the three groups did not differ in gender, education and duration of disease. The three groups did not differ in presence and accuracy summary score (BQSS-CPA), organization summary score (BQSS-ORG). Using Bonferroni correction there were no significant differences between AD and FTD in any of the parameters of qualitative evaluation. Instead we found significantly differences between FTD and DLB, in particular for configural, cluster and detail presence, planning and reduction. **Discussion and conclusions:** BQSS is one of the most comprehensive methods that provide both a comprehensive set of qualitative ratings and important quantitative summary scores. In our study the performance scoring with BQSS did not differ between the tree groups. In particular we confirmed previous findings that figure copy performance using a qualitative methods is not useful in differentiating AD and FTD. However the most interesting and significantly differences have been found between FTD and LBD. Although our sample is small, our work is the first study that has investigated and compared the performance on copy condition of Rey figure in AD, FTD and LDB using BQSS.

Frequency of stereotypies and repetitive behaviors in frontotemporal dementia and Alzheimer's disease: a pilot study with a specific tool

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Background: repetitive behaviors are frequent clinical features of frontotemporal dementia (FTD) and may be divided in simple movements (stereotypies) or complex behaviors (rituals). Lack of specific and standardized clinical scales may hamper recognition and early treatment of these behavioral disturbances. **Aim:** to assess the frequency of stereotypies and repetitive behaviors in patients with behavioral FTD (bvFTD) and in patients with Alzheimer's disease (AD) using a dedicated questionnaire. **Methods:** 25 patients with a diagnosis of bvFTD (mean age 72±8.4 years) according to established criteria and 40 AD patients (mean age 80±7 years; p=0.001) were recruited for this study. Mean MMSE score was comparable in the two groups (FTD:21±7, AD:19±5; p=0.3). An *ad hoc* questionnaire, the Repetitive Behaviors Subscale (RBS), obtained by revising and merging preexisting scales on stereotypies, was administered to each patient. RBS provides frequency and severity scores for nine subitems: motor and verbal stereotypies, verbal perseverations, clock watching, counting, hoarding, routine and rituals, fixed leisure activities and recurrent eating behaviors. **Results:** mean total RBS score was signifi-

cantly worse in the bvFTD group respect to AD (bvFTD:16.8±9.6; AD:8±8; p=0.002). The bvFTD group presented more frequent rituals and fixed adherence to routine (bvFTD:62%, AD:20%; p<0.001) and verbal perseverations (bvFTD:62%, AD:28%; p<0.01). Simple motor stereotypies, instead, were present in a similar proportion of bvFTD and AD patients (bvFTD:42%, AD:46%; p=0.7), as well as verbal stereotypies (bvFTD:25%, AD:10%; p=0.2). Total RBS score weakly correlated with total NPI score (r=0.75) and not with the MMSE score. **Conclusions:** presence of complex rituals and verbal perseverations are core features of the FTD, while simple motor and verbal stereotypies can be also detected in AD patients. A specific questionnaire assessing repetitive and compulsive behavior may help clinicians recognizing and grading this behavioral disturbance and monitor the efficacy of drug treatments.

Alzheimer's disease: an immune-mediated pathology?

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Alzheimer's disease (AD) is a neurodegenerative disorder associated to the accumulation of Beta-Amyloid (Abeta) aggregates within the CNS followed by neuroinflammation. AD is characterised by a deregulation of Abeta protein metabolism and its precipitation in the limbic and associative cortices where it accumulates in extra-cellular plaques. A prominent immune response in the CNS has been shown to be associated with Abeta deposition and plaque formation. It was suggested that the inflammation occurring in the brain of AD patients has systemic parallels, and there are many reports supporting the concept that AD is a systemic inflammatory disease. Regulatory T cells (Treg) are a key cell type for regulating cellular immunity, preventing autoimmune disease in experimental mouse models. The relevance of Treg in regulating human cellular immunity could be demonstrated by the fact that changes in Treg activity or frequency contribute to autoimmune diseases. The assessment of Treg cell frequencies in AD may have relevant implications both in terms of the clarification of their role in the development of the disease and to evaluate the diagnostic power of Treg changes in AD identification. To this end, we stained Treg cells from AD patients and healthy subjects by a polychromatic flow cytometry assay. Results evidenced that the frequency of total Tregs is higher in AD patients respect to healthy subjects. Of note, among total Tregs, the naïve compartment results significantly increased in AD, suggesting a possible role of such cells in the pathogenesis of the disease.

Route learning in Alzheimer's disease

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Background: topographical disorientation (TD) is frequently detected among focal and neurodegenerative diseases; it assumes particular significance in Alzheimer's disease (AD), being often one of its earliest symptoms. However, despite its relevance in the disease, few studies have explored the nature and mechanisms for TD in these patients. **Purpose:** the present study aims to verify the occurrence of TD and to identify the neuropsychological dysfunctions associated with TD in a group of 10 patients affected by AD. **Materials and methods:** ten patients (8 men, 2 women) affected by mild-to-moderate Alzheimer's Disease (AD) were enrolled in the study. A group of 15 healthy subjects (7 men, 8 women), matched with the patients for demographical characteristics, served as reference group. They were administered an experimental Route Learning Task (RLT): during the learning trial the subjects were shown a video in which they were asked, while sitting in the cabin of a car, to follow a real route, along which were placed ten intersections having two possible choices (turn on the left or on the right). Immediately after the learning trial, the pathway was showed again. At each intersection the video was stopped and the subjects were asked to remember if the car had previously turned left or right. **Results:** the t test revealed a significantly lower performance ($p < 0.001$) of AD patients in the experimental Route Learning Task. The performance on the RLT correlated significantly to spatial tasks in the background neuropsychological examination (p=0.01). **Discussion:** the present study showed the presence of topographical disorientation in mild-to-moderate AD. The TD correlated to measures of visuospatial impairment. The present data should en-

courage to examine in detail topographical disorientation in AD even in the mild phase of the disease. It is likely that the visuospatial breakdown plays the prominent role in the genesis of TD.

The applause sign in fronto-temporal lobar degeneration

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Introduction: originally, the applause sign was considered a specific sign of progressive supranuclear palsy (PSP). However, other studies found that the applause sign was highly specific for parkinsonian disorders but not for PSP. Our recent study provides evidence for the presence of the applause sign in cortical dementias such as AD and FTD. The nature of applause sign is still uncertain. It has been interpreted as a motor perseveration or a form of apraxia. The present study aims to clarify the debated nature of the applause sign. **Materials and methods:** the applause sign was detected using the three clap test which was administered and scored according to the literature. During the neuropsychological examination attention was paid to the presence of motor perseverations in copy and memory tasks. They were recorded. We examined the applause sign in 80 patients with Frontotemporal Lobe Degeneration (FTLD): 13 patients with SD; 33 patients with FTD, 9 patients with PNFA, 14 patients with CBD and 11 patients with PSP. **Results:** an abnormal applause sign was present in all patient groups (80% in PSP, 60% in CBD, 48% in FTD, 66% in PNFA and 30% in SD). Correlation analysis performed within the whole patient sample evidenced a significant correlation between the applause sign and the number of perseverations in other neuropsychological tests ($p<0.01$). The only correlation of the applause sign to the background neuropsychology was with the Stroop test. **Conclusion:** the present study shows the presence of the applause sign in the different phenotypic variants of FTLD. The high correlation with motor perseverations make plausible that the appluse sign itself is a motor perseveration, likely consequent to frontal lobe dysfunction.

Does low dose of acetyl-salicylic acid reduce cognitive decline in patient with Mild Cognitive Impairment?

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Objectives: although neuroprotective effect of anti-inflammatory drugs has been claimed, randomised controlled trials have given negative results in decreasing the risk of Alzheimer's disease. We aimed to determine whether low doses of acetyl-salicylic acid (ASA) influence the course of the disease in people with Mild Cognitive Impairment. **Method:** as a part of a longitudinal clinical-neuropsychological study, 90 MCI patients were assessed by a thorough clinical history, neurological and extensive neuropsychological examinations, laboratory tests and neuroimaging. They were divided into two groups, according if they assumed ASA or not. All participants were re-evaluated after 22 months. Differences between two groups were analyzed by the Student's t-test for continuous variables and the Chi-square test for non-continuous ones. **Results:** 31 patients (mean age 72 years old, 38% male and 62% female) assumed ASA, and 59 (mean age 69 years old, 30% male and 70% female) did not. Age and scooling-adjusted Mini Mental State Evaluation (MMSE) did not differ between two groups baseline; however the average MMSE declined over the follow up period was different (0,11 +/- 1,9 and 0,33 +/- 2,7; p=0,045). Worsening in specific tests was similar in both group, except for Digit Span test which almost reach the statistical significance (-0,21 +/- 0,8 in ASA users and 0,18 +/- 1,2 in ASA non- users, P=0,059). After follow-up 9,6% of ASA users and 28,8% of ASA non-users converted in dementia (X=3,2; P= 0.071). **Discussion:** we reported a positive effect on global cognitive function evaluated by MMSE. The analysis of specific cognitive domains suggest that in ASA users attention is less affected by the disease progression. Furthermore our data indicate less converters in ASA users, although without statistical significance. It is therefore possible that ASA might influence cognitive decline. These findings in a small sample encourage larger-scale studies.

Cross-sectional clinical, neuropsychological, neuroimaging, neurophysiological, and biochemical characterization of Mild Cognitive Impairment patients in wp5 pharmacog/e-adni study

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Background: workpackage 5 of PharmaCog (E-ADNI) is a serial multicenter European study aimed to identify new biomarkers of disease progression in 150 patients with amnestic mild cognitive impairment (aMCI). E-ADNI uses core markers of the North American ADNI, and expands them with specific cognitive, neuroimaging, neurophysiological, and biochemical markers, harmonized with markers that are assessed in animal models in PharmaCog. **Methods:** we report preliminary cross-sectional data of the first 41 patients enrolled in 7 memory clinics in Italy (Brescia, Genoa), France (Marseille, Toulouse), Spain (Barcelona), and Germany (Essen, Leipzig). Patients underwent clinical and neuropsychological evaluation, high resolution 3T MRI with MPRAGE, T2*, FLAIR, resting state, and DTI acquisitions, EEG with resting state and auditory P300 recording, lumbar punctures assessing Abeta42, tau and p-tau, and blood samples with PKC conformation and Abeta 1-42 binding on erythrocytes, amyloid precursor protein C-terminal fragments, plasma and lymphocytes biomarkers, and RNA splicing analyses. Each MPRAGE volume was analyzed in FreeSurfer, focusing on automatically segmented regions of interest in neurodegenerative diseases. Patients were divided into Abeta positive (CSF-POS) and negative (CSF-NEG) based on CSF Abeta42 levels. **Results:** clinical features are in agreement with what is expected for patients with aMCI in the absence of functional disability (mean age 69.0+6.5, Mini Mental State Exam 26.2+1.9, Functional Assessment Questionnaire 3.2+2.9). Concerning MR structural data, the segmentation measures of volumes and thickness are consistent across MRI sites and comparable with the US-ADNI data. CSF-POS MCI patients showed higher prevalence of family history of dementia than CSF-NEG, while neuropsychological, MR and EEG biomarkers showed no significant differences with this preliminary dataset. **Conclusions**: the patients enrolled in the European-ADNI have clinical and biomarker characteristics compatible with aMCI. Neuropsychological, MR and EEG differences between patients with high and low CSF Abeta42 levels should be explored in much more depth with larger group sizes.

Test-retest reproducibility of brain morphometry, diffusion and rs-fMRI: a 3T multi-site study

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Introduction: the IMI PharmaCog project is a European industry-academic public-private partnership aimed at identifying reliable biomarkers sensitive to disease progression in patients with Mild Cognitive Impairment. We evaluate the across-session test-retest reproducibility of morphometric [cross-sectional (CS) or longitudinal (LG) (1) FreeSurfer pipeline], diffusion (DTI indeces) and functional temporal signal-to-noise ratio (tSNR) multi-site 3T data on a group of healthy elderly subjects. **Methods:** eight 3T MRI sites (GE, Philips, Siemens) participate across Italy, Spain, France and Germany. Five local healthy (55-90 years) were scanned in two sessions a week apart. Data analysis: i) MPRAGE, Freesurfer; ii) DTI, FSL; iii) SPM8 and FSL. Reproducibility measures: i and ii) absolute percent change relative to the means (abs), spatial reproducibility (DICE) across test-retest; iii) Voxel-wise maps of abs across test-retest. **Results:** Abs and DICE of the LG analysis were significantly better than the CS for all volumes (Wilcoxon test, p=0.01), except for lateral ventricles. Abs of diffusion indeces were highly consistent across structures, metrics and 3T MRI sites, and were mostly ~ 2-3 %. Test-retest reproducibility results

of all the metrics considered showed good consistency with the literature. Functional preliminary data showed a similar full brain tSNR Abs distributions for all sites (error distribution peaks ~20 %) but shifted to lower errors on Philips site (~12 %). **Conclusions:** a multi-site 3T MRI protocol for longitudinal brain morphometric and diffusion analysis was implemented in eight sites covering four countries. Our results confirm the advantages to use the longitudinal FreeSurfer analysis giving an overall improvement in the reliability of the measures. Functional study is ongoing to better understand variability sources across all sites and in connectivity measures. Pharmacog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

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Nonfluent/agrammatic primary progressive aphasia caused by FTLD pathology

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Objective: to identify early clinical and neuroimaging features of sporadic non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA) caused by frontotemporal lobar degeneration (FTLD)-4Rtau (nfvPPA-tau) or TDP-A (nfvPPA-TDP) pathology. **Methods:** we collected prospectively clinical, neuroimaging and neuropathological data in sporadic nfvPPA and non-aphasic frontotemporal dementia (FTD) patients with FTLD-tau (9 nfvPPA and 5 non-aphasic FTD) or FTLD-TDP pathology (2 nfvPPA and 3 non-aphasic FTD). We investigated patterns of grey matter (GM) and white matter (WM) atrophy in nfvPPA-tau and nfvPPA-TDP using voxel-based morphometry (VBM). VBM analyses also compared non-aphasic FTD with FTLD-tau or -TDP pathology and FTLD-tau versus -TDP directly. **Results:** all nfvPPA patients showed apraxia of speech (AOS) and agrammatism. In nfvPPA-TDP, severe AOS, bucco-facial apraxia and spastic dysarthriacaused early mutism and were associated with significant GM loss in left motor and premotor regions. NfvPPA-tau patients showed AOS, dysarthria with prominent hypophonic features and, later in the disease course, generalized motor symptoms. VBM revealed GM and WM damage in the cortical and subcortical anterior motor and language networks in nfvPPA-tau. VBM in the non-aphasic FTD group supported greater involvement of WM in FTLD- tau versus FTLD-TDP cases. **Interpretation:** clinical features in sporadic nfvPPA relate to damage within specific language networks but also to relative neurodegeneration in GM and WM. We propose that early WM damage and hypophonic dysarthria in nfvPPA are highly suggestive of 4R-tau pathology. Instead, early, predominant left motor and premotor GM atrophy with severe AOS, bucco-facial apraxia and early mutism might predict TDP pathology.

Primary progressive crossed aphasia in dextrals: report of three cases

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Primary progressive aphasia (PPA) is a cognitive disorder characterized by a selective impairment of language abilities. It is classified into three distinct variants, that are agrammatic, semantic and logopenic forms. PPA is re-

lated to an asymmetrical degeneration of left frontal and temporal cortical regions. Recently a few cases with an involvement of right cortical areas were described, suggestive for reversed language lateralization. We reported three right-handed patients affected by PPA with asymmetrical dysfunction of right cortical associative areas, fulfilling clinical criteria for crossed aphasia. All patients performed extensive clinical and neuropsychological examination, including standardized battery for language (Aachener Aphasie Test). The patients were 1) a woman affected by non fluent/agrammatic form (onset at 53 years), 2) a woman presenting with semantic aphasia (onset at 66 years) and 3) a man affected by logopenic form (onset at 58 years). Morphological (CT/MRI) and functional (SPECT/PET) brain neuroimaging showed asymmetrical atrophy and hypometabolism of right frontal and temporal areas in all patients, with a relative sparing of left hemisphere. No structural damages such as vascular or expansive lesions were found. Genetic assessment of genes involved in AD and FTD dementia is in progress. Our patients with crossed aphasia span the whole phenotypical spectrum of PPA. To date, agrammatic variant is the most described crossed PPA form, while only one case of logopenic type was reported. In this work, we describe the first case of semantic form of PPA in crossed aphasia. These findings support the reversed lateralization of language brain networks in a subset of subjects, independently to handedness dominance. This variability could allow to study the specificity of neuronal language networks. Patients with crossed PPA might represent a model to evaluate the selective susceptibility of specific functional neuronal networks to neurodegeneration in the three different forms of PPA.

Neuropsychological markers for early detection of cognitive impairment in Parkinson's disease

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Introduction: cognitive impairment is a common feature in PD. A consistent PD subgroup develops dementia along the course of the disease. Recently, clinical diagnostic criteria for defining mild cognitive impairment in PD (MCI-PD) have been proposed; moreover, biomarkers able to predict the progression of cognitive decline and risk for dementia are under investigation. Among CSF biomarkers, reduced levels of Aβ42 have been repeatedly reported as reliable predictor of cognitive decline in PD patients; also, the usefulness of structural and /or functional neuroimaging for improving diagnostic accuracy in early phase of the disease has been proposed. The aim of our study was to assess the cognitive profile in a consecutive series of PD subjects, using a comprehensive neuropsychological evaluation including CANTAB (Cambridge Neuropsychological Automated Test Battery). **Methods:** seventeen consecutive subjects who received the diagnosis of idiopathic PD underwent a comprehensive neuropsychological examination (MoCA, digit span, clock drawing test, verbal fluency, similarities of WAIS-IV, prose recall test, CANTAB). They also underwent unconventional 3T-MRI and lumbar puncture for CSF measurement of classical biomarkers (Aβ42, total tau and phosphorylated tau). **Results**: nine patients were in very early phase – H&Y= 1; out of 17, 2 subjects performed normally in all tests; four patients disclosed minor deficits only in CANTAB subtests; seven patients fulfilled the Level II diagnostic criteria for MCI-PD; four showed an overt dementia. MRI and CSF data are under investigation. **Discussion and conclusions**: there is an increasing need of an early detection of cognitive impairment in PD patients, thus identifying those individuals having a higher risk of dementia. CANTAB represents a sensitive tool for detection of very mild cognitive deficits, even in highly educated people. This information can drive the clinician to further diagnostic work-up by means of CSF and imaging biomarkers, in order to improve diagnostic accuracy in very early phases.

Alien hand syndrome of corticobasal degeneration: involuntary release of primary motor cortex

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Background: corticobasal degeneration (CBD) is a neurodegenerative disorder characterized by asymmetric rigidity, bradikinesia, dystonia, apraxia, myoclonus, cortical sensory impairment and cognitive impairment. Alien hand syndrome (AHS) is a typical phenomenon in CBD. It is usually characterized by unilateral movements of an arm performed without conscious will. This study aimed to analyze the neural correlates of AHS in three patients with CBD. **Methods**: all patients presented left alien hand, bradykinesia, dystonic postures and gait disorders. Two patients had cortical sensory loss, ideomotor apraxia and intentional tremor. One had cognitive impairment and aphasia. Magnetic resonance images were acquired with a Philips scanner at 1.5. The functional session was constituted by two runs. In the first run the sequence of acquisition was: Rest (R), voluntary movement of left hand (VMl), voluntary movement of the right hand (VMr), whereas in the second run was: R, VMr, VMl. When the patients performed VMr, their left hand often started to move spontaneously for several seconds (AHM). **Results:** AHM was associated with the selective activation of the right primary motor area (M1), while VMr and VMl hand involved controlateral primary motor area (M1), bilateral prefrontal and parietal areas, supplementary motor area (SMA) and ipsilateral cerebellum. Moreover higher intensity and larger extension of M1 activity was evident during AHM than VMr, reflecting hyperactivity or reduced inhibition of M1 following the reorganization of intracortical connection from premotor, SMA and parietal cortex. **Discussion and conclusions**: two previous fMRI studies, in single cases, described the isolated activation of controlateral M1 in a patient with parietal stroke and the activation of an extensive network of brain areas in a patient with CBD respectively. Our findings extend the previous studies showing that AHS in CBD, at least in some cases, is associated with the involuntary release of the controlateral M1.

Tissue oxygen saturation and pulsatility index as markers for amnestic mild cognitive impairment: NIRS and TCD study

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Background: there is evidence suggesting that amnestic mild cognitive impairment (aMCI) patients may be in a transitional stage of evolving Alzheimer's disease (AD). Many researchers are trying to identify markers that may increase the diagnostic specificity allowing to identify the dementia in this pre-clinical stage and to anticipate the start of treatment to delay the onset of the disease. **Aim:** to evaluate the utility near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) parameters as potential markers for aMCI. **Methods:** by means of NIRS and TCD, noninvasive and inexpensive technologies, we studied 21 patients with aMCI (10M and 11F, 70.2 ± 7.3 years) and 10 age matched healthy controls. **Results:** by means of NIRS, we found a significant mean decrease of tissue oxygen saturation of cortex microcirculation (TOI), - 27 %, $p < 0.0005$, on the temporal-parietal cortex of both side compared to the controls. By means of TCD, we found a significant mean increase of pulsatility index (PI), $p < 0.0007$, of middle cerebral artery (MCA) of both side compared to the controls. Cerebrovascular risk factors were present in 81% of the aMCI patients. We used the receiver-operator characteristic (ROC) curves to assess the diagnostic potential of TOI and PI for diagnosis of aMCI; for TOI we found ROC area of 0.92, $p < 0.0001$, sensitivity 81%, specificity 95%, cutoff of 59%; for PI we found ROC area of 0.78, $p < 0.0001$, sensitivity 69%, specificity 98%, cutoff of 0.96. **Conclusions:** our study reveals that the TOI reduction on the temporal-parietal cortex of both side and the increase of PI in both MCA are associated with a clinical diagnosis of aMCI patients. The reduction of TOI may be considered a new marker for aMCI, especially when combined with the increase of PI in MCA.

Preserved knowledge of moral rules in patients with dementia and impulsive moral violations

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Background: humans regulate social life through compliance with social norms. Previous studies in patients with neurodegenerative diseases demonstrated that impaired social behavior could be detected in this pathology. Aim of the present study was to investigate knowledge and observance of social rules in patients with Alzheimer's disease (AD) and Frontotemporal lobar degeneration (FTLD) by means of a moral judgment task. **Methods:** six FTLD patients (4 male; mean MMSE=25,84), eight Alzheimer's disease (AD) patients (3 male; mean MMSE=24,82) and a group of matched controls (n=16) were administered with tasks designed to assess their abilities of basic and social emotion (ToM) recognition (Emotion Recognition Batteries, Social Judgments Evaluation Test, Faux Pas Test) and a Social Norms Evaluation Task. **Results:** FTLD patients showed poor performances in Emotion Recognition Batteries, in particular for facial and prosodic expressions of disgust, fear and sadness. AD and FTLD displayed poor ability in the Social Judgment Evaluation Test. Results of the Social Norms Evaluation Test demonstrated that knowledge of social norms was preserved in both groups of patients, but they both showed marked inappropriate social behaviour, as revealed by the results of the same Social Norms Evaluation Test administered to the caregiver. **Conclusions:** AD patients showed preserved performances in social tasks. On the contrary, FTLD patients displayed marked impaired performances both in recognition of facial and auditory basic emotions and in the ability to understand others' feelings and thoughts, loss of empathy, impulsivity and violation of social norms, in spite of a preserved knowledge of moral rules and conventions.

Efficacy of cognitive stimulation on Alzheimer's disease

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Cognitive Stimulation (CS) is a non-pharmacological intervention aimed at managing cognitive deficits of Alzheimer's disease (AD). A Cochrane Systematic Review concluded that CS is efficacious, although the sample size of the studies were small (1). **Objective:** to evaluate the efficacy of CS in a group of AD patients with mild-moderate cognitive impairment. **Methods:** this non-randomized open study investigated 34 AD patients (NINDS-ADRDA criteria). All subjects underwent a detailed neuropsychological battery including Mini Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Activities of Daily Living (ADL) e Instrumental Activities of Daily Living (IADL). Patients participated at two weekly sessions of CS lasting 120 minutes for six consecutive months. Caregiver stress was evaluated using the Caregiver Burden Inventory (CBI).
Results: after 6-month CS neuropsychological performances were: significantly improvement on MMSE (21.76 vs 22.99, $t<0.001$); significant reduction on NPI (16.47 vs 7.88; $t<0.001$). In addition CBI was significantly reduced after the intervention (29.23 vs 22.36; $t<0.001$). **Conclusions:** CS has been effective in cognitive improvement and reduction of behavioural symptoms. Also caregivers stress was reduced after the intervention, indicating an indirect effect of the intervention. Limitations of the study were the small sample size and the design (non randomized and open).

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Italian network for autosomal dominant Alzheimer's disease and Frontotemporal Lobar Degeneration

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Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are two of the most common forms of dementia, that arise with both sporadic and familiar forms. Familiar forms are linked to pathogenic mutations which are transmitted with an autosomal dominant pattern. Specifically, mutations in APP, PSEN1 and PSEN2 gene are involved in AD, leading to altered amyloid metabolism, while mutations in MAPT, GRN and repeated expansion in C9ORF72 gene lead to altered tau metabolism in FTLD. These mutations are rare, thus the involvement of multiple centres is essential. The project, funded by the Italian Ministry of Health, works in close cooperation with US DIAN (Dominantly Inherited Alzheimer's Network) and GENFI (GENetic Frontotemporal Dementia Initiative). It aims at laying the foundations for an Italian network of clinical centres with capabilities to recruit and study persons carrying mutations linked to AD and FTLD. The project will define and validate a standardized protocol for the collection of clinical, imaging, neurophysiologic, and biological samples of patients with familial AD and FTLD. A national registry and a biobank for biological samples of familial AD and FTLD cases will be developed, as well as a common protocol for genetic testing and counselling of these cases. The project will also deploy an Italian hub-and-spoke network for the efficient referral and management of familial cases. A sample of asymptomatic and symptomatic carriers of pathogenic mutations (and non carriers, as controls) will be enrolled to identify neurobiological changes that occur in carriers many years before the clinical symptoms onset. The project will improve the management, diagnosis, and treatment of AD and FTLD, while speeding up the implementation of clinical trials across Italian centres through the registry of cases.

Neuropsychological and functional correlates in Mild Cognitive Impairment (MCI)

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The aim of this study was to evaluate the contribution of cerebral perfusion single-photon emission computed tomography (SPECT) data and event-related potentials (ERPs) recording as tools to serve the neuropsychological and clinical diagnosis of MCI. Fourteen patients (age 66,0±5,1; 8 women; MMSE 27,1±2,7) performed a selective neuropsychological battery to assess general cognitive status, short- and long-term verbal memory, episodic memory, constructional praxia. All patients underwent 99 mTc HMPAO SPECT and ERP recordings (N400 and P300) as well. Neuropsychological testing evidenced a mild impairment on tests exploring verbal short-term and long-term memory in 11/14 of patients. In comparison with controls, 13 out 1 patient showed significant hypoperfusion in the frontal, limbic and temporal lobes mainly on the left side. N400 was abnormal in 11/14 of MCI patients. As a group, no significant differences between the N400 amplitude to incongruous words and congruous words were recorded in MCI patients with respect to the controls. No significant correlations were observed between N400 amplitude with age and depression. P300 was normal in 3/14 of patients. Statistical analyses revealed significant correlations between verbal memory score and incongruent N400 amplitude ($p=0.02$ $r= 0.75$) and left temporal lobe (BA 46, 47) deficit perfusion ($p=0.04$ $r=0.6$). Also, N400 abnormalities and left frontal lobe SPECT hypoperfusion correlated significantly ($p=0.04$ $r=0.7$). Our findings suggest that SPECT and ERP methods are able to detect pathophysiological changes in MCI patients providing functional informations. Both SPECT and electrophysiological recordings may support neuropsychological evaluation in identify earlier functional biomarkers of cognitive deficits in MCI and even in subjective cognitive impairment (SCI). Finally, such functional correlates could provide useful tools in predicting conversion to dementia.

Driving ability in patients with dementia: report from Alzheimer's dementia Assessment Units in Northern Italy

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Aims: aim of the present study was to characterize qualitatively and quantitatively the patients affected by cognitive disorders still driving in an area of Northern Italy. **Patients and methods:** subjects with cognitive disturbances, referred to the Alzheimer Assessment Unit at the IRCCS "C. Mondino Institute of Neurology" Foundation, Pavia, Italy, and the Department of Neurology, Ospedale di Circolo, Varese, Italy, between January and December 2012, were included in the study. Demographic and clinical characteristics and the parameters suggested as the most significant predictors of driving safety were collected throughout a structured interview. **Results:** 198 patients (M/F: 142/56; mean age: 73.8±8.2 yrs) were enrolled, out of these 172 were still driving; in only one patient the driving license was revoked. Mostly of the subjects have modified their driving features: reduced travel time (47%) and driving mileage (63%), avoiding driving at night (57%) and in rush hours (23%), driving on well-known itineraries (50%). Patients' rating of driving ability was significantly higher than caregiver's rating (43% versus 62%). History of crushes was not significant. Patients' avoidance behavior significantly ($p<0.01$) increased with age and worsening of cognitive, functional and behavioral scales (Clinical Dementia Rating, Mini Mental State Examination, Neurobehavioral Inventory, Activities of Daily Living, Instrumental Activities of Daily Living). **Conclusions:** age and the degree of dementia are the best predictors of driving safety. Even if subjects with cognitive impairment overestimate their driving ability, we can suggest that patients in the early stages may remain cognitively competent to continue driving safely at least with limitations.

Neuroanatomical correlates of disease progression in a case of nonfluent/agrammatic variant of primary progressive aphasia due to progranulin (GRN) Cys157LysfsX97 mutation

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Objective: to evaluate the neuroanatomical changes over time in a case of nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) with a progranulin (GRN) mutation and expected underlying TDP type A pathology, using advanced magnetic resonance imaging (MRI) techniques. **Methods**: the patient was a 63 years old, right-handed, female meeting criteria for a diagnosis of nfvPPA and carrying a GRN Cys157LysfsX97 mutation. We collected 2-year longitudinal clinical and neuroimaging data. Voxel based morphometry (VBM) and diffusion tensor (DT) MRI analyses were applied to evaluate grey matter (GM) and white matter (WM) damage. Tensor-based morphometry (TBM) was used to investigate GM loss over time. **Results:** since her first evaluation, the patient showed severe apraxia of speech and mild agrammatism. She developed early mutism but no frank extrapyramidal symptoms during the subsequent disease course. At diagnosis, VBM revealed GM loss in the left cortical speech and language networks while the right hemisphere was relatively spared. At follow up, GM atrophy became more severe in these areas extending also posteriorly to the left temporo-parietal regions and involving corresponding regions on right hemisphere. TBM confirmed the widespread GM loss and ventricular enlargement over time: the highest volume decrease (about 20%) was detected in the left premotor cortex, while atrophy of this region was mild (about 5%) contralaterally. DT MRI tractography showed a subtle involvement of the superior longitudinal fasciculus (SLF) at baseline, which became more severe at follow up. No other WM tracts were injured. **Conclusions:** we demonstrated a differential involvement of distinct brain compartments (GM and WM) over time in a nfvPPA GRN+ patient with expected TDP type A pathology that might explain her

clinical evolution. This approach might be useful for *in vivo* prediction of nfvPPA pathology that might become a central issue with the advent of protein-specific treatments.

Cognitive and affective aspects of Theory of Mind in Mild Cognitive Impairment

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The Theory of Mind (ToM) is the ability to attribute mental states to oneself and others. Two different components of ToM have been identified: the cognitive ToM is the ability of understanding and attributing desires and intentions to others, whereas the affective ToM is the ability of understanding and attributing emotions to others. Until now, these components of ToM and their cognitive correlates have been poorly explored in Mild Cognitive Impairment (MCI). The aim of the study was to investigate the two aspects of ToM in patients with MCI. **Material and methods:** we enrolled 27 patients with diagnosis of MCI and 24 age- and education-matched healthy subjects (HC). Both patients and controls underwent neuropsychological tasks evaluating verbal memory (Immediate Recall and Delayed Recall of the Rey Auditory Verbal Learning Task, IR and DR-RAVLT, Verbal Span), frontal functions (Frontal Assessment Battery, FAB), apathy (Apathy Evaluation Scale, AES), cognitive (Advanced Test of ToM, ATT) and affective ToM (Emotion Attribution Task, EAT; Reading the Mind in the Eyes Test, RME). **Results:** patients with MCI and controls did not differ on demographic aspects. Significant differences were found between two groups on Mini Mental State Examination, IR and DR-RAVLT, FAB and AES. After entering cognitive variables (significantly different in the two groups) as covariates, MANCOVA showed that patients with MCI and controls significantly differed on ToM tasks (Wilk's Lambda=3.626, p=0.021). In detail, patients with MCI performed worse than controls on ATT, EAT and RME. In both groups, EAT significantly correlated with RME but neither were correlated with ATT, in line with evidence suggesting that EAT and RME assess ToM abilities distinct from those assessed by ATT. **Conclusions:** the present results demonstrate that both cognitive and affective components of ToM are impaired in patients with MCI.

Investigating the role of adipokines in Alzheimer's disease

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Introduction: adipokines are adipocyte-derived secretory factors which have functions in immune response, inflammation, overweight, and insulin resistance. Recently, several experimental and clinical studies suggested a role for adipokines in Alzheimer's disease pathogenesis. **Aim of the study:** to measure plasma concentrations of leptin, adiponectin and resistin in patients with AD and non AD dementia, and to search for correlations between plasma adipokines and cerebrospinal fluid (CSF) biomarkers (Aβ-42, T-tau and P-tau). **Materials and methods:** we enrolled in our study 67 patients with mild or moderate cognitive impairment (38 females, 29 males; mean age 68,19 ± 7,94 yrs). Obese and diabetic subjects were excluded. During hospitalization all patients underwent lumbar puncture and were diagnosed with AD (26 patients, 16 females, 10 males; mean age 67,46 ± 8,11 yrs) or non AD dementia (41 patients, 22 females, 19 males; mean age 68,66 ± 7,89 yrs) according to current clinical criteria and CSF biomarkers concentrations. Plasmatic levels of adiponectin, resistin, and leptin were measured by ELISA. Statistical analysis was performed with SPSS version 20. P-values below 0.05 were considered to indicate statistical significance in all analyses. **Results:** we found that serum concentrations of resistin were significantly reduced (p<0,026) while serum concentrations of adiponectin were increased (p<0,035) in AD patients in comparison with non AD patients. No difference was found in serum leptin levels. A significant positive correlation was found between resistin and CSF Aβ-42 concentrations (r= +0,338 p<0,005). In our female patients the serum concentration of leptin is significantly higher than those of male patients (p<0,001). **Discussion:** this study provides preliminary evidences that adipokines may be involved in the pathogenesis of AD. Further studies are needed to provide more information on the relationship between resistin and CSF Aβ-42.

Noun-verb dissociation in primary progressive aphasias

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Introduction: disproportionate impairment of naming nouns versus verbs and the opposite pattern have been reported in cases of focal brain damage or degenerative diseases, indicating that processing of nouns and verbs may rely on different brain regions. Production of nouns is limited in patients with posterior lesions while anterior lesions generally impair production of verbs, although exceptions to this lesion-deficit association have also been reported. The interpretation of the double dissociation between nouns and verbs is therefore not straightforward. **Subjects and methods:** 24 patients with PPA were enrolled: 10 subjects with PNFA, 8 subjects with SD and 6 subjects with LPA. Naming and recognition of nouns and verbs were examined by means of the BADA naming and comprehension tasks. In these tasks nouns and verbs denoting objects and actions are matched for word frequency, length and phonological complexity. A background neuropsychological examination was available for all patients included in the study. **Results:** both in naming and comprehension tasks no significant differences were found in the three samples of patients studied. The single patient qualitative analysis showed that PNFA patients tended to name nouns better than verbs, while SD patients generally named verbs better than nouns. Anyway, no dissociation between nouns and verbs was detected. **Discussion and conclusion**: the present data fail to show differences in noun/verb processing in PNFA, SD, LPA. The results of this study are in contrast with previous studies of this topic in PPA, and reinforces the conclusion proposed by Matzig et al. about language disorders consequent to focal lesions that the double dissociation of noun-verb is perhaps less substantial than expected.

Chronic acquired hepatocerebral degeneration or Parkinson disease? A case report

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Objectives: to describe a man with hepatitis-C-related liver cirrhosis, progressive extrapiramidal syndrome, memory loss and behavioral symptoms responsive to levodopa. **Case report:** a 63-year-old man with hepatitis-C-related liver cirrhosis was referred to our hospital for dysartria, bradykinesia and rest tremor in the left arm started one-year ago associated to cognitive deterioration and behavioral disorders began in the last two months. Neurological examination revealed extrapiramidal syndrome. Mini Mental Status Examination revealed cognitive impairment. Laboratory findings showed chronic impairment of liver function with impaired plasmatic coagulation and hyperammonemia. Brain MRI showed bilaterally increased T1 signal in both basal ganglia. No specific bioelectric abnormalities came out from EEG. He was treated with lactulose and with levodopa 100/25 mg twice daily with symptomatic improvement in particular of motor disturbances. After introduction of therapy a complete neuropsychological evaluation was performed with a normal cognitive profile. It was suspected a CAHD and levodopa was stopped but neurological symptoms worsened again. We reintroduced levodopa with an improvement of disturbances. I-FP-CIT SPECT (DAT-SPECT) was performed showing asymmetrical reduced DAT density suggesting Parkinson's disease (PD). A diagnosis of PD in patient with CAHD was hypothesized. **Conclusion:** CAHD is a progressive and irreversible syndrome associated to chronic liver failure. Neurological signs of CAHD may include impairment of intellectual function, parkinsonism, MRI symmetrical iperintensity in T1 in basal ganglia and poor response to levodopa. Difficulties in the reported case rise from the complex differential diagnosis of CAHD and idiopathic PD onset with memory impairment and behavioral symptoms. Our patient had a good and stable response to levodopa and abnormal DAT-SPECT with a strong suspicion of PD. As in this case, linking neuroimaging data to patient's history, physical examination neuroimaging and laboratory findings are essential clues to make an accurate diagnosis.

Genetic association between APOEe4 and clinical and neuropsychiatric symptoms in Alzheimer's disease patients

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Introduction: the Alzheimer's disease (AD) is a neurodegenerative disorder characterized by impairment in cognitive and activity daily functions. The behavioural and psychological symptoms are also a common feature of the disease. One well-known risk factor for AD, particularly for late onset, is the e4 allele of the apolipoprotein E gene (APOE). Many studies have investigated a possible association between the APOe4 and the presence of cognitive and neuropsychiatric symptoms (NPS) but the finding have been unclear. This study aimed to investigate the role of APOE genotype in clinical, behavioral and psychiatric AD symptoms. **Matherials and methods:** we have studied 138 subjects with probable AD, clinically well-characterized by means neuropsychological assessment and morphological and functional neuroimaging. The NPS were evaluated using NeuroPsychiatric Inventory (NPI). All subjects were undergone to blood sample for APOE genotyping after having obtained written informed consent approved by an institutional ethical board. **Results:** ninety-two were females and 46 males with mean age of onset 68.55±8.27. At first evaluation, the MMSE score was 22.77±5.27 and total NPI 6.30±6.85. Eighty-one patients (58.7%) had not e4 allele in their APOE gentotype whereas eight patients (5.8%) showed e4e4 genotype and 49 patients (35.5%) had e3e4. None differences were found beetwen APOE genotype and sex whereas seems to be a relationship between APOE and age of disease onset (p:0.047) and positive familial hystory for dementia (p:0.046). No difference in the distribution of APOE genotypes was found for MMSE and NPI; however the presence of the allele e4 was significantly associated with apathetic subsyndrome of NPs (p:0.033). **Conclusion:** in the study we found that apathetic subsyndrome in AD occurs more frequently in subjects with APOE e4 allele.

Diagnosis in dementia: sometimes a path with great surprises. A case report

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Background: Creutzfeldt-Jakob Disease (CJD) is a dramatically rapid type of dementia, always fatal within a very short time. It is characterized by changes in behavior, emotional response and intellectual function, often associated with confusion, hallucinations and agitation and usually followed by cerebellar symptoms and myoclonic contractions. Especially in the early stages of disease, it could be considered in differential diagnosis with other dementias, as Alzheimer Disease or Lewy Body Disease. **Material and methods:** we described the case of a 75 year-old woman who referred to our memory clinic in August 2012 for rapidly worsened retentive memory deficits, episodes of temporal-spatial disorientation, bizarre behavior such as speaking with pets and deflection of mood, begun three months before. Speech, swallowing and walking were preserved, while autonomy in IADL was compromised (ADL: 6/6; IADL: 3/8). On neurological examination we noticed anosognosia, temporal-spatial disorientation, severe forgetfulness, incorrect ideation and attentional deficits, but neither focal neurological nor extrapyramidal-cerebellar signs nor involuntary movements. Brain CT revealed generalized atrophy and neuropsychological evaluation severe involvement of multiple cognitive domains. We were about to conclude for Alzheimer disease, when we took EEG outcome which showed diffused sharp wave complexes and triphasic waves. Then we performed brain MRI which revealed cortical hyperintensity in frontal-temporal-parietal regions bilaterally in DWI and FLAIR sequences and lumbar puncture which revealed positivity of 14-3-3 protein and pathological increase of tau protein (1190 ng/L). The patient was discharged with diagnosis of CJD. After two weeks she was bedridden, totally dependent in ADL and IADL, unable to swallow and speech. **Conclusions:** diagnosis of dementia can be sometimes very difficult. Although patient history and neurological examination play a fundamental role in a correct diagnosis, other diagnostic tools, such as EEG, MRI or liquoral analysis, can often prove diriment in the diagnostic approach to a patient with dementia.

CSF biomarkers profile: do they agree with clinical diagnosis?

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Background: CSF biomarkers amyloid-β 1-42 (Aβ42), total tau (tau) and tau phosphorylated at threonine 181 (p-tau) are useful diagnostic markers for Alzheimer's disease (AD) even though still today there are considerable differences in absolute concentrations of these marker results among laboratories, even when the same kit is used. **Objective:** assessment of biomarkers profile fitting clinical diagnosis, of a cohort of cognitive declined patients referred to Neurological Clinic of Santa Chiara Hospital in Pisa. **Method:** 33 patients, with available CSF, were included in this study. Retrospectively, in blind condition, levels of Aβ42, tau and p-tau was been analyze in patients who had received clinical diagnosis of Alzheimer Disease (AD), Fronto-Temporal Lobar Degeneration (FTLD), Lewy Bodies Disease (DLB), and Cortico-Basal Degeneration (CBD). From these measurements, Innotest® Amyloid Tau Index (IATI) was calculated for each patient. **Results:** on the base of clinical picture, neuroimaging and neuropsychological evaluation, 16 patients were initially given diagnosis of AD, 15 were given another type of dementia diagnosis; 3 patients were not demented. 73% of diagnosis were confirmed by laboratory evidences. **Conclusion:** our study showed relatively few cases of diagnosis where clinical and laboratory findings did not fit. Relatively few diagnoses changed after the CSF results were given to the clinician. Before CSF can be widely accepted as a reliable tool, a consensus for processing and handling of the samples is needed.

Diagnosis of sporadic CJD in a man admitted to hospital for suspected cerebellar ischemia

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Introduction: we suppose that rapidly progressive dementia, MRI cortical hyperintensity in DWI, high levels of tau protein and positivity for 14-3-3 analysis in CSF, and finally pattern of periodic synchronous discharge in EEG, concur to diagnosis of sporadic CJD. (Definitive diagnosis is established with histological examination of brain biopsy or autopsy materials). **Case Report:** G.F. male 65 years-old. He was working like entrepreneur till October 2012 without any problem. In December suddenly he showed cerebellar ataxia and dysarthria. He was recovered in the Stroke Unit. In TAC there was cerebellar malacia. There was progressive clinical aggravation with also mutacism, myoclonic jerks in the right arm and allucinations. In MRI there was hyperintensity in temporo-parietal cortical area in the left emisphere in Flair e DWI sequences. That hyperintensity was not clearly relevant. We investigated every possible cause: neoplasia, limbic encephalitis, CJD, vascular lesion. We carried out a massive investigation. The more important date were, in addition to MRI finds, the positivity for protein 14,3,3 and the high levels of TAU protein (> 1200 pg/ml) in CSF; the homozygous for methionine at codon 129; pattern of periodic synchronous discharge in EEG. **Conclusions:** the symptoms and the experimental tests results pointed to a highly likelihood of a sporadic CJD.

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An unusual case of Alzheimer's disease with early onset: interest of CSF fluid biomarkers and PRNP genotype in the differential diagnosis

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Introduction: heterogeneity in Alzheimer's disease (AD) clinical presentation has increasingly been discussed during the last years. Atypical cases have been reported with unusual EEG findings, early-onset and atypical symptoms. In the last decade, there has been a growing interest for the role of PRNP codon 129 polymorphism in relation to AD clinical features. **Case report:** we report a case of unusual cognitive impairment in a 48 years-old woman with no family history for dementia. Clinical features at onset included recurrent episodes of mental confusion, disesecutive symptoms (dysfunction in planning and abstract thinking) and emotional disturbances (depression and apathy). First neuropsychological examination showed a moderate global cognitive impairment. EEG showed fronto-temporal sporadic theta rhythm abnormalities. Brain MRI showed a mild bilateral parieto-temporal atrophy and 18FDG-PET scan confirmed a hypometabolism in the same areas. CSF biomarkers were abnormal, but within a range as expected for classic AD, except for 14-3-3 protein test that was mildly positive. ApoE genotype was ε 3/ε 3. PRNP genotype showed homozygosis for methionine at codon 129. Repeated neuropsychological examinations showed a slow progression over a period of 12 months. **Discussion and conclusion:** atypical presentation can render diagnosis of AD difficult. The early-onset with an initially rapid course of deterioration suggested CSF biomarker and genetic studies. The CSF levels of Aβ-42, total-Tau, phospho-Tau supported an Aβ-related disease in the patient. CSF proteins 14-3-3 are commonly positive in human prion diseases, while not being specific. PRNP gene might be linked to degenerative dementias other than prion diseases. Indeed, a link between the codon 129 and early-onset cognitive impairment or the presence of Aβ-associated lesions in the elderly has been observed. The originality of this report lies in its atypical form and completeness. It also confirmed again the utility of CSF biomarkers and genetics in diagnosis of dementias with unusual onset.

Constructional apraxia and execution strategies of rey-complex figure test in Multiple Sclerosis

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Objective: to describe progression of constructional apraxia (CA) and execution strategies of drawing in patients affected by Multiple Sclerosis (MS). **Background:** CA is defined as deficit of visuo-constructive analysis characterized by the inability to copy drawings in absence of low-level visual and primary motor deficit. Visuo-spatial analysis depends on attention (whose impairment is the central core of cognitive dysfunction in MS), motor planning and working memory and is typically studied using the copy of complex figures. **Design and methods:** a 7 years follow up study of 29 MS patients with CA was conducted. The copy of modified Rey Complex Figure Test (RCFT) was used to study visuo-constructive skills and to describe spatial planning strategies. Patients' performances were compared longitudinally and a cross-sectional assessment of drawing strategies comparing patients and 30 age-and sex-matched healthy subjects was also performed using t-test statistical analysis. **Results:** at follow-up, no significant quantitative difference emerged in RCFT copy scores while qualitative analysis of errors revealed that patients showed more omissions ($p<0.005$). Considering the execution strategies, we showed that 38% of patients and 40% of controls, thus showing no significant differences, started from the central structure of RCFT. Among the execution strategies the following ones distinguished patients from controls: patients juxtaposed details one by one without an organizing structure ($p<0.005$), whilst healthy controls began with a detail attached to the central rectangle, completed it and added remaining details in relation to it ($p=0.02$). Moreover, patients who did not begin by drawing the central structure had a lower performance on Immediate ($p=0.05$) and Differed ($p=0.03$) recall of RCFT if compared to patients using a more integrated approach. **Conclusions:** performances on tests exploring constructive abilities are influenced by visuo-spatial perception and integration, but also by executive skills, such as organization, strategic processing and working memory. We propose that deficit

of visual component of attentional function could be responsible for the execution strategies and, consequently, for impairment of motor planning depending on spatial coordinates.

Two cases of Charles Bonnet syndrome and review of the literature

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Background: visual hallucinations (VHs) can be associated with a variety of clinical conditions being also experienced by health people, when there is inadequate stimulus to the sensory system as occurs in patients with impaired vision due to a ophthalmic disease. This condition is known as the Charles Bonnet Syndrome (CBS). **Aim:** to describe two case of CBS and review of the literature. **Case Report:** patient #1, a 87 year old woman with age related macular degeneration in both eyes presenting with a 15 years history of intermittent VHs. She reported that the symptoms occurred mostly in the evening. At the age of 82 she developed Parkinson's disease and she considerably improved after levodopa treatment (125 mg three times a day). In view of the long history of VHs preceding the onset of the extrapyramidal symptoms, low-dose dopamine introduced only recently, only mild MCI at neuropsychological tests and the all other negative findings, the aetiology of hallucinations was attributed to CBS. Patient #2, a 60 year-old man with acute onset of diplopia and decreased visual acuity. Seven days later his visual acuity decreased and elaborated VHs followed. Laboratory examination indicated hypothyroidism and MRI of the orbits indicated a marked enlargement of the extraocular muscles. He was diagnosed with orbit pseudotumor in autoimmune hypothyroidism. VHs disappeared after the improvement in visual acuity due to methylprednisolone intravenous therapy, and the aetiology of hallucinations was attributed to CBS. **Conclusion:** the circumstances favoring VHs support the hypothesis that sensory deprivation enhances the ongoing activity of the visual system after sensory loss. The course, and treatment of CBS patients vary according to the nature of the visual dysfunction. No pharmacological interventions, such as increasing the lighting at home and reassurance of the benign nature of CBS is essential to support patients and reduce caregiver's burden.

BETA-AMYLOID aggregation in response to modification of membrane fluidity

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Introduction: the deposition of amyloid fibrils as consequence of β-amyloid peptide aggregation, is proved to be related to modification of neuronal membrane fluidity in neuronal membrane of Alzheimer patients (1). Cholesterol and polyunsaturated fatty acids (PUFAs), normal constituents of dietary food, are known to be responsible, respectively for the increase and the reduction of membrane fluidity (2). They indeed play a critical role in modulating membrane fluidity and cell homeostasis. **Objective:** to study the effects of membrane lipid composition on amyloid aggregation pathways. **Methods:** the modification of bilayer fluidity and mobility in the presence and in absence of β-amyloid peptide have been monitored using electronic paramagnetic resonance (EPR) spectroscopy. EPR characterization have been realized by using phosphatidylcholine including nitroxide group close to its hydrophilic headgroup. The modulation of the aggregation pathway on membrane models of different composition was carried out using AFM microscopy; β-amyloid secondary structure modification have been observed using circular dichroism spectroscopy. **Results:** in the present contribution we report a structural investigation of amyloid peptide in membrane models differing for lipid composition and microelement content. Our data based on several different spectroscopy and microscopy (AFM) measurements show that variable quantities of choles-

terol, PUFAs and/or microelements induce β-amyloid peptide to follow distinct aggregation pathways in response to specific qualitative and quantitative compositions.

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CFS biomarkers in FTD with low progranulin serum level (GRNsl)

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Objective: Alzheimer's (AD) and Frontotemporal (FTD) dementias share clinical and neurochemical similarities, which makes difficult differential diagnosis. While the use of CSF biomarkers is considered supportive for AD diagnosis, analogous conclusions are not available yet for FTD. Recent studies have been made to detect GRN mutation carriers assessing by GRNsl. We analyze CSF biomarkers and GRNsl in a group of AD and FTD pts in order to identify a potential pattern of the diseases. **Material and methods:** GRNsl was evaluated in 28 pts with cognitive impairment suggestive for AD (15 pts fulfilled DSM IV and NINCDS-ADRDA criteria; MRI or PET with parieto-temporal atrophy or hypometabolism) and FTD (13 pts diagnosed according to the Neary's criteria; MRI or PET with fronto-temporal atrophy or hypometabolism). CSF was obtained in all patients and biomarkers were measured by ELISAs test. **Results:** normal GRNsl(>70pg/ml) was found in 13AD pts and in 8 FTD pts. In FTD with low GRNsl (7pts), we found the followings profiles: 4 pts demonstrated normal Ab 1-42, p Tau e T Tau levels; 2 pts with mild increase of p-Tau level and one pt showed a typical CSF-AD pattern. FTD pts with low GRNsl obtained significantly poorer scores than FTD pts with normal GRNs, precisely on tests of attention (TMTA), mental flexibility (TMTB), and language (naming test).DISCUSSIONCSF biomarkers efficiently discriminated AD patients from others. As reported by other studies, in our FTD-low GRNsl pts we found normal CSF biomarkers on 57% of cases. Only two pts FTD-low GRNsl showed a possible tau pathology (high p-Tau levels). Then, the analysis of CSF biomarkers may be useful to individuate GRN mutation carriers with low GRNsl whose presentation mimics aMCI or AD. **Conclusion:** CSF analysis needs to be performed in a greater group of patients with low GRNsl to confirm our results.

Kinematic gait parameters in parkinsonian patient's with and without MCI in off and on state: a preliminar motion analysis study

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Introduction: in recent years the relationship between cognition and gait in Parkinson's disease (PD) has received increasing attention. Nevertheless, the specific connections between functional gait parameters and cognitive features are not fully understood. **Objective:** to describe knee kinematic parameters during gait in patients affected by PD with or without mild cognitive impairment (MCI+, MCI-). In order to study the possible effect of cognitive involvement on gait we also analyzed the knee kinematic using a dual task paradigm. **Methods:** using a Motion Analysis system, we compared knee kinematic parameters in PD patients with MCI (n=10) and without MCI (n=10) in off and on state in the following conditions: 1) normal gait; 2) motor dual task; 3) cognitive dual task. We analyzed the two flexion excursions of knee joint. Memory, executive and visuospatial domains were as-

sessed with an extensive neuropsychological battery. **Results:** we find that in MCI+ PD patients in off state, the first angular excursion of knee was larger as compared to MCI- PD. Only the cognitive dual-task condition further increased angular excursion. **Conclusions:** our data suggest that only the cognitive dual-task worsened the angular excursion. Instead during the motor dual-task in MCI+ PD patients the angular excursion was similar to MCI-.

FTD Guidelines

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The publication of the criteria for the 3 variants of primary progressive aphasia (PPA) (nonfluent/agrammatic, semantic, and logopenic) and of the revised diagnostic criteria for the behavioural variant of frontotemporal dementia by two international group of investigators represents an attempt to provide shared guidelines to improve the phenotypic characterization of the heterogeneous presentations of a part of the fronto-temporal dementia spectrum. The background of this attempt lies in the impressive advancements in this area of research in the last decades. Studies of reliability and validity are ongoing in different countries and tyically require the development of multicentric research networks.

Highlights on genetics of FTLD

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Frontotemporal dementia (FTD) is a non-Alzheimer's form of dementia with onset age of mid to late 50s that affects the frontal and/or the temporal lobes. FTD is clinically divided in the two categories of behavioural and/or language variants and is characterized by heterogeneous pathology defined by pathogenic protein inclusions: MAPT (microtubule associated protein tau), ubiquitin/TAR DNA binding protein 43 (TDP)-43, fused in sarcoma (FUS) and p62. MAPT, progranulin (PGRN) and, recently, C9orf72 genes represent the three main genetic factors associated with FTD. Genetic variability in TDP-43, charged multivesicular body protein 2B (CHMP2B), valosin containing protein (VCP), FUS and TMEM106B genes contribute to =5% of cases. Currently, research tools such as genome wide association studies (GWAS), exome and genome sequencing hold promise to further uncover the genetic underpinnings of this complex disorder. A current GWAS is being carried out as a collaborative effort at the University College of London (UCL), the National Institute of Health (NIH) and the Texas Tech University Health Sciences Center (TTUHSC). This study is the largest and most comprehensive International GWAS for FTD to date that collected ~3,500 samples diagnosed with bv-FTD, SD, PNFA and FTD-MND for phase I from ~ 30 international FTD research centers worldwide. Samples were genotyped on 660K/Omni express chips and run on Illumina Infinium platform. Phase I was recently completed and the study has moved to phase II (or replication) for which further ~2,000 samples have been collected. Samples are being genotyped on exome plus – NeuroX – custom content chips, still on Illumina platform. The main aims of this FTD-GWAS are to identify novel loci relevant to the disease and, possibly, to begin understanding the genetic basis of the different subtypes of this disease.

Cortical degeneration and cognitive disorders in multiple sclerosis

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Cognitive impairment (CI) is now recognized as a core feature of multiple sclerosis (MS). It affects 45-65% of MS subjects and mainly involves information processing speed, complex attention, memory and executive functions.

Language and general intelligence are usually preserved. CI has been documented from the earliest stages of the disease and in different disease phenotypes, and has a marked negative impact on patients' lives and lifestyles, including employment, social and everyday functioning. Once established, CI tends to progress over time, independently of physical disability. Indeed, the relationships between the presence and severity of CI and other clinical measures are at best modest. On the other hand, neuropsychological functioning was found to be related with brain damage as detected by Magnetic Resonance Imaging (MRI), particularly with measures of involvement of grey matter areas. In the last few years, there is growing attention towards cortical atrophy and the detection of cortical lesions, which are more diffuse than what believed in the past. Recent evidence has consistently pointed to a relationship between cortical damage and CI in MS subjects, both in cross-sectional and longitudinal assessments.

Implementing Alzheimer's biomarkers in the clinic for the diagnosis of prodromal and atypical cases: the Italian inter-societal approach to clinical, organizational, and ethical issues

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The identification and validation of biomarkers for diagnosing, monitoring progression and predicting onset of Alzheimer's disease (AD) has been a main focus of AD research in the past 10 years. Validated biomarkers to date are Abeta42 and tau in the cerebrospinal fluid, cortical hypometabolism on fluorodeoxyglucose positron emission tomography, hippocampal atrophy on magnetic resonance, and brain amyloid deposition on amyloid imaging with PET. The recent revision of AD diagnostic criteria incorporates the use of biomarkers and operationalizes diagnosis of prodromal AD into four levels of probability, depending on the presence and nature of the biomarker findings. In order to test the criteria, biomarkers should be used for diagnosis in realistic memory clinic patients. However, several hurdles to biomarker implementation should be overcome, and solutions will be different in different Countries according to local regulatory and reimbursement systems. We established a workgroup of representatives of Italian scientific societies (Neurology, Neuroradiology, Nuclear Medicine, Laboratory Medicine, and Psychogeriatrics) that set a roadmap addressing clinical, organizational, and ethical issues that will guide the implementation of biomarkers from research to routine use for AD diagnosis through the steps of: standardization and validation of biomarker collection and measurement; refinement of accuracy data and development of guidelines for the combined use of biomarker; pilot implementation and testing in Biomarker Qualified Memory Clinics; and development of a national program for sustainable access to biomarker-based diagnosis. We propose this can be a model to be translated in other Countries with similar NHS organization.

PET Imaging in the early e preclinical phase of AD

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PET studies have focused on the development of tools improving either detection of people at higher risk of dementia or early diagnosis of Alzheimer disease (AD). Within the two major classes of AD biomarkers currently

identified, i.e. markers of disease state (Abeta amyloid accumulation) and markers of disease stage (neuronal injury), amyloid and [18F]FDG-PET imaging represent decisive tools. In the recent guidelines these are recognized of crucial value to the early and differential diagnosis firmly supporting the final diagnosis of AD. The references based recommendations, however, included also large PET imaging literature based on visual methods that greatly depending on the observer's experience, reduces sensitivity and specificity and lacks a clear cut-off between normal and pathological findings. To overcome these limitations, PET imaging can be assessed using parametric or voxel-wise analyses by comparing the subject's scan with normative data set. It has been shown that such measurements increase sensitivity and specificity of PET molecular imaging and allow a better differentiation between normal subjects, preclinical AD and AD individuals. This is true also for the differential diagnosis among the atypical forms and other neurodegenerative dementia diseases in particular in the early phase. Statistical Parametric Mapping (SPM) of [18F]FDG-PET imaging is the most method in research and clinical set and a new SPM tool has been validated. Its possible use on Grid-SPM system is under development to provide a wide availability to perform single-case analysis in clinical practice. Equally, the development of PET imaging tools for the detection of amyloid deposition is of particular relevance for the early detection of AD and the prediction of patients' outcome. It is mandatory to obtain quantified measures crucial for the confirmation or exclusion of AD and the distinction from normal state. Applying these methods would be crucial also in multicentre studies and for therapy monitoring.

Prospective memory in Mild Cognitive Impairment and Alzheimer's disease

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Prospective memory (PM) is a multifaceted cognitive function allowing the realization of delayed intentions. PM deficits are frequently reported in individuals suffering from brain pathologies in which they may be associated to autonomy and quality of life decrease. Taking medicines regularly, paying a bill or attending to appointments are some examples of routine activities that may be affected by PM weakness. Clinical research documents that PM is early and severely impaired in individuals with Alzheimer's disease. This evidence raises the issue of whether PM impairments may be a precocious sign of cognitive decline in persons with higher risk to develop dementia. Increasing data have being collecting in individuals with mild cognitive impairment (MCI), a condition considered to potentially represent the prodromal phase of dementia syndromes. The available literature, although still sparse, highlights some relevant points. First, in respect to healthy individuals, MCI persons show significant worse performance on both ecological and laboratory PM tests. Second, an analytic examination of data evidences a difference between MCI and healthy individuals indicating, in the average, a moderate-high effect size. Interestingly, preliminary data from a recent research in which a logistic regression model was applied, show that the association of PM with episodic memory scores improves both sensitivity and specificity of neuropsychological assessment of MCI. In conclusion, PM abilities are significantly affected in both Alzheimer's Disease and MCI. Data from the latter population suggest that PM impairment may be a very early sign of cognitive deterioration. However, extant literature suffers from methodological limits mainly represented by the relatively low number of individuals examined in the different studies, and by the heterogeneity of both the samples recruited and PM procedures adopted. Further longitudinal studies should also investigate the predictive value of PM impairments on the risk to develop dementia in the affected individuals.

New insights in molecular aspects of Alzheimer's disease

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5-HT4 agonists have been proved to exert procognitive effects in rodents and to induce the non-amyloidogenic processing of the amyloid precursor protein (APP), leading to an increase of soluble sAPPa (sAPPa). Therefore,

5-HT4 receptors (5-HT4R) could be of interest to delay AD progression. We studied the action mechanism of 5-HT4R ligands and analyzed their effects on Aβ production and amyloid plaque formation. COS-7 cells were stimulated with 5-HT4R agonists and sAPPa release quantified through ELISA. Results were confirmed *in vivo* with i.p. injections in wild-type mice (WT). In addition, chronic administration of 5-HT4 agonists was performed in an aggressive mouse model of AD, the 5XFAD, during the prodromal phase preceding the appearance of behavioural deficits. Following treatments, amyloid plaque load and Aβ burden were measured through ELISA and thioflavin T staining. Astroglial inflammation associated to plaques was revealed through GFAP staining. 5-HT4R agonists induced an increase of sAPPa release both in cell cultures and in WT mice. The chronic and prodromal administration of 5-HT4R agonists to 5XFAD mice reduced the production of Aβ peptides and slowed down the formation of plaques. These effects were prevented by a co-treatment with a specific 5-HT4R antagonist, that was ineffective by itself. Astroglial inflammation was also markedly reduced after 5-HT4R agonist administration. Chronic treatments promoting sAPPa release via the stimulation of 5-HT4 receptors clearly hinder plaque formation and Aβ load while jointly attenuating inflammation processes. We conclude that 5-HT4 agonists administration could represent an interesting and promising strategy for AD prevention.

Physiological activites of amyloid-beta monomers

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Our group suggested that β-amyloid (Aβ), in its non-toxic monomeric state, has a physiological role in the brain. Accordingly, we provided the demonstration that monomeric Aβ is able to activate the insulin/IGF-1 receptor signaling thus behaving as a neuroprotectant agent. More recently, we have investigated whether Aβ monomers have insulin/IGF-1-like metabolic actions either in the brain or in the periphery. We have found that synthetic monomeric Aβ acts as a positive allosteric modulator of type-I IGF receptor, and that participates in the control of neuronal glucose uptake and peripheral glucose homeostasis.

Ionic dyshomeostasis, synaptic deficits and neuronal death in Alzheimer's disease

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The molecular determinants of Alzheimer's (AD) disease are still not completely known; however, in the past two decades, a large body of evidence has indicated that unbalanced homeostasis of two signaling cations, calcium (Ca2+) and zinc (Zn2+), is an important contributing factor for AD development and progression. The two cations can operate synergistically to promote generation of free radicals that further intracellular Ca2+ and Zn2+ rises and set the stage for a self-perpetuating harmful loop that leads to synaptic dyfunction and neuronal death. In recent years, Zn2+ has also emerged as an important signaling ion. Zn2+ signaling is playing a key physiological role in the modulation of neuronal excitability and synaptic plasticity while perturbations in brain Zn2+ pools have been linked to cognitive decline. In this talk, we will discuss novel insights on pathways linking Zn2+ to these pathogenic processes as well as clues for development of new therapeutic strategies aimed at treating AD. We will discuss how restoring Zn2+ homeostasis may affect BDNF signaling and represents an important therapeutic avenue to modify AD onset and progression. Finally, as growing evidence indicates that AD is also associated with increased neuronal excitability and epilepsy, we will present data linking oxidative stress, intraneuronal Ca2+ homeostasis, and the modulation of Kv2.1 channels in a preclinical model of AD.