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ORAL COMMUNICATIONS

The cerebral structural and functional signatures of impulse control disorder in Parkinson's disease

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Introduction: To assess cortical thickness (CT) measures, white matter (WM) microstructural damage, and resting state (RS) functional connectivity alterations in patients with Parkinson's disease and impulse control disorder (PD-ICD) compared with controls and PD no-ICD cases matched for disease stage and duration, motor impairment, and cognitive status.

Methods: 85 PD patients (35 PD-ICD) and 50 controls. All subjects underwent 3D T1-weighted, diffusion tensor (DT), and RS-functional MRI (RS-fMRI). CT measures were assessed using surface-based morphometry. DT metrics were explored using region-of-interest-based and tractography approaches. RS-fMRI data were analyzed using a model free approach.

Results: Compared with controls, both PD patient groups showed a pattern of brain structural alterations involving basal ganglia, pyramidal and associative systems. Compared with PD no-ICD, PD-ICD patients showed reduced CT of the left precentral and superior frontal gyri, and motor and extramotor (limbic) WM tract involvement. Furthermore, compared with controls, both patient groups had an increased functional connectivity within the visual-network. Additionally, PD no-ICD patients showed increased functional connectivity of bilateral precentral and postcentral gyri within the sensorimotor network compared to both controls and PD-ICD cases.

Conclusions: Relative to PD no-ICD, PD-ICD patients are characterized by a more severe involvement of frontal, meso-limbic and motor circuits. Furthermore, in PD-ICD, the lack of increased functional connectivity within the sensorimotor-network together with their cortical thinning in the same regions, suggest a greater disconnection among these systems in this condition.

Combining structural magnetic resonance imaging and neuropsychological tests to classify mild cognitive impairment

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Aims: Alzheimer's disease (AD) is the most common cause of dementia, but it is difficult to detect in its earliest stage. Recently, efforts have been made to combine neuropsychological and brain imaging biomarkers in an attempt to detect AD at its prodromal Mild Cognitive Impairment (MCI) stage [1]. Machine learning approaches have been shown to be extremely suitable to this purpose. In the present pilot study we aimed to test the validity of combining cognitive scores (with a focus on visuo-spatial abilities which appear more sensitive to subtle cognitive changes) and brain structural features in the detection of MCI through a machine learning approach.

Materials: A group of 11 patients with MCI and a group of 11 healthy elderly controls were enrolled into this study. Participants underwent Cognitive test and Magnetic Resonance Imaging assessment.

Methods: All participants underwent standardized cognitive tests and new visuo-spatial experimental

tests, such as object location recognition, map learning and route learning, and self-administered questionnaires, such as Sense of Direction Scale, Spatial Attitude Scale, Spatial Anxiety Scale and Self-Efficacy Scale [2]. All participants underwent the same brain MRI protocol on a 3 Tesla General Electric MR750 scanner, including T1w images stripped and segmented to obtain grey matter maps. A Multi-Kernel-Learning Support-Vector-Machine procedure implemented by PRoNTo software [3] was used to combine structural magnetic resonance imaging and cognitive scores to classify MCI and healthy participants.

Results: Correct classification was achieved in 100% of the participants, suggesting that the combination of neuroimaging with more complex cognitive tests is suitable for early detection of Mild Cognitive Impairment.

Discussion: The results highlighted the importance of the experimental visuo-spatial memory tests battery in the efficiency of classification. Although the number of participants is a limitation of the present study, it outlined a suitable framework to combine neuroimaging and cognitive assessment in early detection of MCI.

Conclusions: These findings suggest that the high-level brain computational framework underpinning the participant performance in these visuo-spatial ecological tests might represent a "natural filter" in the exploration of cognitive patterns of information able to identify early signs of AD.

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Epigenetic profile in FTLD patients C9ORF72 repeat expansion carriers

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Objectives: Methylation analysis of the 5'CpG-island in C9orf72 promoter near the G4C2 repeat expansion in patients with Frontotemporal lobar degeneration (FTLD) and healthy subjects.

Materials: We investigated the CpG methylation profile of genomic DNA from blood of 86 subjects: 45 FTLD patients [17 expansion carriers (mean age at onset 60.3±10.1, 58.8% female), 28 non carriers (mean age at onset 65.4± 6.5, 39.3% female)] and 41 controls (mean age at samples collection 73.15±7.9; 58.5% female). All patients fulfilled the inclusion criteria for FTLD [1,2]. All healthy subjects were carefully assessed using a rigorous clinical and neurological examination to exclude to presence of any neurological disorder.

Method: To assess the level of methylation we performed direct bisulfite sequencing based on the conversion of unmethylated C to T by bisulfite treatment. Direct inspection of sequencing chromatograms showed the total number of methylated CpG sites. Samples were categorized to three methylation levels (no methylation, low methylation and high methylation).

Results: Methylation levels of the CpG island resulted significantly higher in FTLD patients C9orf72 expansion carriers that in non carriers (patients, p value < 0.0001 and healthy subjects p value < 0.00001). Within C9orf72 expansion carriers, no statistically significant difference was found between FTLD than FTLD/ALS patients (p value = 0.6941). Methylation levels did not correlate with the age at onset (42-74 years old; Spearman coefficient = -0.16176, p value = 0.53)

Discussion: Our study provide evidence that hypermethylation of the CpG island is expansion-specific, since a high level of methylation was not observed in any of the 69 non carriers (patients and Controls). The combined analysis of the FTLD and FTLD/ALS dataset reveals that DNA methylation is not a major modifying factor for disease phenotype, although a tendency for more highly methylated samples was detected in FTD/ALS patients.

Conclusions: Further validation will be necessary to confirm the role of this or other epigenetic mechanisms in the C9orf72 linked diseases.

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Alzheimer's disease is a disorder of cortical plasticity independently from age of onset

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Presenile Alzheimer's disease (Early Onset Alzheimer Disease) accounts for less than 10% of all AD cases. EOAD and Senile or Late Onset Alzheimer disease (LOAD) share the same pathological features and are considered the same disorder affecting people at different ages, under 65 years for EOAD, over 65 years for LOAD. Whether the different pathological burden could influence also synaptic plasticity mechanisms has never been addressed yet. The aim of our study is to compare a population of non-genetic EOAD with a LOAD from a CSF bio-markers analysis and a neuropsychological point of view. Furthermore, by comparing these patients with two additional control groups, respectively old healthy subjects and healthy young subjects obviously age-matched, we investigated the neurophysiological characteristics of these patients through transcranial magnetic stimulation protocols. To verify this hypothesis we evaluated a group of 22 sporadic EOAD and 33 LOAD for plasticity induction of LTP/LTD-like effects using respectively intermittent TBS (iTBS) or continuous TBS (cTBS). Central cholinergic activity was evaluated by means of short afferent inhibition (SAI) protocol. Moreover we performed in all the patients a lumbar puncture to study the biomarker profile, and an extensive neuropsychological battery. Patients, both EOAD and LOAD, showed an impairment of LTP mechanisms while healthy controls, showed a normal profile of cortical plasticity. SAI protocol results show a positive correlation between SAI dysfunction and aging, reflecting acetylcholine role in aging. No differences have been observed between EOAD and LOAD about neuropsychological and bio-marker analysis. EOAD and LOAD show similar clinical characteristics both from a psychological than from a bio-marker point of view. The central cholinergic pathway seems to be affected more by age than by the disease process itself. The mechanisms of LTP are altered in AD patients despite the age, thus representing a reliable marker of disease.

Comparative value of [(123)I]-FP-CIT SPECT and [(123)I]-MIBG myocardial scintigraphy in distinguishing between dementia with Lewy bodies and other types of dementia

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Aims: (i) To compare the diagnostic value of FP-CIT SPECT and MIBG myocardial scintigraphy in differentiating DLB from other types of dementia, and (ii) to determine inter-rater reliability for visual assessment for each of the two methods.

Materials/Methods: Our analyses included 30 patients with a clinical diagnosis of DLB and 29 patients with a clinical diagnosis of non-DLB dementia (AD, $n=16$; bvFTD, $n=13$), who were consecutively referred to five memory clinics in Lombardy. All patients underwent FP-CIT SPECT and MIBG myocardial scintigraphy within few weeks of clinical diagnosis. All diagnoses were agreed upon by the local clinician and an independent expert (PT), who did not at any time during the study have access to striatal and myocardial images. Diagnostic appropriateness was re-evaluated after 12 months of follow-up. Unlike prior investigations, our study did not exclude patients with concomitant illnesses that might potentially interfere with MIBG uptake. Striatal and myocardial images were visually classified as either normal or abnormal by independent nuclear physicians who were blinded to the patients' clinical data, except for age.

Results: The DLB and non-DLB groups were comparable ($p>0.05$) for sex, age at onset, and age and global severity of dementia at first visit. As expected, DLB patients showed a greater frequency of all core features, and had lower scores on tests of visuospatial/constructional and attentional abilities ($p<0.05$). Overall, sensitivity and specificity to DLB were respectively 93% and 100% for MIBG myocardial scintigraphy, and 90% and 76% for FP-CIT SPECT. Lower specificity of striatal compared to myocardial imaging was due to decreased FP-CIT uptake in seven non-DLB patients (three with parkinsonism) who had normal MIBG myocardial uptake. Inter-reader agreement was higher for myocardial (Cohen's kappa between 0.89 and 0.96) than for striatal (Cohen's kappa between 0.82 and 0.86) imaging.

Discussion: Striatal and myocardial imaging are equally sensitive to DLB, but the latter method can be more reliable and specific for excluding non-DLB dementias, especially when parkinsonism is the only "core feature" exhibited by the patient. Notably, MIBG myocardial uptake in our non-DLB group was invariably normal, despite the concomitance of diabetes and/or cardiomyopathy in about one fourth of the patients, suggesting that the potential confounding effect of these illnesses on MIBG uptake might have been overestimated.

Conclusions: Our results on MIBG scintigraphy argue in favour of its upgrade from supportive to suggestive DLB features. This needs to be confirmed in further prospective studies with larger unselected samples.

Mapping the statistical dissociation between Alzheimer's disease and normal ageing on the default-mode network

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A considerable proportion of adults without cognitive deficits do have histological evidence of subclinical Alzheimer's pathology (AD). Similarly, patients suffering from AD are also subjected to the inevitable mechanisms of ageing. Based on this dual overlap, it is difficult to disentangle the pattern of exclusivity triggered by the two trajectories when both affect the same neural system. This is the case of the default-mode network (DMN). Although the effects triggered by AD on the DMN are much more pronounced, a qualitative analysis indicates that the maps of regional modifications are substantially comparable. As a consequence, it is not fully clear what the net signatures of ageing and AD are on the DMN. Regression models were run to investigate these patterns. Two-hundred-and-twenty-two adults underwent an MRI protocol inclusive of structural and resting-state acquisitions. These included 151 healthy adults covering the entire age-span and 81 patients diagnosed with either minimal/mild AD dementia or AD mild cognitive impairment. The volume of the left hippocampus was operationalised as index of AD volumetric susceptibility/severity. Days of age at scan were instead used as index of ageing. Subject-specific maps of the anterior and posterior DMN were extracted from a cohort-wise Independent Component Analysis. Multiple-regression models were computed using either index as main regressor, while controlling for the counterpart variable. Education levels, intracranial volume, grey-matter fraction and gender served as additional nuisance regressors, accounting for cerebral and cognitive reserve. Within the aDMN, age was positively associated with connectivity in the superior portion of the anterior-middle cingulate gyri and in prefrontal areas, while hippocampal volume was negatively associated with connectivity in the inferior portion of the anterior cingulate and the left middle frontal gyrus. Within the pDMN, age was negatively associated with connectivity in posteromedial and right temporo-insular regions, and AD was positively associated with cuneal connectivity.

This piece of statistical evidence indicates that AD and ageing converge in the up-regulation of different aspects of the anterior DMN. On the other hand, the typical pattern of posterior DMN down-regulation seen in postero-medial areas seems not to be a product of AD, as connectivity of these regions was associated with ageing. The hippocampal volume was instead associated with connectivity within occipital areas, normally not considered as core target of AD. These findings support the possibility that the influence of AD in experimental studies might be partly masked by the effects of ageing.

Thinking movement: association of motor imagery with the affected side in Parkinson's disease

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Background: Motor imagery (MI) training is increasingly being adopted for improving motor performance in patients with Parkinson's disease (PD). Aim: To assess whether the side-specific motor impairment in PD is reflected by side differences in MI.

Methods: Three MI questionnaires (the Vividness of Visual Imagery Questionnaire, Vividness of Movement Imagery Questionnaire, and the Test of Visual Imagery Control) were administered to subjects with PD. The association between the affected side and MI was assessed through multivariate linear regression, adjusting for levodopa equivalent daily dose (LEDD), MMSE, UPDRS-III, education, comorbidities and duration of the disease.

Results: Among 39 participants (mean age 73 years, 36% females, 56% right affected side), a left affected side was independently associated to lover MI scores for VVIQ (B=-11.89; 95%CI -19.72, -4.07), VMIQ (B=-17.30; 95%CI -31.65,-2.94), and TVIC (B=-10.96; 95%CI -19.02,-2.91).

Conclusions: Side impairment predicts MI ability in PD; this should be considered for rehabilitation programming.

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Together is better: social network and risk of dementia in MCI subjects, a memory clinic-cohort study

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Objectives: To assess the role of social network in the progression from Mild Cognitive Impairment (MCI) to dementia in a memory clinic setting.

Materials and Methods: Four hundred and seventeen MCI subjects (mean age: 75.4 ± 6.9 years; education: 7.57 ± 3.9 years; MiniMental State Examination (MMSE) total score: 25.3 ± 2.4) were screened at baseline for civil status (CS) and domestic environment (DE, i.e. living with someone or not). The population underwent a baseline complete clinical and neuropsychological evaluation and annual follow-up for dementia surveillance. To assess the association between dementia and social network, a Cox proportional hazard regression model was used in order to adjust for the covariates. The role of social interactions in the progression to dementia was assessed estimating Hazard Ratios (HR). Each predictor (CS and DE) was tested separately, with progressive grades of adjustment for covariates, including age at diagnosis, education, gender, MMSE and IADL score, MCI subtype, Apolipoprotein

E (ApoE) haplotype, Geriatric Depression Scale (GDS) and Cumulative Illness Rating Scale (CIRS) scores.

Results: During a mean time of 32.2 ± 23.8 months of follow-up, 245 (58.8%) subjects developed dementia, while 172 (41.2%) remained stable MCI. Univariate analyses showed that MCI subjects who developed dementia were older, had lower MMSE, IADL, GDS, CIRS scores, had more frequently a multi-domain cognitive impairment and were more frequently ApoE ε4 allele carriers at baseline. Cox regression models showed a protective role of both conditions of having a partner (HR 0.74, 95% CI 0.57-0.95, *p* 0.021) or living with someone (HR 0.76, 95% CI 0.58 – 0.98, *p* 0.038). After full correction for covariates, the status of living with someone showed a significant protective role against progression to dementia (HR 0.66, 95% CI 0.44 – 1.00, *p* 0.048), and the protective role of having a partner was maintained (HR 0.75), even if statistical significance was lost (95% CI 0.51 – 1.10, *p* 0.143).

Discussion and Conclusion: The presence of social interactions plays a significant protective role against progression from MCI to dementia, probably acting as an enhancer of cognitive reserve buffer. The effect seems to be particularly relevant for sharing DE with someone, even after correcting for covariates. The protective role of positive social interactions against cognitive decline had already been demonstrated in population-based studies performed on asymptomatic subjects. This study underlines their crucial role even in the MCI condition.

Accuracy of Creutzfeldt-Jakob disease diagnosis using RT-QUIC testing of olfactory mucosa and cerebrospinal fluid samples

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Objective: We previously detected prion seeding activity in olfactory mucosa (OM) of Creutzfeldt-Jakob disease (CJD) patients using nasal brushings coupled with real time quaking induced conversion (RT-QuIC) with high sensitivity and specificity. However, the OM procedure using cyto-brushes may cause mild discomfort or blood contamination of samples. To further evaluate and improve this approach to CJD diagnosis, we tested a softer flocked swab. Moreover, we assessed the diagnostic outcome of combined RT-QuIC analyses of OM and cerebrospinal fluid (CSF).

Methods: We collected OM and CSF samples from 61 possible, probable or definite CJD, 8 genetic prion disease, and negative controls (50 OM and 54 CSF) and analyzed them by RT-QuIC.

Results: OM sampling using swabs was painless and softer than brush with minimal blood contamination. Single cyto-brushings ($n=48$) or swabbings ($n=95$) of sCJD patients gave diagnostic sensitivities of 90-93%. Cumulative results from multiple OM samplings in one session improved sensitivity to 97% (95% confidence interval (CI), 88-99%; $n=61$). CSF testing of the same patient group was 95% sensitive (CI, 84-99%). Collectively, all sCJD patients ($n=61$) were RT-QuIC-positive using OM, CSF, or both, giving an overall RT-QuIC diagnostic sensitivity to 100% (CI, 93-100%). All non-CJD controls were negative giving 100% specificity (CI, 91-100%). For patients with genetic prion disorders, combined OM and CSF testing was 75% sensitive (CI, 36-96%).

Interpretation: OM swab sampling allowed gentler, yet highly accurate, sCJD testing. However, testing both CSF and OM samples increased the diagnostic accuracy to 100%.

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Transient focal neurological episodes due to cerebral amyloid angiopathy: what can we learn from a 19-month follow-up population study

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Background: Sporadic cerebral amyloid angiopathy (CAA) is a common age-related cerebral small vessel disease characterized by progressive deposition of beta-amyloid in the wall of cortical and leptomeningeal small arteries. Transient focal neurological episodes (TFNE) are recurrent, stereotyped, brief, and with a wide spectrum of clinical features ranging from TIAs to "aura-like" symptoms and are increasingly recognized as common clinical presentation of CAA, other than spontaneous lobar intracerebral haemorrhages (ICH).

Aim: (i) to describe demographic and clinical features of patients with CAA presenting with TFNE, (ii) to assess which are the most frequent diagnosis and therapeutic work-up at first event, and (iii) to define risk factors for lobar ICH or TFNE relapse.

Methods: 33 patients with a final diagnosis of probable CAA based on Boston criteria (modified by Linn) recruited from 2010 to 2015 were retrospectively studied. Clinical data and neuroimaging CAA features (TC scan and MRI with GRE or SWI sequences) were collected at onset and for each new CAA-related episode during 19-month follow-up. MRI sequences were reviewed with an expert neuroradiologist to confirm imaging evidences of CAA (lobar cerebral microbleeds, superficial cortical siderosis or acute focal convexity sub-arachnoid haemorrhage (cSAH)).

Results: 21 (63%) CAA patients presented with TFNE, 9 (27%) with lobar ICH and 3 (10%) with CAA-related inflammation. Demographic features and systemic risk factors were not different among groups. TFNE group presented more frequently negative TIA-like episodes (52%), whereas positive aura-like (28%) symptoms were less reported. On MRI, microbleeds were detected in 88% and cSAH in 52% of TFNE cases. The most frequent diagnosis of TFNE at baseline was stroke or TIA (43%), following CAA in 4 and cortical venous thrombosis in 3 patients. At first visit 70% of patients with TFNE was treated with antithrombotics (antiplatelet drugs or vitamin K-antagonists). During follow-up, the risk of ICH after a first TFNE was 42%, being 14% in the first two months. A significant association between TFNE/ICH relapse and antithrombotic drugs use was found ($p = 0.04$).

Conclusions: Misdiagnosis of CAA-related TFNE is frequent given the heterogeneous clinical manifestations (often hardly distinguishable from TIAs), and because differential diagnosis of neuroimaging findings is sometimes very challenging (e.g. cortical venous thrombosis vs cSAH/ superficial cortical siderosis). CAA-related TFNE are associated with high early risk of lobar ICH, hence avoid antiplatelet drugs or anticoagulants in CAA patients is recommended.

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Macronutrients intake in adulthood and risk of dementia in old age: a 20-years follow-up Italian study

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Objectives: A high caloric intake has been associated with an increased risk of cognitive decline. Macronutrients are the main determinants of total caloric intake, thus aim of this study was to investigate the association between daily energy intake derived from carbohydrates, proteins and fats in relation to the risk of dementia.

Materials and Methods: This is a prospective cohort study on a population of residents ($n = 1604$) in two districts of Northern Italy aged 40-74 years old who were examined about dietary habits and other lifestyles during the period 1991-5. Dietary habits were assessed by means of a 158-item food frequency questionnaire at baseline. Occurrence of Alzheimer'

Disease (AD) and Vascular/other forms of Dementia (VaOD) were ascertained using Regional Health Registries. The proportion of daily energy intake (calories) derived from carbohydrates (%), proteins (%) and fats (%) was calculated and participants were ranked as "low" and "high" intake. Cox models were used to assess the associations between % macronutrients and incident AD and VaOD adjusting for potential confounders.

Results: During a median of 18.6 years of follow-up, 73 incident dementia cases had occurred (39 AD and 34 VaOD). In the fully adjusted models the risk of AD was significantly increased in people with high % carbohydrates (HR 2.45, 95%CI 1.08-5.57) but was reduced in those with high % fats (HR 0.34, 95%CI 0.16-0.71) and high % proteins (HR 0.78, 95%CI 0.38-1.60). The risk of VaOD was elevated in subjects with high % fats (HR 1.77, 0.79-3.95) but was decreased in persons with high % protein intake (HR 0.49, 95%CI 0.22-1.08) even though the estimates did not reach the significance. No association with % carbohydrates was observed.

Discussion: High % carbohydrates and low % proteins and fats were associated with an increased risk of AD whereas low % proteins and high % fats increased the risk of VaOD in our cohort. A possible explanation might reside in the food sources. Olive oil, rich in monounsaturated fatty acids, was the main source of fats in AD subjects. Persons who developed VaOD had a high intake of lard and margarine, rich in saturated and trans-unsaturated fatty acids. Regarding carbohydrates, subjects with AD had a higher intake of foods with high glycemic index than individuals with VaOD.

Conclusion: Our data suggest that certain dietary choices and habits in adulthood can play a key role in the prevention of AD and dementia in old age.

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Transcranial brain parenchyma sonography in the diagnosis of dementia with Lewy bodies

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Background: Transcranial sonography (TCS) of the brain parenchyma is used to visualize alterations in the substantia nigra (SN) and it is applied for early diagnosis of Parkinson's disease.

Objective: We aimed to explore specific echogenic alterations of SN in dementia with Lewy bodies (DLB) compared to Alzheimer disease (AD).

Methods: Seventy-one subjects underwent TCS: 22 DLB, 28 AD and 21 healthy elderly controls. Cognitive impairment, extrapyramidal signs, visual hallucinations, fluctuations and REM-behavior symptoms were investigated. TCS assessed SN hyperechogenicity and symmetry.

Results: TCS revealed SN hyperechogenicity in 100% of DLB compared to 50% of AD and 30% of controls. Mean SN echogenic area (cm^2) was 0.22±0.03 in DLB, 0.15±0.03 in AD, and 0.14±0.03 in controls ($p<0.0001$). More than 50% of DLB presented a marked hyperechogenicity (cutoff value >0.22 cm 2) respect to only 10% of AD ($p<0.0003$). DLB had symmetrical SN enlargement, whereas AD were mostly asymmetrical ($p=0.015$). Combination of SN echogenic area and asymmetry index held a sensitivity of 88.9% and a specificity of 81.2% in discriminating DLB from AD (PPV 85.7%, NPV 85.7%). No association was found between SN hyperechogenicity and UPDRS-III, MMSE or presence of visual hallucinations.

Conclusions: TCS may be a valid supportive tool in the diagnostic workup of neurodegenerative dementia helping clinicians distinguishing DLB from AD even at the early stages.

POSTER

Functional connectome organization is altered in PD patients with mild cognitive impairment

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Objective: Investigation of the brain wiring architecture is a powerful approach in the examination of the pathogenic mechanisms of neurodegenerative disease. This study investigated the functional brain connectome organization in Parkinson's disease (PD) with mild cognitive impairment (MCI).

Methods: 54 PD-MCI patients, 54 demographically-matched PD patients with no cognitive impairment (PD-ncog), and 41 healthy controls underwent resting state functional MRI (fMRI). Graph theory analysis was used to measure the global topological properties of functional brain networks. Differences in regional networks among groups were investigated using Network-based statistics (NBS).

Results: PD-ncog patients did not show altered global graph theory measures and regional functional connections relative to controls. PD-MCI patients had lower mean network degree, connection density, and global efficiency as well as higher path length compared to controls and PD-ncog cases. NBS analysis revealed that, relative to healthy subjects, PD-MCI patients showed a large network of reduced functional connectivity that included basal ganglia and the majority of fronto-temporo-parietal areas with the most significant being the precentral, postcentral, superior and inferior frontal, and superior temporal gyri, anterior and posterior cingulate cortices, and supramarginal gyri and insula bilaterally.

Conclusions: The topological properties of brain networks are altered in PD patients with cognitive deficits, suggesting a loss of efficiency of long-distance functional connections. The pattern of the network alterations and their anatomical distribution suggest that network analysis may provide biomarkers of the neuropathological substrate underlying PD-related cognitive impairment.

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Multimodal imaging to distinguish *in vivo* early onset Alzheimer's disease from behavioral variant of frontotemporal dementia

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Objective: The aim of this study was to compare early-onset Alzheimer's disease (EOAD) and behavioural variant of frontotemporal dementia (bvFTD) using a multimodal neuroimaging approach combining structural (cortical thickness [CT] and white matter [WM] microstructural measures) and functional (resting state functional [RS-fMRI] connectivity) MRI.

Methods: Sixty-two probable EOAD patients, 27 probable bvFTD patients and 48 controls underwent 3DT1-weighted MRI, diffusion tensor (DT)-MRI and RS-fMRI. CT measures and DT metrics from the main WM tracts were obtained. RS fMRI data were analyzed using a model free approach. A Random Forest (RF) analysis was applied to explore the role of MRI data in classifying the two syndromes.

Results: Compared to controls, each patient group showed a widespread pattern of brain alterations. Compared to bvFTD, EOAD patients showed reduced CT of the posterior cingulate and inferior parietal gyri bilaterally, WM damage of the splenium of the corpus callosum, and decreased functional connectivity of the posterior cingulum within the default-mode network. Compared to EOAD, bvFTD

patients showed reduced CT of the orbitofrontal cortices and temporal pole bilaterally, and WM damage of the corpus callosum, cingulum, superior longitudinal and uncinate fasciculi bilaterally. RF analysis revealed that the best predictors of differential diagnosis among MRI measures were the CT values of the inferior/medial parietal cortices and right temporal poles.

Conclusions: Multimodal imaging can help understanding differences between early onset dementia phenotypes. Furthermore, RF analysis suggests that CT measures may represent a useful tool to distinguish EOAD from bvFTD at individual patient level in clinical practice.

Structural and functional MRI signatures of ALS patients with C9ORF72 hexanucleotide repeat expansion

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Objective: In order to explore the specific C9orf72 MRI signature in amyotrophic lateral sclerosis (ALS), we investigated structural and functional abnormalities in C9orf72-positive (+) relative to C9orf72-negative (-) ALS cases matched for all main clinical features.

Methods: 21 C9orf72(+) ALS patients were compared with: 22 healthy subjects; 31 C9orf72(-) ALS patients without cognitive impairment [C9orf72(-) motor] matched for ALSFRS-r score; 26 C9orf72(-) ALS patients matched for ALSFRS-r score and cognitive deficits [C9orf72(-) plus]; 20 C9orf72(-) ALS patients matched for disease progression rate [C9orf72(-) rate]. All subjects performed structural, diffusion tensor and resting state functional MRI.

Results: All patients showed cortical thinning of motor and extra-motor brain regions. No cortical areas were more affected in C9orf72(+) compared to C9orf72(-) motor and plus phenotypes, while occipital thinning was observed in C9orf72(+) relative to C9orf72(-) rate cases. All patients showed a damage of the motor callosal fibers and corticospinal tract vs controls. C9orf72(+) patients showed an additional involvement of the right superior longitudinal fasciculus. C9orf72(+) patients exhibited decreased functional connectivity of the motor and dorsal attention networks compared to C9orf72(-) plus patients. In the visual network, C9orf72(+) patients showed increased functional connectivity relative to controls and all sporadic phenotypes.

Conclusions: Early occipital structural and functional alterations appear to be as the C9orf72 specific MRI signatures in ALS. Functional connectivity patterns relative to sporadic cases suggest altered connectivity as part of C9orf72-ALS pathogenesis.

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Modelling trajectories of brain damage in progressive supranuclear palsy: a longitudinal multimodal MRI study

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Objective: To explore clinical, cognitive, and neuroimaging changes in patients with progressive supranuclear palsy syndrome (PSPs).

Methods: We enrolled 21 patients with Richardson's syndrome (PSP-RS) and 10 with PSP-parkinsonism (PSP-P). Patients underwent clinical and neuropsychological evaluations and MRI scan at baseline and after a mean 1.4 year follow-up (FU). Diffusion tensor (DT) metrics of white matter (WM) tracts were assessed in both PSPs groups. Cortical thickness changes were investigated in PSP-RS patients. At baseline, 35 healthy controls underwent MRI.

Results: Both PSPs groups manifested significant motor and cognitive decline (PSP-RS > PSP-P). Apathy worsened in both groups, while depression and behavioral changes in PSP-RS only. At study entry, PSP-RS patients presented focal thinning of frontotemporal and cingulate cortices bilaterally, compared to controls. Over time, these areas and insular cortices showed a progression of thinning. PSP-RS patients exhibited baseline WM damage in midbrain, superior cerebellar peduncles, corpus callosum and main long-range tracts. At FU, damage progressed in corpus callosum, frontotemporal/-parietal connections, but not in infratentorial WM, and correlated with the worsening of disability and cognitive/behavioral dysfunction. At baseline, PSP-P patients had WM damage in the anterior corpus callosum, external capsule, corona radiate, and superior longitudinal fasciculus bilaterally, compared to controls; these same regions showed a subtle progression of damage during FU.

Conclusions: In PSPs patients, the progression of WM microstructural damage is prominent compared to cortical damage and it is related to the worsening of clinical symptoms. DT MRI offers useful biomarkers to monitor the progression of PSPs disease.

Metabolic connectomics targeting brain pathology in dementia with Lewy bodies

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The core clinical features of Dementia with Lewy Bodies (DLB) are a progressive cognitive decline, extrapyramidal signs, and visual hallucinations. This picture reflects selective vulnerabilities, with specific neuronal populations dying consequently to α-synuclein accumulation and degeneration of dopaminergic and cholinergic systems. The link between neurodegeneration and underlying pathology is mediated by the metabolic pathways involved in neuronal function and bioenergetics.

Objective: Using [18F]FDG-PET, our study investigated the metabolic connectomic phenotype in DLB at an early disease stage, tracing for the first time a new scenario of precocious vulnerability in complex functionally connected networks, and also connectivity changes based on spreading of synuclein pathology and damage to the crucially relevant neurotransmission systems.

Materials and Methods: We characterized the metabolic connectome in 42 DLB patients at early disease stages, and compared it with the metabolic connectome of 42 age-matched healthy controls. Using sparse inverse covariance estimation and graph-theory, we performed a whole-brain analysis as well as anatomically-constrained analyses targeting cholinergic and dopaminergic pathways and α-synuclein spreading.

Results: The whole-brain analysis revealed alterations of DLB functional architecture, with overall reduced small-scale and increased large-scale metabolic connectivity in cortical and sub-cortical regions. The global connectivity alteration was associated with changes in the brain modular organization, with a consequent loss of local functional relevance. Metabolic connectivity impairment was found within occipital, thalamic and cerebellar regions and brainstem. The latter regions and the frontal cortex suffered also a long-range disconnection. The anatomically-constrained analyses revealed specific connectivity alterations within structures early affected by α-synuclein pathology. Within dopaminergic networks, nigrostriatal cortical projections were severely affected, whereas the ventrotegmental-limbic pathway was spared. The analysis of the cholinergic networks showed chang-

es in basal forebrain and brainstem projections to the cortex, notably in regions supplied by Ch1-2 and Ch5-6 basal forebrain nuclei. Within Ch5-Ch6 projections, the thalamus was the most affected. Taking our results together, we found a global reconfiguration of brain metabolic connectivity in DLB, affecting brain regions crucially involved in DLB pathology and in its clinical phenotype,. The α-synuclein-based analysis provides *in vivo* evidence for the applicability of Braak's staging system to DLB. Dopaminergic and cholinergic systems analyses showed the presence of a diverse vulnerability of neurotransmission pathways, with metabolic connectivity being mostly affected by neurodegenerative processes in specific neurotransmission networks.

Conclusions: These patterns of metabolic connectome abnormalities unveil a new scenario for the clinical DLB phenotype, representative of its underlying metabolic alterations, spread of pathology, and neurotransmission impairment.

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Validation of an optimized [18F]FDG SPM method for the differential diagnosis of atypical parkinsonisms in a clinical setting

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The clinical differential diagnosis of atypical parkinsonian disorders (APDs) can be challenging as the key symptoms of these neurodegenerative syndromes often overlap with those of other diseases or manifest later on the disease course [1]. [18F]FDG PET, by identifying specific disease-related patterns of regional glucose metabolism, can aid initial clinical diagnosis.

Objective: This study aims to validate a parametric method to assess [18F]FDG PET metabolism and its added value in the early differential diagnosis of APDs [2].

Materials and Methods: Fifty-seven patients with APDs were recruited. Each patient had a clinical first diagnosis and was referred for [18F]FDG PET within 3 months of the first clinical visit. A statistical parametric mapping (SPM) optimized procedure provided the brain hypometabolism maps at single subject level in a comparison to a large normal database [3]. Each SPM map was then classified by three neuroimaging experts, blinded to the clinical diagnosis, as suggestive for a specific APD subtype. The diagnostic power of initial clinical and [18F]FDG PET SPM classifications in predicting the final clinical diagnosis at follow-up was assessed by using indices of diagnostic accuracy and performing a logistic regression analysis.

Results: The low diagnostic power of initial clinical classification is characterized by 1) the 30% of unspecified APD classifications, 2) the 7% of uncertainty, and 3) the 25% of disagreement between initial classification and final clinical diagnosis. The [18F]FDG PET classification revealed high overall accuracy (98%), sensitivity (97%), specificity (99%), PPV and NPV (.92 and .99) in comparison with initial clinical classification. In the logistic regression analysis only [18F]FDG PET classification significantly predict the final diagnosis ($p<0.001$).

Conclusions: This study in a clinical setting validating the [18F]FDG PET SPM procedure in APDs, supports its strong value for the differential diagnosis in single individuals. In comparison to the initial clinical classification, only PET metabolic imaging was able to differentiate APD subgroups, particularly in the cases with atypical presentations or symptoms overlap. These results suggest the inclusion of [18F]FDG PET and the use of SPM procedure in the diagnostic criteria of atypical parkinsonisms, particularly at the time of initial presentation when the clinical ground might be insufficient.

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Functional connectome architecture of Alzheimer's disease, mild cognitive impairment and behavioral variant of frontotemporal dementia: a GRAPH analysis study

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Objective: This study aimed at investigating functional brain network architecture in late-onset (LO) and early-onset (EO) Alzheimer's disease (AD), mild cognitive impairment (MCI), and behavioral variant of frontotemporal dementia (bvFTD).

Methods: The study involved 122 AD patients, 61 MCI patients, and 51 age-matched controls. 35 EOAD patients were also compared with 29 bvFTD patients and 35 age-matched controls. All subjects underwent 3D T1-weighted and resting state functional MRI. Network nodes were defined parcellating the AAL atlas into 262 regions with equal size. Graph theory analysis and Network-based statistic were used to measure, respectively, global topological properties and differences in regional functional networks among groups.

Results: While controls showed high-densely connected modules, AD groups and bvFTD patients showed a loss of long-distance intra-module connections. Regardless the age of onset, AD patients showed altered global network measures (lower network degree, clustering coefficient, and longer path length) compared to controls and to the other patient groups. Compared with controls, MCI patients showed a decreased regional functional connectivity in the fronto-parietal connections. A decreased regional functional connectivity was prominent in the parieto-occipital connections in EOAD and in the fronto-temporal-parietal connections in bvFTD patients.

Conclusions: Global graph properties of brain networks are severely altered in AD, while they are relatively maintained in the other patient groups, thus suggesting that they are promising in distinguishing EOAD from bvFTD patients. Furthermore, the fronto-parietal connectivity disruptions in MCI patients could reflect an early marker of the disease.

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Functional and structural brain alterations in two independent samples of patients with posterior cortical atrophy

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Objective: To assess white matter (WM) damage and resting-state (RS) functional connectivity alterations in two independent samples of patients with posterior cortical atrophy (PCA) compared with healthy controls.

Methods: Sample#1 (1.5T MRI): 8 PCA patients and 21 controls; Sample2# (3T MRI): 13 PCA patients and 20 controls. All subjects underwent 3DT1-weighted, diffusion tensor (DT) and RS-functional MRI (fMRI). Gray matter (GM) atrophy was assessed using voxel based morphometry. DT MRI metrics were explored using tractography. RS-fMRI data were analyzed using a model free approach.

Results: The two PCA groups were matched for age and gender; sample#1 had longer disease duration (5±2 vs 3±1 years). Compared with controls, both PCA groups showed: cortical atrophy in the

occipital-temporal-parietal and frontal regions; WM alterations involving corpus callosum, cingulum, superior and inferior longitudinal fasciculi bilaterally; decreased functional connectivity of the occipital gyri within the visual-network and the precuneus and posterior cingulum within the default-mode network. The pattern of brain alterations of Sample#1 was more widespread than that of Sample#2. Relative to controls, sample#1 showed a further decreased connectivity of the: right superior frontal gyrus and anterior cingulum within the frontal network; left thalamus and hippocampus within the salience network; left superior temporal and supramarginal gyri within the dorsal-attentive network.

Conclusions: In two independent PCA samples, we showed that the WM damage is more widely distributed than expected on the basis of cortical atrophy. Moreover, altered functional connectivity becomes more significant with disease worsening extending from occipital to frontostriatal and temporo-parietal regions.

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CSF biomarkers performance in the differentiation between AD and FTD

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Objective: Cerebrospinal fluid (CSF) concentrations of amyloid peptides ending at positions 42 and 40 (Aβ42 and Aβ40, respectively), total tau (t-Tau) protein, tau phosphorylated at threonine 181 (p-Tau) were measured and Innotest® Amyloid Tau Index (IATI) and Aβ42/40, Aβ42/t-Tau and Aβ42/p-Tau ratio were calculated, in order to compare their accuracy in discriminating patients with AD and Fronto Temporal Dementia (FTD).

Material and Methods: 45 patients with AD and 20 with FTD referred to Neurological Clinic of Santa Chiara Hospital in Pisa, with available CSF, with 3 years of clinical follow-up, were included in this study. Aβ42, t-Tau, p-Tau, IATI and Aβ42/t-Tau and Aβ42/p-Tau ratio medium values of AD patients were compared with FTD patients, as well as, in a subgroup of patients (35 AD and 9 FTD), Aβ40 and Aβ42/40 ratio medium value, using Student T test. Pearson test and regression analyses were carried out to estimate the correlation between the biomarkers and clinical impairment based on MMSE values. Receiver operating characteristics (ROC) curve analysis was used to determine the area under the curve (AUC) including 95% confidence interval (CI) values, and cut-off points were set to achieve highest levels of sensitivity and specificity. Statistical significance was assumed at $p < 0.05$. Data analyses were carried out using SPSS 21.0 software.

Results: We found that, compared with the FTD patients, t-Tau and p-Tau mean value increased ($p = 0.011$ and $p = 0.01$ respectively) and Aβ42, Aβ42/p-Tau and Aβ42/40, ratio decreased ($p < 0.001$, $p < 0.001$, $p < 0.00001$, respectively) in AD patients. When ROC analyses performed the ratio Aβ42/40 represented the best parameter for discriminating AD from FTD (AUC: 0.962, p : 0.05, 95% CI 0.911 – 1; at the best cut-off score of 0,0628, sensitivity 100%, specificity was 89%), followed by Aβ1-42/p-tau ratio (AUC: 0.924, p : 0.05, 95% CI 0.82 – 1; at the best cut-off score of 4,254, sensitivity was 90 %, specificity was 87%). The linear regression performed between MMSE, age of onset, mean disease duration and CSF biomarkers in both the two groups did not show significant association except for Ab1-42 and MMSE ($p = 0.013$) in AD.

Conclusions: Our results are in agreement with the literature, underling that the combination of the different biomarkers, in particular Aβ1-42/p-tau and Aβ42/40 ratio increases the performance of CSF biomarkers to distinguish AD from FTD.

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Longitudinal clinical and brain MRI changes in multiple system atrophy

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Objective: Multiple system atrophy (MSA) is a rare and rapidly progressive neurodegenerative disorder. Longitudinal studies focused on clinical and MRI changes in MSA are still missing.

Methods: We enrolled 25 MSA-pakinsonian variant (MSA-p) patients and 21 matched healthy controls. Patients underwent clinical and neuropsychological evaluations and MRI scan at baseline and after a mean follow-up (FU) of 1.1 years. At baseline, MRI was obtained from controls. Changes in cortical thickness and diffusion tensor (DT)-MRI metrics of white matter (WM) tracts were assessed in MSA-p patients.

Results: During follow up, MSA-p patients showed a worsening of motor impairment, cognitive deficits and behavioural changes. At baseline, MRI study did not detect significant cortical and WM abnormalities in MSA-p patients compared with controls. After 1 year, MSA-p patients showed only a subtle, focal thinning of the frontotemporal cortices. Conversely, they showed significant, severe WM changes involving the corpus callosum, and frontotemporal and frontoparietal connections bilaterally (anterior>posterior). No longitudinal changes were observed in the infratentorial regions. In MSA-p, the progressive involvement of corpus callosum, external capsule, and long-range associative WM pathways bilaterally was associated with the worsening of cognitive deficits and behavioral changes.

Conclusions: This is the first longitudinal, multimodal MRI study of MSAp patients. In MSA-p patients, the progression of WM microstructural damage is prominent compared to cortical damage and may explain the worsening of cognitive and behavioural symptoms. DT-MRI has the potential to offer promising biomarkers for monitoring MSA-p and predicting the clinical evolution.

Functional metabolic temporo-limbic dysfunction in amnestic MCI subjects without amyloid load: a [18F]FDG and [18F]Florbetaben PET imaging study

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Background: Mild Cognitive Impairment (MCI) is a heterogeneous condition not always due to Alzheimer's disease. A subset of MCI subjects characterized by a selective impairment of long-term memory and a very slow progression rate of cognitive decline has been recently identified and considered as a possible clinical expression of the so-called "limbic-predominant" AD variant. We tested this diagnostic hypothesis evaluating the metabolic impairment and amyloid burden by PET in a subset of MCI subjects with a selective long-term memory impairment, slow progression rate and long symptom duration.

Materials and Methods: From a large series of amnestic MCI, we retrospectively selected 32 subjects (age=74.8±4.9) with slow progression, long-lasting symptom duration (>4 and up to 10 yrs). All the subjects had FDG-PET scans, and 20 out of 32 (age=75.6±4.8) also [18F]Florbetaben PET imaging for the assessment of amyloid load. Optimized voxel-based Statistical Parametric Mapping (SPM) was used for the analysis of FDG-PET data at single subject level, and SUVr method was applied for the analysis of amyloid-PET data.

Results: At the clinical follow-up, only a decline of episodic memory was present in each case, without progression to AD dementia. FDG-PET imaging showed in each case a metabolic dysfunction limited to the medial temporal lobe (i.e., hippocampal structures) without the typical AD temporo-parietal hypometabolism. In a few cases additional hypometabolism was evident in the frontomedial cortex, the superior temporal gyrus, and the posterior cingulate

gyrus. Notably, the subjects assessed for amyloid burden by PET had values within the normal range (< 1.45) or borderline (1.51 <x<1.79) SUVr values, well below the mean values reported in AD (1.93Â±0.3) for this tracer.

Discussion: These results indicate that a subgroup of amnestic MCI subjects has a more favorable clinical outcome and no in vivo evidence for AD positive biomarkers. A possible neuropathological correlate of this condition is the argyrophilic grain disease, typically characterized by selective tau pathology spreading throughout the limbic system. FDG-PET imaging has a crucial role in the diagnostic and prognostic algorithm of such patients. Larger clinical and neuropathological studies including in vivo assessment of tau burden by PET are needed to better define the syndrome.

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Amygdala-VMPFC dysfunction as a marker of dementia in parkinsonism

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Aim: Anxiety and somatoform disorders can antedate the first occurrence of the motor signs in Parkinson's Disease (PD) (Friedman, 1998). These early non-motor symptoms are also present in patients with Dementia with Lewy Bodies, in which frontal lobe dysfunction is one of the early features of dementia. Furthermore, somatoform disorders have been associated with the development of dementia in PD patients (Onofrj et al, 2010). In the current study, we aim to investigate whether the fronto-limbic network dysfunction may have predictive value for the development of overt dementia in PD.

Materials: 10 early PD (ePD) with anxiety and somatoform disorders and in 10 age-matched healthy volunteers were clinically evaluated and underwent MR session. Patients were followed for two years to define the disease progression.

Methods: Resting state functional magnetic resonance imaging (rs-fMRI) and Proton MR Spectroscopy (H-MRS) were used to investigate the functional connectivity (FC) and neurochemical profile within fronto-limbic circuits.

Results: ePD showed higher GABA/tCr content in vmPFC as compared to controls. FC between amygdala and vmPFC is altered. Specifically, in healthy volunteers the FC is negative, whereas in ePD it is loss.

Discussion: The interaction between the amygdala and the vmPFC plays a key role in emotional processing and regulation. Particularly, the higher GABA content in the vmPFC could promote the functional imbalance in the fronto-limbic circuit and the over-activation of the amygdala, leading to the somatic manifestation of the anxiety in ePD.

Conclusions: Our findings suggest that the neurochemical and the functional imbalance within the amygdala-vmPFC circuits could be linked with the non-motor disturbances in ePD and with the development of overt dementia in PD.

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The superficial white matter in Alzheimer's disease

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Background: White matter abnormalities have been shown in the large deep fibers of Alzheimer's

disease patients (Sachdev et al., 2013; Matsuda, 2013; Liu et al., 2011). However, the late myelinating superficial white matter comprised of intracortical myelin and short-range association fibers has not received much attention.

Materials and Methods: In order to investigate this area, we extracted a surface corresponding to the superficial white matter beneath the cortex, and then applied a cortical pattern-matching approach which allowed us to register and subsequently sample diffusivity along thousands of points at the interface between the gray matter and white matter in 44 patients with Alzheimer's disease (Age: 71.02+5.84, 16M/28F) and 47 healthy controls (Age 69.23+4.45, 19M/28F).

Results: In patients we found an overall increase in the axial and radial diffusivity across most of the superficial white matter ($p < 0.001$) with increases in diffusivity of more than 20% in the bilateral parahippocampal regions and the temporal and frontal lobes. Furthermore, diffusivity correlated with the cognitive deficits measured by the Mini-Mental State Examination scores ($p < 0.001$).

Discussion & Conclusion: The superficial white matter is uniquely complex in humans and continues to myelinate much later in life than any other primate. Given the distinctive cellular makeup, the superficial white matter likely plays an important role in Alzheimer's disease. To support this conclusion, we have demonstrated that it is damaged across most of the brain in Alzheimer's disease and is associated with Alzheimer's disease-related cognitive impairment.

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Structural brain MRI abnormalities in Kennedy's disease

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Objective: The extent of central nervous system (CNS) involvement in Kennedy's Disease (KD) still needs to be clarified. The aim of this study was to assess cortical and white matter (WM) alterations in a large sample of KD patients compared to healthy subjects and amyotrophic lateral sclerosis (ALS) patients.

Methods: 19 patients with genetically confirmed KD were compared with 27 healthy subjects and 25 ALS patients matched for motor disability. Patients underwent clinical examination, neuropsychological assessment, and MRI. Tract-based spatial statistics (TBSS) was applied to investigate WM damage and cortical thickness analysis to identify cortical atrophy.

Results: KD patients were characterized by pronounced behavioral symptoms. Both ALS and KD phenotypes showed widespread cortical thinning of motor and extramotor brain regions. In addition, KD patients manifested a greater involvement of the anterior cingulate cortex relative to ALS cases. Both KD and ALS phenotypes showed pronounced damage of the brainstem fibers. While in KD patients a characteristic fronto-occipital damage was evident, in ALS patients TBSS revealed a widespread pattern of damage encompassing the corticospinal tracts (CST), left superior longitudinal fasciculus (SLF) and corpus callosum. Moreover, the involvement of these WM fibers was greater in ALS compared with KD.

Conclusions: A prominent involvement of the cingulate cortex was found in KD, probably reflecting the observed behavioral symptoms. Brainstem fibers were equally involved in KD and ALS, while DT MRI measures of the CST, left SLF and corpus callosum were able to differentiate ALS from KD.
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The utility of multimodal imaging in the diagnosis of ALS

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Objective: Advances in statistical learning theory were applied to assess the diagnostic potential of structural and diffusion tensor (DT) MRI in amyotrophic lateral sclerosis (ALS).

Methods: 3D T1-weighted and DT MRI were obtained from 113 sporadic (probable, probable-laboratory supported, definite) ALS patients, 22 patients with ALS mimic disorders, and 40 healthy controls. The diagnostic accuracy of precentral cortical thickness measures and DT MRI metrics of the corticospinal tract and motor callosal fibers were assessed in a testing cohort and externally proved in a validation cohort using a random forest analysis.

Results: In the testing set (64 randomly selected sporadic ALS patients and healthy controls), precentral cortical thickness showed 0.85 accuracy, 0.76 sensitivity, 1.00 specificity in differentiating ALS patients from healthy controls, while DT MRI measures distinguished the two groups with 0.77 accuracy, 0.84 sensitivity, 0.65 specificity. In the same group, the combination of cortical thickness and DT MRI metrics improved the classification pattern as follows: 0.87 accuracy, 0.88 sensitivity, 0.84 specificity. In the validation cohort (remaining 49 sporadic ALS vs ALS mimic disorders), the diagnostic accuracy was higher for DT MRI than cortical thickness measures (0.80 vs 0.65), and the combined approach improved the classification only minimally (accuracy 0.83).

Conclusions: A multimodal imaging approach that incorporates motor cortical and white matter alterations yields statistically significant improvement in accuracy over using each modality independently in the individual ALS patient classification. DT MRI technique may be a useful tool in distinguishing ALS from ALS mimic disorders.

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A new qualitative MRI-DWI score provides useful insight into clinical phenotype, molecular subtype and survival in Creutzfeldt-Jakob disease

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Objectives: Neuroradiological criteria for diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) include hyperintensity on DWI or FLAIR sequences in at least two cortical regions (parietal, temporal or occipital), or in the caudate nucleus and putamen. However, there are only few studies exploring which MRI sequences and brain regions are more informative to support CJD diagnosis. Aim of this study was to validate a new qualitative MRI score in CJD diagnosis and to study the relationship between MRI lesion patterns and clinical features.

Materials and methods: 32 patients with diagnosis of definite or probable CJD (either by autopsy or with RT Quick-CSF technique) and 16 healthy subjects were included. All participants had a MRI study with both DWI and FLAIR sequences. Clinical features and PRNP gene polymorphism were also recorded. MRI images were evaluated with a semi-quantitative score, which separately considered the extent and degree of MRI signal intensity in 22 brain regions, both in DWI and FLAIR.

Results: In CJD patients the semi-quantitative score showed a better definition of MRI lesions (extent and hyperintensity) in DWI compared to FLAIR for cortical regions ($p < 0.01$). Insula and cerebellum were the only regions that did not differentiate CJD patients from controls, neither in intensity nor in extent of MRI signal. Among CJD patients the VV subgroup had the lowest scores in the cortical regions while the MM subgroup showed lower scores in the thalamus. Involvement of pulvinar and hockey stick sign were prevalent in MV2 subgroup. The cognitive-behavioral clinical phenotype was associated with a greater extent ($p = 0,01$) and hyperintensity ($p < 0,01$) of cortical lesions in respect to the ataxic phenotype, in which the subcortical lesion load was prominent. A positive correlation between the cortical lesion load and disease duration (signal intensity: $r = 0,60$; $p < 0,01$; lesion extent: $r = 0,47$; $p = 0,02$) and an inverse correlation between the extent of cortical ($p = 0,04$) and subcortical ($p = 0,05$) lesions and survival were found.

Discussion and conclusions: Our results suggest that MRI analysis for suspected CJD should analyze DWI-based images, observing all cortical regions including frontal lobes and excluding insula and cerebellum. Moreover, analysis of extension and degree of signal alterations in DWI provides information on the likely molecular subtype and also have prognostic value for survival.

Cortical thinning associated with mild cognitive impairment in Parkinson's disease

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Objective: Parkinson's disease (PD) is often associated to cognitive deficits. Aim of the study was to investigate patterns of cortical thinning associated with mild cognitive impairment (MCI) in PD and to explore relationships with cognitive deficits.

Methods: We studied 108 PD patients (54 without cognitive impairment [PD-ncog], and 54 with MCI [PD-MCI]), and 41 healthy controls. All subjects underwent structural magnetic resonance imaging (MRI) and clinical and neuropsychological evaluation. The cortical thickness analysis was performed on the 3D T1 weighted.

Results: Compared to PD-ncog and healthy controls, PD-MCI showed cortical thinning of superior temporal sulcus, inferior parietal, middle and superior temporal gyri bilaterally, as well as left frontal pole and supramarginal gyrus. Bilateral precentral gyri and left enthorinal cortex and superior frontal gyrus as well as right inferior frontal gyrus revealed reduced thickness only when PD-MCI were compared to controls. When compared to PD-ncog, PD-MCI showed additional cortical thinning of the postcentral gyri bilaterally. PD-ncog did not show differences relative to controls. Lower scores on global cognition tasks were associated with widespread cortical thinning. Cortical thinning of fronto-temporo-parietal regions was correlated to lower executive and visual spatial scores.

Conclusions: Our results demonstrate that MCI in PD has a neuroanatomical substrate of cortical thinning which correlates with performance in neuropsychological evaluation. The atrophy pattern identified in this study might be used as a surrogate marker of cognitive impairment in nondemented PD.

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From Parkinson's disease to dementing α-synucleinopathies: subcortical "matter"

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Introduction: α-synucleinopathies, such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB), are characterized by an ascending

accumulation of α-synuclein extending from brainstem structures to the neocortex. Clinically, PD and DLB are clearly distinguished, while discrimination between Parkinson dementia (PDD) and DLB can be subtle and actually based on temporal relationship between motor and cognitive symptoms. Study of subcortical structures with MRI techniques could provide in-vivo information on the spread of pathology among these different clinical conditions.

Objectives: To explore the patterns of atrophy at the subcortical level in PD, PDD and DLB. In particular, we were interested in the markers of evolution from PD to PDD and in the discrimination between DLB and PDD.

Methods: 16 PD, 11 PDD and 16 DLB patients were recruited and underwent 1.5T MPRAGE MRI scanning. Segmentation of subcortical structures was performed with the fully-automated FMRIB's Integrated Registration and Segmentation Tool (FIRST) implemented in FSL. Then, volume and shape of each structure were compared between groups.

Results: PDD and DLB patients showed a global subcortical atrophy as compared to PD patients. When comparing PD to PDD, hippocampal atrophy was found to be the best predictor of dementia, while PDD and DLB were discriminated by overall normal pallidal volumes in PDD patients. Vertex analysis revealed specific shape differences in the involved structures.

Conclusions: Our results expand previous findings obtained with manual and automated segmentation of subcortical structures in PD, showing a widespread subcortical atrophy when dementia is overt. Moreover, it shows new radiological evidences that PDD and DLB could be two distinct entities in the spectrum of α-synucleinopathies.

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Atypical variant of Alzheimer disease with mismatching biomarkers of β-amyloid pathology: a case report

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Introduction: According to the model of dynamic biomarkers of Alzheimer pathology, amyloid Positron Emission Tomography (PET) and Cerebrospinal Fluid (CSF) biomarkers positivity can be regarded as nearly interchangeable early biomarkers of β-amyloid burden, so that they are expected to be positive at the same time in a patient with Alzheimer Disease (AD). Positive CSF values may precede amyloid PET, but the other way round has not been reported yet.

Case description: A 57-year-old man came to our attention with a 2-year history of progressive difficulties in everyday duties of his job (carelessness in ordinary tasks, poor concentration during work-overload periods in person with a meticulous premorbid personality), progressive apathy, motor inertia, which led him to resign. One year later, he developed a mild speech disorder, without impairment of the instrumental Activities of the Daily Living. Neither neurological examination nor MRI scan revealed remarkable findings. The neuropsychological assessment showed an impairment in executive functions. The clinical presentation was suggestive for a Frontotemporal Lobar Degeneration (FTLD) or for a frontal variant of AD (fvAD). A FluoroDeoxyglucose PET (FDG-PET) supported the diagnosis of FTLD, as a bilateral right prevalent frontotemporal hypometabolism was evident. CSF analysis showed normal levels of β-amyloid (1-42) Aβ42, very high levels of total-Tau protein t-Tau, high phosphorylated-Tau protein p-Tau and very high levels of β-amyloid (1-40) Aβ40. He also underwent a Florbetaben PET which revealed a massive cortical β-amyloid deposition, suggesting Alzheimer pathology.

Discussion: Our data showed a discrepancy between β-amyloid CSF values, which were normal, and a positive Florbetaben PET. To explain this discrepancy, a number of assumptions were made: 1) PET tracer could bind different types of A-β plaques, 2) a possible FTLD–AD comorbidity, 3) true AD clinically mimicking an FTLD. Using an algorithm

to differentiate AD from non-AD CSF profile (INNOTEST® Amyloid Tau Index (IATI)<0.8 and p-tau>50 pg/ml), a biochemical profile compatible with AD was found. Normal CSF Aβ42 level might be explained as an unusual case of basal higher production of β-amyloid (as confirmed by Aβ1-42/Aβ1-40 ratio <0.05); higher t-tau and p-tau levels might be a feature of atypical AD, as expression of greater neuronal degeneration and stronger aggressiveness of the disease.

Conclusion: This clinical case highlights the importance of imaging and biohumoral biomarkers in the differential diagnosis of unusual variants of AD, suggesting the need of better understanding the role and the relationships between β-amyloid biomarkers.

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Obesity as a risk factor in the early-stage of neurodegeneration: relation between body mass index and brain structure

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Objectives: The prevalence of being overweight and obesity is increasing worldwide and numerous longitudinal studies are linking this condition with higher risk of developing dementia, such as that due to Alzheimer's disease (AD). However, the mechanisms by which obesity may impact cognitive decline are not clearly explained and a better understanding of this association might elucidate the role of obesity as a risk factor for AD. The goal of this study was to explore whether using Body Mass Index (BMI), as a proxy of obesity, it is possible to clarify the pattern of associations with dementia risk by studying brain structure in the prodromal stage of AD.

Materials: A total of 15 Mild Cognitive Impairment (MCI) patients (8 overweight and 7 non-overweight) and 17 healthy older adults (10 overweight and 7 non-overweight) were included in this study. All participants underwent a complete neuropsychological assessment and brain MRI.

Method: Voxel-Based Morphometry analyses were carried out on three-dimensional T1-weighted scans to calculate the association between brain structure and BMI. Specifically, a full factorial model with all participants and between-sample t-tests were run to test the association in the entire cohort or in the sole MCI group.

Results: Lower grey matter volumes in the frontal and limbic lobes and in some cerebellar regions were found in the overweight MCI subgroup (BMI > 25). Specifically, a significant reduction of grey matter volumes ($p < 0.001$, FWE-corrected) was found in middle and superior frontal gyri, parahippocampal gyrus, culmen and cerebellar tonsil. Furthermore, this subgroup also showed significant white matter volumes reductions ($p < 0.05$, FWE-corrected) in fronto-temporal areas (e.g. middle and superior frontal gyri and fusiform gyrus).

Discussions and Conclusions: These changes in brain white matter and in regional grey matter volume highlighted a different patterns of associations in the subgroup of overweight MCI patients, highlighting the presence of interactive processes between the prodromal stage of AD and vascular burden due to excessive body mass.

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Intraventricular tumor presenting as progressive supranuclear palsy-like phenotype

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Objective: Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by early postural instability with falls, supranuclear ophthalmoplegia, parkinsonism with axial rigidity and frontal dementia [1]. However, PSP-like phenotypes secondary to vascular injuries, paraneoplastic syndromes, toxic factors, or infectious diseases have been reported [2,3].

Materials and Methods: Here, we report a case of a 70 years-old woman with a 2-years history of postural instability, spontaneous falls and vertical supranuclear gaze palsy.

Results: Brain MR imaging showed midbrain compression and dislocation due to a large tumor in the left lateral ventricle. DAT SPECT imaging revealed normal striatal dopamine transporter binding.

Conclusions: Midbrain compression by an intraventricular mass should be considered as a rare determinant of a PSP-like phenotype.

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APOE polymorphism induces different clinical presentations and different brain metabolic patterns in Alzheimer's disease

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Objectives: Several genes have been implicated in influencing Alzheimer's disease (AD). APOE E4 allele increases the risk of AD and lowers the age of disease onset, but alone is neither necessary nor sufficient for the development of AD. Several reports demonstrate that E4 variant associates with a faster cognitive decline and a greater cerebral atrophy in AD, suggesting a key role of this polymorphism in delineating different disease course. To better understand the effect of APOE polymorphism on the brain functional impairment in AD we investigated, through18F-fluorodeoxyglucose positron emission tomography (FDG-PET), whether different brain regions glucose consumption rates (GCr) were observed within different AD patients divided by APOE variants (E2, E3, E4) and between AD APOE patients and healthy subjects (HS). Furthermore we analyzed the neuropsychological profiles of AD patients divided by APOE variants.

Materials: PET to assess FDG brain distribution. ELISA for determination of cerebro-spinal fluid (CSF) protein concentrations. Standardized cognitive neuropsychological battery. Methods. One-hundred-forty AD patients underwent lumbar puncture for CSF analysis, APOE polymorphism analysis, neuropsychological evaluation and FDG-PET. Fifty-eight HS underwent FDG-PET.

Results: As compared to HS, E4 AD showed a significant reduction of GCr in a wide cortical area involving left and right limbic, left parietal and frontal regions, while E3 AD showed a limited reduction of GCr in the right parietal cortex/precuneus. Moreover E2 AD showed a wide reduction of GCr that involve the temporal and parietal cortex as compared to HS. Within AD patients we found a reduction of GCr in the left frontal lobe comparing E4 to E2 while no differences were found when comparing E3 to E2. Comparing to E4, E3 AD showed a significant reduction of GCr in right parietal lobe/precuneus. No difference was found in CSF biomarkers profile within the APOE variants group. Neuropsychological evaluation showed significant differences only in memory assessment when comparing E2 to E3 and E2 to E4, with E2 AD patients having better performances.

Discussion: These results demonstrate that AD patients exhibit different patterns of brain glucose metabolism with a wide cortical involvement for E4 and a selective right parietal/precuneus involvement for E3 patients. No difference was found in CSF biomarkers profile within APOE variants, while the neuropsychological assessment showed less impairment of memory functions in E2 AD group.

Conclusions: APOE polymorphism drives different patterns of cortical metabolic activity and clinical presentation. These findings could be of interest for future pharmacological treatment strategies.

Gender-related biomarkers in Alzheimer's disease

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Objective: Alzheimer's Disease is more prevalent in women than in men. Women getting AD also demonstrate greater cognitive declines compared with men. This even includes verbal skills that are stronger in healthy females compared with males. These conditions suggest that there may be important sex differences also among the possible biomarkers for AD, more specific in women or in men and that their discovery is important not only for the diagnosis and progession of disease, but also when studying the pathways involved in AD pathology. The aim of this study was to analyze some biomarkers focusing on possible differences between men and women.

Materials: This study enrolled 734 subjects including subjects diagnosed with AD ($n=338$), MCI ($n=181$) and healthy controls ($n=215$).

Methods: After obtaining informed consent, blood samples were taken from patients and control subjects. Genomic DNA was extracted from peripheral blood leukocytes. Genetic analysis was performed using Direct sequencing by DNA sequencer Beckman CEQ 8000. Plasma levels of PGRN were measured, using an ELISA kit according to manufacturer's instructions.

Results: We carried out a genetic analysis on SORL1 gene in rs641120, rs1010159 and rs641120 SNPs in AD, MCI and healthy controls. SNP rs641120 is associated with MCI progressing but only in men sub-sample, as observed by the comparison of both genotype and allelic frequencies between progressing and stable MCI. Moreover, we evaluated progranulin (PGRN) in plasma samples, finding higher levels in females compared to males; furthermore, in AD patients, a positive correlation between PGRN levels and age was observed in females.

Discussion: Currently, some authors found a significant interaction between sex and biomarkers associated to Aβ42 and total tau on longitudinal hippocampal atrophy, longitudinal decline in memory and executive function. Moreover, the Alzheimer's Disease Neuroimaging Initiative (ADNI) program described that plasma leptin values in men were approximately half those of women in MCI and AD. Our data on biochemical and genetic biomarkers confirm the existence of sex dependent differences in AD patients. This leads us to consider that a more thorough study of sex differences in the functional, cognitive, and neural changes that occur across the AD spectrum is needed.

Conclusions: The attention on sex-specific differences might improve the use of biomarkers and enhance the understanding of the physiological differences between men and women in AD.

Neural correlates of frailty in behavioral variant frontotemporal dementia

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Background & Objectives: Frailty is a common clinical syndrome in older adults and carries an increased risk for poor health outcomes, incident disability, hospitalization, and mortality. There is a complex relationship between frailty and dementia. Population studies have shown that increasing frailty is associated with incident Alzheimer's disease (AD), vascular dementia, nonAD dementias, and the rate of cognitive decline [1]. In patients with dementia, frailty may be a predictor of disability as well as

a long-term predictor of mortality. At present, neurobiological mechanisms underlying frailty in patients with dementia have been scarcely investigated. The objective of this study was to investigate the neural correlates of frailty in patients with the behavioral variant of Frontotemporal Dementia (bvFTD).

Material & Methods: Eighteen bvFTD patients (7 men, 11 women; mean age ± SD: 67.0 ± 9.2 yrs), attending the Memory Clinic of the Department of Neuroscience of the University of Torino, were selected for the study. Diagnosis was made according to the International Behavioral Variant FTD Consortium Criteria [2]. Patients underwent extensive clinical, neuropsychological, and neuroradiological (including brain structural MRI and 18FDG-PET) investigations. The clinical diagnosis was supported by CSF biomarkers. A group of 18 healthy subjects (11 men, 7 women; mean age ± SD: 64.5 ± 8.6 yrs) served as controls. Frailty was assessed using the Multidimensional Prognostic Index (MPI), a cumulative index derived from a standardized comprehensive geriatric assessment [3]. Voxel-based statistical analyses of both MRI and FDG-PET data were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) running on MATLAB 7.5 environment. SPSS 21 was used for all additional statistical analyses.

Results: MPI scores were significantly increased in bvFTD patients when compared with controls ($p<0.01$). A significant correlation between MPI scores and gray matter reduction in the left Superior Frontal gyrus, left Orbital Frontal gyrus, left Inferior Frontal gyrus, and left Superior Temporal gyrus was found ($p<0.001$ and $p<0.002$). In addition, a significant correlation between reduction in cerebral metabolic rate of glucose consumption and frailty scores was found in the left Insula, and left Superior Frontal gyrus ($p<0.001$).

Discussion & Conclusions: Our study shows that, in patients with bvFTD, there is a significant correlation between functional and structural impairment of different regions of the Salience Network, like left frontal, insular and temporal regions, and a comprehensive frailty index. Further studies are needed to explore clinical relevance of our data.

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A new [18F]FDG-PET molecular approach for the study of connectomics in Parkinson's disease

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Idiopathic Parkinson's Disease (iPD) is a neurodegenerative movement disorder, characterized by progressive loss of nigral dopaminergic neurons and abnormal accumulation of α-synuclein. Projections to the striatum are affected, but synaptic dysfunction is thought to propagate to other brain regions, damaging motor and cognitive systems. The heterogeneous events contributing to synaptic dysfunction can be captured *in vivo* by [18F]FDG-PET. 36 iPD patients (age=64.63±10.74; disease duration=5.27±3.14) and 36 age-matched healthy controls (HC) (age=64.75±10.70) were included. Using sparse inverse covariance estimation [1] and graph-theory on brain metabolism measures, we performed 1.whole-brain, 2.anatomically-restricted and 3.functional networks analyses. Anatomically-restricted analyses were conducted in the dopaminergic systems (nigrostriatal and mesolimbic) and on the basis of the spreading of α-synuclein pathology hypothesized by Braak [2]. Using interregional correlation analysis [3], we extracted functional networks belonging to motor and cognitive domains. 1. The whole-brain analysis showed alterations in the overall organization of iPD brain metabolic architecture in comparison to HC, with reduced short-range and increased long-range metabolic connectivity. The region undergoing the most relevant reconfigurations was the cerebellum, with a complete disruption of both short and long-range connectivity. Metabolic connectivity within striatal, thalamic and frontal regions also underwent reconfigurations. 2. The anatomically-restricted analyses

revealed that connectivity was mostly affected within structures affected by precocious α-synuclein accumulation, i.e. medulla, pons and midbrain, supporting *in vivo* Braak's staging hypothesis. Nigrostriatal dopaminergic system showed a diffuse metabolic connectivity impairment. The mesolimbic system was disorganized as well, in particular the connections between ventral striatum, orbitofrontal cortex and amygdala, suggesting that this dopaminergic pathway is also affected and dysfunctional early in iPD. 3.Functional networks analysis showed alterations in the default mode network and in the subcortical components of executive and sensorimotor networks. This new perspective in network-oriented and pathology-based analysis showed that neurodegeneration in early iPD affects several brain metabolic networks at short and long distance, with specific vulnerability patterns reflecting spreading of neuropathology and specific neurotransmission system damage.

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Microstructural damage of the white matter in the frontal aslant tract account for visuo-spatial performances in patients with Alzheimer's disease

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Purpose: Constructional praxis relies on a network consisting of inferior parietal and pre-motor regions, and it is thought to require transformation of spatio-temporal representation (parietal regions) into movement sequences (pre-motor regions). The Frontal Aslant Tract (FAT) has been recently described as a bundle connecting the Broca's area to the Supplementary Motor Area (SMA) and to the pre-SMA in both hemispheres [1; 2]. The functional properties of this connection are currently unknown especially in dementia, such as Alzheimer's disease (AD). We aimed to explore the micro-structural integrity of the FAT in patients with AD and its potential relationship with cognitive functioning.

Materials and Methods: 23 patients with AD, and 25 healthy subjects (HS) were enrolled. All subjects underwent cognitive evaluation and MRI examination at 3T. MRI including diffusion sequences used for probabilistic tractography analysis. We reconstructed individual FAT bilaterally and assessed their micro-structural integrity by both mean fractional anisotropy (FA) value and by voxel-by-voxel analysis using SPM-8. Then, we used mean FA values for correlations with cognitive measures.

Results: There were no differences in demographic variables between groups. Both analysis on mean FA and voxel-wise analyses revealed that patients with AD showed decreased FA in the bilateral FAT respect to HS. In addition, we showed in AD patients positive association between bilateral FAT and tests assessing constructional praxis and visuo-spatial logical reasoning.

Discussion: The present results revealed a bilateral damage of FAT in patients with AD. Moreover, we found association between damage to the FAT and constructive abilities, and it fits well with the knowledge of a functional involvement of SMA and pre-SMA in the movement sequences required to successfully execute the constructive praxis task. We speculate that praxis tasks can be mediated by integrity of the FAT in patients with AD.

Conclusions: The FAT is an associative bundle critically involved the network sub serving the constructional praxis in patients with AD.

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Functional connectivity changes in MCI: a magnetoencephalography study

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Objectives: Finding a reliable, non-invasive and early biomarker for Alzheimer's disease (AD) is important to improve clinical management. Magnetoencephalography (MEG) is a neurophysiological technique detecting the magnetic fields generated by the neuronal activity. Previous findings suggest a reorganization of the brain network in AD. Aim of our work is to find reliable, objective and replicable network metrics to distinguish subject affected by mild cognitive impairment (MCI) from healthy controls.

Materials: We recruited 11 patients affected by MCI and 13 control healthy subjects that underwent a 5 minutes resting-state magnetoencephalographic recording.

Methods: The raw MEG signals underwent principal component analysis (PCA) and independent component analysis (ICA) to improve the signal to noise ratio. Ten clean epochs were bandpass filtered in the canonical frequency bands (delta, theta, alpha1, alpha2, beta, gamma). To assess functional connectivity we used the phase lag time, since it quantifies to what extent a given channel is leading of lagging other channels. An adjacency matrix, for each epoch in each frequency band, was obtained. The Minimum Spanning Tree (MST) was calculated for each adjacency matrix. Several network metrics were computed, and compared by permutation testing corrected for multiple comparison.

Results: Several MST metrics were found to be altered in the delta band. In detail, the tree hierarchy (Th) and the leaf fraction (L) were found to be higher in the MCI as compared to controls. The Th is a measure that captures the fine tuning of the network between a star–like conformation (where all the nodes are near to each other, but the whole network relies heavily on the central node) and a line–like network (that is less integrated but has a much lower risk of hub overload). The leaf fraction is the fraction of nodes that have degree (the number of links) equal to 1.

Discussion: These results suggest a compensative mechanism occurring in the early stages of the disease. It is possible to hypothesize that global measures (Th) might be able to identify early alterations of brain networks. The leaf fraction confirms that the change in hierarchy is driven by a global feature of the network rather than by changes in a specific area (since we failed to show any difference in centrality measures).

Conclusions: Although further studies are needed, our preliminary findings suggest a useful role of network theory applied to MEG analysis in discriminating patients with MCI from healthy subjects.

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Brain FDG-PET in mild cognitive impairment: a retrospective longitudinal study

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Background: Brain metabolism alteration represents one of the earlier neuroimaging biomarkers of dementia.

Aim: This study aimed to describe different FDG-PET patterns in a cohort of Mild Cognitive Impairment (MCI) patients, also exploring their prognostic value in the prodromal phase of dementia.

Methods: Seventy-four MCI patients underwent brain F18-FDG-PET and clinical and neuropsychological follow-up for about two years and a half.

Statistical comparisons of FDG-PET scans at baseline were compared between patients who convert to Alzheimer's type Dementia (MCI-AD) or to Fronto-Temporal Dementia (MCI-FTD) and those who remained Stable MCI.

Results: Compared with Stable MCI, MCI-AD patients had hypometabolism in the left middle and inferior temporal gyri and a suspected increased metabolism in the bilateral postcentral gyri, in the right precentral gyrus, insula and in the left lentiform nucleus. MCI-FTD showed hypometabolism in the right inferior, middle, superior frontal gyri and inferior, middle and superior temporal gyri. Compared with a group of matched controls, MCI-AD showed a hypometabolism in the left cingulate gyrus, the left cuneus, the left posterior cingulate and the left superior parietal lobule, whereas MCI-FTD exhibited a pattern of hipometabolism involving the caudate nucleus bilaterally, the superior frontal gyrus bilaterally, the cingulate gyrus bilaterally, the inferior frontal gyrus bilaterally, and in the left insula.

Discussion: Already in MCI patients, FDG-PET is able to detect specific patterns of hypometabolism among dementia subtypes, respectively involving posterior cingulate cortex and precuneus in AD and anterior frontal regions in FTD. Moreover, in the prodromal phase, compared with stable MCI, AD was characterized by temporal hypometabolic activity indicating synaptic dysfunction and by higher sub-cortical metabolic activity as possible expression of compensatory mechanisms, whereas FTD by hypometabolic frontal and temporal regions.

Conclusion: In MCI patients, FDG-PET is not only an excellent and early diagnostic biomarker, but also a good tool to describe neurobiological correlates of dementia subtypes in time.

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Diagnostic utility of [18F] Florbetaben PET and its concordance with amyloid-β1-42 in cerebrospinal fluid in patients with dementia

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Aims: Brain amyloid deposition is considered one of the main hallmark of Alzheimer's Disease (AD). Nowadays, two approaches are available for assessing AD pathology "*in vivo*": Aβ1-42 cerebrospinal fluid (CSF) levels and more recently amyloid load visualized by Amyloid beta Positron Emission Tomography imaging (Amy-PET) probes. Studies evaluating concordance between these two methods have provided conflicting results. Under specific conditions, Amy-PET may be of great clinical utility, especially in conflicting diagnosis. This study aimed to determine concordance between CSF and PET in detecting amyloid pathology. Moreover, we wanted to explore the impact of Amy-PET scan information on diagnostic confidence and clinical diagnosis.

Materials: We included 20 patients (age 67.55 ±9.75; 9 males, 11 females), 9 suspected for AD pathology and 11 suspected for not-AD pathology.

Methods: All patients underwent CSF analysis including Aβ1-42 dosage and Amy-PET with [18 F] Florbetaben. CSF biomarker was considered abnormal based on Aβ1-42 < 600 pg/ml. A semiquantitative visual scan assessment were used to quantify amyloid deposition in the brain. Brain Amyloid Plaque Load (BAPL) was rated as negative (BAPL 1 absence of amyloid) or positive (BAPL 2 and 3 presence of amyloid).

Results: Concordance between Amy-PET and CSF was 80%. In 2 out of 4 discordant cases, Amy-PET was positive and CSF Aβ1-42 levels were close to the cut-off. In 3 out of 4 discordant cases, Amy-PET was in accord with suspected clinical diagnosis. In the remaining case with positive Amy-PET and Aβ-1.42 high levels in the CSF, the patient had a concomitant mild normal pressure hydrocephalus. Considering Amy-PET results, clinical diagnosis

were changed in 2 out of 20 patients and diagnostic confidence increased in 16 out of 18.

Discussion: Our preliminary results shown a good concordance between CSF biomarker and Amy-PET in detecting brain amyloid load. In discordant cases, clinical diagnosis were more often in agreement with Amy-PET results. In suspected AD, Amy-PET could provide more evidences of AD pathology, especially when CSF levels are just above cut-off. In our experience, after a proper diagnostic work-up, Amy-PET significantly modifies clinical diagnosis only in few cases, but it can improve diagnostic accuracy and confidence.

Conclusions: CSF Aβ1-42 dosage and Amy-PET are both useful biomarkers to detect AD pathology. In selected patients, Amy-PET represents a good tool in the differential diagnosis of dementia.

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Hippocampal vascularization patterns: a high resolution 7T time-of-flight magnetic resonance angiography study

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Aims: Since Spielmayer and Uchimura studies, the hippocampal vascularization has been considered one of the possible main determinants involved in the hippocampal degeneration. The intrahippocampal vascular network has a sort of "vascular vulnerability" with a relative small number of capillary anastomoses and an inadequate ability to cope with hypoperfusion. Arterial vascularization of the hippocampus is dependent on the collateral branches of the posterior cerebral artery (PCA) and the anterior choroidal artery (AchA), but numerous variations have been described concerning the origin of hippocampal arteries. Currently, what we know on hippocampal vascularization is provided by autopsy studies. In these studies, different vascularization patterns have been detected post mortem. Using 7T TOF MRI image data, we wanted to detect "*in vivo*" hippocampal vascularization patterns, trying to compare our results with previous autopsy remarks.

Materials: 41 healthy subjects

Methods: All subjects underwent a 7T MRI scan, including a high resolution (isotropic resolution 0.28 mm) 7T TOF MRA sequence focused on the hippocampal area. 2D and 3D reconstructions were used, as well as a vessel representation by skeletons for diameter analysis. A distinction between posterior supply (PCA), mainly anterior supply (AchA) and mixed supply (PCA+AchA) was analyzed according to literature data. Moreover, we tried to detect the three different branching patterns of the PCA involved in hippocampal and temporo-mesial supply (Pattern 1: temporal branches; Pattern 2: temporal branches+anterior hippocampal artery; Pattern 3: common trunk).

Results: In 79 out of 82 hemispheres it was possible to detect the three distinct PCA patterns (Pattern 1: 54%, Pattern 2: 22%, Pattern 3: 24%). In 62 out of 82 hemispheres we was able to describe the different hippocampal supply based on only PCA supply (45%), mainly AchA supply (5%) and mixed supply (50%). The distribution of vascularization patterns shown a very good concordance with post mortem data. We also found a close relationship between PCA patterns and hippocampal patterns, and differences in the left-right distribution among different patterns.

Discussion: For our knowledge, it's the first time that it was possible to describe "*in vivo*" hippocampal vascularization patterns. While taking into account MRI spatial resolution limits, the good concordance with neurosurgical data seems to confirm the accuracy of our classification.

Conclusions: The possibility to compare "*in vivo*" individual differences in hippocampal vascularization with perfusion and clinical data may represent an important first step to better clarify the relationship between vascular and degenerative pathology. Moreover, our results may provide further information about hippocampal angiographic patterns and their distribution to other research areas like training effects and cognition.

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Progressive choroidal thickness attenuation in patients with Alzheimer's disease: results from a 12-months prospective study

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Objectives: To compare the 12-month choroidal thickness (CT) change between Alzheimer's disease (AD) patients and normal subjects.

Materials and Methods: In this prospective, observational case series, 23 patients with a diagnosis of mild to moderate AD and 23 age-matched control subjects were included. All the subjects underwent neuropsychological (MMSE, ADAS-Cog and CDR) and ophthalmological evaluation, including spectral domain optical coherence tomography (SD-OCT), at baseline and after 12 months. Choroidal thickness was measured manually using the caliper tool of the OCT device.

Results: The cut-off value of baseline subfoveal choroidal thickness to discriminate AD from controls was 222 microns, with 83% sensitivity and 78% specificity. After 12 months, AD patients had a greater reduction of choroidal thickness than controls ($p \leq 0.01$, adjusted for baseline choroidal thickness, age, gender, axial length, and smoking). Patients with thinner choroid at baseline also had lower MMSE score at 12 months (B=0.088, $p<0.0001$).

Discussion: In a precedent cross-sectional study we demonstrated a significant reduction of choroidal thickness in AD1. In this study we demonstrated that AD patients showed a significant reduction in choroidal thickness over time. Furthermore, we showed that baseline choroidal thickness was a significant predictive factor for patients' cognitive decline at follow-up.

Conclusions: Choroidal thinning observed in AD might be related to a series of pathologic events triggered by local Aβ deposition. Our data suggest that repeated measures of choroidal thickness could be a useful marker of the disease progression over time. Further investigations are needed to establish the diagnostic and prognostic role of OCT analysis of the choroid in appropriate prospective comparative studies of larger patient populations.

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

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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: To investigate whether the presence of VH in DLB is associated with microstructural changes of the white matter tracts studied with diffusion tensor imaging (DTI) MRI sequences, and if is related with cortical grey matter damage atrophy.

Methods: 30 DLB patients, 12 with VH (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), 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). Cortical thickness (CT) analysis was performed with Freesurfer and QDEC application was used to individuate statistically significant differences among cortical regions. Results were

corrected for multiple comparisons by using a pre-cached cluster-wise Monte-Carlo Simulation and mapped on the surface. Significance level was set at p corrected<0.05.

Results: The DLB VH+ group had significantly decreased FA and increased MD values in the right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus compared to VH- group. Radial diffusivity values were significantly increased in all the major WM fasciculi and in the body of the corpus callosum in VH+ patients. An increased MD values in the right inferior longitudinal fasciculus, superior longitudinal fasciculus in patients with DLB VH+ correlated with scores on test exploring visual attention. No differences in diffusivity and FA values have been found between DLB and AD patients. CT analysis shows gray matter damage bilaterally in fronto-temporo-parietal regions.

Discussion: This study was the first to explore diffusivity and FA values in the whole white matter in DLB patients with VH. The findings of diffuse microstructural alterations of white matter particularly in the right hemisphere in VH+ patients, and its correlations with visual attentional performances may give insight into the physiopathology of VH genesis.

Cognitive and functional metabolic profiles in primary progressive aphasia variants

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Background and Objective: Primary Progressive Aphasia (PPA) represents a heterogeneous group of neurodegenerative conditions in which language impairment is the main symptom at onset and remains the prominent clinical feature during the following years of disease. Three main variants exist: the semantic (sv-PPA), the non fluent/agrammatic (nfv-PPA), and the logopenic/phonologic (lv-PPA). In this study, we aimed at investigating the different cognitive profiles and FDG-PET hypometabolic patterns in PPAs series with aim to provide a comprehensive view on the cognitive-functional correlates in the three variants, paying attention also to case-to-case variability. Since the clinical picture may be confounding in the early disease phases, the supportive diagnostic role of a functional biomarker, such as FDG-PET imaging, at the individual level can be fundamental.

Material and Methods: 48 PPA patients (i.e., 11 sv-PPA, 19 nfv-PPA and 18 lv-PPA) were included. The nfv-PPA group included pure nfv-PPA cases ($n=8$) as well as combined cases with atypical parkinsonism ($n=11$). Neuropsychological information as well as FDG-PET scans were acquired at close time. FDG-PET data were analysed using an optimized voxel-based SPM method at the single-subject level. Second-level group analysis was performed to evaluate commonalities in brain metabolic patterns.

Results: Different language profiles characterized the PPA variants. Different scores on naming and oral comprehension (sv-PPA<nfv-PPA, sv-PPA<lv-PPA), as well as repetition (nfv-PPA<sv-PPA, lv-PPA<sv-PPA) were found in the PPA groups. No significant difference emerged at the verbal fluencies and Token test. Deficits in non-language domains (i.e., short-term memory, attention, executive functions, and visuo-spatial abilities) were evident only in nfv-PPA and lv-PPA groups. Different patterns of brain hypometabolism characterized at the single-subject level analysis each variant with specific regional dysfunctions. Namely, the temporal poles in sv-PPA cases, and the inferior parietal and precuneus often bilaterally in the lv-PPA cases, the inferior frontal gyrus, insula and perisylvian cortex in nfv-PPA patients. Whole brain group analyses on PPA variants confirmed the patterns of brain hypometabolism characterizing each variant in agreement with literature reports.

Discussion and Conclusion: The study highlighted the distinctive cognitive and functional features of the three PPA variants at the single subject level, adding novel evidence to current literature mainly limited to MRI studies in group analysis distinguishing the PPA variants. Our data provide first evidence for the utility of the FDG-PET SPM single-subject analysis to support early differential diagnosis of PPAs.

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Intracranial arterial dolichoectasia: a new disease entity?

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Objectives: Intracranial arterial dolichoectasia (IADE) may be detected by neuroimaging and be associated with extracranial arterial abnormalities of which neurologists may be unaware [1]. Some evidence suggests a possible association with cerebral small vessel disease (SVD) [2]. Our aims were to identify patients with IADE and describe: clinical and neuroimaging SVD-related features; the possible coexistence of extracranial arteriopathy.

Materials and methods: Starting from December 2014, we prospectively identified IADE patients among those attending the Florence VAS-COG Clinic and Stroke Unit of our Hospital. If IADE was identified, we assessed: familiar and clinical history, with particular focus on stroke and vascular risk factor profile; neuropsychological performances; brain MRI, with visual rating of SVD features, including white matter hyperintensities (WMH, Fazekas scale), count of lacunar infarcts, enlarged perivascular spaces, and, if T2* gradient-echo sequences were available, count of microbleeds. Each patient underwent a neck, thoraco-abdominal aorta, and lower limbs CT angiography, according to a predefined protocol.

Results: IADE was detected in 5 patients by means of neuroimaging performed for ischemic stroke (4 patients) or cognitive impairment (1 patient). All were males, with a mean age of 73 years; none were current smokers, 4 had hypertension, 1 had diabetes, 2 had hypercholesterolemia, and 2 had a history of myocardial infarction. All patients had dolichoectasia of the basilar artery, 1 also with middle cerebral arteries ectasia, and 1 with carotid siphons and middle cerebral artery involvement. Functional and cognitive performances were normal in 1 and abnormal in 4 patients; 2 patients had mild cognitive impairment and 2 had dementia. On brain MRI, all patients had WMH (mild in 1, moderate in 2, severe in 2 patients), at least one lacunar infarct, and dilated perivascular spaces. At least one microbleed was detected in 3 out of 3 patients with available dedicated MRI sequences. Based on extracranial CT angiography, 2 patients had abdominal aortic and iliac ectasias, 2 had both thoracic and abdominal aortic ectasias, 1 did not have any enlargement.

Discussion: Preliminary data from this small group of IADE patients confirm the possible association with cerebral SVD. Systemic arterial abnormalities may coexist and deserve consideration by neurologists.

Conclusions: These data are in line with the current hypothesis that IADE should be considered as a disease entity, different from atherosclerosis, in which the involvement of the brain-supplying arteries may be only part of a systemic arteriopathy [3]. The relationship with cerebral SVD needs further evaluation.

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The network signature of cognitive efficiency in Alzheimer's disease

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Cognitive efficiency refers to the maximisation of performance obtained by minimising the use of metabolic resources. This construct has been widely studied in healthy adulthood but it has never been investigated in patients suffering from Alzheimer's disease (AD), a condition which down-regulates the processes of neural plasticity and renders the brain progressively inefficient. Although most cognitive functions are subjected to inexorable decline, there are some cognitive domains in which, very often, patients with clinically-established AD dementia show performance levels within the range of normality. This is the case of the Letter Fluency test, a task of linguistic and executive abilities which is mainly sustained by left posterior prefrontal regions, areas relatively spared by AD pathology during the prodromal stages of the disease. In this study we investigated the network peculiarities of AD patients who show high levels of performance on this test, to clarify how the neural systems maintain efficiency after the onset of neurodegeneration. Ninety participants (45 patients in the prodromal stages of AD and 45 healthy controls, matched for demographics at a group level) had resting-state functional MRI. Of the list of neuropsychological tests included in an extensive battery administered to each participant, the Letter Fluency test was the sole measure not showing any significant group difference. A median split carried out on the entire cohort served to separate high-performing from low-performing participants. Dual regression procedures were implemented to extract the maps of functional connectivity of task-negative, task-positive, and control networks. Factorial ANOVAs were then modelled to test the interaction between diagnostic group and performance level. Specifically, we inferred the contrast by which the connectivity of high-performing patients supersedes that of low-performing patients, net of the same difference seen in healthy adults. An effect of the interaction was found in the anterior default mode network and in the two fronto-parietal circuits. As confirmed by post-hoc t t-tests, in all these three maps enhanced connectivity was prevalently found in the peristriate areas of high-performing patients. In AD, cognitive efficiency is pursued in association with increased network connectivity within both task-negative and task-positive networks. Although the occipital lobe is not normally part of these circuits, its involvement can be interpreted as a plastic attempt to exploit regions of the brain not severely affected by AD, and located within synaptic reach to remould the patterns of functional connectivity in support of optimal cognitive performance.

Cortical activation during levitation and tentacular movements of corticobasal syndrome

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Introduction: Corticobasal Syndrome (CBS) is a term coined to indicate the presence of predominant progressive asymmetric rigidity and apraxia, which may be due to different underlying pathologies, including Corticobasal Degeneration (CBD), Alzheimer, Frontotemporal lobar, Progressive Supranuclear Palsy and prion diseases [1]. CBS is mostly seen with asymmetric brain atrophy [2]. Alien Hand (AH) is listed among possible symptoms of CBS [2], in the recent revision of criteria for the diagnosis of CBS and CBD1, yet "what behaviors constitute alien limb phenomena remains a matter of debate". Levitation and tentacular movements (LTM) are considered specific, yet rare (30%) [1], features of Corticobasal Syndrome, and are erroneously classified as alien hand.

Objectives: Our study focuses on these typical involuntary movements and aims to highlight possible neural correlates. LTM were recognizable during functional Magnetic Resonance Imaging (fMRI) in four CBS patients. FMRI activity was evaluated during rest and during voluntary movements (VM), consisting of voluntary levitation and finger wriggling. FMRI acquisition blocks were balanced in order to match LTM blocks with rest and VM conditions.

Results: Despite variable intensity and range of involuntary movements, evidenced by videos, fMRI

showed, during LTM, a significant ($p<0.05$) activation only of the contralateral primary motor cortex (M1).

Discussion: Voluntary movements of the affected and unaffected arm elicited the known network including frontal, supplementary, sensory-motor cortex and cerebellum. Willed movements of the LTM-affected arm induced higher and wider activation of contralateral M1 compared to the unaffected arm.

Conclusion: The isolated activation of M1 suggests that LTM is a cortical disinhibition symptom, not involving a network. Higher activation of M1 during VM confirms that M1 excitability changes occur in CBS. Our study calls attention to the necessity to separate LTM from other alien hand phenomena.

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Identification of incident dementia with a case passive follow-up in a cohort of 1693 subjects in Northern Italy: reliability of a classification algorithm querying the health information system

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Objectives: Health Informative Systems constitute a powerful resource to produce epidemiological results from large scale population-based studies.

Scientific literature reports an increasing number of studies investigating through their use different health outcomes. Aim of this study was to evaluate the reliability of an algorithm in identifying Dementia cases from Health Information System of ASL-Mi1 (HIS-Mi1) by comparing the observed incidence with the expected in the general European population (EuroDem).

Materials and Methods: A cohort of 1693 persons living in the north-west area of Milano was recruited in 1991-1995 and screened in a baseline visit. The mean age at enrollment was 56.6 years. After twenty years, administrative data were queried by means of an algorithm addressed to identify Dementia cases newly diagnosed. The fiscal code was used as key for each subject of the original cohort in a deterministic record linkage with the HIS-Mi1. Incident Dementia was defined in case of retrieval of i) diagnosis coded ICD9-CM=3310, ICD9-CM=290-2909, ICD10-CM=G30-G309 or ICD10=F00-F03 from the Hospital Discharge Registry or the Mortality Registry, ii) two consecutive drug prescription coded ATC N06D from the Pharmaceutical Prescription Registry, iii) payment exemption. The date of Dementia was established as the first occurrence of any of the previous conditions.

Results: Out of the 1693 subjects, the procedure identified 1604 persons; this cohort contributed 20,034 p-y to passive follow-up. The observed incident Dementias were lower than expected from the EuroDem study (73 vs 90) with an overall incidence rate (IR) of 3.7 x 1,000 p-y in people aged 60 or more. When comparing age-specific IR with the expected, we found dissimilar results for the ages of more than 80 years, while the IR were consistent for the ages 60-64 (1.2 vs 1), 65-69 (1.3 vs 1,1), 70-74 (3.0 vs 2.7) and 75-79 (9.3 vs 9.7).

Discussion: The performance of this algorithm should be validated through direct observation in a random sample of this cohort or in other similar cohorts, since misclassification may have occurred. The discrepancy in the incident rates for the older ages might be explained by under-reporting issues due the occurrence of other severe comorbidities. However our results are consistent with the expected for the ages 60-79 years, suggesting that the use of this procedure can be reliable when investigating these categories of age.

Conclusions: Administrative data are a valid resource to conduct large epidemiological studies and reliable results can be obtained with a dramatic cost reduction.

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Reversible dementia: neuropsychological and neuroradiological picture of a case of anti-NMDA-receptor encephalitis

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Aims: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a paraneoplastic syndrome that mainly affects young women. There are few reports concerning detailed neuropsychological profile during the disease and long-term cognitive outcome. The aim of this report is to describe neuropsychological and neuroradiological features and time course of a case of NMDAR encephalitis

Materials: We report a case of NMDAR encephalitis involving a 31-years-old female who exhibited a severe acute short-term episodic memory impairment and neuropsychiatric symptoms.

Methods: A detailed diagnostic work-up including complete clinical and laboratory examinations, neuropsychological assessment and neuroradiological investigation has been done at the onset and during follow-up immediately after surgical treatment and one month later.

Results: Neuropsychological evaluation revealed a global cognitive impairment characterized by pathological performances in immediate and delayed verbal memory, visuo-spatial memory, visual naming, semantic verbal fluency and verbal working memory. A brain 3T-MRI showed abnormal hyperintense signals on fluid-attenuated inversion recovery (FLAIR) sequences, asymmetrically involving the medial region of the temporal lobes which were suggestive for limbic encephalitis. An abdominal CT scan revealed the presence of an ovarian teratoma. The cognitive impairment and neuroradiological findings reversed after medical (intravenous steroids and immunoglobulins) and surgical treatment (annessiectomy). The definitive histological examination revealed a low-grade immature ovarian teratoma. Antibodies directed against NMDAR were detected in serum and in cerebrospinal fluid.

Discussion: The present report supports the central role of NMDARs in several neurological functions such as learning and memory acquisition and consolidation.

Conclusion: This study underlines the possibility of a rapid and complete clinical, neuropsychological and neuroradiological recovery when the disease is promptly diagnosed and treated.

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A structured group-based cognitive rehabilitation program for executive dysfunction

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Objective: The aim of this study was to evaluate the effects of a brief and structured group-based cognitive rehabilitation program in patients with executive dysfunction of different etiologies.

Materials: The rehabilitation program combined Goal Management Training (GMT), psychoeducation and cognitive training of attention. It lasted 6 sessions and was administered once week during a consecutive 6-weeks period. Each session lasted 90 minutes and was divided into a psycho-education phase, a modified GMT phase and a cognitive training phase. The GMT procedure was derived from the one described by Levine and colleagues [1], adapted to our patients difficulties and needs. Psycho-education was centered on problems related to attention and executive functioning in daily living and coping strategies for these situations. Cognitive training was focused on attention. Inclusion criteria were subjective complaints suggesting poor executive functioning and impaired performances in at least two tests sensitive to frontal lobe dysfunction. Exclusion criteria were presence of dementia and/or

major psychiatric disorders. Seven consecutive patients were so recruited.

Methods: Before and after the treatment the patients were assessed using a series of standardized neuropsychological tests, an everyday paper-and-pencil task (two parallel versions) and questionnaires for deficit awareness, anxiety and depression symptoms. Mean raw scores of tests and scales before and after the treatment were compared using Wilcoxon signed-rank test.

Results: The comparison of patients performances as a group before and after the treatment revealed statistically significant differences ($p<0.05$) in the everyday paper-and-pencil task and in several attention and executive functions tests but not in memory measures. Significant differences were also found in the Self Awareness of Deficit Index, State Trait Anxiety Inventory, and Beck Depression Inventory.

Discussion: After the treatment the patients showed a better performance on attention and executive measures. We also found evidence of improvement in deficit awareness, which is considered the most important prognostic index for a successful rehabilitation [2]. Finally, our patients showed amelioration of anxiety and depression symptoms, confirming the influence of cognitive training on emotional states, as previously reported [3].

Conclusions: Our study supports the issue that the combination of Goal Management Training, psychoeducation and cognitive training may improve cognitive performance, deficit awareness and psychological status in patients with executive dysfunction of various etiology, even in a relatively brief intervention. The present study highlights the importance of non-pharmacological strategies in the treatment of neurocognitive disorders.

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Metabolic correlates of free and cued selective reminding test (FCRST) in prodromal AD and mild behavioral variant of FTD

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Aim: The Free and Cued Selective Reminding Test (FCRST) could be particularly useful to evaluate episodic memory in prodromal AD (pAD) because it both controls the encoding and facilitates the recall task through semantic cues. However, a non-negligible part of patients with FTD overlapped AD dementia patients in a recent study (Bertoux et al., 2014) which may reduce the FCRST accuracy in AD versus other dementia. We evaluated whether the FCRST is able to discriminate between pAD and very mild bvFTD and furthermore assessed its brain metabolic correlates in each patient group.

Material and Methods: Forty-three pAD patients (age:75.6±4.9; MMSE score:25.3±2.9; education:9.9±4.1) and thirteen very mild bvFTD patients (age:73.6±8.9; MMSE score:24.1±2.8; education:8.3±3.6) underwent neuropsychological evaluation and 18F-FDG-PET. The scores derived from the FCSRT (Girtler et al., 2015) and 18F-FDG-PET data were compared between groups. Furthermore, 18F-FDG-PET was correlated with the FCRST scores in each group.

Results: As compared to bvFTD, pAD showed significantly lower FCRST index scores ($p<.007$), the Facilitation Index (FI; $p<.001$) and the Delayed Total Recall (DTR $p<.0001$) scores being the most significant indexes. The ROC curves of FI and DTR between pAD and bvFTD groups yielded an AUC (FI)=.777 and an AUC (DTR)=.857, respectively. Sensitivity and specificity were 60% and 92% for FI (mean accuracy=66.1%), and 74% and 84% for DTR (mean accuracy=77.7%). In pAD, FI was positively correlated with brain metabolism in bilateral mesial and orbito-frontal cortex ('frontal VROI') while TDR was positively correlated with metabolism in left medial temporal cortex ('temporal

VROI', including parahippocampal gyrus and uncus) (SPM8, uncorrected $p<.001$ at voxel level, $p<.05$ FDR-corrected at cluster level; nuisance: age, education). In bvFTD, FI and DTR did not reach statistical significance. The frontal VROI (normalized to global uptake) showed a higher metabolism ($p<.006$) in pAD compared with bvFTD while the temporal VROI showed a lower metabolism ($p<.024$) in pAD versus bvFTD.

Discussion and Conclusion: The FCSRT has a good specificity in differentiation between AD and bvFTD already at the early stages, although FI sensitivity is limited. Brain metabolism in mesial and orbito-frontal cortex appears as the pathophysiological basis of FI failure in pAD, highlighting the role of these frontal cortices in the semantic facilitation phenomenon. More intriguingly, impairment of DTR is significantly dependent on left hippocampal/parahippocampal metabolic levels, thus being a possible probe of the mesiotemporal functional failure in pAD. Accuracy of FCSRT in pAD versus other neurodegenerative disease remains to be investigated.

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Reversion from mild cognitive impairment to normal cognition: a systematic review of literature and meta-analysis

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Objectives: Despite its clinical and scientific relevance, the reversion of mild cognitive impairment (MCI) to normal cognition (NC) has to date attracted limited attention, and there are no conclusive data concerning the rate of its occurrence. The aim of the present study was to systematically review, discuss, and meta-analyze data coming from longitudinal studies on MCI with the purpose of retrieving more precise estimates concerning the proportion of subjects reverting to NC.

Materials and methods: We performed a systematic review, using PubMed, the Cochrane Library, and the ISI Web of Science databases, of all the longitudinal studies on MCI published from 1999 (year of the first MCI operationalization) up to October 2015. Only articles in English language were retained. After a first screening based on title and abstract, the remaining articles were singularly assessed based on the following inclusion criteria: 1) longitudinal design; 2) follow-up longer than 2 years; 3) enrolling subjects with MCI; and 4) reporting the number or percentage of subjects exhibiting a reversion to NC. Study quality was assed through the QUIPS tool. Both data extraction and critical appraisal of studies were independently performed by 2 couples of Authors. Meta-analysis was carried out using Metaprop. Subgroup analyses were conducted considering the following factors (where available): setting; length of follow-up; and mean age of MCI participants at baseline.

Results: A total of 2,338 articles were examined, leading to the final inclusion of 25 studies. The quality of included studies resulted moderate. We observed an overall MCI reversion rate of 18% (95% Cis 14-22), with a relatively high heterogeneity across studies (I2 96.1%, $p=0.000$). Estimates were relevantly affected by study setting, with an 8% (95% CIs 4-11) reversion rate in clinical-based studies and a 25% (95% CIs 19-30) rate in population-based studies (after excluding 2 outliers). Length of follow-up and mean age of participants did not substantially influence the observed rates.

Discussion and Conclusion: To our knowledge, this is the first attempt to systematically review, discuss, and meta-analyze available evidence concerning the reversion of MCI to NC. Based on our findings, reversion to normality is a common trajectory among MCI populations, with an overall estimated rate of 18%. That is, nearly one out of five

subjects with MCI exhibits a complete remission of cognitive symptoms and deficits over time. These findings impose extreme caution and require a more balanced view when approaching the MCI construct, both in clinical and research contexts.

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Socio-demographic and clinical modifications over time of subjects evaluated for cognitive disturbances in a memory clinic between 2002 and 2014

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Objectives: The adoption of preventive strategies against age-related pathological conditions is repeatedly solicited. In particular, in recent years, the concepts of "prevention" and "early diagnosis" have been growingly discussed and explored in the field of cognitive disorders, as confirmed by the recent operationalization of conditions based on subjective complaints. Such increased attention to cognitive disturbances and neurodegenerative conditions may constitute a key step for achieving early/timely diagnosis of dementing illnesses. In fact, raising awareness in the general population about the nature of diseases and empowering individuals for the detection of preliminary signs/symptoms is crucial for targeting the early stages of the condition of interest. However, prevention may also generate some issues to be acknowledged by healthcare systems. For example, an excessive use of medical and diagnostic resources may occur in informed persons undergoing screening procedures. In this report, we present exploratory analyses aimed at investigating the socio-demographic and clinical changes over time of all the individuals who have been cognitively assessed in a Memory Clinic between 2002 and 2014.

Material and methods: We retrospectively reviewed the clinical charts of all subjects undergoing a neurological and neuropsychological assessment at the Memory Clinic of the Department of Neurology and Psychiatry, "Sapienza" University (Rome, Italy) between 2002 and 2014. We also estimated the incidence of subjective cognitive complaints (SCC), operationalized as self-experienced cognitive disturbances associated to normal performance in an extensive neuropsychological evaluation.

Results: Overall, 3,856 subjects attended our Memory Clinic over the considered period of observation. Among them, 13.9% reported SCC. A significant increase of SCC incidence over time (from 2.1% in 2002 to 22.8% in 2014; Figure 1) was observed. Age was found to significantly decrease during the observed timeframe ($p<0.001$). Moreover, a significant increase of education level, global cognitive performance, and physical function were reported (all p values <0.001). A reduction of severe dementia cases (MMSE<=10) and a concomitant increase of individuals with normal global cognitive performance (MMSE>=24) were found.

Discussion and Conclusion: In these last years, individuals attending our Memory Clinic have gradually become younger, more educated, and less impaired in cognitive and physical functions at their first cognitive assessment. To date, nearly one out of four subjects undergoing a neuropsychological evaluation has no objective cognitive deficits, thus presenting subjective cognitive complaints. Based on our findings, the development and implementation of strategies for improving the referral to memory clinics is urgent.

Strengths and weaknesses of national dementia plans around the world

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Introduction: The number of actual and expected people with dementia is increasing worldwide. As a

reaction, a growing number of governments is developing comprehensive public health strategies. Many countries have developed and implemented National Dementia Plans (NDPs), considered as the most powerful tools to transform national dementia care and support. Bupa, the largest international provider of specialist dementia care, and Alzheimer's Disease International (ADI), the global federation of Alzheimer's associations, have drawn up a global report to help policy makers to develop a good NDP (In Pot, A. M. & Petrea, I., Bupa/ADI report: 'Improving dementia care worldwide: Ideas and advice on developing and implementing a National Dementia Plan'. London: Bupa/ADI, October 2013). We analyzed and compared existing international NDPs based on the elements recommended by the Bupa/ADI report.

Methods: A systematic search was performed between November 2015 and February 2016 on databases and websites, using the terms Alzheimer/Dementia and National Plan/Strategy. Only documents and articles published in English were selected and included. Content, development and implementation were the 3 areas of policy identified by Bupa/ADI as those that should be addressed in a good plan and might affect its actual impact. We analyzed and compared published NDPs using the core elements of best practice identified for each area of policy.

Results: We identified and analyzed available NDP documents, including plans from England, Scotland, Northern Ireland, Australia, Denmark, Finland, France, South Korea, USA, Norway, Netherlands, Luxembourg, and Italy. The analysis of the NDPs showed some overlap in the core elements of best practice when analyzing and comparing the content, development and implementation areas. Nevertheless, a relevant overall heterogeneity was observed. Only few countries resulted having moved towards a second plan or phase of implementation.

Conclusions: While most of the NDPs embrace the international aims to raise awareness and to improve access to a formal diagnosis and support, variability exists between the plans in terms of implementation, in particular for what concerns the effective monitoring, evaluation and update as well as the commitment of funding. Such variability, although expected and valuable in order to capture the international diversity in defining NDPs, is still a limitation of the whole, global strategy against dementia.

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Organization and efficiency in integrated cognitive rehabilitation: a specific treatment to rehabilitation of cognitive functions

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The indication of cognitive rehabilitation for degenerative, focal and inflammatory neurological disease [1], encouraged us to examine results of our patient's cognitive rehabilitation. Our training is an integrated cognitive rehabilitation that consist of three treatments, cognitive, ecological-behavioral and physical therapy, with the same target on weak cognitive areas, to keep result for a long time. We recruited 100 subjects at own first rehabilitation, 62 male and 38 female, the average age was 62,82 years, and an average of 10,01 years of school. All recruited subjects received a neurological examination and neuropsychological tests administered before and after our integrated cognitive rehabilitation. We used these neuropsychological tests: MMSE, FAB, digit span, spatial span, Rey's learned word list immediate, attention matrix, Raven Colored Progressive Matrices, constructional apraxia, clock drawing test and verbal fluency. We used t-test for statistical examination of data of neuropsychological tests gave before and after treatment. We found statistically significant results at MMSE (p = 0,00084), FAB (p = 0,00027), Raven CPM (p = 0,00093), clock drawing test (p = 0,02471) and verbal fluency (p = 0,04548). Data divided based on disease, age, sex, years of school, MMSE level, FAB level, month of therapy and weekly frequency, and results were corrected with Bonferroni's correction with cut-off = 0,005. We always founded significant results in all of these divisions in executive cognitive areas, also with Bonferroni's correction. This means that therapy has an effect on executive cognitive areas independently of disease or age or sex or years of school or MMSE or FAB level. Subjects took drug therapy

with acetyl cholinesterase-inhibitor or memantine. Some authors found a decline of executive cognitive areas during this drug therapy as predictive factor of future decline [2]. Subjects in drug therapy with acetyl cholinesterase-inhibitor or memantine improved in rehabilitation because the actions of the drug therapy and of the rehabilitation operated on different cognitive domains. Another consideration regards on the cognitive reserve: age and years of school are inversely proportional to the advantages of cognitive rehabilitation. The best frequency is twice weekly. At last on the duration of cognitive rehabilitation we have an improvement until to four months of treatment, a stationary level in following five months and a soft impairment above ninth month. In conclusion on the basis of previous considerations we can affirm a central role of the executive cognitive area in management of demented patient and in indication to cognitive rehabilitation.

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Daily function as predictor of dementia in mild cognitive impairment. An 8-year follow-up in the ILSA study

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Objective: To evaluate the predictive effect of daily functioning and motor performance (MP) on the progression to dementia in normal cognition and mild cognitive impairment (MCI).

Methods: The study cohort was identified within the Italian Longitudinal Study on Aging, a large population-based survey on age-related functional changes and diseases of the cardiovascular and nervous systems in a representative cohort of older Italians [1]. After the baseline assessment, to detect prevalent cases of cognitive impairment and dementia, participants were re-examined at 4-year and 8-year follow-ups [2, 3]. Functional independence was evaluated using the Index of Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADL) Scale. A six-test battery were used to assess MP.

Results: Overall, 2,386 individuals were included, for a total of 16,545 person-years. Eight-year incidence of dementia (per 1,000 person-years) was 12.69 in total sample, 9.86 in subjects with normal cognition at baseline, and 21.43 in MCI. Progression to dementia was significantly higher with increasing baseline ADL and IADL impairment, and with a worse MP. In Cox regression analyses controlled for demographics and major age-related conditions, increased IADL impairment was the stronger predictor of progression to dementia ($P<0.001$), with HR ranging from 2.16 (95% CI, 0.82-5.70) to 9.57 (95% CI, 3.40-26.91) in subjects with MCI at baseline.

Discussion: IADL impairment is a predictor of transition to dementia in MCI. Controlling for demographics and major age-related disease reduced the significance of ADL and MP. This was not the case for IADL, confirming their validity in the MCI construct.

Conclusions: Inclusion of IADL in the MCI construct significantly improves the prediction of dementia. Individuation of different transition rates is required to plan cost-effective interventions.

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Survey of the neuropsychological tools for the diagnosis of dementia in the Italian centers for cognitive disorders and dementias

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Introduction: A national survey of health and social health services for dementia, totally or partially covered by the public healthcare service, has been carried out within the project assigned by the Ministry of Health (CCM 2013) to the National Institute of Health. A map of these services was also created and is currently available through the thematic website "Dementia Observatory" (www.iss.it/demenze). The use of neuropsychological tools for the diagnosis of dementia was assessed, within the survey, in 501 Centers for Cognitive Disorders and Dementias (CCDDs).

Materials & Methods: A total of 536 Alzheimer's Units (AU), renamed CCDDs within the Italian National Dementia Plan (NDP), have been surveyed between February 2014 and August 2015 at a national level. A standard form, defined to build up structure, process and outcome indicators, has also been used to gather information on the neuropsychological assessment (NPA). It included questions on scales, neuropsychological tests and batteries used for the diagnosis of dementia, presence of psychologists in the service team, and inclusion of a neuropsychological assessment among the services offered by the center. The forms were gathered through a specifically designed online platform.

Results: Response rate to the survey was 93.5% (excluding sub-AU), including all Italian regions. Psychologists were present in 61.1% of the centers, with a significant difference among geographical areas and the lowest frequency in southern Italy; one out of 2 psychologists were not structured. The CCDD reporting to administer a NPA were 93.2%. The most frequently used scales, neuropsychological tests and batteries were: Mini-Mental-State-Examination (93.2%), IADL (89.2%), ADL (87.8%), Clock-Drawing-Test (83.4%), Short-story (69.3%), Rey-15-words (64.9%), Geriatric-Depression-Scale (63.9%), Controlled-Oral-Word-Association (61.5%), Category - Naming (60,9%), Rey-Complex-Figure – copy (55.3%) and recall (51,9%), Neuropsychiatric-Inventory (55%), Frontal-Assessment-Battery (54.5%), Attentional - Matrices (54.3%), Digit-span (52.3%), Drawings' copy (52.1%), Trail-Making-Test (51.5%). A total of 230 (46%) of the CCDDs reported having administered NPA to at least 75% of the referred patients with dementia. Further analyses were carried out on data from the NPA according to geographical area, location of services and presence of psychologists.

Discussion and Conclusions: Data on the availability of NPA, presence of psychologists, and test used for the diagnosis of dementia in Italian CCDDs allows to rise a debate on the current status of NPA in clinical practice. The NPA for the diagnosis of dementia should rely on adequate, standardized and validated tools, and on specifically trained professionals. It should be part of a wider debate, even in the context of the NPD.

Heterogeneity in MCI and early-AD. Abnormal levels of CSF biomarkers and presence/prominence of impairment in memory or other cognitive domains

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AD is a progressive disorder: prior to developing dementia, affected subjects show for long no symptoms or only a mild cognitive impairment (MCI) that do not affect significantly their functional independence. Memory compromission is specific to AD but some patients show 'variant' presentations with prominent impairment of other cognitive domains (CD). The amnestic variant of MCI seems to evolve more frequently to AD dementia, however, persons with prominent impairment in other CD may underlie an AD pathology. Specific CSF biomarkers exist (changes of Abeta1-42, tau and p-tau levels) to support AD diagnosis. Aim of the present

study was to verify, in patients with MCI and early-AD, the association between CSF concentrations of Ab and the presence/prominence of cognitive impairment in memory or in other CD. The neuropsychological assessments of 78 elders with MCI or mild-dementia (MMSE≥20) who underwent CSF examination were collected. The corrected scores (CS) of the Rey Auditory Verbal learning test delayed recall were considered representative of memory domain, The CS of the Rey-Osterrieth complex figure copy were considered representative of visuo spatial functions, language was assessed with semantic fluency test (if not present, the letter fluency CS were considered representative of the language domain and the Frontal Assessment Battery (if not present, the Stroop test interference times/errors) was used to assess the executive domains. Enrolled individuals were categorized according to the presence and prominence of impairment in one of the 4 CD. The association between the presence/prominence of impairment in a CD and abnormal levels of Abeta1-42, tau and p-tau was assessed by chi-2 analysis. Parametric comparisons of the means of biomarker-levels across groups were also performed. Four groups of patients of comparable numerosity could be identified, according to the severity of the CD-specific impairment. No differences in global severity of cognitive impairment measured at the MMSE were observed between them. The prominence of memory alterations was not associated with abnormal levels of CSF biomarkers. By comparing presence or prevalence of cognitive impairment in memory and other domains with CSF abnormalities, we can observe that only 50% of the subject with altered biomarker concentrations were memory predominant or performed bad in memory test. Findings emphasize heterogeneity in MCI and early-AD. A neuropsychological prominent compromission, involving primarily, visuo spatial, language, executive domains prominent over memory decline might characterize early AD. Progetto Giovani Ricercatori GR-2011-02349822

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Parkinsonism in frontotemporal dementia: data from a Sardinian cohort

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Objective: In clinical practice, parkinsonism appears to be quite frequently associated with frontotemporal dementia (FTD) but few studies focused on its prevalence and characteristics [1,2]. We aim to describe data on parkinsonism in a cohort of Sardinian patients affected by FTD.

Methods: We investigated our cohort of FTD patients diagnosed using Rascovsky criteria(BvFTD) and Gorno-Tempini criteria(PPA). Parkinsonism was identified by the presence at least of two clinical features between bradykinesia, rigidity, resting tremor and postural instability. Iatrogenic parkinsonism were excluded. All patients were screened for C9ORF72 and TARDBP gene mutations and 25 also for progranulin mutations.

Results: In our Sardinian cohort of 69 FTD patients 48 were affected by BvFTD, 8 by semantic dementia, 8 by the non-fluent primary progressive aphasia (PPA) and 5 by unspecified PPA. Among patients with BvFTD 13 patients were carriers of C9ORF72 mutation and 5 of the p.A382T missense mutation of the TARDBP gene. 1 other patient with unspecified-PPA was TARDBP mutated. No mutations in progranulin gene were found. 26 patients (37%) in the whole cohort showed parkinsonism of whom 23 had BvFTD, 1 unspecified PPA, 0 SD and 2 PNFA. Patients with parkinsonism had a trend to be more frequently familial cases (13/26vs12/43, p0.06). Parkinsonism was in most cases an early onset feature during the disease course and was mainly of the rigid-akinetic type. Tremor PD-like was present only in two patients with BvFTD and one patient with PPA. 5 patients had a CBS-like parkinsonism and 2 PSP-like. C9ORF72+BvFTD patients had mostly symmetric (6 patients) or mildly asymmetric (4 patients) parkinsonism. C9ORF72- BvFTD patients had more frequently asymmetric (6 patients) rather than mildly asymmetric (3 patients) or symmetric (4 patients) parkinsonism. The comparison between C9ORF72+ BvFTD and the C9ORF72- BvFTD groups showed a significant prevalence of parkinsonism in the former group (10/13vs13/35,

p0.03)(3). None of the patients with TARDBP mutation had parkinsonism. Dat-scan was altered in 4 out of 5 of C9ORF72+patients with parkinsonism and 3 out of 3 C9ORF72- patients with parkinsonism. Levodopa response was negative in all but one patients in which was administered.

Conclusion: In our population we found a little higher prevalence of parkinsonism (37%) than previously reported in literature (16-30%) (2). Parkinsonism is largely more frequent in BvFTD than other FTD variants and particularly in C9ORF72+BvFTD. We found a prevalence of parkinsonism in C9ORF72+BvFTD patients much greater than previously reported in literature. Clinical features of parkinsonism were different in C9ORF72+ and C9ORF72- patients.

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Prevalence of social cognition disorders in relapsing-remitting multiple sclerosis patients

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Objectives: Despite converging research in MS has recently shown disturbances of social cognition abilities, their prevalence in clinical settings is unclear. Moreover, studies in MS exploring different facets of social cognition within the same population still lack. The primary aim of this study was to assess the prevalence of social cognition dysfunctions in Relapsing Remitting Multiple Sclerosis (RR-MS). Secondarily, we explored possible correlations with demographic, clinical and cognitive variables.

Materials and Methods: We prospectively collected forty-five RR-MS patients (MS center, BioNeC, University of Palermo, Italy). Clinical rating scales (i.e., EDSS, FSS, MusiQoL, HADS) were administered to each patient, as well as standardized measures of executive functioning, the Italian standardized versions of Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and three social cognition tasks (i.e., Ekman 60-Faces test, Story-based Empathy Task, Reading the Mind in the Eye). Additionally, an experimental task of moral dilemmas was performed by patients and forty-five matched healthy control subjects (HC). We considered MS patients as "social-impaired" when scores on at least two social tasks were below the 5th percentile of controls.

Results: The 7% of RR-MS patients presented a "social-impaired" profile. In particular, impairments of negative emotion recognition (fear, angry and disgust) and deficit in affective ToM were consistently present (i.e., 16% of the sample). Compared to HC, patients showed poorer emotional arousal on moral dilemmas. No significant correlations with disease severity or other clinical variables as well as with basic cognitive functions emerged.

Discussion and Conclusion: The clinical assessment of socio-emotional processing abilities in MS patients is crucial for a better definition of their cognitive profile. Besides, early recognition of such disorders may push the development of new therapeutic targets and non-pharmacological interventions for a benefit to patient's social behavior and quality of life.

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The multidimensional prognostic index based on a comprehensive geriatric assessment predicts caregiver burden in Alzheimer's disease

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Objectives: To evaluate the prognostic accuracy of a Multidimentional Prognostic Index (MPI) derived from a standardized Comprehensive Geriatric Assessment (CGA) for evaluating caregiver burden in Alzheimer's disease (AD).

Design: Prospective study.

Participants: A total of 253 consecutive AD patients attending the Alzheimer's Evaluation Unit of the IRCCS "Casa Sollievo della Sofferenza" in San Giovanni Rotondo, Italy were included in this study. Of these, according to MPI grades, 122 patients showed a low (MPI-1), 107 a moderate (MPI-2) and 24 a severe (MPI-3) risk of mortality.

Measurements: All patients underwent a comprehensive evaluation with standardized CGA, Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Geriatric Depression Scale (GDS), and Neuropsychiatric Inventory (NPI). To all caregivers were administered the Caregiver Burden Inventory (CBI), a 24-item multidimensional questionnaire in which 5 subscales explore 5 dimensions of caregiver burden: (1) CBI-Objective, (2) CBI-Developmental, (3) CBI-Physical, (4) CBI-Social, and (5) CBI-Emotional.

Results: No significant difference were showed between the three MPI groups on sex. Patients with MPI-3 were older ($p<0.0001$) than patients with MPI-1 and MPI-2. Clearly, significant difference were showed between the three groups of patients on scores in CGA ($p<0.0001$) with an higher impairment in patients with MPI-3. Moreover, patients with MPI-3 showed a significantly higher cognitive impairment in MMSE ($p<0.0001$), and an higher score in GDS ($p<0.0001$) and NPI ($p<0.0001$) than MPI-1 and MPI-2 patients. Caregivers of patients with MPI-3 devoted significantly more length of time care (in months, $p<0.0001$) and time of daily care (in hours, $p<0.0001$) and showed a significantly higher burden level in CBI-Objective ($p<0.0001$), CBI-Developmental ($p<0.0001$), CBI-Physical ($p<0.0001$), CBI-Social ($p<0.0001$), CBI-Emotional ($p<0.0001$), and CBI-total score ($p<0.0001$) than caregivers of patients with MPI-1 and MPI-2.

Conclusions: MPI should be a useful measure for predict the caregiver burden in patients with AD.

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Longitudinal assessment of frontal cognitive impairment in patients with motor neuron disease

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Objective: Motor neuron disease (MND) is now widely recognized as a multi-system pathology. Despite the prominence of motor symptoms, indeed, up to 50% of MND patients also manifest a broad range of neuropsychological deficits. The majority of cognitive studies of MND are cross-sectional and little is known about the longitudinal course of cognitive disturbances in these patients. We tested the progression of frontal cognitive impairment in patients with MND, accounting for the effect of progressive verbal and/or physical disability.

Methods: 26 non-demented patients with recently diagnosed sporadic MND were followed prospectively with clinical and neuropsychological evalua-

tion every 3 and 6 months respectively, for a maximum follow-up of 24 months. Cognitive assessment was performed using the MMSE, verbal fluency tests, and the Test of Attentional Performance (TAP). The TAP, which is administered through an automated computerized system, permits to investigate the whole spectrum of frontal involvement in ALS, reducing verbal and/or physical disability. Alertness (in terms of its intrinsic and phasic components), divided attention, sustained attention, behavioural control and interference tendency (in terms of stimulus-reaction incompatibility) were evaluated. Scores were analyzed in terms of performance speed and performance accuracy (valid responses and omissions). Longitudinal linear models were used to assess clinical and cognitive variable changes over time and the relationship between baseline clinical features and cognitive deterioration.

Results: During follow up, MND patients experienced a progressive worsening of motor disability, with a statistically significant decrease over time of the ALSFRSR scale score ($p<0.001$), total MRC ($p<0.001$) and ALS severity scale ($p<0.001$), and increase of the upper motor neuron score ($p<0.001$). MND patients also showed a significant deterioration of the global cognition ($p=0.04$), and several frontal measures (p ranging from <0.001 to 0.04). The TAP showed that sustained attention, behavioural control and interference tendency significantly decreased over time. The progressive cognitive decline was independent of baseline motor clinical characteristics.

Conclusions: Longitudinal analyses using computerized-based, sensitive executive measures revealed a progressive cognitive decline in MND patients, which appeared relatively early in the course of MND and is not associated with baseline motor disability. Cognitive deterioration in MND encompasses both executive performance accuracy and speed.

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The Italian version of cognitive functioning instrument (CFI): reliability and validity in healthy elderly subjects

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Objectives: To validate the Italian version of the Alzheimer's Disease Cooperative Study (ADCS)-Cognitive Functioning Instrument (CFI) 1, a simple questionnaire useful to detect early changes in cognitive abilities in individuals without clinical impairment 2, thus also used for monitoring cognitive functioning in prevention trials, by comparing current to previous performance observed one year before. It consists of 14 questions administered to both the subject and the referent (study-partner). The score ranges from 0 to 14, where responses are coded as Yes = 1, Maybe = 0.5, No = 0 and summed to calculate a total score.

Materials: CFI was translated from English into Italian by using forward-backward translation. Each item was set after agreement was reached. We also administered the Mini-Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Geriatric Depression Scale (GDS).

Methods: The Italian version of CFI was administered to a consecutive group of 109 cognitively healthy and functionally independent subjects (age: 60-85; mean: 70, M:51 F:67) recruited either among relatives of patients attending our Memory Clinic or as volunteers after advertisement. We wanted to assess (i) the internal consistency of the Italian version of CFI, by means of corrected item–total correlations and Cronbach's α; (ii) the correlation between CFI and global cognition measurements such as MMSE and RBANS – i.e., criterion validity; (iii) the correlation between CFI and GDS – i.e., discriminant validity.

Results: Internal consistency: corrected item–total correlations ranged between 0.21 and 0.62 in self-report, and between 0.28 and 0.61 in partner-report. Cronbach's α was 0.71 in self-report and 0.72 in partner-report. The correlation between total partner- and self-report score was significant ($r=0.37$, $p<0.001$). Criterion validity: gender, age, and education did not show any influence on CFI scores. CFI self-report total score was not correlated with MMSE but with RBANS ($r=-0.26$, $p=0.007$). Discriminant validity: CFI self-report total score was correlated and GDS ($r=0.51$, $p<0.001$).

Discussions: Cronbach's α was adequate but lower than the original, both in self- and partner report. Criterion validity was reached only partially, since we found a significant correlation with RBANS index, but not with MMSE. Finally, the strong correlation of self-report CFI with GDS score threatens discriminant validity. The correlation with

depressive symptoms was not evaluated in the original version and further analyses to identify the meaning of this correlation is needed.

Conclusions: The Italian version of CFI still needs further investigations in large cohorts, including longitudinal observation.

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Longitudinal observation of neuropsychological and diffusion tensor imaging tractography alterations caused by herpes simplex virus encephalitis

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Objectives: Herpes Simplex Virus Encephalitis (HSVE) is one of the most common causes of sporadic necrotizing encephalitis, caused by the herpes simplex virus (HSV-1) which affects particularly the limbic and medio-temporal regions. The present study aimed to investigate the longitudinal neuropsychological and brain tractography changes associated with HSVE-1.

Materials: The patient (female, 70 years old, 5 years education) at onset had global amnesia, confabulation and anosognosia. After few days she showed severe global cognitive deterioration with persistent anterograde and retrograde episodic amnesia, spatio-temporal disorientation and daily-living functional loss. Conventional MRI showed selective bilateral atrophy in hippocampal and parahippocampal regions.

Methods: The patient underwent ad-hoc second-level neuropsychological assessment and diffusion weighed imaging (DWI) acquired on a 3T GE MR scanner in the sub-acute phase, after six months and one year later. Diffusion Tensor probabilistic tractography was used to reconstruct the white matter tracts. By using the Crawford and Garthwaite procedure (Crawford et al., 2010), t-test analysis comparing the mean Fractional Anisotropy (FA) between the patient and a group of healthy elderly controls ($N = 17$) was carried out.

Results: At onset the patients showed severe loss of episodic and semantic memory, autobiographical and visuo-spatial memory and wayfinding deficits. Neuroimaging analysis showed significant reduction of FA in bilateral inferior longitudinal fasciculus (ILF), left uncinated fasciculus (UNC), left inferior fronto-occipital fasciculus (IFOF) and right superior cingulum (SUP-CING), compared with the control group. After six months, the patients showed global cognitive improvement, persistent severe amnesia, semantic deficits and spatial disorientation, paralleled by reduced diffusivity in left UNC and IFOF. One year later, the cognitive profile remained quite stable with mild worsening in temporal orientation, persistent memory deficits and improvements in extra-mnestic domains, such as visuo-constructional abilities. Diffusivity reduction was detected in bilateral ILF and left UNC.

Discussion: Diffusion Tensor tractography revealed that HSVE is characterised by reduced brain diffusivity in the longitudinal evolution of viral infection.

Conclusion: The pattern of white matter damage seems to represent a plausible neural substrate of the cognitive deficits of this single case after HSVE, presenting not only extensive amnesia, but also severe deficits in visual recognition, spatial representation and navigation. Alterations to the UNC fasciculus seems to be consistent in time across observations in this patient with moderate-severe sequelae.

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Qualitative patterns at Raven's colored progressive matrices in mild cognitive impairment and Alzheimer's disease

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Background: Visuo-spatial and problem-solving abilities are commonly impaired in patients with Alzheimer's disease (AD). Conversely, subjects with amnestic Mild Cognitive Impairment (aMCI) do not exhibit overt involvement of cognitive domains other than memory. As consequence, a detection of an impairment at the Raven's Colored Progressive Matrices (RCPM) could be useful to discriminate aMCI from AD and to mark the progression from one condition to another.

Aim of the study: To describe the pattern of errors at RCPM in patients suffering from AD as compared with those of aMCI.

Methods: Fifteen patients with AD, 15 subjects with aMCI and 31 normal subjects (NC) received the RCPM. The errors were classified as: 1) Difference (D); 2) Inadequate Individuation (II); 3) Repetition of the Pattern (RP); 4) Incomplete Correlation (IC).

Results: No difference approached significance between aMCI and NC. AD always exhibited a higher number of errors as compared with NC. AD showed higher number of errors as compared with aMCI only on RF and IC errors.

Conclusions: The results suggest that the visuo-spatial and problem solving impairment that characterize AD, and probably subtend the progression from aMCI to dementia, do not affect to the same extent all cognitive dimensions explored by RCPM.

Occurrence of seizures and EEG interictal epileptiform discharges in AD patients and their correlation with clinical features: a cross-sectional study

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Aims: Several studies have shown that seizures and epilepsy have a higher incidence in Alzheimer's disease (AD) than in the general population, even though with contrasting data (1), and the prevalence/incidence of interictal epileptiform discharges (IEDs) in AD is still unclear. The aims of our study were: 1) to analyse the prevalence of seizures in a group of AD patients, 2) to investigate the prevalence/types of IEDs, 3) to assess whether IEDs/seizures occurrence correlate with any clinical features of patients.

Materials: We included 167 patients with probable AD according to NIA-AA (2011), mild/moderate dementia, from a total sample ($n=245$) of consecutive demented outpatients seen at the Memory Center of the University of Pisa. Exclusion criteria where CDR>2, vascular lesions or other relevant CT/MRI lesions potentially affecting seizure threshold. In a subgroup of AD patients a further diagnosis of mixed dementia (MD) with mild-moderate vascular burden was performed by the mFazekas scale score. Detailed clinical/treatment data were collected. A validated questionnaire for anamnestic seizures screening (SQ)(2) to identify previous seizures of patients was administered to patients and caregivers; SQ was administered also to caregivers (controls). 85 patients were randomized for standard EEG recording blindly to their SQ.

Method: Cross-sectional analysis and correlation of collected data.

Results: Age was 72,73 ± 6,52 y at AD onset, and 76,92 ± 6,38 y at observation; mean MMSE was 17,63 ± 6,03. 19.8% of patients had MD. A positive SQ was found in 12,6% AD and 1,8% controls ($p < 0.01$). A higher prevalence of neuroleptic intake in the previous 3 months was found among patients with positive SQ than in those with no previous seizures ($p = 0.009$). Seizures reported were tonic-clonic generalized (52,38%), partial complex (42,86%), and simple partial ones (33,33%) (often co-existing). Seizures prevalence/types were similar in AD with and without MD. IEDs occurred in 14.12% of patient EEG (sharp-waves: 75%; spikes: 18%; spike-waves complexes: 8%) and were mainly focal/multifocal. In patients without IEDs, cognitive impairment was higher than in those with EEG IEDs ($p=0.017$).

Discussion: We confirmed AD is associated with higher risk of seizures. As seizure prevalence was

similar in AD with and AD without MD we speculate that AD pathology is per se a crucial risk factor for seizures. The inverse relation between IEDs occurrence and cognitive decline might be in line with some data in AD experimental models.

Conclusion: This cross-sectional study shows that AD pathology increases seizure and IEDs prevalence.

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Frontotemporal dementia in the Marche region: an attempt to estimate incidence and prevalence

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Frontotemporal dementia is a group of heterogeneous neurodegenerative disorders, less frequent than Alzheimer's Disease but a common cause of young-onset dementia. About 25% of cases are late-life onset. Population studies are rare. The estimated incidence is 2.7–4.1/100,000 and prevalence is 15–22/100,000 with nearly equal distribution by gender. FTD is frequently familial and hereditary. Five genetic loci for causal mutations have been identified, all showing 100% penetrance. Up to now non-genetic risk factors are missing. There is still need for descriptive populations studies, to fill gaps in our knowledge about FTD distribution. The aim of the present project is to estimate incidence and prevalence of FTD among the population of Marche region of Italy. All Dementia and Cognitive Disturbance Centres (CDCD) of the Marche Region were involved in this project. They were asked to fill a form for each new patient with a diagnosis of FTD. The form addressed several points: clinical history, neuroimaging, genetical analysis and family history. Recruitment started in September 2015. Preliminary data are calculated on a six month period: forms were available from 6 out 9 centers. A total of 11 new cases were recruited in the 6 CDCDs leading to an incidence of 9.4/100.000 subjects/six months. 9 patients were affected by bvFTD, one patient by PNFA and a third by PNFA/CBD. A positive family history was present in 4/11 patients. Genetical analysis was available in 7 patients and did not reveal known mutations, even in two patients showing family history for dementia.

The use of benzodiazepines in people with cognitive complaints: a cross-sectional study in the remind cohort

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Objective: Evidence is not conclusive to impute to benzodiazepines (BDZ) a negative impact on cognition. We aimed to evaluate the use of BDZ in the cohort of the REMIND study, which is a 3-year pragmatic population-based prospective cohort study in Milan, which aims to implement an Integrated Care Pathway (ICP) for dementia.

Materials and Methods: From April 2013 to March 2014, 4249 subjects with first cognitive complaints underwent the Mini Mental State Examination (MMSE) administered by 353 General Practitioners (GPs). All 353 GPs underwent a strict training for the correct performance of the MMSE,

in order to gain the highest level of reliability of the score. Drug history was collected and the BDZ score was created (BDZ=0, receiving no BDZ drugs; BDZ= 1, receiving at least one BDZ drug). A MMSE ≤24 was considered relevant for the present study.

Results: Out of 4249 subjects, 782 (18.4%) received at least one BDZ. Subjects with BDZ score=1 were older (78.2 ± 7.6 vs. 76.7 ± 8.3; $p<0.001$) and were more frequently female ($p<0.001$). No statistically significant differences were observed for what concern education, MMSE total score and impact on sub items of MMSE. To assess the association between cognitive impairment and the use of BDZ, a multivariate analysis was used in order to adjust for the covariates. In the multivariate analysis, no statistically significant differences were found between subjects who took BDZ drugs and the risk of cognitive impairment (OR= 0.90, 95% CI 0.73-1.11). The results did not change with a MMSE cut-off of 27.

Discussion: About one fifth of the population of the present study with first cognitive complaints received BDZ medication in the primary care setting. In the present study, we did not find any association between BDZ use and a worst performance in the MMSE score. The conflicting results from various longitudinal studies suggest that further investigation are needed in order to better understand the role of BDZ use and the impairment in cognitive performance.

Early and late effects of cognitive stimulation in Alzheimer's disease patients: evidence from a 12-month prospective cohort study

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Objectives: To investigate the early and late effects of long-lasting cognitive stimulation (CS) in a large sample of patients with Alzheimer's disease (AD) compared with non-stimulated AD controls.

Materials and methods: 200 consecutive patients with a diagnosis of mild-to-moderate AD (NINCDS-ADRDA criteria, $1 \leq CDR \geq 2$, $19 \leq MMSE \geq 24$) were randomly assigned to two groups containing 100 participants each. One group (treated group-TG) received CS training for six months. The other group (non-treated group-CG) did not receive either CS or any other non-pharmacological treatment. All the subjects underwent a clinical and neuropsychological evaluation at the baseline (T0), at the end of the CS (T1) and six months later (T2). The CS intervention consisted of several cognitively-stimulating activities (memory training, speech therapy, occupational therapy, reading and logic games). It was administered in group sessions (6/7 participants) lasting 60 minutes held twice a week for 24 consecutive weeks. The statistical analysis was based on the data from all the subjects in the TG that attended at least 80% of the CS sessions and all the subjects in the CG. We used the t-test and a post-hoc analysis (Tukey's HSD) after ANOVA for repeated measures to analyse the data. P values of less than 0.05 were considered significant.

Results: 73 patients in the TG attended at least 80% of the CS sessions. Their data and those from 94 subjects in the CG (6 subjects were lost to follow-up) were analysed. At T1, the statistical analysis revealed a significant improvement in cognitive scores of the TG, whereas those of the CG significantly worsened. Sixty-two participants in the TG (11 subjects were lost to follow-up) and 80 in the CG (14 subjects were lost to follow-up) completed the study (T2). Cognitive scores worsened in both groups at T2, though to a lesser extent in the TG.

Discussion: Our study confirms that CS consistently improves cognition in AD patients. These beneficial effects appear to partially persist six months after the end of the CS period, as demonstrated by differences in cognitive decline between the two groups at T2.

Conclusion: Our data confirm that long-lasting CS may temporarily postpone cognitive decline in AD patients1. Furthermore, evidence of the persisting effects of CS after the end of the stimulation highlights the effectiveness of this kind of non-pharmacological intervention in AD.

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Cognitive reserve in cognitive aging: what we can learn from Parkinson's disease

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Introduction: Parkinson's disease typically occurs in elderly people; and while we know the typical cognitive profile of Parkinson's disease (PD) is not clear how the cognitive reserve might influence cognitive profile of Parkinson's disease in later life; indeed one research strategy that can be used with the cognitive reserve is to establish groups of elderly persons with Parkinson's disease who differ in key variables that affect the cognitive reserve and then compare their performance in cognitive tests.

Aims: To determine which of the variables that have an influence on the cognitive reserve (measured by means of the cognitive reserve questionnaire) are related with performance in executive function and verbal episodic memory performance in elderly parkinsonian people.

Subjects and Methods: The study tested the cognitive reserve hypothesis by quantifying cognitive reserve (CR) and subsequently determining its role in executive function and verbal episodic memory performance. A comprehensive neuropsychological battery was administered to 35 non demented elderly persons with PD (77% males, mean age 77 (SD 7.1), mean education 9 (SD 4.6); mean MMSE score 27 (SD 3.1). Raw test scores were adjusted based on Italian normative data. All participants underwent the Brief Intelligence Test (TIB) and the Cognitive Reserve Index (CRI) questionnaire as proxies for CR. Relationships between TIB, CRI and CI were investigated by logistic or linear regression analyses.

Results and Conclusions: At logistic regression analysis, only CRI (OR 0.94; 95% CI 0.91-0.97; $p=0.001$) and TIB (β 0.39; 95% CI 0.71-0.90; $p<0.01$) were significantly associated with performance at word fluency test. These associations were also confirmed for the Digit Span Test (backward) (both $p<0.02$).Our data provides empirical support for the CR hypothesis in PD but findings supported only limited role of CR in reducing the direct negative effect of Parkinson's disease on cognition in elderly subjects with PD. CR was significantly associated especially with cognitive areas affected in PD. A lifestyle characterized by experiences of mental stimulation may help to cope aging and Parkinson's disease neurodegeneration.

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Progressive aphasias: might language tests play a role in early diagnosis?

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Aims: Clinical evaluations of patients presenting with language disorders are challenging especially at early stage of neurodegenerative disorders. The syndrome of Progressive Primary Aphasia (PPA) is a decline in language functions that remains isolated during the first 1-2 years. Progressive aphasias can arise as part of neurodegenerative disorders such as Alzheimer's Disease (AD), Posterior Cortical Atrophy (PCA), Frontotemporal dementia (FTD). The aim of the study was to identify potential marker in language tests performed at first evaluation, related to different syndromic evolutions in patients exhibiting language deficits as early and main symptom.

Materials and Methods: 38 patients initially presenting with language impairments were selected retrospectively from the database of the Memory Unit of Neurological Clinic of University of Pisa. All patients performed neuropsychological assessment, including formal language evaluation (Aachener Aphasie Test-naming subtest – AATn, phonemic and semantic verbal fluency, Token test), CT or MRI, FdG PET and a subgroup Lumbar Puncture. Clinical follow-up ranged from 2 to 10 years. The syndromic diagnosis was made during a period

ranging from 2 to 4 years from the first observation. On the basis of PPA criteria1, 4 subjects presented logopenic aphasia (L-PPA) and 4 patients semantic variant (S-PPA). FTD has been developed in 5 patients, AD in 17 subjects, while 3 patients evolved into Corticobasal Syndrome (CBS) and 5 subjects had PCA. A chi-square test was performed to evaluate the association between performance on language tests (under/over the cut-off) and syndromic evolution.

Results: Between the selected language test only the ATT-n revealed a significant association ($\chi 2$=16,823, p=0.005). In particular, all patients with AD showed impairment on AATn, while DCB and FTD patients revealed preserved performance. Most of PCA and PPA patients showed a performance under the cut-off (3 patients, respectively, for PCA, PPA-L and PPA-S).

Discussion: The heterogeneity of neuropsychological and clinical presentation of progressive aphasias hinders an early classification and a syndromic diagnosis. Our preliminary data suggested that naming impairment at baseline (measured with AATn) was related to syndromic evolution, while impairment in verbal fluency and sentence comprehension tests did not.

Conclusion: Although the small samples size, these results suggested that naming might be a potential helpful marker of syndromic evolution in progressive aphasias. Future studies would develop classification system able to capture the complexity of syndromic characterization of aphasia merging useful markers.

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Voluntary inhibitory control and impulsivity in Parkinson's disease patients with and without levodopa-induced dyskinesias

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Levodopa therapy is the most effective treatment for Parkinson's Disease (PD) motor symptoms, however, some complications such as levodopa-induced dyskinesias (LIDs) and impulsive behavior frequently occur in combination with its use. This suggests the development of behavioral disinhibition parallel to LIDs that could be ascribed to alterations of prefrontal functionality. The aim of the current study was to determine if PD patients with LIDs show features of altered voluntary motor inhibition in parallel with increased impulsivity when compared to PD patients without LIDs. Two matched samples of PD patients with (n=8) or without LIDs (n=8) according to the Abnormal Involuntary Movement Scale (AIMS) were enrolled in the study. The two groups of patients were evaluated by Barratt Impulsivity Scale-11 (BIS-11) to assess impulsivity traits. Furthermore, participants performed a stop signal task at baseline condition and following experimental manipulations. We used continuous theta burst stimulation (cTBS), a form of repetitive TMS known to induce long-lasting inhibition of the stimulated area, over the right inferior frontal gyrus (r-IFG) in order to verify behavioral modifications occurring when interfering with prefrontal activity in the two groups of PD patients. The results showed similar performances between groups to the stop signal task at baseline, albeit PD with LIDs resulted clearly more impulsive than PD without LIDs according to the BIS-11 total score. Following the combined effects of prefrontal cTBS and levodopa intake, Go reaction times were prolonged in all PD patients compared to all others conditions. The present findings show that although PD patients with LIDs are clearly more impulsive than PD patients without LIDs, they do not differ for voluntary inhibition performances. Furthermore, the present results

suggest that it is possible to improve motor initiation control in PD patients combining levodopa intake with prefrontal cTBS. In conclusion, the present data demonstrate the absence of a correlation between voluntary motor inhibition and impulsivity, while confirming the hypothesis of behavioral disinhibition in patients with LIDs. The current study proposes the involvement of r-IFG activity in motor initiation in PD patients but not in motor inhibition.

Descriptive study on the willingness to undergo predictive genetic testing in subjects at risk for familial Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is the most cause of dementia and affects all ethnic groups. The clinical manifestation of AD are preceded by a 15-20 years period of silent pathology during which the accumulation of fibrillar beta-amyloid and the development of neurofibrillary tangles occur. Subsequently, the synaptic and neuronal loss produce cognitive impairment. In the recent years, there are increased effort at identifying interventions to prevent the clinical manifestation of AD. However, prevention studies must recruit thousand participants that more likely to develop AD and follow them for many years. An example of this population are persons with family history of the disorder. Currently, the number of such individuals who decide to undergo predictive, pre-syntomatic testing, however, is relatively low.

Material and Methods: We have performed a questionnaire for determining whether these subjects with family history of AD would be willing to undergo genetic testing, learn the results and participate in preventive studies. We also explored the reasoning behind their decision and which is their life-style in an attempt to modify the wrong ones. The first part of the questionnaire concerned the demographic aspects and the emotional and social impact that the disease of the relative has had on their life. The questionnaire were administered by the same doctor during the medical visit or a telephone interview.

Results: One hundred and thirty-five subjects with positive family history for AD (3 first-degree relatives) were enrolled in this study. The middle age is 54.06 ± 10.14 and the schooling is 13.70 ± 3.49. Eighty-nine subjects (65.9%) are female and the 86.7% of the participants are sons of AD patients and only 31 subjects (23%) are cohabitants. One hundred and twelve (83.0%) have expressed willingness to undergo genetic test and the main reason was linked to the offspring. The 85.7% of those who responded in a negative way, would change idea if there were preventive therapies or disease modifying drugs.

Discussion and Conclusions: The availability of prevention studies and/or disease modifying drugs might serve as incentive for person at risk for FAD to undergo genetic testing. Female subjects, especially if with children, are more motivated, possibly related to their expressed interest in helping offspring. At the same time, it is crucial to create genetic counselling because these vulnerable subjects need to be thoroughly educated prior to making decision regarding the predictive testing and, especially, when the genetic result will be communicated to them.

Acute akinesia in dementia with Lewy bodies

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Objectives: Neuroleptic Malignant Syndrome (NMS) and Akinetic Crisis (AC) of parkinsonisms are considered identical expression of the same idiosyncratic unpredictable and possibly lethal clinical event. NMS is precipitated by exposure to neuroleptics, AC can appear because of medical or surgical comorbidities. It is not clear whether the Neuroleptic hypersensitivity observed in Dementia with Lewy Bodies (DLB) [1] implies an increased incidence of NMS and AC crises, and whether AC can appear in DLB without a preceding neuroleptic exposure. We assessed the incidence of AC in a large cohort of patients affected by DLB as compared to incidence in Parkinson Disease (PD) patients [2].

Methods: 614 PD patients and 236 DLB patients were recruited from consecutive afference to the

Memory and Movement Disorder Clinics of University of Chieti, Italy during 2007-2014. AC was diagnosed as sudden severe akinetic state unresponsive to dopaminergic rescue drugs, dysphagia, serologic alterations without recovery for 48 hours or more, leading to hospital admission. Among analyzed variables, exposure to neuroleptics was specifically considered, because of the high implicit risk in DLB.

Results: A total of 24 PD and 16 DLB patients developed AC. 77 DLB and 32 PD patients were exposed to neuroleptics, all presented with worsening of parkinsonism, but only 8 DLB and 3 PD patients presented with AC. Disease duration before AC was lower in the DLB group than in the PD group. The annual incidence of AC was 3‰ in the PD population and 1.5% in the DLB population. Outcome was fatal in 12 DLB and 3 PD patients.

Conclusion: AC in DLB is more frequent, occurs earlier than in PD and is more frequently fatal. AC in DLB can appear, same as in PD patients, despite no exposition to neuroleptics and no treatment withdrawals. The significant rate of mortality in our cohorts, due to medical complications precipitated by the transient refractoriness to dopaminergic rescue drugs administration, suggests that the use of typical neuroleptics in DLB patients should be avoided. The use of neuroleptics in DLB should therefore be limited to quetiapine or clozapine, which showed an acceptable safety profile [3], and possibly complemented with alternative pharmacological approaches, including the use of cholinesterase inhibitors.

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Fronto-parietal network and anosognosia in cognitive decline: a resting state FMRI study

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Introduction: Neuropsychological studies support the hypothesis that anosognosia in MCI and AD might reflect a failure to update self-awareness system based on the set of beliefs of one's own capacities and traits with external experiences. Therefore, we may speculate that self-awareness relies upon different networks that are functionally correlated and that support communication between an "external" source of information and an "internal" personal knowledge. In this study, we used Independent Component Analysis (ICA) to investigate neural connectivity networks involved in self-awareness in cognitive decline.

Methods: Forty-two elderly participants took part in the fMRI study: 8 patients with a diagnosis of mild AD, 14 patients with a diagnosis of amnesic MCI, and 20 healthy elderly. The presence of anosognosia was assessed by means of Clinical Insight Rating Scale (CIRS) and Anosognosia Questionnaire Dementia (AQ-D) and patients with score ≥ 2 at CIRS and score ≥ 14 at AQ-D were classified as unaware. Analysis of resting data was carried out with the toolbox MELODIC, part of the FSL software package (www.fmrib.ox.ac.uk/fsl), and dual regression approach.

Results: The two groups of aware and unaware patients only differed for AQ-D and CIRS score; no statistical significant difference was detected in global measure of cognitive impairment and demographical data. Group comparisons analyses showed increased functional connectivity between fronto-parietal networks and posterior cingulate cortex, bilateral precuneus, right mesial temporal lobe, right inferior temporal gyrus, right paracingulate, and bilateral middle and superior frontal gyrus in controls and aware subjects compared to unaware patients. No significant differences were found in the reverse condition and between controls and aware patients. No significant differences between any of the groups in any direction were found within the other RSN.

Conclusion: Fronto-parietal network represents a functional interplay between "internal" personal knowledge and "external" source of information; therefore, disruption of this control network may reflect impaired self-awareness in AD and MCI patients.

Frontal deficits and behavioral disturbances in patients with Alzheimer's disease and chronic obstructive pulmonary disease: a comorbidity problem

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Aims: Chronic obstructive pulmonary disease (COPD) may be associated with worsening of cognitive performance. We studied patients with Alzheimer's Disease (AD) with and without COPD, and we analyzed, in a retrospective way, clinical and neuropsychological variables to verify if COPD plays a pejorative role on cognitive or functional autonomy in patients with dementia.

Materials: We enrolled 17 adult patients (AD-COPD) with probable AD (according to NINCDS-ADRDA criteria) and COPD (according to Global Initiative for COPD guidelines) and 17 with AD only (AD); they were matched for sex, age, educational level and Mini Mental State Examination (MMSE) at the disease onset.

Methods: Global cognitive status was estimated using MMSE at the first assessment and after 24 months. Memory, executive functions, praxia and language were the other cognitive domains analyzed. The two groups were also compared for the presence of behavioral disorders (anxiety, depression or delirium).

Results: AD-COPD had worse results in executive functions screening than AD; no significant differences were found comparing other cognitive domains; moreover no significant difference there was between the two groups considering the decrease in MMSE score. Regarding behavioral disorders, the most remarkable result was a higher incidence of delirium in AD-COPD than in AD (53% vs 12%), with a statistical significance (p 0.025); AD-COPD also showed an higher presence of depression (35% vs 18%).

Discussion: COPD is known to be associated with the development of cognitive deficits, in particular regarding for executive functions and attention, memory and logical reasoning. In this context, MMSE has a low diagnostic accuracy to underline effective cognitive impairment in AD-COPD. It's also clearly documented an association between COPD and behavioral disorders, such as depression, anxiety and delirium.

Conclusions: Our study shows a higher frequency of frontal deficits and behavioral disturbances in patients with AD and COPD than patients with AD only. Furthermore we found a greater incidence of delirium, just in the early stages of the disease. COPD could complicate the management of AD patients, thus necessitating a closer and multidisciplinary monitoring.

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Neuropsychological profile of amnestic MCI patients with selective medial temporal lobe FDG-PET hypometabolism

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Background and Objective: Mild cognitive impairment (MCI) is defined as subjective cognitive complaints with objective evidence of cognitive impairment in the setting of normal general functioning. A subset of MCI characterized by slow disease

progression and prevalent episodic memory impairment has been identified and considered as possible clinical expression of the so-called "limbic-predominant" Alzheimer's disease (AD). Given the precise location of the degenerative process mainly involving the medial temporal lobe, apart from the memory impairment of the hippocampal type, a deficit in recognition of basic emotion could be hypothesized. No study, however, systematically explored such neuropsychological aspects.

Material and Methods: We enrolled 14 single-domain amnestic MCI patients (11M/3F, age in years =75.2±5.07, years of education = 11.57±4.55, MMSE raw score=25.43±2.06) with long-term disease duration (47.64±23.6 months). All patients underwent a FDG-PET scan that showed a pattern of regional metabolic dysfunctions limited to medial temporal lobe structures without the typical AD temporo-parietal hypometabolic pattern. An in-depth neuropsychological evaluation assessed general functioning and basic cognitive abilities. The Italian standardized versions of the Free and Cued Selective Reminding Task (FCSRT) and the Ekman-60 Faces Test (Ek60F) were additionally administered to test episodic memory and emotion recognition. A mean follow-up of about 2 years evaluated possible progression of cognitive decline.

Results: At follow-up, no patients progressed to dementia, but five patients were classified as multiple-domain MCI. The 93% of patients poorly performed in the free recall trials of the FCSRT, with the 80% of the sample presenting an index of sensitivity below the cut-off score (0.74±0.20). Global emotion recognition was impaired in the half of sample (43%), with deficits in the recognition of fear, anger, sadness and surprise. The recognition of fear was the most impaired among the six basic emotions. Patients progressing to multiple-domain MCI showed a more spread impairment at the Ek-60F task.

Discussion and Conclusion: In this study, we provided evidence that amnestic MCI patients with very slow disease progression and medial temporal lobe dysfunctions as shown on FDG PET, are characterized by amnestic syndrome of hippocampal type and impairments in basic emotions recognition. A heterogeneous cognitive profile, however, partly emerged in this MCI population, suggesting possible different pathological substrates as well as additional phenotype-modifiers features that need to be further investigated.

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Picture interpretation task in dementia

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Picture Interpretation Task (PIT) was used by Luria (1966) in pre-frontal impairment as a tool for assessing active visual exploration and its relation with understanding of meaning. A similar method was adopted in Italy for simultaneous agnosia (Bisiach 1983) using Giacomo Favretto's picture "Il Sorcio", in which, even if no animal appears, one can surmise a mouse being hunted. Rosci et al. (2005) validated this picture, for interpretation processes, in a normative sample and in patients affected by prefrontal lesions. The aim of our study is to validate PIT in clinical use with cognitive impairment. 126 patients consecutively examined for cognitive impairment in the Neurology Unit of MultiMedica, Castellanza (Va), were administered a reproduction (29x21 cm) of the picture, along with traditional neuropsychological battery. Our sample includes patients with Alzheimer Disease (N 38), amnesic Mild Cognitive Impairment (N 7), Fronto-Temporal Dementia (N 11), Parkinson Disease (N 14), Vascular Dementia (N 26) and mixed cognitive impairment (N 30); mean age was 75.2±9.7 (range 47-90), mean MMSE raw score was 20,7±4,7 (range 9-30). We calculated and grouped equivalent scores proposed by Rosci based on response time (0-1 pathological; 2-3-4 normal). As incorrect answers present a large heterogeneity in content, we tried to classify responses on the basis of the prevalent process conveyed: correct answer (C), incorrect interpretation (I), description (D), mixed description and interpretation (ID). Two examiners evaluated the content of verbal production with an high inter-rater reliability: k (.04)=.763; $p \leq .001$. Parametric (ANOVA) and non

parametric (Chi-square) tests were used at convenience. According to equivalent scores distribution, significant impairment was found in 83% of the whole group, with no significant difference between dementia groups at chi square. Significant interaction between equivalent scores and MMSE was found [ANOVA: $p \leq .001$]. Kind of responses showed significant interaction with MMSE at ANOVA [$p \leq .001$], showing a decrease of quality of verbal productions along with MMSE scores reduction (C> ID, I, D). Our experience indicates that the test can be easily used in a large sample of patients with different types of dementia, even illiterate and along different stages of disease. Furthermore it seems a good marker of early disorder of logical-inferential abilities. At last, qualitative analysis of the responses may contribute to a better comprehension of the cognitive processes involved in finding of meaning.

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Evaluation of retinal thickness in Alzheimer's disease

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Objectives: It is plausible that degenerative changes occur in both optic nerve fibers and retina in patients with Alzheimer's Disease (AD) in early phase of the disease, even prior to the hippocampal damage [1]. The objective of this study is to assess whether retinal deterioration is an early biomarker of AD pathogenesis and to clarify the possible functional correlation with cognitive decline.

Material: The study was conducted at the "Azienda Ospedaliera S. Andrea" of Rome. We enrolled 25 subjects with probable AD (mean age, 74 ± 3,9 years) and MMSE score ≥ 15 and 17 healthy controls (mean age, 70 ± 6,7 years).

Method: All subjects underwent the Mini Mental State Examination (MMSE) to assess the global cognitive functioning and the Optical Coherent Tomography (OCT) to assess the retinal thickness. In each eye the following parameters were evaluated: Retinal Nerve Fiber Layer (RNFL); perimacular Ganglionar Cell Complex (GCC); Macular Volume (MV). All AD patients underwent a neuropsychological battery. On the basis of the result of each neuropsychological test, we created an index to better estimate the predominantly impaired cognitive functions (memory VS executive functions) in each patient.

Results: Mean MMSE ± SD score was 24,2 ± 3,8 in the AD group and 29,2 ± 0,7 in the healthy group. Thickness of RNFL was significantly reduced in AD subjects compared to controls, with more relevant difference in the nasal (-22,3%) and superior (-17,4%) quadrants. Moreover, GCC and MV values in AD subjects were significantly lower than the ones of the controls. However, no correlation between MMSE score and RNFL and GCC degeneration rate was found in AD subjects. Neuropsychological data did not show any correlation with the retinal modifications.

Discussion and Conclusion: In agreement with previous studies, our results suggest that optic nerve is involved in the early phase of AD [2,3]. At this regard, since amyloid pathology begins many years before clinical manifestation, finding manageable biomarkers for early diagnosis has progressively become of paramount importance. We can hypothesize that retinal characterization using non invasive methods could accurately reveal cortex pathology over time, since its atrophy may be the result of a retrograde transinaptic degeneration. However the relationship between optic nerve degeneration and the clinical progression of the AD still remains unclear. Longitudinal studies on larger sample of patients are needed to clarify if retinal changes might represent an eligible biomarker for developing a non invasive, low-cost, patient-friendly screening tool.

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Computer-based cognitive training for dementia. Results from a randomized controlled trial on MCI, mild AD and healthy ageing

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Objectives: Assessing the efficacy of a novel computer-based cognitive training program in patients with mild Alzheimer disease (mAD), mild cognitive impairment (MCI) and in healthy elderly (HE) subjects.

Materials: The training was administered using a software that resulted from a project co-funded by the European Union (CIP-ICT-PSP) (http://www.cognitivetraining.eu) called Sociable and operating on a touch-screen computer. The software included exercises for the process based cognitive training (pb-CT) for the different cognitive abilities and an electronic book called Book of Life for the reminescence therapy (RT).

Methods: A multicenter, randomized, controlled trial involved 348 participants with mAD, MCI and HE from four European countries. Participants were randomized in two arms of a crossover design: arm A consisted in 3 months of computerized cognitive training focused on memory and executive functions combined with RT and 3 months of rest; those in arm B underwent the reverse. All participants were followed up for 6 months, with assessments at baseline, at 3 months and at 6 months. The training consisted in 24 one-hour treatment sessions (individual or group) twice weekly for 12 weeks. The primary outcome was the effect of the training on cognitive functions, with specific focus on memory and executive functions performance in the experimental group, compared with the control group. The secondary outcome was the effect of the training on functional abilities assessed with Instrumental Activities of Daily Living (IADL).

Results: We found a significant effect of the training for memory in all three groups on delayed recall of the Rey Auditory Verbal Learning Test and for executive functions in HE on the phonological fluency test. MCI and HE participants maintained these effects at follow-up. MCI and mAD participants also showed a significant effect of the training on the Mini Mental State Examination scale. Participants with mAD showed more stable instrumental activities of daily living during the training versus the rest period.

Discussion: The study showed the efficacy of the computerized cognitive training program combined with reminiscence therapy in mAD and MCI and healthy elderly participants. Effect sizes on memory measures, consistently with previous evidence, were in the medium range. Further studies are needed to assess the specificity of this combined training.

Conclusions: Our results corroborate the positive effect of pb-CT and its maintenance primarily on memory in HE and MCI participants that did not seem to be potentiated by RT. Moreover, our results are very promising for the mAD participants.

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Risk of suicide in patients with frontotemporal dementia: a pilot study

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Objectives: Frontotemporal dementia (FTD) is a clinically heterogeneous syndrome associated with circumscribed degeneration of the prefrontal and anterior temporal cortices and characterized by changes in personality and social conduct. The risk of suicidal behaviour was reported to be more likely among FTD patients as compared with age and gender-matched controls1. The aim of this study was to determine possible risk factors associated to suicidal

thoughts in FTD patients using an extensive neuropsychological and neuropsychiatric evaluation.

Materials & Methods: 20 FTD patients [M/F =11/9; age=70±7.6] diagnosed according to McKhann et al. criteria 2, were recruited at the neurological division of the Department of Neuroscience in Turin. FTD patients were divided in two groups according to the score obtained at the Scale for Suicide Ideation: 9 FTD patients with risk of suicide [5 subjects with suicide ideation and 4 patients who have attempted suicide] and 11 FTD patients without risk of suicide. 9 controls were included in this study. Each group underwent a neuropsychological assessment (including tests on attention, language and executive functions). Neuropsychiatric aspects were investigated using questionnaire on behavioral mood changes. Neuropsychological and neuropsychiatric aspects were compared between groups using one-way ANOVA with a Bonferroni correction. T-test was used for analysis within group of FTD patients with suicide risk.

Results: FTD patients with suicide risk present higher levels of anxiety, stress, depression and hopelessness compared with FTD patients without risk of suicide ($p<.001$) and with control group ($p<.05$). We didn't found a significant difference in levels of apathy and cognitive impairment between the three groups. Both groups of FTD patients present higher levels of impulsivity than controls ($p<.001$). FTD patients without risk of suicide show a lower levels of anxiety and stress compared with control group ($p<.005$). Interestingly, within the group of FTD patients with risk of suicide, subjects who have attempted suicide present a longer disease duration than FTD patients with only suicide ideation ($p=.001$).

Discussion & Conclusions: Our study shows that, in FTD patients, there is a high association between risk of suicidal behaviour and neuropsychiatric aspects such as anxiety, depression and stress. We didn't found a significant difference in level of apathy between the three groups. In line with stress-diathesis model, proposed by Mann3, we can speculate that FTD patients present a neurobiological vulnerability to suicide behaviour; moreover we can assume that disease duration could be a good predictor for future suicide attempts in FTD patients with suicide ideation.

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Prevalence of the cave of septum pellucidum in Alzheimer's dementia: a retrospective case-control study

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Aims: The cave of septum pellucidum (CSP) is an often overlooked cystic anomaly of the median line that is supposed to develop following traumatic brain injury (TBI), which is a well-known risk factor for Alzheimer's dementia (AD). Starting from this premise, our primary aim consisted in assessing CSP prevalence in AD with respect to matched non-demented controls (CTRL). Secondary aims consisted in studying clinical and imaging correlates of the CSP in the recruited AD.

Materials and Methods: A preliminary power calculation was made for this retrospective case-control study and 207 AD and 162 CTRL were recruited at the moment, granting 81% power. Demographical (age, sex and history of TBI) and radiological data (cortical atrophy, Evan's ratio, Fazekas score) were collected. CSP presence and dimension were assessed in double.

Results: CSP was present in 42.5% of AD and 23.5% of CTRL (X2=14.67, $p=0.0001$); furthermore CSP vertical and horizontal dimensions nearly doubled. Comparing AD CSP+ vs. CSP- the only found difference was that the former group was on average two years older but this was not present in CTRL.

Discussion and Conclusion: CSP is increased in AD and might represent a novel risk factor for the disease, albeit this anomaly represents a putative surrogate marker for TBI. This might be especially interesting when thinking that minor repeated

traumas often do not result from patients' medical history. Further studies with different designs should be performed for clarifying this relationship.

Bilateral hippocampal lesions without amnestic syndrome in VGKC limbic encephalitis

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Introduction: Very few studies investigated the neuropsychological profile in autoimmune limbic encephalitis (LE) and showed specific verbal memory deficits in autoimmune LE due to antibodies to the voltage-gated potassium channel complex (VGKC). The aim of this study was to present the cognitive profile of a patient with evidence of bilateral hippocampal alterations due to VGKC-LE.

Case description: A 63 year-old man with a six-month history of autobiographical memory impairment and emotional lability was admitted to the Neurology Unit. The patient underwent brain MRI revealing bilateral increased FLAIR signal intensity in the amygdala and anterior part of the hippocampus, and PET/MRI-FDG scan showing a mild increased tracer uptake in the mesial temporal regions and no body neoplastic lesions. EEG revealed bitemporal bursts of sharp waves. Serum tests were unremarkable except for an increased title of antibodies to VGKC. Baseline neuropsychological evaluation, comprehensive of an extensive test battery for memory (digit span, prose memory and Rey auditory verbal learning test) demonstrated deficits only for sustained attention, processing speed and working memory (MMSE:28/30). Immediate and delayed verbal memory and learning abilities were normal.

Discussion: Despite structural and functional alterations of limbic structures as amygdala and hippocampus, the profile of cognitive impairment in VGKC-LE may not include deficits of verbal memory and learning abilities. This may be due to a partial alteration of the hippocampus involving the anterior part only.

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Pseudobulbar affect in ALS is associated to cognitive impairment

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Aims: Pseudobulbar affect (PBA) is often found in amyotrophic lateral sclerosis (ALS) patients and represents a difficult problem to treat for physicians since the proposed treatments are largely unsatisfactory. This is part might be due to the fact that PBA exact determinants are still uncertain. Aim of this study consisted in attempting to clarify the role of PBA determinants in ALS, characterizing both, cognitive, behavioral and UMN dysfunctions variably expressed by these patients.

Materials and Methods: 50 ALS outpatients were recruited for this study. Each patient underwent to the UMN score including the center for neurologic study lability scale (CNS-LS) and to the ALS-cognitive behavioral screen (ASL-CBS). Furthermore, finger tapping (two trials of 10 sec, dominant hand) were video-recorded for subsequent quantification, and three primitive reflexes tested (PR, i.e., palmomental, corneomandibular and Myerson's sign, assigning one point for each present PR, total score from 0 to 3).

Results: 11 patients (22%) showed CNS-LS scores compatible with PBA (≥13, PBA+). Comparing PBA+ versus PBA-, the former displayed lower cognitive ALS-CBS scores (12.9 ± 3.7 vs. 10.5 ± 2.6, $p=0.03$); accordingly, a negative correlation between CNS-LS and cognitive ALS-CBS scores was found ($r=-0.32$ $p<0.05$). PBA+ patients also had increased expression of PR (45% vs. 15% of subjects that totalized the maximum score, $p<0.05$) and UMN score (5.4 ± 1.0 vs. 10.3 ± 2.6, $p<0.05$). On the other hand, albeit behavioral ALS-CBS and finger tapping scores were lower in PBA+ patients, these differences were not significant.

Discussion and Conclusions: PBA in ALS is related to cognitive dysfunction, besides the already previously reported association with UMN involvement. Increased knowledge on PBA determi-

nants might aid in different strategies for treating this often disabling condition.

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"Probable" cerebral amyloid angiopathy under 55 y.o.: case report

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Background: Cerebral amyloid angiopathy (CAA) is a progressive microvascular amyloidosis affecting the small- and medium-sized arterioles and the capillaries of brain parenchyma and leptomeninges. Most individuals with CAA are asymptomatic; however, some can present with focal neurological symptoms from lobar intracerebral hemorrhages or superficial siderosis. The revised Boston diagnostic criteria for CAA take into account these two clinical-radiological characteristics and an age > 55 years [1]. Few cases of symptomatic CAA in younger adults have been reported so far [2].

Case Report: A 51- year old man with severe intellectual disability due to meningitis in childhood, without mention of additional disorders in his medical history, not taking any drug at home, was hospitalized for sudden onset of psychomotor slowing and transient weakness of his left limbs associated with dyspnea. Chest X-ray showed an overloading of the small circle and left pleural effusion. A first brain CT scan showed a right frontal hypodensity and a subsequent brain MRI with gadolinium enhancement confirmed an intracerebral hemorrhage at the level of the right first frontal gyrus. Epileptiform abnormalities were excluded by EEG. A control CT scan performed after 2 weeks, documented a new minor bleeding in the superficial right temporal region. The caregiver reported additional behavioural changes in the last few days with deflection of mood tone, apathy and a tendency to hyperphagia. A new brain MRI (with T2 * GRE sequences) documented the coexistence of haemosiderin deposits in the prerolandic right frontal gyrus and in the ipsilateral temporo-parietal areas, likely from another previous minor bleeding. Furthermore, blooming black dots were founded in the left parieto- temporal region and right cerebellar hemisphere. Few days later, an acute confusional state with lethargy (GCS : 11/15) suddenly appeared. An urgent CT scan documented a large hemorrhagic area on the left cerebellar hemisphere with surrounding edema and a compression of the fourth ventricle leading the next day to death.

Discussion and Conclusions: The present case fulfills all revised Boston criteria for "probable" CAA, except for age. We suggest that sporadic CAA may be an underdiagnosed entity in younger adults and should therefore be considered in the differential diagnosis of lobar ICH, even in presenile age.

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A novel GRN G.1642_1645DELTGAG mutation is associated with frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP)

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Objectives: The clinical presentation in progranulin gene (GRN) mutation carriers is extremely heterogeneous in terms of symptoms, disease duration and age at onset. The majority of genetic defects in GRN are loss-of-function mutations, causing haploinsufficiency, and are associated with very low plasma progranulin levels. Here we described an American family, which presented a novel mutation in a putative donor splice site, predicted by bioinformatics splice-site analysis (g.1642_1645delTGAG; IVS7+6delTGAG).

Materials: Plasma and DNA were obtained from relatives of the proband; moreover, RNA was directly extracted from three different brain areas of the index case after an autopsy was performed.

Methods: Progranulin plasma levels were evaluated using an ELISA kit (Adipogene, Korea; normality reference >61ng/ml). GRN genotyping was carried out by direct sequencing; Spliceport website was used for bioinformatics splice-site analysis (http://spliceport.cbcb.umd.edu/). A PCR and Real Time PCR was performed to test cerebral progranulin gene expression in comparison with three housekeeping genes.

Results: The index case was a female diagnosed with Frontotemporal Dementia (FTD) with parkinsonism at the age of 66 years. Her family history was positive for dementia (mother died with dementia; a sister aged 73 has Alzheimer's disease; another sister aged 76 has expressive and language dysfunctions). GRN analysis in the proband and two symptomatic sisters showed progranulin plasma levels below the reference threshold. Gene sequencing led to the identification of a novel mutation in a putative donor splice site. All three affected subjects carried the variant. The proband died a few months ago and the autopsy showed the presence of TDP-43 in the brain; PCR and RT-PCR confirmed the lack of progranulin gene expression in association with the variant, but not in control.

Discussion: The segregation of the variant with the disease, the low progranulin plasma levels, and the TDP-positivity in the brain suggest that the variant is pathogenic. Nevertheless, genotipyng in a large cohort of healthy subjects is needed to exclude the possibility that the variant is a rare polymorphism or is in linkage disequilibrium with an unknown pathogenic variant.

Conclusion: We identified a novel GRN mutation in three carriers of the same family, associated with extreme heterogeneous phenotype, including expressive language disorder, FTD, AD, and parkinsonism. In particular we demonstrated the lack of progranulin gene expression in the proband to indicate that the variant is pathogenic according to the GRN loss-of-functions' mechanism and the predictive splice-site analysis.

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Repetitive TMS of the default mode network: a randomized, double-blinded, cross-over study trial in MCI patients

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Objective: Mild cognitive impairment (MCI) has been identified as the earliest clinical condition associated with an increased risk for developing Alzheimer's Disease (AD). The most common clinical presentation of MCI is associated with memory loss as the predominant symptom (amnesic MCI). Recent evidences support strong structural and functional disconnection of the parietal Default Mode Network (DMN) nodes in patients with AD, and less remarkably in those with aMCI. Recent finding suggests that the application of transcranial magnetic stimulation (TMS) over posteromedial cortex including Precuneus (PC) in healthy subjects is able to modulate memory performance. The present double blind randomized cross-over clinical study investigated the efficacy of two weeks of repetitive TMS in modulating cognitive performances in patients with MCI.

Materials: Eleven MCI patients were enrolled in the study.

Method: TMS was applied over PC at 20 Hz, in a 10-session course over 2 weeks in a sham-controlled crossover design. Subjects were randomly assigned to real stimulation or control stimulation (sham). A 2-week washout period was applied following which subjects were crossed over to the alternate treatment for an additional two weeks. Neuropsychological tests (cognitive performances), TMS-EEG co-registrations (cortical activity and reactivity), RS-fMRI (functional connectivity), DW-MRI (structural connectivity) acquisition were obtained at baseline and after two weeks of treatment for real and sham condition.

Results: The patients demonstrated an improvement in episodic memory performance following real stimulation compared to sham stimulation. DISCUSSION: These results support the role of medial parietal region in memory process likely due to modulation of DMN connectivity in aMCI patients.

Conclusions: These findings suggest that TMS may be a potential effective strategy in treatment of MCI patients for whom, currently, there is no available therapy.

RBD in patients with essential tremor: a predictive factor for Lewy body disease?

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Introduction: REM sleep behavior disorder (RBD) is a non motor symptom of Lewy body disease. It can precede the onset of synucleinopathies or occur in their context. RBD is also more prevalent among patients affected by essential tremor (ET) as compared to the general population [1].

Objectives: To evaluate in a cohort of prospectively followed ET patients the conversion rate to Parkinson's disease (PD) or Dementia with Lewy bodies (DLB), and to retrospectively evaluate among the converted patients the presence of RBD in their history. In this way it could be possible to infer the possible predictive value of RBD for the development of PD/DLB among ET patients.

Materials and methods: 106 patients who were diagnosed with ET have been observed for 5 years. Patients underwent MSD-UPDRS part III, CAF, MMSE, TRGRS and EMG. The REM Sleep Behavior Disorder Screening Questionnaire was administered to all patients using the cut-off score of 5. 52 patients developed parkinsonism during the 5 years (29 PD and 23 DLB). 32 patients had a history of RBD and among them 9 evolved into PD and 14 into DLB.

Results: The presence of RBD in patients with ET was found to have a sensitivity of 46% and a specificity of 84% for the progression of these patients to PD or DLB. Finally, the presence of RBD in patients with ET showed a sensitivity of 32% and a specificity of 71% for the occurrence of PD while the presence of RBD in patients with ET showed a sensitivity of 64% and a specificity of 79% for the development of DLB.

Conclusion: The results are significant in the direction of a good specificity attributable to RBD as predictor of the development of a parkinsonian disorder (PD or DLB) in patients with ET. RBD has a high specificity and a high sensitivity in indicating the progression of patients with ET to DLB, but not to PD. This could be explained by the hypothesis that the presence of RBD is mostly connected to the akinetic-rigid form of PD rather than the tremorigen one [2]. The greater sensitivity and specificity for DLB could be explained by the known association between RBD, hallucinations and dementia. Recent studies have re-evalued the prevalence of tremor in DLB [3], strengthening our findings.

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Costs associated with Alzheimer's disease in Italy: baseline results from the GERAS II observational study

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Objectives: To assess baseline Italian costs associated with Alzheimer's disease.

Methods: GERAS II was a prospective, multicentre, observational study reflecting routine care in AD, planned for a 6-month period in Italy and Spain. Community-dwelling patients aged ≥55 years presenting within the normal course of care, with a diagnosis of probable AD (NIA–AA) and a Mini-Mental State Examination (MMSE) score ≤26, were included along with their primary (informal) caregiver. Patients and caregivers were stratified according to patient AD severity (MMSE scores: mild, 21–26; moderate, 15–20; or moderately severe/severe (MS/S), <15). Patient resource use and caregiving hours for the month before baseline were obtained using the Resource Utilization in Dementia instrument; monthly societal costs (caregiver informal care, patient healthcare, patient social care) were estimated using unit costs (year 2013) of services and products. Statistical methods included analysis of variance (for continuous variables).

Results: Overall, 198 patients and their caregivers were included (mild: $n=29$, moderate: $n=80$; MS/S: $n=89$). Mean (SD) patient age was 77.5 (7.23) years, 119 patients (60.1%) were female. No overall clear pattern (according to AD severity) was observed for acetylcholinesterase inhibitor (AChEI) or memantine use ($p=0.086$), although memantine only was taken by a numerically larger proportion of patients with mild AD (33.3% of patients versus 19.1% moderate and 23.5% MS/S). Mean (SD) total caregiving hours/month were 210.9 (177.12), 173.6 (177.82) and 324.2 (197.31) for patients with mild, moderate and MS/S AD, respectively ($p<0.001$ between groups). Mean (SD) total monthly societal costs were €1,850 (1,900.54) for mild AD, €1,552 (1,321.98) for moderate AD, €2,728 (2184.23) for MS/S AD ($p<0.001$ between groups). Caregiver informal care (basic and instrumental caregiver hours) contributed the highest proportion of costs for all severities (€1,370 mild; €1,223 moderate; €2,223 MS/S), followed by patient social care (€270 mild; €199 moderate; €399 MS/S) and patient healthcare (€210 mild; €130 moderate; €106 MS/S).

Discussion: Total Italian societal costs, to which caregiver informal care was the highest contributor, generally increased with higher AD severity. However, costs were slightly lower for moderate than mild AD, which may reflect the observed unusual trend for higher use of caregiver time and memantine in patients with mild versus moderate AD. Our small sample size limits the conclusions that can be drawn.

Conclusions: This study provides information on real world AD patients and cross-sectional cost data that may be useful to the Italian public and decision makers.

Specific measures of verbal memory performances may distinguish Alzheimer's disease from dementia with Lewy bodies

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Introduction: Standard neuropsychological assessment may sometimes not be able to offer useful information for the differential diagnosis of neurodegenerative diseases with cognitive decline. Specific measures of verbal memory and learning could increase diagnostic accuracy of Alzheimer's disease (AD) versus other neurodegenerative dementia.

Objective: To comprehend if measures of verbal memory (learning, forgetting and serial position effects) in a widely used specific cognitive task (Rey's Auditory Verbal Learning Task [RAVLT]) could distinguish dementia with Lewy bodies (DLB) from AD.

Method: 32 AD, 29 DLB, 21 frontotemporal disease (FTD) patients were enrolled in the study and followed longitudinally for 3 years until the diagnosis were made according to standard criteria. 28 normal elderly subjects served as controls (NC). All subjects underwent a baseline neuropsychological assessment including the RAVLT. A part from standard scores of immediate and delayed recall, specific

verbal memory measures were evaluated: verbal learning [immediate recall test: trial 5 minus trial 1], verbal forgetting [trial 6 of delayed recall minus trial 5 of immediate recall], percentage of verbal forgetting [verbal forgetting/trial 5 *percentage] and the serial position effects of immediate (trial 1) and delayed recall (trial 6).

Results: Standard delayed memory scores were worse in AD patients than in DLB ($p=0{,}01$) and FTD ($p=0{,}04$) and each disease group was worse than NC ($p<0.01$) while immediate recall scores were similarly impaired among all disease groups. Rate of verbal learning was normal in DLB and FTD and impaired in AD ($p=0{,}02$) while verbal forgetting scores were pathological in AD, mildly impaired in DLB and normal in FTD. With a cut-off of ≥75% at the verbal forgetting percentage, AD and DLB patients were differently distributed ($z=2.5$, $p<0{,}01$) with 58% of AD versus 21% of DLB patients lying above the cut-off. Considering the serial position effects, AD showed an increased recency effect in the immediate recall respect to DLB and FTD ($p<0{,}01$).

Discussion: Delayed recall, verbal learning, verbal forgetting percentage and immediate recency performances are measures that could help in differentiate AD from DLB. This type of memory deficits in DLB resembles the prevalent encoding deficits of FTD patients.

Evidence for axonal damage in dorsal and ventral dopamine pathways in early Parkinson's disease

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Progressive loss of dopamine neurons in the substantia nigra (SN) is considered the main aspect of neurodegeneration in idiopathic Parkinson's disease (iPD). Recent evidence suggests that axons are more vulnerable to α-synuclein pathology, indicating that degeneration may start in the projections to the striatum, only subsequently affecting SN neural cell bodies. Damage to the mesolimbic system in early disease phase is still controversial, notwithstanding the possible presence of neuropsychiatric symptoms even years before motor onset.

Objective: We measured Dopamine Transporter (DAT) binding potentials in both the nigro-striatal and ventrotegmental-mesolimbic dopaminergic pathways in iPD at the initial clinical stages, in order to specifically assess for different regional vulnerability, and to test the recent hypothesis that considers synaptic dysfunction and axonal damage due to α-synuclein aggregation as a key feature of iPD.

Materials and Methods: We used [11C]FeCIT-PET to measure DAT in 32 iPD patients (disease duration: 20.8±11.5 months) in comparison to 15 healthy controls. The iPD cohort was further divided into three subgroups based on the presence and degree of depressive mood as assessed by UPDRS-I depression scores (=0; =1; ≥2).

Results: We found a predominant impairment in the dorsal putamen (60.4% reduction in DAT availability), whereas the dorsal caudate and ventral striatum were less affected (37.7% and 31.1% DAT reductions). Notably, the SN and ventral tegmental area (VTA) showed an even more limited DAT binding decrease (21.3% and 23.6% DAT reductions, respectively). iPD patients with more severe depressive mood showed a more reduced DAT availability in the VTA, a crucial part of mesolimbic system.

Conclusions: These results support the hypothesis that neurodegeneration in iPD is initially more prominent in the basal ganglia axon terminals. This evidence of a relatively spared neuronal dopamine cell bodies would justify neuroprotective interventions even if patients have already manifested clinical symptoms.

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Semantic and nonfluent aphasic variants are predominant frontotemporal lobar degeneration phenotypes in TBK1 carriers

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Objectives: TBK1 loss-of-function mutations were reported in rare patients with ALS, isolated or secondarily associated with dementia [1, 2] and in patients with frontotemporal lobar degeneration (FTLD) [3]. In this study, TBK1 was studied in a French cohort of 302 FTLD patients. We described in detail the clinical, cognitive and neuroimaging characteristics of the four TBK1 mutation carriers presenting a FTLD clinical phenotype.

Patients and Methods: We studied 302 unrelated FTLD patients (143 familial) including 182 probands with isolated FTLD and 120 that secondarily developed ALS. The main FTLD and ALS gene have been previously excluded. TBK1 gene has been sequenced in the probands, and was secondarily analysed in family members of mutation carriers when DNA was available. Sanger sequencing of the 20 coding exons (2 to 21) of TBK1 gene (NM_013254.3) was performed.

Results: Four probands carried loss-of-function mutations (p.Thr156ArgfsX6, p.Tyr482X, p.Gln655X and IVS18-2A>G). Two patients initially presented semantic variant of frontotemporal dementia (svFTD); two other developed non-fluent variant of FTD (nfvFTD) and corticobasal syndrome (CBS), associated with severe anterior temporal and opercular atrophy. All patients secondarily developed ALS.

Discussion and conclusion: We demonstrated that TBK1 FTLD phenotypes are larger than initially reported, and are mainly characterized by semantic dementia, speech apraxia and nfvFTLD/CBS. This study will have important impact for clinical practice, enlarging the phenotypic spectrum of the disease. Aphasic presentations seem to be more characteristic of TBK1 mutations than the bvFTD phenotype. TBK1 mutations should be thus searched for in patients presenting isolated FTD at onset, particularly in rare aphasic cases who secondarily develop ALS.

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"Alimentalamente (feed-your-mind)" project

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Introduction: Every human being starts his development from a determined genetic set on which he builds, through the years, his own characteristics. This set can contain a predisposition to cognitive decay, which can either or not manifest, depending on one's own behaviors. Literature confirms that the accumulation of "cognitive reserves" can significantly postpone such a decay. We developed and built an educational project addressing middle and high schools' students. The project was born after a couple meetings with groups of teenagers in April and September 2015. The meetings were organized as cultural drink-breaks called "Alimentalamente (feed-your-mind)".

Equipment's and Methods: We firstly consider to realize a project addressing the last two years of high school's students. We will involve volunteers associations to help us enter the schools. The project will be made up off six meetings of the duration of a couple of hours each. The meetings' title are:

1) Regular working of the human brain
2) Negative consequences of alcohol and tobacco on the brain
3) Negative consequences of natural and synthetic drugs on the brain
4) Negative consequences of compulsive gambling on the brain
5) Negative consequences of cyber-addiction and of "trash mass culture" on the brain
6) A proper lifestyle of health alimentation, physical activity and cultural stimulation

The choice to divide the different topics has the goal to enforce the delivered messages. The two hours duration of a meeting is intended to permit also an open discussion with the audience about the discussed themes. In conclusion of the last meeting we will address to the audience a learning-test, without the intent to express a school mark, but to quantify the reception of our message. The learning-test will be made up off 12 multiple-choice questions, two questions about each meeting. Assuming we can manage to start the project both in technical institutes and lyceums, we will also be able to compare the results to quantify the interest and concentration of the students belonging to different realities.

Conclusions: Our message contains clear and documented explanations which can make the kids aware of the biological consequences of certain behaviors. This awareness make them informed and so directly responsible of their both positive and negative choices. The real effectiveness of the project will be evaluated only with time as we aren't anyway able to preventively quantify individual choices.

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Bioimpedance vector analysis in mild cognitive impairment and Alzheimer's dementia: a cross sectional study

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Objective: The aim of this study was to analyze variations of nutritional status in patients with Alzheimer's disease (AD) and subjects with Mild Cognitive Impairment (MCI) by means of bioelectrical impedance vector analysis.

Methods: In a University-Hospital setting, we performed a cross-sectional study recruiting 59 patients with AD (38 women, 24 men), 34 subjects with MCI (20 women, 14 men) and 58 elderly controls (29 women, 29 men). Nutritional status was evaluated by anthropometry (body mass index; calf, upper arm and waist circumferences), Mini Nutritional Assessment (MNA); bioelectrical impedance vector analysis (BIVA). Variables were analysed by analysis of variance with subjects grouped by cognitive status within gender.

Results: Sociodemographic variables did not differ among AD, MCI and elderly controls, except for females' age (AD patients were older than MCI and controls), whereby age was used as covariate in a general linear multivariate model. The phase angle, ratio of reactance to height, ratio of impedance to height were significantly different in AD patients than in controls in both sexes. MNA (total score) in both sexes was significantly lower in AD patients, but not in MCI subjects with respect to controls; BIVA detected a lower ratio of impedance to height (Z/h) in men with MCI with respect to controls. No differences in BIVA analysis were found in women with MCI with respect to controls.

Conclusions: Bioelectrical characteristics were significantly different in patients with AD with respect to controls. Longitudinal studies will be required to determine if BIVA could reflect early AD-changes in body composition in MCI.

Controversial role of NOTCH3 gene cysteine sparing mutations associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) phenotype: are they causative of the disease?

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Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common hereditary subcortical vascular dementia. CADASIL is a cerebral small vessel disorder caused by NOTCH3 gene mutations affecting cysteine residues. However, some NOTCH3 variations involving other residues than cysteine are known and their pathogenic role remains actually debatable [1]. This study described 8 CADASIL-like patients carrying 3 different missense cysteine sparing NOTCH3 mutations.

Methods: Eight patients showing a CADASIL-like phenotype were addressed to genetic analysis, according to the CADASIL scale for diagnostic suspicion (cut-off >14) [2]. NOTCH3 exons 2-24 and splice junctions were directly sequenced on genomic DNA; in patients carrying the P496L variant, all 33 exons were investigated. Skin biopsies on 5 patients were performed from the upper arm. Ultrathin sections, stained with uranyl acetate and lead citrate, were observed in an electron microscope.

Results: The known NOTCH3 variant A1020P was found in two unrelated patients, affected by late onset-mild cognitive impairment associated to parkinsonism and epilepsy, respectively. In other 4 patients (two siblings and two unrelated patients), A1020P was associated with the known variant V1183M. In three of them, clinical pictures consisted in early onset dementia and parkinsonism; the fourth patient was affected by ischemic stroke at young age. Finally, other two siblings carried the known variant P496L and were affected by vascular dementia. In silico analysis predicted A1020P as "tolerated", whereas V1183M and P496L were predicted as "damaging". A familial history for dementia, headache or stroke was present in the V1183M and P496L carriers. Clinical features were suggestive for CADASIL (CADASIL scale score range: 14-18). Brain MRI showed a severe leukoencephalopathy diffuse to external capsule and subcortical infarcts in all patients. Granular osmiophilic material (GOM) deposits in vascular smooth muscle cells resulted absent in 5 examined patients (A1020P, A1020P/V1183M and P496L carriers).

Discussion and Conclusions: The A1020P variation seems to be not causative of CADASIL, as confirmed by both in silico data and the lack of positive familial history. The role of P496L and V1183M variations is controversial: the two variations could be pathogenic, given the recurrent clinical phenotype in families of the carriers and the in silico finding about a damaging role of these variations on the protein; GOM analysis resulted negative, but their sensitivity in CADASIL is contradictory and not conclusive for the diagnosis [3]. This is the first description of clinical CADASIL-like phenotype associated to the P496L and V1183M mutations.

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Cognitive trajectory of psychosis subtypes in Alzheimer's disease: preliminary results from non linear mixed effect (NLME) models in Alzheimer's disease neuroimaging initiative (ADNI2)

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Objectives: The psychosis phenotype in Alzheimer's disease (AD) may be comprised of two subtypes: paranoid (persecutory delusions) and misidentification (misidentification phenomena +- visual and auditory hallucinations), and each subtype may have distinct neuropathological underpinnings. There is robust evidence that psychosis is associated with a faster speed of cognitive decline using linear and non-linear models of disease progression, but whether the trajectory is subtype dependent has not been explored. This study aimed to investigate the impact of psychosis subtypes on the rate of disease progression evaluated by the Alzheimer's Disease Assessment Scale (Adas-cog), in a longitudinal dataset ADNI2.

Materials and Methods: Data on ADNI2 participants who were categorised as late mild cognitive impairment (LMCI) or AD over a 4 years observation period were included in the analysis ($n=528$). There were 96 psychotic subjects, among these 38 with pure paranoid subtype, 29 pure misidentification subtype and 29 with both. Potential confounding covariates, including Mini Mental State Examination, Functional Activity Questionnaire, Clinical Dementia Rating, Neuropsychiatric Inventory, age, education, gender, apoE4 status and concomitant medications were also explored. Data were fitted with logistic models based on Richard's function (Samtani 2012). Estimation was performed using the SAEM algorithm implemented in the Monolix software (version 4.3.3). Model selection was made using visual predictive checks and likelihood ratio test. The effect of psychosis and paranoid and misidentification subtypes were explored on the rate of disease progression.

Results: The presence of psychotic symptoms significantly increased the rate of disease progression, indexed by an increase from 1,3 to 3.0% in ADAS-cog scores per year (P-value=0.00061): Hallucinations increased the rate of progression from 1.5 to 3.8% (P-value=0.0012) and delusions from 1.4 to 3.2% (P-value=0.0017). The presence of both psychotic subtypes increased the rate of progression from 1.3 to 3.9% (P-value=0.0016) misidentification subtype alone from 1.3 to 2.8% (P-value=0.021), whereas paranoid subtype was not significantly associated with change in the rate of progression.

Discussion: We found that the presence of psychosis determinates faster cognitive decline, confirming previous findings. The presence of both subtypes, and of the misidentification subtype alone, is associated with faster disease progression, after controlling for potential confounding factors. Instead paranoid subtype was found not to have impact on disease progression.

Conclusions: We presented a disease progression model in AD and LMCI incorporating the impact of psychosis subtype on the worsening of ADAS-cog scores over the time.

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Phenomenology of GBA gene mutation: Chieti experience

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Background: The GBA gene encodes the lysomal hydrolase glucocerebrosidase. Bi-allelic GBA mutations cause Gaucher disease; both mono- and bi-allelic mutations are associated with increased risk for Parkinson's disease (PD) [1]. The GBA mutations occur in 5-10% of PD patients [2]. If the clinical features of PD patients with or without GBA mutations are different is still unclear. In the present work, we describe the clinical phenomenology of six PD patients with GBA mutation followed in our Center for Movement Disorders.

Methods and results: Six patients of our cohort of 155 PD-DLB-PDD patients analyzed for genetic mutation, presented with GBA mutations (1 homozygous pattern, 5 heterozygous pattern). Three patients had a family history of parkinsonian disorders. At the onset, all patients showed a good levodopa response with a reduction on UPDRS III scores of at least 45%. Rigidity and bradykinesia (asymmetric in 83.3% of the patients) were more frequent than tremor (100% vs 50%). Vertical gaze palsy with limitation and fragmentation of saccades was found in all. All the six patients had neuropsychiatric disturbances, characterized by depression. Eating disorders were reported by 50% of patients. Visual hallucinations (VH) were present in 4 patients. At the PD onset, only two patients had a normal score on MMSE and only two had a normal visuo-spatial functions. REM sleep behavior disorder (RBD) were present in 50% of the patients. In GBA-patients, in comparison with our cohort of PD patients, were present slightly earlier age of onset (67.6±4.9 vs 73.0±7.2) and greater frequency of cognitive impairment (MMSE 22.6±7.6 vs 26.0±3.8), together with behavioral symptoms. Four GBA mutated patients received a clinical diagnosis of dementia with Lewy Bodies, one patient was diagnoses as affected by PD with dementia. Our patients also showed vertical gaze palsy with limitation and fragmentation of saccades, never previously described in GBA-mutation associated parkinsonism.

Discussion: PD patients with GBA mutations were indistinguishable from idiopathic PD as related to motor symptoms, but seemed to be more prone to develop cognitive and behavioral symptoms [3]. In conclusion, in our case series we found a high incidence of parkinsonian dementia features. Pathologic GBA mutations causing reduced enzymatic functions, cause increased α-synuclein deposition and accumulation of β-amyloid and amyloid-precursor protein, neuronal susceptibility to metal ions, oxidative stress, microglial and immune activation. Further studies are needed to illustrate the relationship between these genetic and histopathological findings and consequent clinical phenotype of GBA mutations.

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Estimating the association of 5HTTLPR polymorphism with delusions in Alzheimer's disease

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Objectives: To determine whether the 5HTTLPR serotonin transporter gene polymorphism is associated with delusions in patients with Alzheimer's disease (AD).

Design: Prospective cohort study.

Participants: A total of 257 consecutive AD patients attending the Alzheimer's Evaluation Unit of the IRCCS "Casa Sollievo della Sofferenza" in San Giovanni Rotondo, Italy were included in this study. Of these, 171 AD patients with delusions (AD-D) and 86 AD patients without delusions (AD-noD).

Measurements: All participants underwent a comprehensive evaluation with standardized CGA,

Mini-Mental State Examination (MMSE), and Neuropsychiatric Inventory (NPI). Individuals were genotyped for the 5HTTLPR polymorphism in blinded fashion.

Results: No significant difference were showed between the two groups on sex, mean age, educational level and scores in CGA. AD-D patients showed significantly an higher cognitive impairment in MMSE ($p = 0.047$), and an higher score in NPI ($p < 0.0001$) and NPI-Distress ($p < 0.0001$) than AD-noD patients. Homozygosity for the L/L genotype were associated with a lower MMSE ($p = 0.011$) and an increased risk for delusions ($p < 0.0001$).

Conclusions: This study showed that the 5HTTLPR polymorphism is associated with delusions in AD, with important implications regarding the mechanisms underlying this symptom. Because of this, it could be possible to implement a personalized therapy for AD patients with delusions.

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Cognitive and behavioral effects of tDCS in frontotemporal dementia

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Objective: Pharmacological treatment for dementia is limited (Hansen N., 2012), alternative therapeutic approaches are worth pursuing, such as non-invasive brain stimulation with transcranial direct current (tDCS). tDCS has been demonstrated to affect the neuronal excitability and reported to enhance cognitive performance in dementia and in other neurological and psychiatric diseases (Ferrucci et al., 2008, Hansen N., 2012). The aim of this study is to evaluate the cognitive and behavioral effects of tDCS in patients with Fronto Temporal Dementia (FTD).

Methods: We recruited 13 patients (mean age±SD: 70.8±4.9, 6 men) with FTD according to the by published criteria (Lund/Manchester, 1994) (MMSE score mean±SD: 25±3.4). We delivered anodal tDCS (AtDCS) and sham tDCS (StDCS) over the temporo-parietal cortex (2 mA intensity, 20 minutes) for 5 consecutive days. In each session Visual Recognition Task (VRT), Phonemic Fluency Task (PFT), Picture Naming Task (PNT), and Neuropsychiatric Inventory (NPI) were administered at baseline (T0) after the last tDCS cycle on day 5 (T1), one week (T2) and one month (T3) after the end of the treatment. Non parametric Wilcoxon was used to compare anodal versus sham condition.

Results: Our results showed that AtDCS produced a significant improvement in NPI scores compared to sham condition at T1 and T2 (Anodal vs Sham: T1: $p=0.02$; T2: $p=0.04$; T3: $p=0.064$), but not change in cognitive functions was found ($p >0.05$).

Discussion: Our findings showed that AtDCS, over the temporo-parietal cortex, improves behavior in FTD patients but fail to improve cognitive functions. Because preliminary data showed that tDCS could interfere with several mechanisms potentially altered in neurodegenerative diseases, it is reasonable to investigate tDCS effects as a therapeutic instrument in dementia.

Conclusion: Future large-scale clinical and mechanism-oriented studies may enable us to identify its therapeutic validity in dementia disorders.

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Spirochetes infection and frontotemporal dementia: a potential link to pathogenesis?

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A potential link has been hypothesized between spirochetal infection and Alzheimer's Disease (AD). A potential slow-acting unconventional infectious agent acquired in youth becomes active after years leading to the pathogenetic cascade responsible of beta amyloid production. This issue has never been explored in other forms of degenerative dementia. By contrast it is acknowledged that neurosyphilis can cause slowly progressive dementia and there is mention in the literature of neurosyphilis presenting with the features of primary progressive non-fluent aphasia (NFPA). We decided to review clinical records of patients studied in our Centre for Cognitive Impairment and Dementias from January 2011 and August 2015 during a day-hospital session to explore the frequency of syphilis positive serology. All patients underwent routine blood exams including syphilis screening (VDRL and TPHA test), neuropsychological evaluation, electroencephalogram and carotid ultrasonography. All patients had available neuroimaging (CT or MR scan) and some of them cerebral PET/SPECT scan. A total of 817 consecutive patients were reviewed. Nine patients of 817 showed positive syphilis serology. In these patients syphilis screening revealed very low titres and were judged as expression of a remote infection. The FTA-IgM test was negative in all cases. Clinically, five patients showed progressive memory loss; four of them showed a neuropsychological pattern in keeping with AD and a fifth showed isolated memory impairment (MCI). One patient was diagnosed as behavioural variant of Frontotemporal Dementia (FTD). Three patients presented with NFPA. All patients had a normal neurological examination. MR imaging in all patients revealed no signs of neurosyphilis. Five patients agreed to undergo a lumbar puncture, which proved negative for syphilitic infection. Patients who declined lumbar puncture had a one year follow-up: syphilis titres did not increase with time and patients did not develop other neurological signs in keeping with neurosyphilis. Statistical analysis was performed in the two dementia groups (AD and FTD) in which patients with positive syphilis serology were present. Fisher's Exact Test revealed a trend towards more frequent syphilitic infection in FTD ($p=0.49$). The present retrospective data suggest a higher frequency of spirochetal infection in frontotemporal dementia compared to Alzheimer's Disease. Patients with NFPA seem to show a particularly high presence (23% of cases) when compared to other variants of the FTD. In view of the relatively small numbers we cannot exclude the possibility that this finding arose by chance. Nevertheless, the findings suggest that further study is merited.

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Unusual phenotypic patterns in familiar frontotemporal dementia

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Background: Frontotemporal lobar degeneration (FTLD) shows heterogeneous clinical phenotypes. Approximately 40% of FTLD patients have a history that is suggestive of familial transmission and the most common genes associated are GRN, MAPT and C9ORF72. We describe an Italian family showing different clinical phenotypes of the FTD spectrum without a known genetic mutation.

Case Report: The family was native of Ancona, Italy. Three siblings, two sisters (S1 e S2) and one brother (B1) came to our attention and are described in details. History of dementia characterized by prominent behaviour problems was reported in other 7 members of the family (father,grand-father, three uncles and two cousins). S1 is a 64 year-old, right-handed lady with an atypical semantic dementia. She presented with a two year history of progressive language disturbance, mainly characterized by world finding problems, semantic and phonological

paraphasias, associated with behavioural alterations such as impulsiveness and verbal aggressiveness. The neuropsycological evaluation revealed an atypical language disturbance characterized by a prevalent semantic impairment together with phonological and syntactical errors. Semantic breakdown was present also in the non-verbal domain with associated agnosia and prosopoagnosia. MRI showed predominantly left temporal atrophy. PET revealed decreased metabolic activity in left frontal and temporal areas. S2 is a 65 year-old, right-handed lady with behavioral variant of FTD. It was referred a two year history of attention disturbance and behavioural problems including verbal aggressiveness, impulsiveness, binge eating, compulsive attitudes together with psychosis (delusions and visual hallucinations). Neuropsycological evaluation showed sever frontal behavioural syndrome. CT scan showed predominantly right fronto-temporal atrophy. B1 is a 61 year-old, right-handed man with Corticobasal syndrome. He referred a two year history of progressive motor impairment in his left arm associated with mild behavioural alterations such as verbal dishinibition and irritability. Neurological examination showed an extrapyramidal syndrome. Neuropsycological evaluation revealed ideomotor apraxia and astereognosia in his left upper limb. MRI scan showed right fronto-parietal cortical atrophy and FDG-PET revealed decreased metabolic activity in the same regions. Genetical analysis, including C9ORF72, MAPT, GRN, did not reveal mutations in the three siblings.

Conclusion: Likely the family described carries still unknown genetic mutation and permit to infer that FTD Italian families should carry different mutations from the ones described in other countries.

Genetic Creutzfeldt-Jakob disease presenting with insomnia

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Background: E200K is the most frequent cause of genetic Creutzfeldt-Jakob disease (CJD). Usually patients with this mutation present at the onset a rapidly progressive dementia, hallucinations or walking difficulties. Insomnia has been reported only later in the disease.

Objective: To report a 59 years old patient with genetic CJD presenting with insomnia.

Methods: The authors characterized clinical, neuroradiological and neurophisiolocial features of the disease using MRI, EEG and prion protein (PrP) gene (PRNP) analysis.

Results: The patient presented a drug resistant insomnia and this was the only symptom for one month. He later developed tremor in right hand that rapidly spread to all four limbs. When he was referred to our hospital he was dysatric, disfagic, dysmetric, had bilateral tremor and memory loss. He rapidly progressed developing myoclonus, vertical gaze palsy and tonic-clonic seizures. EEG showed sharp waves and periodism bilaterally with left prevalence. Brain MRI revealed DWI abnormalities in basal ganglia and talami bilaterally and cortical ribboning. Genetic testing demonstrated a E200K mutation with Methionine-Methionine at codon 129 of PRNP. The patient died eight days after the admission and three months after the first symptom onset.

Conclusion: Insomnia may be the first and only symptom at onset. This report confirms the heterogeneity of symptoms at presentation in genetic CJD.

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The JPND-MEETINGDEM project: a combined support programme for people with dementia (PWD) and their caregivers: first results in Italy

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Background: The MEETINGDEM Project (MCSP) aims to implement an innovative approach to support people with mild-moderate dementia (PWD) and their families in Italy, Poland and UK. This person-centered approach has already been implemented in the Netherlands and demonstrated benefits (reduced behavioural and mood problems -BPSD-, delayed admission to residential care, higher levels of carer competence and lower levels of burden). MCSP proposes activities to stimulate PWD, services and support for caregivers and for both.

Objectives: To investigate differences between PWD and caregivers participating in the MCSP (MCSP; 12+12) and a control group (usual care; 10+10).

Method: A pretest-posttest control group design was applied (ANOVA repeated measures 2x2). PWD and caregivers were recruited according to the Global Deterioration Scale score (GDS:4-5). Dyads of the experimental group were assessed at the start of participation in MCSP (t0) and after 7 months (t1) to evaluate behavioural disturbances, quality of life and global cognitive level; dyads of the control group ($n=7$, 3 dyads dropped-out) were assessed with the same tools at t0 and t1.

- Neuropsychiatric Inventory -NPI-
- Ucla Loneliness Scale -UCLA-
- General Health Questionnaire -GHQ 12-
- Short Sense of Competence Questionnaire -SSCQ-
- Dementia Quality of Life -D-QoL-
- Quality of Life in Alzheimer's Disease -QOL-AD-
- Mini Mental State Examination -MMSE-

Results: Statistically significant differences between MC and control group (at t0 and t1; no baseline differences) were identified in:

- NPI (FxG – p= 0,005 and Distress of caregiver p = <0,001)
- UCLA Loneliness Scale (p = 0,006)
- GHQ (3 factor model, total score; Factor "anxiety and depression") (Total score p = 0,004; Domain 1 – anxiety and depression- p = 0,001)

Discussion: Significant differences were found in perceived distress, loneliness and general health: these pilot data seem support the efficacy of the MC approach to sustain caregivers of PWD. A significant difference was also found as far as FxG of BPSD is concerned. This finding is in agreement with previous studies demonstrating the efficacy of multidimensional approaches to reduce BPSD. There was no statistically significant difference in global cognitive level (MMSE) as expected.

Conclusion: MEETINGDEM started in March 2014 and will end in February 2017. We present the preliminary results in Italy. Currently there is no cure for dementia, but possibly its impact on quality of life of caregiver can be changed and BPSD can be reduced by combined support for PWD and caregivers.

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The relationship between homocisteine and cognitive profile in Alzheimer disease

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Background: There is growing evidence that a high level of homocysteine (Hcy) is a risk factor for Alzheimer Disease (AD). It has been demonstrated that individuals with high-Hcy levels have lower gray matter thickness and volumes in several brain regions. There is evidence that behavioural symptoms in AD (BPSD) are positively correlated with Hcy plasma level. To our knowledge, the potential impact of high levels of Hcy in specific cognitive functions in AD has never been investigated.

Objective: To determine the influence of Hcy level on cognitive profile in AD.

Methods: 323 patients with AD were enrolled in a prospective study; they underwent an extensive neuropsychological examination exploring many cognitive domains (memory, language, visuoperception, visuospatial abilities, executive function, constructional praxis, ideomotor praxis). The effects of Hcy levels and of other risk factors (including cholesterol, smoking habits, triglycerides, apoE) were analysed.

Results: Generalized Liner Model showed a significant drop in performance with increasing Hcy that was highly specific for memory tests (of both verbal and visuo-spatial material, and on both short and long term recall) and for Luria's motor planning test; these were pure effects of Hcy as effects of all other predictors were partialled out.

Conclusions: We showed for the first time that high Hcy levels correlate with poor performance in long- and short- term spatial and verbal memory and with motor planning in AD. These results may support the hypothesis that Hcy has an impact on medial temporal and dorsal frontal areas, and are in line with neuroimaging studies showing reduced thickness of temporal cortex in patients with AD and hyperhomocysteinemia.

Are raw scores on memory tests better than age- and education-adjusted scores for predicting progression from amnesic mild cognitive impairment to AD ?

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Objectives: We investigated the recently advanced proposal that unadjusted test scores obtained at baseline on long-term memory tests are more reliable than age- and education-corrected scores in predicting progression from aMCI to AD.

Materials: 270 aMCI patients underwent extensive neurological and neuropsychological examinations both at baseline and at the follow-up, conducted at least 3 years later.

Methods: Predictive capacity of raw, age-corrected, education-corrected and fully corrected scores on RAVLT immediate and delayed recall was compared by examining the area under the ROC curves (AUCs) of all of these scores to assess which scores achieves the better reliability in predicting conversion to dementia. The condition (aMCI stable vs converted) was analyzed to assess the odds ratios resulting from a logistic regression on the corrected and uncorrected scores of RAVLT immediate and delayed recall.

Results: At the final follow-up 190 patients were stable or had reverted to normality and 80 patients (29.6%) had converted to overt dementia. In a logistic regression analyses for RAVLT immediate recall, conversion was predicted by the 'raw' (OR 0.950, $p=0.041$) and the 'age corrected' scores (OR 0.952, $p=0.047$) but not by the 'education corrected'(OR 0.965, $p=0.161$) and the 'age-and-education-corrected' scores (OR 0.973, $p=0.271$). For RAVLT delayed recall, all the condition were able to predict conversion with a variation in risk ranging between 32.4% (uncorrected scores) and 24.8% (age and education corrected scores). The AUC of the ROC curves for the RAVLT immediate recall were 0.6063 for corrected score; 0.6409 for age-corrected score; 0.6407 for education-corrected score; and 0.6549 for the raw score; the AUCs were all comparable ($\chi2=6.41$; $p = 0.0933$). The AUC of the ROC curves for the RAVLT delayed recall were 0.7191for corrected score; 0.7301 for age-corrected score; 0.7268 for education-corrected score; and 0.7402 for the raw score; the AUCs were all comparable ($\chi2=2.70$; $p = 0.4396$).

Conclusion: Even if both in immediate and in delayed recall the ROCs of 'raw scores' were generally higher than the other ROCs on corrected scores, these differences did not reach the level of statistical significance, failing to support the claim that unadjusted test scores are superior to age- and education-corrected scores in predicting progression from aMCI to AD.

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Angela R before Auguste D: a case of familial Alzheimer's disease before Alzheimer's description

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Twenty years ago, Sherrington et al discovered Presenilin 1 (PSEN1), the main gene responsible for familial Alzheimer's disease (AD). An important contribution to the PSEN1 cloning was given by the rebuilding of the N family, a large Calabrian kindred affected by early onset autosomal dominant AD, encompassing 11 generations and 138 affected subjects1. The identification of many patients in this pedigree was achieved throughout the study of medical records in the archives of the Psychiatric Hospital of Girifalco, Italy. We reported the clinical record of an ancestor of the N family, dating back to 1904. Angela R was born in 1865 in Nicastro. Her mother and two maternal aunts were reported as "mad". The first signs occurred at 35 years, after a pregnancy, when she did not recognize her friend's infant daughter and tried to strangle her in the cradle. Over the following years she became aggressive and disoriented, she wildly beat her children because she did not recognize them and she often ran away from home. At admission to the Psychiatric Hospital, she looked like an old woman with deep wrinkles; she was paratonic, voluntary movements were slow. The clinical record reports: "she doesn't recognize anybody, she doesn't understand anything, she doesn't answer any questions, she is emotionally flat. She stays in bed moving her eyes around, without any kind of thoughts driving her mind or triggering any movements of her limbs. She mumbles incomprehensible words. She seems astonished and scared". She died because of marasmus, at 40 years. The clinical picture is consistent with a diagnosis of non-amnestic probable AD2. Bruni et al described four different phenotypes in the N family and the clinical features of Angela R mirror the "dysexecutive" one1. The evidence of the causative genetic mutation PSEN1-Met146Leu in her genealogically proven descendants together with their neuropathological features, made certain the a posteriori AD diagnosis in Angela R. The case of Angela R precedes of three years Alzheimer's description of Auguste D3, representing the first known case of familial AD, and crucially contributed to the genealogical reconstruction of the N family, allowing to include in the same kindred several patients and branches with the same clinical picture, but apparently separated. The enormous archives of the Girifalco Hospital represented a wealth of medical and historical knowledge and the starting point of the AD italoamerican researches that finally led to one of the main discoveries in neurogenetic field.

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Cognitive decline and late-life depression in the elderly: Alzheimer's disease or pseudodementia?

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Background and Objective: Cognitive impairment and depression are two of the most important burdens for elderly people. Therefore, elderly can be potentially affected by two different patterns of mixed affective-cognitive deficits, which can be scarcely distinguished: pseudodementia (PDEM), in which psychiatric disturbances cause secondary cognitive decline; Alzheimer's Disease (AD), representing a primary, progressive, irreversible dementia process showing secondary psychiatric symptoms. Considering that criteria for an early differential diagnosis between PDEM and AD are lacking, the aim of this study was to evaluate the usefulness of cerebrospinal fluid (CSF) AD biomarkers (Aβ42, t-tau and p-tau) analysis as a potential approach to early discriminate PDEM from neurodegenerative AD dementia in clinical practice.

Methods: We observed untreated elderly patients (≥65 year old) affected by cognitive decline (MMSE

15-24) coupled with major depressive symptoms. Patients underwent laboratory tests, neuropsychological testing, EEG, brain MRI, 18FFDG-PET, and lumbar puncture for CSF analysis. At the end of the diagnostic workup we divided patients affected by mixed affective-cognitive disturbances in two subgroups, named AD and PDEM groups, according to standard criteria (1-2). We follow those patients for you years in order to check the early diagnosis performed. We also enrolled a control group similar for age and sex with AD and PDEM groups.

Results: 154 AD patients and 47 PDEM patients underwent the study protocol and completed the two-year follow up. Control group 1 counted 58 patients. PDEM patients showed significant higher CSF levels of Aβ42 (813.33±232.96 vs 313.34±126.69, $p<0.001$) coupled with significant lower t-tau (205.41±83.22 vs 676.60±373.53, $p<0.001$) and p-tau (33.46±9.56 vs 86.67±51.28) CSF levels with respect to AD patients. Notably, all the PDEM patients showed normal CSF Aβ42 levels (> 550 pg/mL). Moreover, PDEM patients showed no differences in the assessment of CSF Aβ42 (813.33±232.96 vs 845.10±231.41), t-tau (205.41±83.22 vs 209.48±87.63) and p-tau (33.46±9.56 vs 39.62±12.22) concentrations than controls.

Discussion and Conclusion: The key finding of this study is that in case of co-existence of cognitive impairment and depressive symptoms in the elderly, CSF biomarkers are useful to discriminate PDEM from AD. In this study, in fact, PDEM patients, unlike AD ones, showed no changes in CSF beta-amyloid and tau proteins contents, exhibiting a CSF biomarkers profile similar to that of the control population. Thus, we suggest that the assessment of CSF biomarkers can be an helpful instrument in achieving the differential diagnosis between PDEM and AD patients at an individual level.

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A case of genetically confirmed diagnosis of Alzheimer disease with neuropshychological, CSF and metabolic pattern of frontotemporal dementia

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A 51 years old Italian man was admitted to our Clinic because of the occurrence of change in behaviour and personality, cognitive problems, urinary incontinence. His family history concerning dementia was negative, except for a maternal aunt who was affected by cognitive decline. Neuropsychological assessment showed significant apathy, anosognosy, impairment in verbal initiative and verbal fluency, deficit in long term memory. The MMSE score was 21. An MRI showed diffuse fronto-temporal-parietal atrophy with bilateral involvement of hyppocampus, especially on the right side, in absence of vascular lesions. Neurological examination showed resting tremor of the left hand and the occurrence of primitive reflexes. The FDG PET scan showed hypometabolism in the bilateral anterior prefrontal cortex, anterior cingulate cortex and medial frontal cortex, especially on the right side; there was evidence also of bilateral hyppocampal hypometabolism, whereas the metabolism in the posterolateral parietal cortex, posterior cingulate cortex and in precuneus was preserved. These results were suggestive of FTD. A lumbar puncture was performed in order to dose CSF biomarkers: the level of beta-amyloid (1-42) (771 pg/ml) and p-Tau (35 pg/ml) were normal, whereas total-Tau was slight increased (354 pg/ml). Genetic analysis revealed APP A713T mutation. Following this result, according to the current diagnostic criteria (IWG2, NIA-AA), a genetically confirmed diagnosis of AD was made.

Conclusions: 1)This case suggests that familial AD may be considered a disease with both dominant and recessive traits of inheritance. 2)The biomarkers profile was indicative of an FTD pathology, whereas the occurrence of genetic evidence of APP mutation was indicative of definite AD diagnosis (Dubois B. et al, 2007). This mutation has been described both

in late onset Alzheimer's disease cases with cerebrovascular lesions (Bernardi L. et al, 2009) and in familial early-onset Alzheimer disease cases (Armstrog J. et al, 2004). The lack of evidence of AD profile in this case suggests that APP A713T mutation may clinically occur also with an FTD-like profile. 3) However, in this case other biomarkers (CSF and FDG-PET) are supportive of FTD diagnosis, so it could be conceivable that this specific APP mutation (APP A713T) may be causative of FTD pathology too.

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A possible role of AD CSF biomarkers in the diagnostic work up of normal pressure hydrocephalus

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Objectives: To evaluate the existence of a typical CSF profile in NPH that could differentiate it from AD and other kinds of dementia.

Material and Methods: We analyzed the concentration of AD CSF biomarkers (Aß42, tau and p-tau) in a sample of 344 subjects: 170 with a clinical diagnosis of Alzheimer's Disease (AD), 34 with Normal Pressure Hydrocephalus (NPH), 106 with other types of dementia and 34 with a not neurodegenerative disorder (CONTROL).

Results: The mean concentrations of Aß42 in AD and NPH patients are significantly lower than in controls, while there are no statistically significant differences between AD and NPH patients. Moreover in AD and NPH groups the number of patients with pathological Aß42 levels is significantly higher than in control and other type of dementia groups. Tau and phospho-tau concentrations are significantly lower in NPH subjects than in AD and other dementias, while there are no statistically significant differences between NPH and controls.

Discussion: Aß42 mean concentrations in AD and NPH patients are quite overlapping and the frequency of patients with pathological amyloid levels is significantly higher in AD and NPH groups with respect to control and other type of dementia groups. This could indicate a possible accumulation of beta amyloid also in NPH subjects. Moreover tau and p-tau concentrations in NPH are significantly lower than in AD and other type of dementia groups and are quite similar to CONTROL group, thus suggesting the possible absence of a marked neuronal damage.

Conclusions: NPH subjects seem to show a typical liquoral pattern characterized by low levels of all the three CSF biomarkers, that seem to guarantee a good reliability in differential diagnosis between NPH and other neurodegenerative disorders. Further studies are nevertheless necessary to confirm these preliminary data and better investigate the role of amyloid in NPH.

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Beta-amyloid 1-42 monomers, but not oligomers, produce PHF-like conformation of Tau protein

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Objective: The mechanistic relationship between Amyloid β1-42 (Aβ1-42) and the alteration of Tau protein is debated. Aβ1-42 polymerization is believed to occur in sequential phases: first Aβ monomers aggregate into soluble oligomers that then form insoluble oligomers, generating protofibrils and fibrils. Soluble Aβ1-42 oligomers constitute the more toxic form of the peptide. Monomers have been proposed to be involved, preferentially, in physiological processes. This study's purpose was to investigate whether and how Aβ1-42 modifies the conformation of Tau to render it prone to aggregate, in a PHF-like state.

Materials and Methods: We investigated the effect of Aβ1-42 monomers and oligomers on Tau, using mice expressing wild type human Tau that do not spontaneously develop Tau pathology. After intraventricular injection of Aβ1-42, mice were sacrificed after 3 hours or 4 days. The short lasting treatment with Aβ monomers, but not oligomers, showed a conformational PHF-like change of Tau, together with hyperphosphorylation. The same treatment induced activation of GSK3 and MAP kinases. The inhibition of the kinases rescued the Tau changes. Aβ monomers increased the levels of total Tau, through the inhibition of proteasomal degradation. Aβ oligomers reproduced all the above mentioned alterations only after 4 days of treatment. At that time, Aβ oligomers break into dimers and monomers.

Discussion: It is known that Aβ1-42 monomers foster synaptic activity. Our results suggest that Aβ monomers physiologically favor Tau activity and dendritic sprouting, whereas their excess causes Tau pathology. Moreover, our study indicates that anti-Aβ therapies should be targeted to Aβ1-42 monomers.

Conclusion: Our results have practical implications; currently the major efforts of Alzheimer's disease therapy are focused on removal of Aβ oligomers, and not monomers.

Primary progressive aphasia with C9ORF72 expansion and AD-like CSF: a case report

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Objectives: The hexanucleotide expansion in the gene C9ORF72 is one of the most common FTLD spectrum genetic causes, although leading to a wide phenotipic variants. Here we describe a subject carring the expansion with a phenotype of logopenic aphasia.

Materials and methods: Subject underwent neurological examination, neuropsychological testing, genetic investigation, lumbar puncture and neuroimaging.

Results: Neuropsychology showed an impairment more in language and executive functions rather than memory, with no hyppocampal amnesic syndrome; his language troubles were repetition deficit, anomia and non-fluent speech, temporal disorientation that converges to logopenic variant of PPA. PET findings reveal left temporal (inferior and lateral, fig.1), left parietal (dorso-lateral, fig.2) and left occipital hypometabolism. The analisys of cerebrospinal fluid (CSF) showed low amiloid (484 pg/ml) and high tau protein (1005 pg/ml) values. Genetic investigation revealed C9ORF72 gene expansion.

Discussion: The results of CSF, the PET and neuropsychology could lead to a diagnosis of logopenic aphasia that is codified as a variant of Alzheimer Disease. Presence of a C9ORF72 expansion orientates the diagnosis toward a frontotemporal degeneration.

Conclusions: Here we described a case of logopenic PPA due to an expansion of C9ORF72, with low amiloid value. This report enlarge the spectrum of C9ORF72 expansion phenotype. Therefore, genetic investigation should be possibily included in diagnostic examinations also of patients with an Alzheimer-like syndrome.

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The development of a home-based and computerized cognitive stimulation therapy for person living with dementia

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Objectives: Cognitive Stimulation Therapy (CST; Spector et al., 2006) is an evidence-based psychosocial intervention proven to be effective in mild to moderate dementia (Spector et al., 2003; 2010). Further studies are needed to investigate the effectiveness of computer-based cognitive stimulation treatments in dementia care (García-Casal et al., 2016). This project aimed to develop and test effectiveness of a Home-based and Computerized version of CST to be performed by the Person With Dementia (PWD) with the support of the caregiver and guided by the Tablet.

Materials: The group CST protocol (14 structured sessions) was adapted for the individual and computerized administration, respecting the CST guiding principles, and then implemented on the Tablet. A manual of instructions and toolkit (e.g. lyrics book, whiteboard, map of Italy) were arranged to be provided with the Tablet. Before starting the treatment, caregivers had a personalized training to use the Tablet and the manual, following the CST guiding principles, such as person-centred, respect and choice.

Methods: All the fourteen sessions are usable through a Tablet, with Android v. 4.4 as operating system, and define an Android application (shortly APP). The APP has been developed in JAVA programming language. Each session is introduced by a video where an operator speaks about the daily activities. Each activity is introduced by a synthesized voice that reads a message shown on the screen. Each session is always introduced from four based activities: Welcome, Karaoke, Reality Orientation and News. Then, the PWD performs the main activity of the day, mostly usable through the tablet and occasionally using some materials in the toolkit, with the support of caregiver. All the sessions are sequential, respecting the order of the CST protocol.

Results: Fourteen software sessions have been implemented favoring the interaction between the users and the application, and giving the users the possibility of choice between different stimulation activities in each session. The testing pilot phase showed that the platform is user-friendly and satisfactory for the PWD and caregiver.

Discussion: The developed home-based and computerized version of CST seems to be a promising tool in offering CST at home to PWD with the help of their caregivers.

Conclusions: The individual and computerized CST application is a complete platform and it is ongoing the study of effectiveness of this intervention in mild to moderate dementia.

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APOE polymorphism and cortical plasticity are independently associated with cognitive decline in Alzheimer's disease

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Objectives: The potential effects of APOE isoforms on lipid metabolism, cell signalling, and neurotoxicity in the central nervous system can influence Alzheimer's disease (AD). Several studies demonstrate that APOE E4 allele associates not only with AD risk and a lower age onset, but also with faster cognitive decline and greater cerebral atrophy,

suggesting a key role of this polymorphism in modulating both disease risk and clinical outcome. In the current study, we investigated the correlation between cognitive decline, motor cortical plasticity and cerebrospinal fluid (CSF) biomarkers profile of AD patients divided by APOE polymorphism in E4 allele carriers (E4) and homozygous E3 carriers.

Materials: A monophasic Magstim 200 device was used to deliver intermitted/continuous theta burst stimulation (iTBS/cTBS) protocols. ELISA was used for determination of CSF biomarkers level. Methods: Forty-one AD patients underwent lumbar puncture for CSF withdrawal, blood screening for APOE polymorphism, stimulation protocols applied over the primary motor cortex and mini mental state examination (MMSE) at baseline and at 6-, 12- and 18-months.

Results: No difference was found in CSF biomarkers profile within the APOE variants group. Conversly iTBS after effects were significantly reduced in E3 AD in comparison with E4 AD patients. MMSE progression, evaluated as delta between 18-month and baseline MMSE score (delta-MMSE) was higher, although not significantly, for E4 AD patients. Correlation analyses revealed that the individual amount of iTBS induced plasticity did correlate with delta-MMSE and total Tau (t-Tau), showing that a less pronounced LTP-like plasticity and higher t-Tau CSF levels were associated with a higher delta-MMSE. Finally a multivariate analysis showed that APOE polymorphism and LTP-like plasticity, but not t-Tau levels, are independently able to predict delta-MMSE in AD patients.

Discussion: These findings demonstrate that cortical plasticity impairment in AD patients is significantly different according to APOE variants. Moreover APOE polymorphism and LTP-like plasticity are both independently associated with clinical progression in AD patients.

Conclusions: APOE variants show different level of cortical plasticity and are independently associated with clinical progression in AD patients.

PRNP P39L variant is a rare cause of frontotemporal dementia in italian population

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Background: Prion protein (PRNP) gene mutations have recently been associated with Frontotemporal Lobar Degeneration (FTLD). In particular, a novel missense P39L mutation in the PRNP has recently been reported in 2 patients with clinical FTLD negative for other causative gene mutations. PRNP gene encodes for PrP protein and a strong association between this protein and Transmissible spongiform encephalopathy (TSEs) has been reported. Moreover, PRNP gene mutations have been associated with clinical pictures mimicking different neurodegenerative diseases, thus an involvement of PRNP in FTLD pathology would be conceivable.

Aim: To test P39L mutation as causative of disease in a large Italian FTLD cohort of patients in order to better investigate the role of this gene in FTLD pathogenesis.

Materials and Methods: P39L mutation was investigated by allelic discrimination using

TaqManTechnology in 761 patients clinically diagnosed with FTLD (374 male and 387 female patients, mean age ± standard deviation: 67.9±8.04 years) as well as in 719 age-matched controls (343 male and 376 female patients, mean age ± standard deviation: 67.8±9.3 years). The presence of this variation was confirmed by directing sequencing.

Results and Discussion: We found one FTLD patient (age 67, behavioral variant), carrier, P39L mutation in heterozygosis status. The patient was a 67-year-old male, with a positive family history for dementia, who developed apathy, short term memory deficit and postural instability at 66. Clinical and instrumental workup excluded prion disease. At MRI, bilateral frontal lobe atrophy was present. A diagnosis of FTD was made, with a mainly apathetic phenotype. Considering the location of this variant, in the N-terminal domain, out of the pathologic core of the prion protein, and its low frequency in our population (0.13%), P39L could be considered as rare cause of FTLD. Likely there would be, other causes, such as environmental factors, that could contribute in association with P39L to FTLD pathogenesis. Moreover, it is possible that this mutation is causative for FTLD patients originating from a limited geographic area. Nevertheless, further studies are required to determine whether and how this mutation exert its pathogenic effects.

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Patients with mixed location (deep and lobar) cerebral macrobleeds and microbleeds: baseline characteristics and follow up data

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Background: Lobar intracerebral hemorrhage (ICH) and microbleeds (MB) are hallmarks of cerebral amyloid angiopathy (CAA) whereas deep ICH/MBs of hypertensive small vessel disease (SVD) in elderly. The predominant type of SVD and clinical outcomes of patients who present with a combination of lobar and deep intracerebral hemorrhage (ICH)/microbleed (MB) locations (Mixed-ICH) is unknown.

Methods: We analyzed 75 Mixed-ICH patients: a) 40 with lobar ICH AND one/more deep MB, b) 29 with deep ICH AND one/more lobar MB, and c) 6 with deep and lobar ICHs. Demographics, clinical/laboratory features, and SVD neuroimaging markers of Mixed-ICH were compared to 191 probable/definite Cerebral Amyloid Angiopathy (CAA-ICH; according to modified Boston criteria) and 125 Hypertensive deep-ICH (HTN-ICH; strictly deep micro/macrobleeds) patients. ICH-recurrence, ischemic stroke (IS)-occurrence and case-fatality on follow up were analyzed.

Results: Baseline risk factors, clinical characteristics and imaging features were similar between patients who had a primarily lobar vs deep ICH, among the Mixed-ICH cohort. When compared to CAA-ICH, Mixed-ICH patients had a higher prevalence of hypertension, diabetes, left ventricular hypertrophy rates, and higher creatinine values (all $p<0.05$), while they resulted older and with higher rate of WMH volume, number of MBs, lacunes count, and CSO PVS than HTN-ICH (all $p<0.05$). In multivariate models, Mixed-ICH diagnosis was associated with higher creatinine, more lacunes and basal ganglia perivascular spaces (PVS), than CAA-ICH (all $p<0.05$). When compared to HTN-ICH, Mixed-ICH patients were older and had more lacunes and MBs in multivariable models (all $p<0.05$). Among 90-day survivors, adjusted case fatality rates were similar for all 3 categories. Annual risk of ICH-recurrence was 5.1% for Mixed-ICH, higher compared to HTN-ICH but lower than CAA-ICH (1.6% and 10.4%, respectively). IS-occurrence for

Mixed-ICH was similar to HTN-ICH but higher than CAA-ICH.

Conclusions: Our study showed that Mixed-ICH patients, commonly seen when MRI obtained during etiologic workup, could be considered as a relative homogeneous group that share similar clinical/radiological profiles. Mixed-ICH appears to be mostly driven by vascular risk factors similar to HTN-ICH, but demonstrates more severe parenchymal damage. The reported hemorrhage recurrence risk, case-fatality estimates, and ischemic stroke occurrence can be helpful in clinical situations that involve antithrombotic decisions.

Topographic distribution of lacunes in cerebral amyloid angiopathy and hypertensive deep intracerebral hemorrhage

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Background/Aim: To evaluate whether lacunes in lobar (LLs) and deep (DLs) locations, defined similarly to microbleed distribution, would differ between intracerebral hemorrhage patients (ICH) with cerebral amyloid angiopathy (CAA) and hypertensive deep-ICH (HTN-ICH).

Methods: Consecutive patients with SVD-related intracerebral hemorrhage (ICH) from a single center prospective cohort were analyzed. We compared presence/absence of LLs and DLs between definite/probable CAA (defined with modified Boston Criteria) and HTN-ICH patients (strictly lobar micro/macrobleeds). Their associations with baseline demographic/clinical characteristics and both MRI markers of SVD severity [white matter hyperintensity (WMH) volume and microbleed counts (MB)] and SVD type [MB location, perivascular spaces (PVS), and WMH patterns] were assessed using multivariate models.

Results: We analyzed data from a cohort of 316 primary ICH patients composed by 191 definite/probable-CAA and 125 HTN-ICH patients. CAA-patients were older, with higher rates of total MB counts, lobar MB, WMH volume, presence of multiple spot WMH, centrum semiovale (CSO) PVS and cortical superficial siderosis (all p-value <0.05). Conversely, Deep HTN-ICH had more hypertension and diabetes, higher creatinine levels, presence of left ventricular hypertrophy, peri-basal ganglia (BG) WMH patterns, BG PVS, and deep MB (all p-value <0.05). In all the cohort lacunes were frequent (30.4%) with similar rates in CAA and HTN-ICH patients (29.3% vs 32%, $p=0.62$). LLs were more commonly present in CAA (23% vs 7.2%, $p<0.001$) while DLs more frequent in HTN-ICH (16.8% vs 3.1%, $p<0.001$). In logistic regression model, higher creatinine, WMH volume, and the diagnosis of HTN-ICH (all $p<0.05$) but not microbleed counts were associated with lacune counts. LLs were associated with CAA diagnosis ($p<0.001$), older age ($p=0.018$), and presence of centrum-semiovale PVS ($p=0.033$). Conversely, diagnosis of HTN-ICH ($p=0.001$), higher WMH volume ($p=0.012$), presence of peri-BG WMH pattern ($p=0.019$) were predictors of DLs. When SVD subtype was used as outcome variable, diagnosis of CAA-ICH was associated with older age ($p<0.001$), more LLs ($p=0.003$), and severe CSO PVS ($p<0.001$) while diagnosis of HTN-ICH with DLs ($p<0.001$), BG PVS ($p=0.01$), hypertension ($p=0.014$), and creatinine (β:2.64, CI 1.4-5.1, $p=0.004$).

Conclusions: Distinguishing CAA from HTN-SVD is important as they are associated with significantly different bleeding risk with important implications in therapeutic decisions. Our results show that different lacunes location (lobar vs deep) in ICH patients might provide insights into the dominant underlying microangiopathy, thus be clinically useful in the appropriate context.

Neurotransmission in Alzheimer's disease: a comprehensive paired pulse TMS investigation

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Objectives: Effects of age on the assessment of intracortical inhibition with paired-pulse transcranial magnetic stimulation (TMS) have been investigated

and have been produced highly variable. On the basis of these previous studies we decided to investigate differences in short intracortical facilitation (SICF), short (SICI) and long intracortical inhibition (LICI) and short-latency afferent inhibition (SAI) protocol in a group of patients with a probable diagnosis of Alzheimer's Disease (AD) compared to a group of age-matched healthy-subjects (HS).

Materials: Ten patients with a diagnosis of probable AD according to the NINCDS-ADRDA Criteria and 10 age-, sex- and education-matched HS were recruited for this study.

Methods: Using TMS methods, we tested SICI, SICF, LICI and SAI on the left motor cortex (M1) at rest in each subjects. In each test, the coil delivered two stimuli: a conditioning stimulus (CS) and a TS. For SICI, the intensity of CS was set at the 80% of active motor threshold (AMT) at different interval interstimulus (ISI) of 1,2,3,5,7,10,15 ms where the CS preceded the TS. For SICF, CS was set at 90% of resting motor threshold (rMT) at ISIs of 1, 1.1, 2.1, 2.5, 3.3, 4.1 ms. For LICI, CS was set at 110% of rMT at ISIs of 50, 100, 150 ms. For SAI protocol, conditioning stimulus, that preceded TS at ISIs of 16,20,24,28 ms, was applied on the right median nerve to evoke a visible twitch of the thenar muscles. Short-latency afferent inhibition (SAI) protocol was performed to indirectly assess central cholinergic activity applying.

Results: Data were assessed measuring the percentage of change of peak-to-peak amplitudes of the mean MEPs produced by test stimulus alone compared to the mean MEPs produced by conditioned stimulus for each subject in each condition. Results showed that long intracortical inhibition were characterized by a decreased efficiency at ISI of 100 msec in AD patients compared to HS ($p=0.005$). Cholinergic activity, assessed by SAI test, were characterized by an impaired inhibition at 20 and 24 ms in AD patients compared to HS. No significant differences were found in SICF and SICI compared AD patients respect to HS.

Discussion: Our results provide evidence of an increased inhibition in long intracortical inhibition circuits and of a cholinergic involvement in AD patients compared to HS.

Conclusion: These data suggest that AD could be related to GABA-B mediated intracortical inhibition and cholinergic activity.

Very slow course of Alzheimer dementia in a family with APP A713T mutation: clinical history of index case

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Background/Objective: Mutations in the amyloid-β protein precursor (AβPP) gene can cause autosomal dominant early-onset Alzheimer's disease, Alzheimer's disease (AD) associated with cerebral amyloid angiopathy (CAA), cerebral hemorrhage, or both. We have previously reported, for the first time, a new large consanguineous FAD family segregating the A713T mutation with patients, either homozygous than heterozygous, that show a large span of onset. Aim of this work was to study the evolution of disease in the index case of the family described and the role of potentially protective factors against the disease.

Subjects/Methods: The index case belongs to family in which a history of AD had been reported. Clinical and genealogical methods were used to identify affected relatives and to reconstruct the pedigree, over six generations. NINCDS-ADRDA criteria were used to establish the diagnosis of Alzheimer's disease. Sequencing of causative AD genes was performed. The index case was observed two times in year for 15 years, through an extensive clinical and neuropsychological evaluation, including standardized battery for cognitive decline. The severity of the disease was assessed through MMSE, CDR score and daily activities scales. Vascular risk factors were monitored. Patient underwent to MRI examination. He started drug therapy at 2008 (rivastigmina 3mg/day); from 2012 has been added memantina (20 mg/day).

Results: On two consecutive generations, five affected persons alive were identified and A713T mutation (GCGtoACG) was found in this patients. In our index case, the A713T mutation was detected in heterozygous state, vascular risk factors were well controlled; Apo E genotype was 3-3. Currently he is 90, MMSE 16,4/30, ADL 4/6, IADL 1/5; CDR 2. Since he shows a moderate degree of disease, he still assumes therapy (rivastigmina 3 mg/day and memantina 20 mg/day).

Discussion and Conclusion: Despite the pathogenic role of the APP A713T mutation, in our patient the dementing process evolves slowly: he is able to participate at neuropsychological assessment, after a long history of illness (about 28 years). It's difficult to establish causes for which the dementing process evolves so slowly. This disease's course is likely attributable to a specific genetic background of modifier genes and/or to epigenetic effect, which in the future would be useful to investigate.

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Experienced usability and adherence to treatment in a technology-enhanced continuum of care program with respect to usual care in MCI and outpatients with Alzheimer: the Ability program

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Background and aims: An increasing body of evidence shows that cognitive stimulation programs benefit cognition in people with mild to moderate dementia over and above any medication effects (Woods et al., 2012). Little is known however as to potential benefits and clinical significance regarding long term continuum of care programs in PWD. Information and Communication Technologies have been increasingly provided as a support for PWD and their careers, although lack of familiarity of elder people with technologies is often considered as a criticism. Within the framework of the Ability project (Ability - Telerehabilitation, Smart Cities and Communities regional funding program, Miur-Por 2007-2013), we tested the usability of the technology-enhanced Ability platform and the adherence to a home-based motor-cognitive rehabilitation program delivered with two different approaches: the Ability platform versus usual care.

Methods: 20 MCI and 10 PWA were randomized in the Ability program and in the usual care program groups. The Ability program is an at home technology enhanced platform a) delivering tablet-based intensive (five days/a week) motor and cognitive activities; b) monitoring from remote vital and physical health parameters (i.e., weight, Heart Rate, O2 saturation, daily steps, sleep activity). We evaluated the platform usability in the Ability group through the computation of phone contacts between the Support Service Centre and Ability participants. Moreover we administered the System Usability Scale (SUS; Borsci et al., 2009) to both MCI/PWA and respective caregivers after the intervention. We tested adherence to treatment through statistical comparison of the number of daily sessions completed between the two groups.

Results: The Ability group showed a better adherence to treatment in comparison to the usual care group by performing a significantly higher number of corrected sessions (number of sessions per day/subject; $p < .007$) and a significantly higher "Pause index" (number of correct pause periods/subject; $p < .001$). As expected, the Ability platform was rated differently in usability (caregiver > MCI/PWA; $p < .05$) and learnability (caregiver < MCI/PWA; $p < .005$).

Discussion and conclusions: The Ability program provides a usable and accessible way to empower participants in their own care. As a positive technology (PT) able to create a smart health community, it also promotes interpersonal connectedness and

engages dyads in effective treatment adherence. Moreover, it has the potential to provide a cost effective long term intervention for MCI and PWA within continuum of care programs.

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Intermediate CAG repeat expansion in the ATXN2 gene influences the clinical characteristics of frontotemporal lobar degeneration

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Objectives: There are several evidences that common genetic risk factors underlie frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Intermediate CAG repeat expansions (27-33 CAG repeats) of the Ataxin2 (ATXN2) gene are a risk factor for ALS and influence ALS phenotype, while expansions >34 repeats are known to cause spinocerebellar ataxia type 2 (SCA2) [1,2]. At present, the role of ATXN2 in FTLD has been scarcely investigated. The aim of this study was to assess whether ATXN2 is a risk factor for frontotemporal lobar degeneration or influence the clinical presentation.

Material and Methods: 243 unrelated patients with FTLD attending the Memory Clinic of the Department of Neuroscience "Rita Levi Montalcini" of the University of Torino were involved in the study. Patients with corticobasal degeneration and progressive supranuclear palsy were not included. Controls were 171 healthy subjects, resident in the same geographical area. The ATXN2 CAG repeat in exon 1 (Ref Seq NM_002973.3) was amplified according to previously described protocols. All patients were screened for mutations in known FTLD-related genes. Finally, the presence of a pathologic expansion in the C9ORF72 gene was also evaluated. Data were analyzed using SPSS version 21.

Results: No difference in the frequency of intermediate polyQ expansions in ATXN2 was found between FTLD patients and controls (7% vs 3%). No allele was detected with more than 32 CAG repeats. Patients with intermediate polyQ repeats presented more frequently with parkinsonism ($p<0.01$), in comparison with patients not carrying intermediate polyQ repeats. Patients with an increased number of polyQ repeats have an earlier onset of the disease than those without intermediate expansions ($p=0.037$).

Discussion and conclusions: In this large series of FTLD patients, we found that intermediate polyQ repeats of the ATXN2 gene are not a genetic risk factor for frontotemporal lobar degeneration, a finding consistent with previous studies [3]. However, intermediate CAG repeat expansions influence FTLD clinical phenotype, being associated to a significantly earlier onset of the disease and parkinsonian features. Further studies are needed to confirm our results.

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Combining cerebrospinal fluid biomarkers and neuropsychological assessment to detect patients with mild cognitive impairment who will progress to Alzheimer's dementia

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Objective: To evaluate diagnostic accuracy of CSF biomarkers, neuropsychological assessment and their combination in detecting subjects with MCI due to AD.

Materials and methods: 115 consecutive patients with a clinical diagnosis of Mild Cognitive Impairment (MCI) admitted to the Neurology Department of San Raffaele Hospital in Milan between January 2009 and January 2015 were selected. At baseline all patients underwent neuropsychological assessment and lumbar puncture with CSF analysis of A-beta 42 (Aß42), total tau (t-tau) and phosphorilated tau (p-tau) levels. Each patient underwent clinical and neuropsychological follow-up, in order to identify the possible progression from MCI to AD. Accordingly, MCI subjects were sub-grouped into converters (MCI-c) and non converters to AD (MCI-nc, including both stable MCI and MCI due to other dementias).

Results: MCI-c had lower Aß42 concentrations and higher t-tau, p-tau, t-tau/Aß42 and p-tau/Aß42 ratios than MCI-nc. Both single biomarkers and biomarker ratios showed excellent accuracy in distinguishing MCI-c from MCI-nc. MCI-c had lower scores in psychometric tests for memory, executive functions, and language in comparison with MCI-nc. These tests showed a good diagnostic accuracy in distinguishing between MCI-c and MCI-nc. Summing z-scores of 16pR-D test, TMT-b and FVS test we obtained the Composite Cognitive Score (CCS) which showed an excellent diagnostic accuracy in detecting those MCI patients who would progress to AD. Combination of CSF and CCS increased the accuracy of the single progression markers.

Discussion: Our results are in line with data from other major international works and confirm utility of CSF biomarkers, both as a single progression index and in combination with neuropsychological assessment.

Conclusion: Diagnosing AD in prodromal phases would reveal of great importance for the future development of new therapeutic strategies which could selectively interrupt the pathogenetic process before damages get irreversible. Therefore, if pharmaceutical research will find effective molecules for AD treatment, it will be fundamental to correctly and early detect subjects with AD pathology to avoid underestimation of their real therapeutic power. Relatively low cost and accessibility of CSF biomarkers measurement and neuropsychological assessment make them essential tools to face the great and growing challenge Alzheimer's disease represents.

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A cluster of progranulin C157KFSX97 mutations in southern Italy: clinical characterization and genetical correlations

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Objectives: Fronto-temporal lobar degeneration (FTLD) is a group of neurodegenerative diseases displaying high clinical, pathological and genetic

heterogeneity. FTLD cases are characterised by an elevated degree of familial aggregation and the main genes involved are the genes coding for microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9ORF72). Several autosomal dominant GRN mutations have been reported, accounting for 5-10% of FTLD cases worldwide. In this study we described the clinical characteristics of seven Italian patients carrying the GRN C157KfsX97 null mutation and demonstrated the existence of a founder effect by means of haplotype sharing analysis.

Methods: All the patients, coming from Southern Italy, were recruited from the Neurological Clinic of the Second University of Naples (Italy), except one, recruited from the Neurological Département Hôpital Pitié-Salpêtrière of Paris (France). They underwent a complete clinical, neuropsychological and instrumental assessment, including morphological and functional brain imaging and CSF biomarkers assay. Clinical diagnoses were Fronto-temporal dementia, behavioural variant (bv-FTD), in 5 cases and Cortico-basal syndrome (CBS) in 2 cases. Five cases were familial. We performed plasma progranulin dosage, GRN gene sequencing and haplotype sharing study, analysing 10 short tandem repeat (STR) markers, spanning a region of 11.08 Mb flanking GRN on chromosome 17q21.

Results: We found the deletion g.101349_101355delCTGCTGT, resulting in the C157KfsX97 null mutation, in all the patients. Concerning haplotype sharing analysis, we observed shared alleles among 6 patients for 8 consecutive STR markers spanning a 7.29 Mb region. This common haplotype strongly supports a founder effect. One patient showed a different haplotype, making impossible to determine for him the presence of the ancestral chromosome common to the other patients.

Discussion: Our observations substantially confirm the elevated clinical variability described among GRN-mutated FTLD cases. Besides the clinical diagnosis, the most consistent aspects are a strongly asymmetric pattern of atrophy and hypometabolism, frequent behavioural, dysexecutive and linguistic deficits and extensive parietal lobe involvement. The absence of evident familiarity in 2 cases may be a consequence of the incomplete penetrance of those mutations. As in previous works with other GRN mutations, the haplotype sharing analysis demonstrated the likely existence of a founder effect for C157KfsX97 mutation.

Conclusions: This is the first study that describes a cohort of apparently unrelated individuals carrying the GRN C157KfsX97 null mutation. Here we evidenced the lack of genotype-phenotype correlation and the possible reduced penetrance of this mutation. Finally we demonstrated the presence of a founder effect in Southern Italy.

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Power of neuropsychological and SPET biomarkers in predicting the conversion of amnestic MCI(AMCI) to AD

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The early detection of patients prone to develop Alzheimer's disease(AD) is the main objective in clinical investigations. The present study aimed at evaluating the power of different neuropsychological and SPET biomarkers to predict the conversion of amnestic MCI(aMCI) to AD. We have investigated the combined use of the abovementioned biomarkers, in order to identify a diagnostic algorithm that can be the best predictor of MCI conversion in AD. 42 aMCI subjects (Winblad 2005) were enrolled in the study using a rather rigorous cut-off (< 1.96 ΔS) in at least one long term episodic memory task. These subjects were assessed at baseline with an extensive neuropsychological test battery including also language, praxis and executive tasks. Performances obtained in four episodic memory tasks (RAVLT immediate, delayed recall, and recognition and Rey-Osterreith Figure memory) were synthesized in the Episodic Memory Score (EMS). EMS takes into account both the number and severity of memory scores of any patient. Patients at baseline underwent also 99mTC-HMPAO cerebral SPECT examination. Neuroimaging data were

analyzed using SPM8 software with a MATLAB 6.5 platform. Neuropsychological assessment was repeated every six months for two-year to detect conversion to AD. Neuropsychological and neuroimaging data from aMCIs who converted to AD (MCI-C) and who did not (MCI-NC) were compared. EMS score of 8 was characterized by good sensitivity (0.77) and high specificity (0.83). Comparison between all the regions of interest at the SPECT examination showed a significant reduced tracer uptake in the posterior cingulate cortex in the MCI-C. A semiquantitative index of perfusion in the abovementioned region of interest, called PCC-P, was estimated. The best theoretical cut-off value was PCC-P = 91.5 that reach a specificity of 0.87 and a sensitivity of 0.63. Correlation analysis shows that EMS and PCC-P are not related, hinting that these two biomarkers measure different phenomena in the degenerative process. At last, we evaluated the combined use of EMS and PCC-P. Assessed simultaneously (in "parallel"), these biomarkers reach great diagnostic sensibility (1.00), but low specificity (0.33). We then investigated the potential use of these biomarkers "in series", simulating that cerebral SPECT were only evaluated in patients with pathological EMS. The combined evaluation of EMS and PCC-P increases markedly sensitivity (0.80) and specificity (0.96), allowing optimal prognostic assessment of the patient. The rationalized use in everyday clinical practice of these neuropsychological and SPET biomarkers can allow an effective, economic and early detection of AD.

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The pitfall of GWA in Alzheimer disease: an Italian case-control study

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Objective: Recent advances in genomic tools drove great expectations in understanding the genetics of sporadic Alzheimer's disease (SAD) and the future use for its prevention, diagnosis, and treatment. However, despite a plethora of translational researches all these studies failed this goal. In particular the role of these studies has been recently discussed since their costs and since they had provided correlation, not causation (1,2,3). Objective of the present study is to replicate the already reported association of CLU, PICALM, TFAM and TNK1 loci in a case control series from Centre and South Italy.

Patient and Methods: On the basis of APOE genotype frequencies, we set a priori a power of the study ≥80%. Accordingly, three cohorts n>500 subjects, i.e. 517 SAD patients (M/F: 174/343, mean age 73.77±9.59y, MMSE score range 0-to-23), 552 cognitively intact age and sex-matched old controls (OC) (M/F: 206/346, mean age 72.52±11.40y, MMSE score range 28-to-30), and 513 cognitively intact sex-matched young controls (YC) (M/F: 195/318, mean age 30.19±3.19y, MMSE score range 28-to-30) were enrolled in the study. The single-nucleotide polymorphisms rs11136000 (CLU), rs541458 (PICALM), rs2306604 (TFAM), and rs1554948 (TNK1) were investigated in blinded fashion with the allele discrimination methodology by using real time technology and the commercially available assays. The common APOE polymorphism was also investigated.

Results: At first glance the following situations were observed: 1) Heterosis at CLU (in both control groups), TFAM (in all cohorts), and TNK1 (only in age-matched controls) loci; 2) A different genotype distribution at TNK1 locus (SAD) in respect to the genotype frequencies expected from the HWE for one locus (p = 0.027); 3) A difference in genotype distribution at PICALM (p = 0.017, pwr = 0.801)

locus; 4) A difference in genotype distribution at TNK1 ($p = 0.003$, pwr = 0.902) locus; 5) A difference in genotype distribution at the APOE ($p < 0.001$, pwr = 1.000) locus. These differences at PICALM and TNK1 loci were missing when the analysis was adjusted for the APOE polymorphism.

Discussion: This is the first study investigating CLU, PICALM, TFAM, and TNK1 loci in SAD patients from Centre and South Italy. In these patients the already described associations appeared as the result of an interaction with APOE rather than independent associations.

Conclusions: The role of genomic SNPs still represented a challenge for the genetics of SAD, having an effects in increasing the risk for SAD, if any, much smaller than those of APOE.

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Autosomal dominant and sporadic frontotemporal lobar degeneration: from non-coding RNAS to the identification of preclinical biomarkers and therapeutic targets

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Objective: Recently, an active role of ncRNAs, miRNAs and long non-coding (lnc)RNAs, was observed in different neurodegenerative diseases including Alzheimer's disease or Parkinson's disease. Therefore, the main aims of this study were to investigate a specific profile of miRNAs and lncRNAs in serum and PBMCs of FLTD patients (sporadic and genetic forms) and to identify possible preclinical biomarkers in order to better understand pathogenic mechanisms.

Methods: Specific PCR arrays containing 84 most common miRNAs and 90 well characterized lncRNAs were used to screen miRNA serum levels and PBMC lncRNAs expression levels in a population composed by: 5 healthy subjects, 5 sporadic FTLD patients, 5 GRN mutation carriers and 5 C9orf72 expansion carriers.

Results: Statistically significant decreased serum levels of miR122-5p, miR22-3p ($P<0.001$) and significant increased levels of miR-31-5p and miR-103a-3p ($P<0.05$) in FTLD patients compared with controls were observed. The down-regulation observed, appears even stronger when C9orf72 FTLD expansion carriers were considered. Regarding lncRNAs PBMC expression, results showed a generalized up-regulation of several molecules in sporadic FTLD patients compared with controls. In particular this upregulation is shown with a lesser extent when C9orf72 carriers or GRN mutation ones were compared to controls. Interestingly, BC200 resulted to be upregulated in sporadic patients or C9orf72 carriers compared to controls (5.09 and 5.7 fold change increase respectively, $P<0.05$). This trend was not confirmed when GRN mutation carriers were compared with controls (1.9 fold change, $P>0.05$). Moreover, ANRIL showed opposite trend between sporadic FTLD, C9orf72 and GRN mutations carriers; it shows a robust upregulation in sporadic FTLD patients compared with controls (29.68 fold change, $P<0.05$) whereas it appears to be downregulated in GRN mutations carriers compared with controls (0.7 fold change, $P<0.05$).

Conclusion: These preliminary data suggest that a number of miRNAs and lncRNAs are dysregulated in FTLD patients, and that different pathways may be involved in genetic forms as compared with sporadic ones. Moreover, these molecules, such as circulating miRNAs, could be useful as biomarkers, to identify in life the ongoing pathology and develop disease modifying tailored treatments. However, further studies addressing this topic are required.

Response to treatment with cholinesterase inhibitors and cognitive reserve in Alzheimer' disease: is there a relationship?

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Background: Cholinesterase inhibitors (ChEIs) represent the main pharmacological treatment of mild to moderate Alzheimer's disease (AD), able to slow down clinical progression of disease. However, the efficacy of such treatments varies widely among individuals and it would be useful to identify predictors of response to therapy.

Aims: The aim of this study has been to investigate whether cognitive reserve influences the clinical response to ChEIs therapy.

Methods: We collected baseline data of 69 newly diagnosed patients with AD. In particular, subjects were assessed using the Mini-Mental State Examination (MMSE), the Cognitive Reserve Index questionnaire (CRIq), the Instrumental Activities of daily Living (iADL) scale and the Neuropsychiatric Inventory (NPI). Differences in MMSE, NPI and iADL within subjects before and after one year of treatment with ChEIs (T0 and T1) were tested using a generalized linear model adjusted for CRIq and age. Patients were considered responders if their delta score T0-T1 was equal or inferior to 2 points of MMSE, while non-responders were those with a delta score higher than 2 points. Differences in socio-demographic variables were tested using t-test and chi-square test.

Results: 48 patients were responders and 21 non-responders. No significant differences were observed between the two groups, regarding demographical characteristics and functional parameters (CRIq, MMSE, IADL scores). Multivariate analysis did not reveal any significant difference regarding MMSE, NPI and iADL between T0 and T1. Univariate analysis showed an interaction effect between CRIq and MMSE ($F=7{,}054$, $p < .01$). Correlational analysis revealed a positive correlation between CRIq score and MMSE's delta score ($r = 0.31$, $p>0.005$).

Discussion: Our results suggest that there is a relationship between cognitive reserve and MMSE's change during the first year of drug treatment. Studies on ChEIs showed that they are beneficial for both cognitive and non-cognitive symptoms of AD, but few evidences are available in literature on possible predictors of response to drug therapy. We know from several researches that a high cognitive reserve is able to delay the clinical onset of AD and that it is associated with a more rapidly progressive disease. Our results confirm these latter observations and suggest that cognitive reserve can probably influence the response to ChEIs treatment.

Group intensive rehabilitation in patients with major and mild neurocognitive disorder

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Objective: No standard protocols are available for cognitive rehabilitation in Major and Mild Neurocognitive disorder (M-NCD, m-NCD); however, preliminary data indicate that such interventions might have cost-effective beneficial effects and are free from side effects or adverse events. The aim of this study was to assess the efficacy of a protocol of Group Intensive Cognitive Activation (g-ICA) in patients with both M-NCD and m-NCD.

Materials: Neuropsychological instruments and the g-ICA protocol. Sixteen patients with M-NCD and 15 patients with m-NCD were enrolled. Eleven patients with M-NCD merely receiving daily care were used as a control group.

Method: The protocol was arranged in in the Oasi Research Institute and is based on the principles of the central role of the patient and the mediation pedagogy. The intervention was carried-out by a neuropsychologist with daily group sessions over a period of two months. Cognitive functions stimulated were: global functions (everyday), ideomotor praxis (Monday, Thursday), visual, auditory and spatial memory (Monday, Friday), auditory and visual selective attention (Tuesday, Thursday), verbal language (Tuesday, Friday), and constructional praxis, semantic memory, ecological problem solving (Wednesday). Neuropsychological assessment was performed at baseline and after the completion of the program.

Results: General cognitive functioning, attention, ideomotor praxis and visual memory scores were

found to be significantly increased in all patients. Beneficial and significant effects were also found for constructive praxis in M-NCD and for executive functioning in m-NCD. All areas of the language function ameliorated in m-NCD and partially (syntax-grammar comprehension) in M-NCD.

Discussion: Our findings seem to indicate that g-ICA might induce beneficial effects on the general cognitive functioning and other specific functions in patients with both m-NCD and M-NCD.

Conclusions: The limited efficacy of drug therapy and the plasticity of human central nervous system are the main reasons that explain the growing interest in rehabilitation[1]. This kind of treatment is cost-effective and can be easily implemented in a hospital setting.

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BPSD severity in Alzheimer's disease is independent from vascular impairment and white matter lesions burden

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Background and objective: BPSD affected almost all AD patients, decreasing quality of life for patients and caregivers. Understanding pathogenetic background and risk factors is the primary step to a better BPSD management [1]. The aim of this study was to analyze a possible relationship between BPSD severity and vascular, genetic and cognitive variables.

Subjects and methods: 135 patients diagnosed as Probable AD, according to NINCS-ADRDA criteria, were enrolled from two different Alzheimer Unit (Catholic University of Rome and Sant'Eugenio Hospital). Each subject underwent: clinical/instrumental examination (including brain MRI), neuropsychological evaluation (including MMSE), behavioural assessment (NPI). Modified Fazekas Scale (FS) and Hachinski Ischemic Score (HIS) were applied to the whole sample in order to analyze the white matter lesions burden and the global vascular impairment. ApoE genotype was analyzed in 92 patients. Data analysis was obtained by Spearman correlation coefficient and by Principal component analysis.

Results: Demographic and clinical characteristics of the whole sample were: mean age = 74.5±7.16 ys, female/male ratio=1,14, mean MMSE Score = 18.6±4.80, mean FS = 1.14±0.86, mean HIS = 2.82±2.08. Patients were stratified, according to the presence/absence of at least one e4 allele in ApoE4 carriers (44) and non carriers (48). BPSD severity (estimated by NPI total score) was independent from cognitive impairment (MMSE), vascular impairment (HIS), white matter lesions (FS) and ApoE status.

Conclusions: Our data do not confirm a possible role for vascular impairment in BPSD pathogenesis as previously reported [2]. In order to better evaluate BPSD it will be necessary to analyze bio psychosocial environmental factors (taking into account that NPI is a caregiver dependent measure). Furthermore, several studies show that grouping BPSD into "clusters of symptoms" (such as depression/anxiety; delirium/hallucinations…) a relationship with different variables might be established suggesting a different role in BPSD pathogenesis for vascular, genetic and environmental factors [3].

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Author Index

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