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Non-conventional Neuroimaging Techniques to Investigate Brain Tissue Modifications in Alzheimer's Disease

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Introduction

Neuroimaging has become a increasingly popular tool for the investigation of dementias. In clinical settings, it plays the prominent role of excluding secondary causes of cognitive decline, which can, in some cases, mimic the occurrence of neurodegenerative dementia. On the other hand, neuroimaging has strongly contributing in clarifying the relationship between clinical, neuropsychological, and behavioural aspects of dementia and the distribution of brain tissue damage. The combination of several non-conventional neuroimaging techniques providing both, measures of regional grey matter (GM) loss and measures of functional and structural brain disconnection offer the opportunity to investigate *in vivo* the pathophysiological modifications in different forms of dementia, and across their clinical evolution. Voxel-based-morphometry (VBM) is one of the most suitable techniques to assess regional GM loss in a data-driven fashion; it allows group comparisons and correlation analyses with clinical/neuropsychological/behavioural variables [1]; ii) Diffusion tensor imaging (DT-MRI) plays a key role for the investigation of white matter (WM) changes, by providing quantitative measures of microscopic tissue damage (i.e., reduced fractional anisotropy, FA; increased mean diffusivity, MD), and allowing the reconstruction of specific tracts (diffusion-tractography) [2]; iii) resting-state functional-MRI (RS-fMRI) provides information on the functional connectivity between brain regions or within neuronal networks, which can be selectively affected by neurodegeneration; disruption of specific networks, such as the so-called default mode network

(DMN) in Alzheimer's disease (AD) [3] or the salience network in frontotemporal dementia [4], have been consistently reported.

This paper reviews some relevant contributions given by non-conventional MRI techniques for the pathophysiological understanding of AD, which represents the most common form of cognitive decline.

Voxel-based morphometry

VBM analysis is based on a series of automatic steps, the main ones including normalization of individual T1-weighted volumes to a standard template, their segmentation and extraction of GM maps, which can be used for statistical analysis. Since its earliest applications to AD, VBM has revealed a much more widespread pattern of GM loss than that previously observed by manual volumetric techniques [1]. Most consistent findings indicate an involvement of the whole association cortex in fully developed AD, with a relative preservation of the sensory–motor cortex, occipital, and cerebellar cortex [4–6]. Some regional GM atrophy has also been regarded as 'clinically eloquent' in terms of explaining symptoms. A negative association was reported between GM density in hippocampal regions and measures of global cognition (as assed by Mini Mental State Examination; MMSE) in patients with AD and mild cognitive impairment (MCI) [5]. More recently, VBM has further highlighted a strict correspondence between patients' disabilities in specific cognitive domains and the level of regional GM atrophy in expected brain regions [6]. Additionally, it was recently shown that behavioural symptoms, such as disinhibition and occurrence of delusions are also associated with regional GM loss [7].

Diffusion MRI

Since the first applications to AD, DT-MRI has shown the ability to detect microscopic WM abnormalities (FA and MD changes), mainly in the corpus callosum, temporal, frontal, and parietal lobes, and their correlations with patients' cognitive performance

[8, 9]. More recently, Tract-Based-Spatial-Statistics (an unbiased method of DT-MRI data analysis), revealed a progressive spread of WM damage from the amnestic-MCI stage to fully developed AD [6]. Interestingly, in some brain regions, FA changes were adjacent to areas of GM loss (as assessed by VBM), suggesting a strict relationship between GM atrophy and axonal degeneration. As mentioned above, DT-MRI based tractography allows a selective investigation of specific WM tracts. The cingulum is the main pathway connecting the medial temporal lobes (MTLs) with the rest of the brain, and is therefore of critical interest for the clinical progression of AD. FA changes have been reported in the cingulum of both, patients with AD and MCI, suggesting an early implication of this tract in the disease course [10]. Moreover, a recent study demonstrated an increasing deterioration of the cingulum when moving from MCI to AD patients [11]. Interestingly, linear regression analyses revealed that MD in the cingulum is able to predict patients' measures of episodic memory in combination with GM density of hippocampal/parahippocampal areas (as measured by VBM), while GM density in the PCC is critical to predict the global cognitive impairment of the same patients [11]. These findings suggest a posterior-anterior progression of AD pathology that parallels the progression of cognitive deficits: episodic memory deficits first; then more and more cognitive deficits until conversion to dementia. Another interesting WM tract explored by DT-MRI tractography is the uncinate fasciculus, which connects anteriorly the temporal and frontal lobes. This tract was found to be implicated by AD pathology [10, 12], and correlations between DT-MRI measures and cognition were reported [12]. DT-MRI based tractography was also recently used to assess changes in structural connectivity across the whole brain, by using the so-called anatomical-connectivity-mapping (ACM) method [13]. Probabilistic tractography is initiated from each voxel of the brain, and the number of connections passing through each voxel are counted and used as a measure of strength in structural connectivity between each voxel and the rest of the brain. An exploratory investigation revealed that ACM is more sensitive than FA in detecting subtle brain tissue changes in AD. Moreover, ACM is also able to detect changes that are likely to represent phenomena of brain plasticity [13].

Resting-state fMRI

RS-fMRI has been extensively used to investigate AD, in the view of a disconnection syndrome hypothesis. Earlier studies suggested that functional connectivity is disrupted between the MTLs and the association cortex in AD. More recent studies, based on the independent component analysis (a data-driven approach that automatically indentifies different neuronal networks), have mainly focussed on the DMN, showing reduced connectivity especially within its posterior node (i.e., PCC) [2, 15]. These findings are interesting for at least two reasons. First, reduced metabolism was previously found in the PCC of AD patients even in the absence of local atrophy. Second, the PCC is directly connected to the MTLs through the cingulum, which represents the most relevant connection of the limbic system. In this perspective, structural/functional disconnection are likely to be critical for the conversion from preclinical to clinical AD. As recently shown, functional disconnection of the PCC is already present at the stage of amnestic-single-domain-MCI, but it associates to local GM atrophy only at the AD stage [15].

Conclusions

It is becoming increasingly clearer that the clinical manifestations of AD are not only due to regional GM loss, but also to abnormal integration between cortical regions by disconnection mechanism. This concept comes from the evidence that WM damage (as assessed by diffusion MR imaging) can be observed in patients with AD since the early clinical stages, and it correlates with clinical measures of cognitive disability. In this perspective, several functional imaging studies have provided evidence that brain hypometabolism/disconnection may precede the occurrence of GM atrophy in certain regions of AD brains. In this context, the cingulum is likely to play a remarkable role in the transitional stage between MCI and dementia. This subject seems to be relevant for both, speculative aspects of neurology and clinical applications.

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Somatic Comorbidity and Alzheimer's Disease Treatment

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In the last 20 years, many efforts were pursued to elaborate a therapeutic strategy able to modify the natural history of Alzheimer's disease (AD). At present, Cholinesterase inhibitors (ChEIs: donepezil, rivastigmine, galantamine) and, most recently, the noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor blocker, memantine, represent the main pharmacological strategy effective in reducing the progression of cognitive decline and functional loss in people affected by Alzheimer's Disease (AD).

Alzheimer's disease typically occurs in elderly people, and its prevalence rises with age. Consequently, therapeutic strategies in AD must take into account the characteristics of older population, often presenting with more chronic conditions. At 2005 in Italy approximately one person on two over 65 years had at least one chronic disease, 34,9% of male and 47,4% of female resulted affected by three or more chronic conditions (ISTAT 2007). In the Swedish population, 55% of subjects beyond the 76 years had at least two chronic conditions with the most common hypertension (38%), dementia (21%), heart failure (18%) and neurosensorial deficits (about 15%) [1]. Among elderly population, Alzheimer's disease patients have often concurrent diseases, mostly cardiovascular, genitourinary, musculoskeletal and neurological, that in comorbidity tend to accelerate cognitive and functional decline [2]. Moreover, demented patients have a higher number of admissions to hospital and prevalence of complications such as pneumonia, hip fracture and, secondarily, pulmonary embolism, renal failure, septicaemia, urinary infections, with consequently an increased risk of death during hospitalization [3].

Therefore, people affected by Alzheimer's disease must be considered frail. Therapeutic decisions for these frail patients must be cautious: the elevated comorbidity index, the consequent multiple medication, the impairment of homeostasis and functions of multiple organs due to aging, contribute to enhance the risk of pharmacological adverse events (AEs) and drug interactions, also increasing the potential occurrence of side effects leading to a cascade of adverse events. In addition, almost all studies, verifying safety and tolerability of AD treatments, were conducted within clinical trial settings, where patients' inclusion was restricted by a low comorbidity and/or polytherapy index. So, it is uncertain if such results can be applied to patients in clinical practice, in a real world setting.

ChEIs are widely recommended as standard therapy in mild to moderate AD from the most important neurological societies [4, 5]. Some recent studies demonstrated that donepezil is effective also in severe AD, particularly on improvement or stabilization of the cognitive functions, on global functionality and, even if controversial in literature, on behavioural symptoms [6]. Among the others ChEIs, galantamine improved only cognitive function in severe AD failing to significantly ameliorate functionality in activities of daily living [7]; a trial on rivastigmine is ongoing [8]. Recently the FDA approved use of donepezil in severe AD although data on lifetime cost utility analysis and duration treatment are limited [9].

Memantine is a treatment effective in reducing the rate of cognitive and functional decline in moderate to severe AD [10] and its use has been approved for these stages. In addition, it has been demonstrated that memantine reduces behavioral symptoms, particularly in the affect, physical behavior and psychosis domains [11] and seems to have some efficacy on aphasia, especially on non-fluent subtypes [12].

ChEIs, because of their cholinergic activity, produce mainly gastrointestinal (GI) and cardiovascular (CV) side effects. Serious AEs are rare.

Common (1–10%) or very common side effects (>10%) are nausea, diarrhea, vomiting, abdominal pain/disturbance, fatigue, dizziness and headache. Agitation is common with donepezil and rivastigmine, rare with galantamine. The incidence of GI symptoms, higher for women, is lower for donepezil compared with galantamine and rivastigmine. Rivastigmine GI-related AEs persist during the long-term treatment, although its transdermal patch formulation shows no very common side effects. GI adverse events are the main cause of discontinuation therapy in ChEIs, mostly nausea. Non-GI AEs have low frequencies and a similar incidence with the different ChEIs.

Due to their vagotonic effects, ChEIs have warnings for use in patients with many cardiovascular comorbidities such as sick sinus syndrome, sino-atrial or atrio-ventricular block, myocardial infarction, unstable angina or congestive heart failure. Moreover, demented patients that assume ChEIs, even in absence of cardiovascular diseases and with a normal pretreatment ECG, have a greater risk of developing hypotension, hypertension, atrial fibrillation or, more rarely, bradycardia. Bradycardia, that is dose-depend-

ent for donepezil, consequently increases the risk to fall, experience syncope or need pace-maker implantation, also enhancing the risk of hospitalization due to bones fractures [13]. Caution must used for patients with pulmonary diseases (asthma, obstructive pulmonary disease), urinary outflow obstruction, seizures, peptic ulcers and severe hepatic impairment. More rarely, ChEIs may cause REM sleep behavior disorder (rivastigmine), worsening or occurrence of extrapyramidal symptoms (mainly rivastigmine), movement disorders (rivastigmine-induced dystonia, donepezil-induced chorea) and toxic hepatitis with or without cholestasis (rivastigmine, donepezil). There are no available prescribing information in severe AD, but literature data indicate that they are probably similar to that of others AD stages.

About drug interactions, ChEIs enhance the effect of succinylcholine-type muscle relaxant during anaesthesia. Their common contemporary use with bladder anticholinergics, due to urinary incontinence in demented patients, occurs in one third of patients and causes a greater functional decline than their use alone. There are no data about efficacy of ChEIs in their concomitant use with anticholinergic agents for others frequent conditions (i.e. depression). Galantamine may interact with digoxin and beta-blockers, reducing heart rate. Levels of donepezil and galantamine are modified by inhibitors (such as paroxetine or fluoxetine) and by enhancers (such as rifampicin, alcohol or phenytoin) of CYP3A4 and CYP2D6 [14].

Memantine has a better profile of safety and tolerability. AEs are very low and similar to placebo. Very common symptoms are no reported; common adverse events are constipation, headache, hypertension and somnolence. Memantine, moreover, can reduce or prevent agitation/aggression and has a withdrawal rate lower than placebo. Warnings for its use concern the presence of epilepsy, raised urinary pH, myocardial infarction, uncompensated congestive heart failure, uncontrolled hypertension and severe hepatic impairment. Among its interactions with others drugs, Memantine can enhance anti-parkinsonian and anticholinergic agents, reducing effects of barbiturate and neuroleptics. Memantine is contraindicated in concomitant use with amantadine, ketamine or other agents acting on the same NMDA receptor; interacts negatively with phenytoin, reduces hydroclorothiazide levels and may increase warfarin levels [14]. In any case, its use in add on with ChEIs in Alzheimer's disease is safe enhancing their effect in delaying time to admission in nursing home and also decreasing costs for health care system and society [15].

Conclusions

Many conditions, very common in the elderly, may restrict ChEIs use and/or efficacy in Alzheimer's disease patients. Memantine has a good profile of efficacy and tolerability with a better safety in pulmonary, cardiovascular and central nervous system comorbidities compared to Cholinesterase inhibitors. Memantine's drug interactions are more favourable since they concern mostly drugs of uncommon use in the elderly. Moreover, having some effects in behavioral symptoms and language disturbances, Memantine is probably useful in AD subtypes overlapping with Frontotemporal Lobar Degeneration.

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Pathogenetic Similarities Shared by Alzheimer's Disease and Multiple Sclerosis

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Neuroscience is a rapidly-changing field of knowledge and understanding the basis of central nervous system (CNS) diseases can benefit from continuous improvement in diagnostic tools and more effective experimental approaches. This has allowed in recent years to overcome several paradigmatic distinctions regarding the pathogenesis of different neurological disorders. A typical example is represented by the rigid separation once postulated between neuroinflammatory and neurodegenerative CNS diseases which is now strongly challenged. In fact, although two frequent neurological disorders such as multiple sclerosis (MS) and Alzheimer's disease (AD) are fundamentally different diseases, recent data suggest that at least some their pathogenetic mechanisms are common [1].

Several examples of these similarities could be provided. Neuroinflammation is defnitely the main driver in MS pathogenesis, particularly in the relapsing-remitting phase and it represents a major target for current therapy. The role of neuroinflammation, once considered largely as an harmful and noxious event, is now being reconsidered. In fact, emerging evidence suggest that it can be both protective and detrimental, depending also on several concomitant and environmental circumstances. Among the possible beneficial effects of neuroinflammation neuroprotection, remyelination, axonal regeneration and mobilization of neural precursors have been suggested [2]. Neuroinflammatory features have now been firmly established also in AD, where they can contribute to amyloid clearance as well as to the propagation of neurodegeneration, and in other neurodegenerative disorders such as Parkinson disease, dementia with Lewy bodies and Huntington's disease. Similarly, reactive oxygen- and nitric oxide intermediates-induced oxidative stress with mitochondrial activity impairment, a potential noxious event able to induce neuronal degeneration, has been primarily investigated in neurodegerative diseases, but has also been recently demonstrated to act in MS. A third, well-established feature described in both AD and MS is glutamate-mediated excitotoxicity, a pathogenetic mechanisms able to damage neurons and commonly linked to neuronal loss in neurodegenerative diseases. However, glutamate-mediated damage can also target glial cells, particularly oligodendrocytes, and it has been advocated as a major event in axonal loss in the progressive stages of MS [3].

Most pathological features of MS markedly differ from those observed in AD. In most stages of MS there is prominent infiltration of various leukocyte subsets into the CNS, particularly at the peak of a disease relapse when neuroinflammation is particularly evident, while this is clearly not a feature of AD. However, in AD (as well as in MS) there is an elevation of several inflammatory mediators coupled with a marked activation of microglia, and regarding oxidative stress it is noteworthy that free radicals are known to be produced through the induction of the respiratory burst in the activated microglia.

Besides these results indicating a possible common and not completely understood role of well-characterized pathogenetic mechanism in AD and MS, recently reported experimental data suggest that other intriguing relationships could be discovered investigating less obvious targets, such as blood platelets, the complement system and the endothelium.

Platelets have long been considered just as a physiological keystone in primary hemostasis and a critical player in arterial thrombosis when their function is dysregulated. However, this perspective is likely to be too simplistic, since increasing evidence supports a much wider role in health and disease. In fact, platelets are able to store and release several biologically active substances potentially able to influence inflammation and neurodegeneration such as growth factors, chemokines and cytokines. As an example, they are a major source of pro-inflammatory molecules (e.g. P-selectin, tissue factor, CD40L, metalloproteinases) and they are now considered as relevant cell types not only in atherosclerosis and related diseases, but possibly also in AD and MS [4–6].

The complement system provides an innate defensive mechanism against pathogenic microorganisms. For several years the role of this system has been rather neglected in CNS disorders, mostly due to the concepts that brain is an immune-privileged organ and that research could be more fruitful if focused primarily on adaptive rather than on innate immunity. By contrast, it is now clearly established that CNS not only contains several components of the immune system, but also that many factors of innate immunity are

expressed throughout the brain [7, 8]. In fact, neuronal and glial cells express Toll like receptors as well as complement receptors and virtually all the components of the complement system can be detected in the CNS where they are synthesized by astrocytes, microglia and also neurons. It has been postulated that the complement system may be useful in eliminating aggregated and toxic proteins associated with AD and other neurodegenerative diseases of the CNS. However, a dysregulated activation of the complement system can have deleterious effect through the activation of microglia, secretion of many proinflammatory cytokines and generation of oxidative products.

Although the cause of MS is unknown, a large body of evidence converges in indicating that MS is a multistep mechanism. Since considerable interdependence and functional overlap has been demonstrated among inflammatory response, coagulation system, and endothelial perturbation, the initial trigger could be a facilitated "movement" of lymphocytes and demyelinating antibodies from the systemic circulation into the CNS through disruption of the blood brain barrier [9, 10]. It has been hypothesized that these phenomena could be ascribed to a damaged "neurovascular unit" that may support neurodegeneration leading to cognitive deficits, as already demonstrated in AD [11, 12], but also be related to multifocal areas of demyelination and chronic inflammation.

Nowadays, new investigational strategies can be explored at the gene and pathways levels using appropriated animal models to deepen the understanding on pathogenetic mechanism. It can be hypothesized that since the CNS responds to injury and infection by activating innate defensive and tissue repair mechanisms, these brain defensive responses can involves common genes and pathways across diverse CNS diseases. Using this experimental approach, global gene expression was assessed in brains obtained from mouse models of MS and AD. Interestingly, DNA microarray expression profiling discovered dysregulated common genes and pathways including, key components of estrogen and TGF-β signaling pathways that have been associated with neuroprotection as well as a neurodegeneration mediator, transient receptor potential cation channel, subfamily M, member 7 (TRPM7) [13]. This type of analysis, if confirmed by further similar and complementary studies might provide a reliable tool for exploring the fine molecular mechanisms underlying different aspects of CNS neurodegeneration and, possibly, also a new approach for identifying new targets for therapy. For example, it has been recently demonstrated that brain atrophy in MS patients is greater in patients bearing the PCK1 allele associated with AD susceptibility [14].

In conclusion, as suggested by the few examples briefly described, the scenario in neuroscience research is rapidly evolving and it is clear that an open-minded experimental approach is mandatory to overcome rigid and no longer tenable borders between the pathogenesis of several frequent and severe chronic diseases of the CNS, also in order to rationalize any therapeutic attempt.

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18F-FDG and Amyloid PET imaging in Alzheimer's Disease

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The patophisiological hallmark of Alzheimer's disease (AD) is the accumulation of amyloid plaques in the brain with a fairly constant distribution pattern involving the basal portions of the frontal, temporal and occipital lobe with a partial saving of the hippocampal formation and primary sensory areas [1]. In vivo 2-deoxy-2-(^{18}F) fluoro-D-glucose (^{18}F-FDG) PET is a minimally invasive diagnostic imaging procedure used that evaluate cerebral glucose metabolism [2] while SPECT with 99mTc-exametazime (HMPAO) and 99mTc-bicisate (ethyl cystine dimer [ECD]) reflects regional cerebral perfusion [3]. ^{18}F-FDG PET is superior to perfusional SPECT in its ability to separate healthy controls from patients with true dementing illnesses [2] detecting functional changes that results in a reduced brain glucose metabolism due to amyloid deposition as neuronal injury and disfunction and cell death [4] .

Several cross-sectional case control, longitudinal assessment and cohort studies with postmortem diagnosis have been performed in the last years using ^{18}F-FDG PET [2] and this technique received approval in the United States for Medicare reimbursement to aid in the distinction of AD from Fronto-Temporal Dementia (FTD) [2]. For diagnosing AD, accuracy of ^{18}F-FDG PET (sensitivity, 84%; specificity, 74%) is better than that of initial clinical evaluation (sensitivity, 76%; specificity, 58%) [5]. Silverman et al found that 88% of 97 cases with clinical suspicious of AD presented positive ^{18}F-FDG PET findings (sensitivity 94%; specificity 73%) then confirmed histopatologically with a diagnosis of AD [6]. Only 20% of the patients with a negative PET scan present a progressive dementing process in long term clinical follow up and ^{18}F-FDG PET has also a better NPV than the initial clinical evaluation (78% vs 65%) [5]. In Mild Cognitive Impairment (MCI), different brain glucose metabolism patterns have been found between converters and non converters patients [7]. MCI converters usually show a greater brain glucose metabolism involvement in parietal, cingulated hippocampus and parahippocampus cortex as compared to MCI non converters which brain metabolic pattern is characterized by a selected involvement of dorsolateral frontal

cortex [7]. It has been suggested that ^{18}F-FDG PET findings may be useful in predicting short term conversion to AD [5, 7]. Part of the previously mentioned results are obtained by means of computer-assisted quantitative interpretation of images [7], being the visual rating of functional brain ^{18}F-FDG PET images heavily dependent to the lack of clearly defined cutoffs to distinguish between normal and pathologic findings especially at the early stage of the disease [2]. Several semi-automated tools initially developed for research applications [8] have been developed (i.e. statistical parametric mapping, SPM, Wellcome Department of Cognitive Neurology, London, UK) for clinical interpretations of a large number of neurologic disorders [9]. In our experience, the application of these tools leads to a greater diagnostic accuracy (Fig. 1), but the process is a little time consuming and images derived from different scanners and with different acquisition parameters cannot always be compared.

^{11}C labelled PET tracer (Pittsburg Compound B) PiB is the most widely used radiotracer for amyloid imaging in human beings [10]. Due to short ^{11}C half-life, three ^{18}F labelled tracers are being investigated in clinical trials for amyloid imaging. Flutemetamol (GE-067) is the 3′-fluoro-derivative of PiB , whereas florbetaben (BAY-94-9172, AV-1) and florbetapir (AV-45) are stilbene and styrylpyridine derivatives, which exhibit high affinity binding for fibrillary amyloid similar to PiB [10]. The regional retention of ^{11}C-PiB appears to be reliable to the regional density of Amiloid plaques in AD [11]. A good correlation between florbetapir brain uptake scores and the postmortem amyloid burden measured by immunohistochemistry and silver stain neuritic plaque scores has been found and florbetapir uptake in region analysis agrees with postmortem measurement of amyloid [11]. While in AD a gray matter atrophy was confined to the medial temporal lobe, a diffused ^{11}C-PiB uptake was widespread to frontal, temporal parietal and posterior cingulated areas while MRI didn't reveal atrophy in these areas [12] suggesting that in AD, hippocampal atrophy can be due to corticohippocampal connectivity disruption and not to in loco β-amyloid presence [13]. In MCI patients, follow-up studies have shown that 70% of ^{11}C-PiB positive MCI subjects will progress to dementia due to AD over 3 years [14]. Less than 10% of ^{11}C-PiB negative MCI patients progress to a clinical diagnosis of AD, whereas about 20% of ^{11}C-PiB negative MCI subjects progress to another type of dementia such as dementia with Lewy bodies or frontotemporal dementia [14]. As a result,

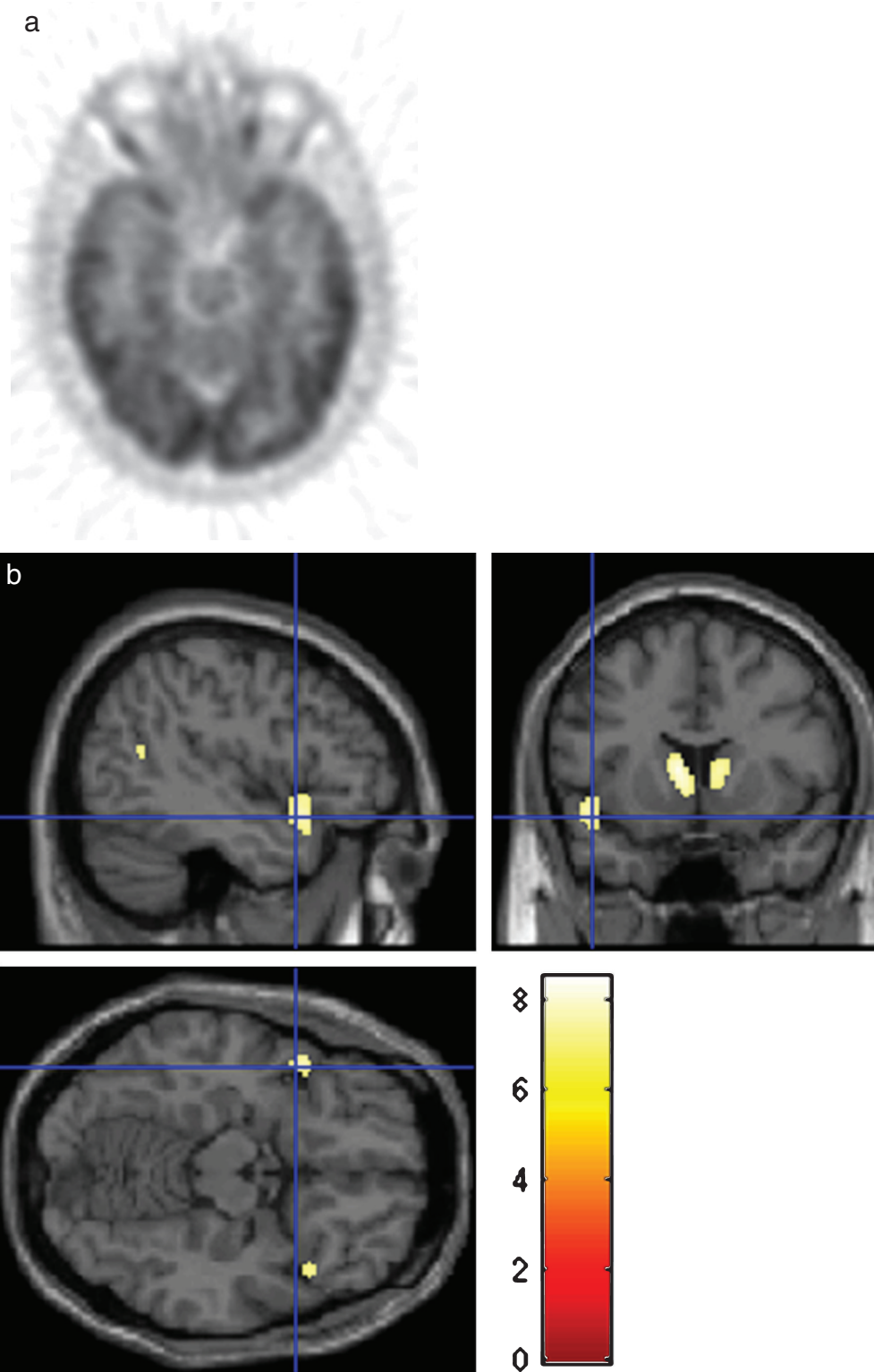Fig. 1. Comparison between visual and quantitative analysis. ^{18}F-FDG Brain PET SCAN of a male patient with clinical diagnosis of MCI showing a preserved brain glucose metabolism at visual examination (a). (b) T1 MRI superimposition showing a decreased ^{18}F-FDG uptake in temporal lobes and basal ganglia detectable using SPM2 when the images were compared with a control group of healthy volunteers.

tracers for amyloid imaging could be helpful in early identification of MCI patients that will convert in AD [14].

To our knowledge, only few studies evaluated the diagnostic accuracy of glucose metabolism and amyloid deposition as demonstrated by Lowe et al which compared ^{18}F-FDG and ^{11}C-PiB PET in the evaluation of subjects with cognitive impairment [15]. In a population composed by healthy controls, amnestic MCI, nonamnestic MCI and AD subjects, the ability to discriminate controls from AD was modestly improved for PiB (ROC area, 0.92), as compared with ^{18}F-FDG (ROC area, 0.84) although this was not a statistically significant difference and the most important contribute of PiB imaging in comparison with ^{18}F-FDG imaging is that separation of the groups is more distinct with PiB in visual examination [15].

In conclusion the high sensitivity and specificity ^{18}F-FDG PET in the diagnosis of AD is implemented by software programs for the quantitative interpretation of scans especially in the early stage of the disease and when considering MCI patients. Several early reports suggest a strong predictive value of amyloid tracers for progression from MCI to AD, and this tracer could represent a useful tool in the diagnosis of AD and its differential diagnosis from FTD [2].

It is our opinion that current advances in functional imaging awaits the development of an effective therapy to slow, halt or possibly reverse the amyloid-based disease process.

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Structural Neuroimaging in Dementia

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Abstract

Dementia is a common and growing problem, affecting 5% of the over 65s and 20% of the over 80s. Dementia is a clinical diagnosis, but often neuroimaging is crucial for proper assessment. Structural imaging by computed tomography (CT) and magnetic resonance (MRI) may help clinicians by identifying nondegenerative and potentially treatable causes of cognitive impairment which, however, account for only 1% of all causes of dementia.

In the last years the focus of imaging in patients suspected of having dementia has shifted from an exclusionary to an inclusionary approach.

The availability of new treatments for dementia, as well as the importance of subtype-specific management, has renewed interest in the use of brain imaging techniques that can assist in the accurate recognition of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), vascular dementia (VaD) and frontotemporal lobe degeneration (FTLD).

In many cases, the specific pattern of cortical and subcortical abnormalities on MRI has diagnostic utility. Furthermore new imaging techniques carry the hope of revolutionizing the diagnosis of neurodegenerative disease so as to obtain a complete characterization (i.e. molecular, structural, and metabolic), which could be used to improve diagnosis and to stage each patient and follow disease progression and response to treatment.

Although only clinical assessment can lead to a diagnosis of dementia, neuroimaging is clearly an invaluable tool for the clinician in the differential diagnosis.

Introduction

The risk for cognitive decline increase with age. When such decline interferes with daily functioning, a diagnosis of dementia is generally present. Therefore dementia is a common illness with an incidence that is rising as the aged population increases.

There are a number of neurodegenerative diseases that cause dementia. According to recent publications and consortium meetings Alzheimer's disease (AD) is the considered to be the most frequent dementia (60% to 70%), but numerous other neurodegenerative illnesses have an associated cognitive impairment, such as dementia Lewy bodies (DLB), frontotemporal lobe degeneration (FTLD), corticobasal degeneration (CBD), Creutzfeldt–Jakob disease (CJD) and other atypical parkinsonian dementias [1]. Vascular etiologies of dementia (VaD) are the third most common cause (8% to 10%), following AD and DLB (10% to 25%), but these numbers vary considerably according to the different criteria used for VaD [2].

Diagnostic criteria of this dementing conditions have relied on a constellation of symptoms, but the definite diagnosis remains a pathologic one.

NEUROIMAGING

Computed Tomography and Magnetic Resonance Imaging

There is strong evidence that structural imaging influences patient management during the initial evaluation of dementia. All current criteria stipulate that structural imaging needs to be done at the initial evaluation of a patient suspected to have dementia [3].

The role of imaging by computed tomography (CT) and magnetic resonance (MRI), historically has been directed at ruling out treatable and reversible nondegenerative etiologies and not to use imaging to better understand the pathophysiology of the different dementias.

In particular, imaging should be performed when a potentially treatable disorder is suspected (hemorrhage, stroke, hydrocephalus), when signs or symptoms suggest superimposed pathology (stroke, multi-infarcts, trauma), or when an abrupt onset of dementia or acute deterioration of mental status occurs [3]. Evidence is lacking for the choice of either CT or MRI.

Besides the potential causes of dementia mentioned above structural neuroimaging can also identify anatomic changes that occur due to the pathologic involvement in neurodegenerative disease. In fact the focus of structural neuroimaging, in the past years, has shifted from its use to rule out certain disease towards a supporting role for the clinical diagnosis [3].

Neuroimaging correlates with gross pathology, characterized by neuronal loss. The result is: cerebral

atrophy, with enlarged lateral ventricles and widened sulci, in the neurodegenerative cause of dementia; cortical and subcortical infarcts with white matter lesions in VaD.

Moreover the topography of the atrophy in the neurodegenerative dementias provides information about the specific type: atrophy of the medial temporal lobe is predominant in AD, while atrophy of the frontal and anterior temporal lobes is seen in FTLD; VaD is marked by infarction, lacunae, and signal abnormalities in the white matter and sometimes microbleeding. When structural imaging is equivocal or does not lead to the diagnosis, functional imaging (i.e. single-photon emission computed tomography, positron emission tomography, diffusion or perfusion MRI) may add diagnostic value [4].

Focus of structural neuroimaging

The high prevalence of AD and VaD means that the suggested first aims in the imaging evaluation of a patient suspected of having dementia are to:
– exclude a structural lesion which may be amenable to neurosurgical intervention;
– assess the extent and pattern of brain atrophy, especially medial temporal lobe atrophy;
– determine the degree of vascular damage, including the occurrence of strategic vascular lesions.
The choice between CT and MRI depends on many factors, including clinical suspicion, controindications, costs and quality of scanners, claustrophobia, and the ability of the patient to keep still for the time needed for the MRI.

Exclusion of a surgically treatable cause of dementia can be ascertained by using CT, but it is also possible to evaluate the presence and extent of cerebrovascular disease than, with appropriate techniques, to assess atrophy of the medial temporal lobe. It is important to realise that the long axis of the medial temporal lobe is somewhat tilted with respect to the transverse plane. In order to obtain slices that are either parallel or perpendicular to the hippocampus, the acquisition protocols need to be adjusted. With the advent of multi-slice CT the possibilities to evaluate the pattern of brain atrophy have increased due to availability of high resolution coronal multi-planar reconstructions (MPR) perpendicular to the long axis of the hippocampus, for the evaluation of medial temporal lobe structures, and sagittal reformatted images to evaluate the paramedian cerebral cortex, such as the precuneus.

Nevertheless MRI is certainly the method of choice [5] and the sequence that will provide the information required are: coronal 3D T1w GE isotropic voxels (to evaluate atrophy), transverse T2w TSE/FSE and transverse FLAIR (to assess white matter alterations), transverse GE T2* (to assess microbleeds). Diffusion weighted imaging (DWI) frequently used in clinical setting for evaluate oedema (suspicion of CJD, recent infarct, transient global amnesia or metabolic dementia).

Visual evaluation in workup of dementia

In clinical practice, the pattern of atrophy across the entire brain should be taken into account, rather than an isolated evaluation of the medial temporal lobe. Besides atrophy, cerebrovascular pathology has been associated with AD, especially in the late onset form. Overlap with VaD may occur and patients may actually fulfil both criteria for AD and VaD [6].

Therefore the first step of neuroradiologic visual evaluation is to determine the degree and pattern of general cortical atrophy (GCA): abnormal or not, symmetric or asymmetric, regional pattern, posterior or anterior gradient. To quantify the degree of GCA can be used a simple rating scales proposed by Pasquier [7] ranging from no atrophy (score 0) to knife-blade atrophy (score 3).

Then evaluate focal regional atrophy in medial temporal lobe (MTA), temporal pole, frontal lobe, parietal lobe, occipital lobe, posterior cingulated and precuneus, brain stem atrophy, cerebellar atrophy.

For the MTA can be used the score suggested by Scheltens. This score can be done on coronal MRI by visual assessment of width of choroid fissure, width of temporal horn and height of hippocampus. Rating of MTA has been shown to be very sensitive to the occurrence of AD, but is not specific for this disease [8].

Many AD patients with early age of onset (before 65 years) often present with visuospatial problems, apraxia, or language deficits, that reflecting a different pattern of cortical involvement in comparison with AD with late age of onset. Several structural MRI studies localize the pattern of the atrophy in early-onset AD to more posterior regions with prominent involvement of the precuneus and posterior cingulated. To appreciate this posterior/parietal atrophy, a specific rating scale has recently been designed, evaluating the posterior cingulate, precuneus and superior parietal regions [9].

In addition to the visual rating scales a number of linear measurements for specific structurers of interest (i.e., radial temporal horn distance, interuncal distance, ventricular width, intercaudate distance) have been proposed in the last decades, but none of these have been widely adopted.

In clinical situations, a *qualitative* visual assessment of images is sufficient for diagnostic purposes. However, a *quantitative* assessment gives more detailed information because the most important structural imaging feature of AD is not only the atrophy but also "progression" of atrophy. Neuroanatomical changes over time may be too mild, diffuse, or topographically complex to be detected by simple visual inspection or even with manually traced measurements of regions of interest.

New volumetric imaging techniques developed in the last years represent an added value to identify subtle structural brain changes which have brought extensive neocortical changes to the fore. The most widely used techniques are: regional volumes and Region-of-Interest approaches, segmentation/registration/deformation-based analyses, and fusion-automatic diagnostic systems. However routine use of these volumetric techniques for the diagnosis of AD may be time-consuming and cumbersome in a clinical setting.

For the evaluation of white matter changing (WMC) many scales have been proposed to examine the amount, size and distribution of vascular WMC in ageing and dementia. In routine patient care a four-step Fazekas scale may suffice [10]. Alternatives include the Scheltens WMC scale (with more step for region). Structural neuroimaging can help to identify vascular dementia or vascular component of AD (mixed dementia) by increasing the sensitivity of the clinical evaluation and management of the vascular component may in turn slow down cognitive decline.

Structural neuroimaging in early diagnosis

Although CT and MRI are commonly used for dementia workups, they are particularly limiting when no structural changes are observable, like in early stages of dementia or Mild Cognitive Impairment (MCI). In these cases, the neuropathological disease process may not have yet affected the overall structure of brain tissue; however, cognitive difficulties and symptoms may be present due to functional changes in brain tissue chemistry or metabolism that have yet to affect the structure of brain that can be seen on MRI or CT. Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from normal (typically 10–15% per year – compared to rates of 1% with normal ageing) but is clearly not the invariable clinical outcome at follow-up [11, 12].

Study of MCI subjects and asymptomatic individuals at risk for familial AD show that hippocampal, cingulated and generalised neocortical losses are all present at an early and even presymptomatic stage. Highly predictive MRI biomarkers for AD are the atrophy and/or volume loss of medial temporal lobe and entorhinal cortex [13].

Serial registration of MRI scans to identify cerebral volume changes over time using the patient as his own control seem to be highly accurate for predicting the transition from MCI to AD in individuals. However to achieve diagnostic certaintly this would require repeated imaging possibly for more than two years [14].

In this pre-clinical stage of dementia functional imaging can provide valuable information about biological and chemical changes occurring in the brain and can support clinicians in early detection and diagnosis of dementia when structural changes are absent. It is important to remember that neuroimaging is only one piece of information that clinicians use when conducting a dementia workup, making a diagnosis, and providing treatment [15].

Conclusions

Neuroimaging is no longer optional in diagnosing the underlying disease in dementia.

The diagnosis of a patient with suspicion of dementia may require input from many disciplines: clinicians, neurophysiologists, psychologists as well as radiologists.

The increasing need for an earlier and more specific diagnosis to guide management and treatment poses a burden on the diagnostic skills of the team involved. The appropriate use of neuroimaging may help to advance diagnosis and alleviate burden for the patient and the carer.

New neuroimaging methods facilitate diagnosis of most of the neurodegenerative conditions after symptom onset and show promise for diagnosis even in very early or pre-symptomatic phases with some diseases.

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Resting State Functional Magnetic Resonance Imaging in Mild to Moderate Alzheimer Disease and Amnesic Mild Cognitive Impairment

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Introduction

Since the human brain is organized into parallel, interacting systems, understanding how they behave in neurodegenerative pathologies may lead to seminal advances in neurosciences. In the last 20 years, functional magnetic resonance imaging (fMRI) has become a predominant technique to evaluate brain function and neuronal functional connectivity (FC) [1, 2]. FC can be defined as the co-activation over time between spatially distinct cerebral areas that show synchronized low frequency fluctuations in cerebral blood oxygen level dependent (BOLD) signal at fMRI, and can be assessed by resting-state fMRI (RS-fMRI) [3]. This technique allows to explore the so called Resting State Networks (RSNs), whose dynamics are independent from external stimuli and reflect intrinsic functional properties [3, 4].

Among the RSNs, the most appealing in the field of cognitive neurosciences is the Default Mode Network (DMN) which includes Posterior Cingulate Cortex (PCC), Anterior Cingulate Cortex, Inferior Parietal Lobe and Medial Prefrontal Cortex. This RSN is active at rest, deactivated during the engagement in cognitive tasks and is strongly negatively correlated with other brain regions usually engaged in the performance of cognitive tasks requiring sustained attention to external stimuli [3]. Moreover, converging evidences indicate that the DMN is involved in spatial orientation, stream of consciousness, episodic, autobiographical and prospective memory [5, 6].

Prior fMRI studies have shown loss of DMN integrity in Alzheimer's Disease (AD) as well as in Mild Cognitive Impairment (MCI) [7, 8, 9]. Although medial temporal lobe structures such as enthorinal cortex and hippocampus are involved in the earliest stage of AD and are responsible for episodic memory impairment, more recent studies suggest that memory is sub served by a broadly distributed network, including specific regions of DMN, such as precuneus and PCC [10, 11]. Nowadays, MCI is interpreted as the possible prodromal stage of AD, and its amnestic form (aMCI) is the most frequently studied because of the high rate of progression to AD.

Objectives

The aims of the present study were to explore the FC of DMN in aMCI and mild to moderate AD, and to evaluate the correlation with global brain atrophy and neuropsychological performances.

Subjects

We recruited 15 aMCI patients, 14 AD patients and 14 healthy controls (HCs). We excluded patients with abnormal MRI, Hachinski scores lower than four, neurological, and psychiatric disorders or major medical conditions (such as diabetes, hypertension or cardiac disease) that could determine cognitive impairment.

aMCI patients were classified according to Petersen et al. criteria as having aMCI single domain; their Clinical Dementia Rating global scores (CDR GS) were 0.5 and Mini Mental State Examination (MMSE) scores ranged from 24 to 26.

AD patients met diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD. We included patients with mild to moderate AD whose MMSE median score was 21.2 ± 4 and whose CDR GS scores ranged from 1 to 2.

HCs had no memory impairment, cognitive disorders or abnormal finding at conventional brain 1.5 Tesla MRI; their CDR GS scores were was 0 and their MMSE scores ranged from 28 to 30.

MRI data

RS-fMRI data were acquired by 3Tesla scanner, and analyzed by Independent Component Analysis (ICA). Such an approach excludes any a priori hypothesis in determining the origin of FC dysfunction. The maps of DMN connectivity were compared with an external template DMN map constructed from HCs to obtain goodness of fit (GOF) indices of DMN expression and
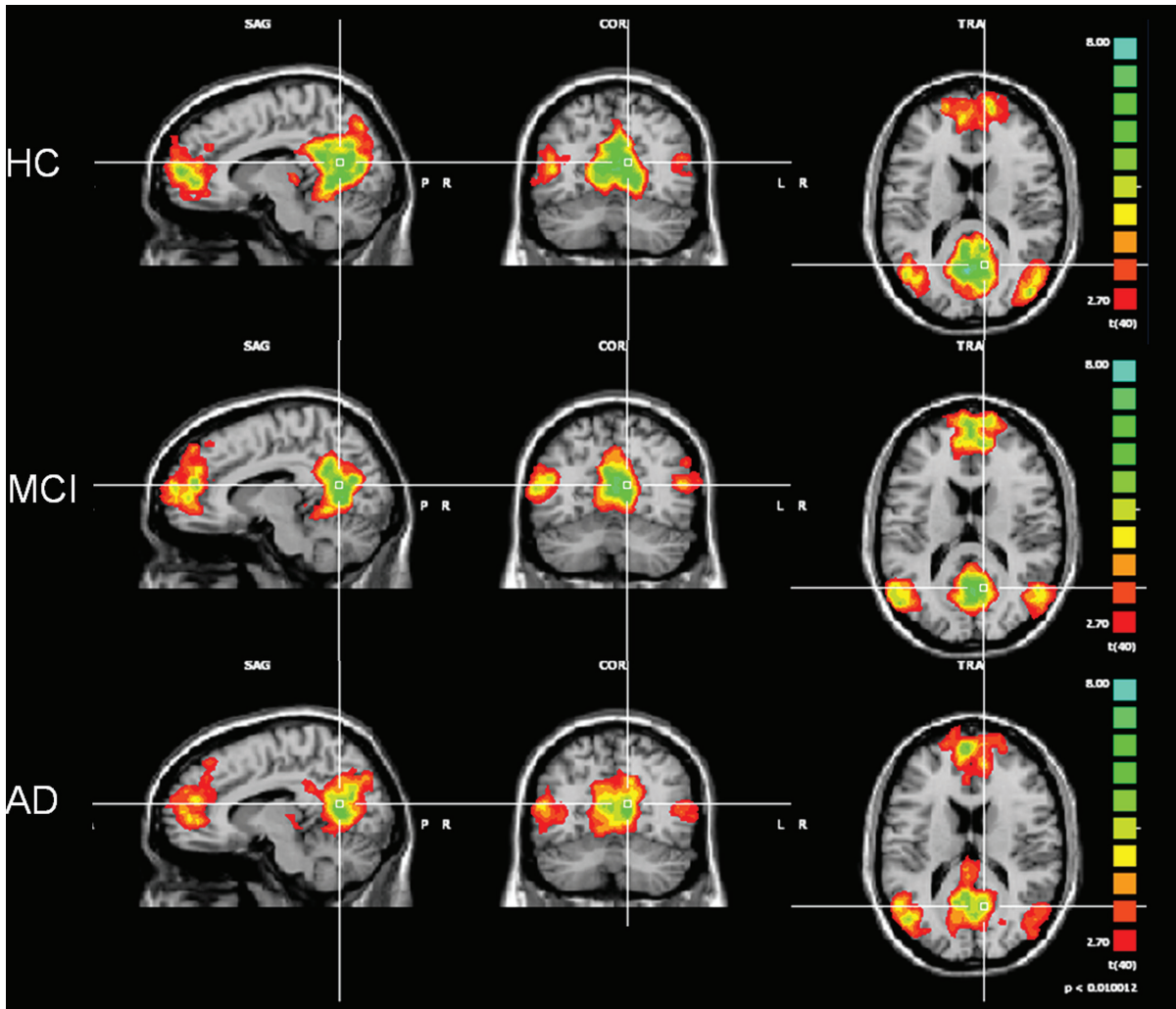
Fig. Single-group DMN maps for HC, MCI and AD groups.

to select the best fit DMN map in each patient. The selected DMN maps entered in a second level population analysis of variance with three groups (HC, AD, aMCI). To assess whole brain atrophy, brain parenchymal fraction (BPF), was measured by SIENAX analysis of the T1-weighted anatomical series acquired in the same MRI sessions.

Statistical correlations between DMN, and BPF measures with neuropsychological data were performed by Pearson's correlation test.

Neuropsychological assessment

All recruited subjects underwent an extended neuropsychological battery including MMSE, Mental Deterioration Battery, Frontal Assessment Battery, Rey Complex Figure Test, Digit Span, Corsi Block Test, Babcock Test, Categorical Fluency, Trial Making Test forms A and B to explore several cognitive domains (global cognitive efficiency; verbal and visual episodic short term memory; verbal and visual episodic long term memory; visuo-constructive abilities; executive functioning: Problem solving; attention).

The functional status and the ability to perform activities of daily living of each patient were assessed by a semi-structured interview with care-givers (Activities of daily living [ADL], and instrumental activities of daily living [IADL]).

The Behavioral and Psychological Symptoms of patients were evaluated by the Neuropsychiatric Inventory (NPI).

The rate of patients' awareness of reason for the visit, memory deficits, functional deficits and progression of the illness was tested by the Clinical Insight Rating Scale (CIRS).

Finally, to detect very early stages of cognitive impairment and to discriminate aMCI from very early AD, we used the CDR Sum of Boxes Score (CDR-SB).

Results

RS-FMRI, BPF and neuropsychology
As expected, aMCI and AD patients were significantly more atrophic than HCs. Nonetheless, the DMN was present and detectable at rest in both aMCI and AD patients. The overall FC of DMN, as expressed by the mean GOF indices, was highest in HCs, intermediate in aMCI and lowest in AD (Figure). At a regional level (comparing DMN maps between groups on a voxel by voxel basis), FC was significantly lower in AD than aMCI and HCs in the PCC.

Moreover, in the AD group DMN measures were linearly correlated with MMSE, while in the aMCI group, PCC activation was linearly correlated to performances on tests exploring delayed recall of verbal memory and executive functions..

Discussion

As expected, the AD patients recruited in the present study were more atrophic than aMCI and HCs. Our neuropsychological data, in agreement with previous studies [12, 13], support the hypothesis that problem-solving and working memory are selectively impaired even in patients with "pure" aMCI and sustain the notion that some aspects of control functions such as social cognition, theory of mind, strategic processes of episodic memory, insight and metacognition could be variably incorporated into the domain of executive functions. In line with previous works [14, 15], we highlight the existence of mechanisms of interplay between explicit (executive) and implicit (introspective mental processes, episodic memory) brain processes, early affected in neurodegenerative diseases.

The present RS-fMRI findings highlight the significant differences in the DMN between HCs, aMCI and mild to moderate AD patients. Furthermore, the significant positive correlation between FC of PCC, and delayed recall of verbal memory and executive functions in aMCI patients, strengths the notion that in aMCI there is a significant infraclinical disruption of the networks involved with executive functions.

Finally, we believe that the present DMN results support the role of RS-fMRI study in the evaluation of aMCI and mild to moderate AD patients in clinical trials as well as in the diagnosis of borderline, dubious and very early cases.

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Vascular Damage and Neurodegeneration

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Alzheimer (AD) and Vascular (VD) dementias are clinical entities defined by specific diagnostic criteria, based on history, clinical presentation, neuroimaging and pathologic features.

AD is the most common form of dementia (about 60%), characterized by a progressive chronic neuro-degenerative disease linked to beta-amyloid deposition (senile plaques and vascular angiopathy), tau-pathology, death of cholinergic neurons, micro-glial activation and inflammation. Conversely, cognitive impairment in VD is produced by cerebrovascular disorders, such as previous clinically apparent or silent strokes, strategic lacunar infarcts, leucoaraiosis.

However, "pure" AD and VD are rare conditions, the majority of syndromes encountered in clinical practice being a mixture of both pathologies. Pure cases of VD without neurodegenerative changes are very rare and autopsy of clinically diagnosed VD cases showed that they had important pathological signs for AD. Indeed, AD pathology may be present in 40%-80% of VD patients and, conversely, vascular comorbidity may be present in 30%–60% of AD patients [1].

Moreover, both conditions share common risk factors, such as old age, atherosclerosis, stroke, transient ischemic attacks, hypertension, cardiac disease, the epsilon 4 allele of the apolipoprotein E (ApoE), elevated homocysteine levels, hyperlipidemia, metabolic syndrome, obesity and diabetes. All these common risk factors suggest common pathogenetic mechanisms, and more specifically a role for cerebrovascular mechanisms in the development and progression of AD.

Cerebral accumulation of a 4-kDa peptide termed beta-Amyloid (Abeta), a 37–43-amino acid fragments (predominantly Abeta40 and Abeta42) derived by serial proteolysis of the amyloid precursor protein (APP) by beta- and gamma-secretase, is widely accepted as the key neuropathological event in AD.

In the last decades, the enormous efforts to understand the pathogenic potential of Abeta have provided new insights into the pathogenesis of AD, raising the idea that the neuro-vascular unit could be the site of early damage. Abnormalities in the vascular system of the brain could contribute to the onset and/or progression of neurodegenerative events in AD. It seems that microvascular endothelium is the primary site of interaction of abeta peptide with endothelial cells, triggering inflammation, endothelial damage, hypoxia, with a vicious cycle between amyloid accumulation, hypoxia, inflammation [2].

The "two-hit" hypothesis of AD pathogenesis emphasize the primary role of vascular damage in triggering neurodegenerative mechanisms of AD.

As an example, hypercholesterolemia and inflammation are the dominant mechanisms implicated in the development of atherosclerosis and have emerged as key factors implicated in AD pathogenesis as well [3]. Chronic inflammation is a pathogenetic mechanism common to vascular and degenerative diseases. Numerous studies have shown the presence of markers of inflammation in brain, cerebrospinal fluid and plasma of AD patients.

A wide range of inflammatory cytokines and chemokines which have been shown elevated particularly in early stages of AD, play a role in the evolution of the atherosclerotic plaque and directly interact with endothelial, microglial and neuronal cells. Elevated levels of cytokines and chemokines are found in or near pathologic lesions in the AD brain and may exacerbate Tau pathology. Retrospective epidemiological studies have shown that non steroidal anti-inflammatory drugs (NSAIDs) may significantly reduce the risk of developing AD, although trials with these drugs failed to demonstrate therapeutic effects in AD patients, suggesting a specific role of inflammation as an early event in AD pathogenesis.

Quite interestingly, Tibolla et al. have recently shown that the vascular pro-inflammatory effects of CNS-localized APP overexpression may lead to atherogenesis before parenchymal Abeta deposition and neuronal dysfunction, confirming a possible primary role of the vascular impairment in AD pathogenesis [3].

This is consistent with the link between ApoE4 and the presence of cerebral amyloid angiopathy (CAA) as a common feature of advanced dementia in AD [4, 5].

The deposition of Abeta in the walls of capillaries, arteries and arterioles, known as cerebral amyloid angiopathy, is an important factor in the severity of AD, as it provokes endothelial degeneration, affects cerebral blood flow, and enhances neuroinflammation. These effects are thought to be caused either by a weakening of the vessel wall through local Aβ-induced inflammation or an impairment of the BBB, even though clinically silent or under the detection threshold. Indeed, cerebrovascular deposition of Abeta

might be cause and consequence of alteration of peptide trafficking across the BBB. However, as an intriguing alternative possibility, it should be taken into account the hypothesis that Abeta accumulation in the cerebral microvascular endothelium may be an outcome of a potential local Abeta production in the vascular domain [6]. In agreement, our group has recently show that after mimicking ischemia in-vitro, by oxygen and glucose deprivation, Abeta accumulates into the brain capillary endothelial cells as a consequence of *in loco* production, and most of the produced peptide may be retained within the cells (unpublished data).

However, the potential molecular mechanisms by which these processes may contribute to AD pathogenesis are today largely unknown.

Recent studies seem to suggest a patho-physiological relevance to the hypoxia/HIF-1 pathways regulation of β-secretase 1 (BACE1) expression and activity in the hippocampus and cortex, demonstrating an important role of hypoxia/HIF-1α in modulating the amyloidogenic processing and providing a molecular mechanism for increased incidence of AD following cerebral stroke [7, 8]. Another potential mechanisms linking stroke and traumatic brain injury with APP metabolism has been elegantly described by Tesco et al., where they have shown that increases in BACE1 and beta-secretase activity are due to post-translational stabilization of GGA3, an adaptor protein involved in BACE1 trafficking during cerebral ischemia [9, 10].

The demonstration of a direct connection between chronic vascular impairment and AD pathogenesis should usher us to focus on new biomarkers and new therapeutic targets, addressing specifically the interactions of Abeta and endothelial cells. Various markers of endothelial damage have been already described in AD patients and we recently demonstrated that Tissue Factor Pathway Inhibitor (TFPI), produced by damaged endothelial cells, should be a suitable marker of endothelial perturbation in AD, increasing up to 60% compared to healthy controls [11]. Since TFPI, like the naturally occurring antibodies against Abeta, has been found to be associated to senile plaques and activated microglia in AD brains, we are now investigating their relations with neurodegeneration and

Abeta toxicity, in order to candidate their evaluation as future biomarkers during the ongoing disease modifying therapies in AD [12].

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Neuropsychological Pattern of Presentation of Alzheimer's Disease

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Sporadic Alzheimer's disease (AD) represents the most frequent type of dementia in both adults and elderly, thus it has been largely studied in a large amount of papers. Although AD is considered a unitary disease, both the neuropathological and neuropsychological investigations on one hand, and the different well-known genetic risk factors on the other, provide reasonable grounds to support the clinical heterogeneity observed in AD clinical presentations.

Undoubtedly memory disorders, due to the earlier involvement of hippocampal and temporal mesial regions [1], are the first and most recognized symptoms of sporadic AD. From the neuropsychological point of view the pivotal role of memory deficits has been recently underlined by the revised criteria for the diagnosis of AD by Dubois and colleagues [2] that also define the quality of this disorder. Specifically memory disorders in AD affect long term memory, but in particular AD patients do not present improvement after semantic cueingwith respect to other dementias.

In an attempt to describe a neuropsychological staging of sporadic AD, connected to the diffusion of the neuropathological process, the cognitive domains are supposedly impaired in a rather predictable order. As a consequence, after episodic memory the semantic domains are mainly involved. Thus knowledge of words and people and cultural notions will be lost. Anomias are frequent in this stage whereas evident language disorders as transcortical aphasia, the loss of grammar rules and mutism appear in later stages.

Executive disorders are frequent in the initial stages of AD [3] but in an early phase only divided attention disorders [4] and deficits in tests of conjunction search [5] are present. Decision making and set-shifting tasks are involved in the early or intermediate phase due to the primary deficit in on going memory. While only in the later stages the behaviour in tasks exploring frontal abilities does not differ between AD and patients with Frontotemporal dementia.

Agnosia appears in the later stage of the disease and it is related to the extension of the neuropathological process to the temporo parietal and temporo occipital regions [6]. Similarly praxis and visuo-spatial skills are the final cognitive domains impaired and their involvement is often correlated with the disruption of the functional abilities [7].

The staging of AD reflects a standard model based on the clinical criteria of NINCDS-ADRDA and DSM-IV-TR mainly used in the diagnosis of AD.

Although this classic cognitive progression of sporadic AD is usually acknowledged, atypical presentations and progressions are frequently described. An atypical presentation can create a source of confusion and difficulty in the differential diagnosis with other dementias. Furthermore numerous patients present rather peculiar trajectories in disease progression with only a few cognitive domains involved over time and a long plateau before the classic AD final condition is reached. In the following section we will briefly describe some of these conditions

Atypical neuropsychological presentation and progression of AD pathology

In the last fifteen years growing interest has been focused on one hand on the observations of patients with dementia related to AD neuropathology that do not have memory disorders at onset and on the other hand, of patients that do not show the classic AD neuropsychological progression [8–11].

Atypical-AD clinical features are associated with an unusual pattern of NFT or SP formation that predominantly involves cortical areas usually spared in the early stages of the degenerative processpresentations. These presentationsare usually defined on the basis of their neuropsychological onset and progression over time and different pattern have been described.

Linguistic onset

Recent neuropathological studies show that 30-40% of patients with clinically diagnosed progressive aphasia have Alzheimer's disease pathology, while the remainders have pathology in the Frontotemporal dementias (FTD) spectrum. The pattern of linguistic disorders in AD cannot easily be distinguished from those observed in FTD [12] and the involvement of other cognitive domains does not help in discerning the two groups either. The prevalence of neuropsychiatric features in Progressive Aphasia syndrome due to FTD pathology seems to be the only distinguishing aspect.

At variance with this observation, the recent classification of PPA (Progressive Primary Aphasia) identifies three subtypes of PPA: Agrammatic, Logopenic and Semantic [13].

In particular, Logopenic PPA is characterized by good comprehension, anomic pause, circumlocutions and poor repetition of sentences. This subtype is strictly related with AD pathology and amnesic symptoms invariably appear in these patients leading to an overt AD over time [11].

Visuo-spatial onset

AD pathology limited at onset to the posterior parietal cortex and occipital cortex has been defined as Posterior Cortical Atrophy (PCA) [11].

The clinical pattern consists of impairment of visuo-spatial function, visual agnosia, poor orienting, till optic ataxia and Balint syndrome.

Actually the clinical pattern of PCA is rather heterogeneous; some patients present mainly agnosia and/or prosopoagnosia while other patients show visual and praxis disorders with a wide spectrum between them. Commonly biparietal subtype is the most frequent with some patients presenting symptoms overlapping with Corticobasal syndrome.

Regularly long term memory disorders appear in 1–3 years, rapidly followed by linguistic disorders, leading to an overt AD diagnosis [10–11].

Other atypical onset

AD and Mild Cognitive impaired patients may display depression and anxiety at the appearance of their cognitive disorders but a specific Behavioural Onset is quite rare. However the diagnosis of AD should be considered if apathetic and/or disinhibited behaviours are followed by memory disorders [8].

On the contrary the occurrence of a Corticobasal Syndrome characterized by a prevalence of cortical signs (alien limb, heminegligence, visuo-spatial deficits, linguistic disorders, apraxia), with respect to extrapyramidal symptoms, has been related to AD pathology in 50% of patients in a neuropathological correlation study [11].

Focal Temporal Lobe Dysfunction (TLD)

From a different perspective, some typical amnesic patterns of AD, mainly characterized by massive long term episodic and semantic memory disorders without executive, visual-spatial and praxis disorders (TLD), deserve some comments. Formerly TLD patients were described as patients with a very slow progression [9] and with a restricted functional pattern of temporal hypoperfusion at the SPET examination

[14]. Recently a longitudinal neuropsychological observation confirmed the slow rate of progression of these patients over time without any switch of TLD to the classic AD condition in a 24 months period [15]. At a whole these reports suggest that TLD may represent a phenotypic subtype of AD with a different pattern of cognitive progression.

Conclusions

AD represents a cognitive and neuropathological disease with a specific pattern of presentation and evolution. Nevertheless atypical presentation and atypical progressions of AD pathology are nowadays well-known. They deserve particular attention in the clinical approach being sources of difficulties in the differential diagnosis with other dementias due to different neuropathology. As a consequence their identification represents not only a merely diagnostic exercise but is critical for the choices of therapeutic strategies in dementia management.

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Non-invasive Brain Stimulation Offers New Prospects in Cognitive Neurorehabilitation for Alzheimer Patients

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Cognitive deficits are a common consequence of brain injury, stroke, neurodegenerative and other neurological disorders. The rehabilitation of neuropsychological disorders of cognitive function, such as language, attention, and other functions, represents an expanding area of neurological rehabilitation [1, 2]. Cognitive deficits that cause significant personal, social and functional burden have recently attracted a growing political, social, and ethical focus. Improvements in these domains have been observed after highly intensive and targeted cognitive training [3]. However, studies in this field to date are scarce, their findings are frequently inconclusive, and, most intriguingly, the neural correlates of training-induced improvement in cognitive functions remain to be fully understood. Moreover, from a clinical perspective, highly intensive treatment is often impractical.

Alzheimer's disease (AD) is a progressive disorder that impacts memory, language and several other cognitive functions, and severe problems manifest early in the progression of the disease. In addition, with disease progression, behavioral symptoms such as delusions, agitation, changes in personality, and mood disturbances may also occur. All these cognitive and behavioral symptoms arise in close relation to the slowing of the electroencephalogram, and it is likely that the inability of cortical circuits to maintain an activated state contributes to the behavioral disorganization. At first site, one would define cognitive neurorehabilitation for AD patients as an inappropriate target since it is a progressive disorder and any improvement would be "vanished" in a short time [4]. Nevertheless if we define the goal of rehabilitation as enabling people to 'achieve an optimal level of physical, psychological and social functioning' then it is clear that this is an appropriate goal at any stage of a progressive disorder. Improving well-being implies an enhancement in quality of life, not only for the person with dementia but also for his or her family or caregivers [4]. Moreover, some aspects of cognitive functions are preserved until later in the disease and can therefore be targets of rehabilitation interventions.

Given the limited effectiveness of pharmacological treatments, non-pharmacological interventions in AD have gained attention in recent years, and there are currently many different approaches under study, ranging from multi-strategy approaches to cognitive training [see 5]. Recent studies have reported enhanced performance on specific cognitive tasks in patients with several types of neurological diseases after receiving non-invasive brain stimulation (NIBS), i.e., repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) to specific cortical areas depending on stimulation characteristics. Converging evidence has indicated that continuous rTMS below 1 Hz (low frequency) causes a reduction in neuronal firing and decreases cortical excitability locally and in functionally related regions. By contrast, intermittent rTMS above 5 Hz (high frequency), which leads to increased neuronal firing, appears to have the opposite effect [6]. Moreover it has been shown that also during tDCS, the neurons respond by altering their firing rates, i.e., cathodal stimulation reduces spontaneous neuronal firing rates, whereas the anodal tDCS exerts the opposite effect [7]. Therefore both techniques induce effects at the cerebral level that are comparable in many aspects.

Specifically, it has been showed that NIBS reduces vocal reaction times for picture naming in normal subjects [8–10] and improves the number of correct responses in AD patients affected with mild to moderate [11] and moderate to severe [12] dementia. Using tDCS, it has also been recently shown that a single tDCS session can ameliorate visuospatial attention deficits in stroke patients [13], naming abilities in vascular aphasia [14, 15] but also memory in patients with AD [16, 17] and many others pathologies [18].

It has been hypothesized that NIBS modifies cortical plasticity and has effects that may outlast the stimulation period itself. Therefore the general idea behind NIBS is that inducing changes in cortical excitability leads to a recovery or reorganization of the functional network responsible for the impaired cognitive function. Function may be restored or compensated for by mechanisms that involve both structural and functional changes to the brain circuits. In addition, the restored function might be based on the same general rules that were valid during the devel-

opment of the nervous system or during learning-dependent plasticity.

We performed two studies with the aim of assessing the long-term effects, on cognitive performance, of rTMS or tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) in AD patients during a resting state. The patients were randomly assigned to one of four study groups. One group underwent a two-week real rTMS stimulation protocol, the second underwent a two-week real tDCS stimulation protocol, while the other two groups underwent a two-week sham treatment, one with rTMS and one with tDCS. Each session consisted of the application of high-frequency rTMS or anodal tDCS over the DLPFC for 25 minutes. Sessions occurred once daily, five days/week.

A significant difference was found between groups over sessions in terms of the percentage of correct responses of auditory sentence comprehension but only in one group. Only real rTMS treatment induced an improvement in performance with respect to baseline, anodal tDCS or sham. Moreover, the improved performance, on sentence comprehension, was present at six months after the end of treatment [19].

These facilitation effects seem related to the possibility of inducing changes in cortical excitability and therefore reorganization of a functional network from which cognitive performance may benefit. An enhancement of cortical excitability by focal brain stimulation of a given network might change AD's performance through a specific potentiation-like phenomenon, which would enable synaptic plasticity and promote recovery of the degraded function. It was claimed that applying electrical stimulation could benefit patients with dementia by altering the activity of various neurotransmitters or by increasing brain activity, thereby retarding neural degeneration and stimulating regenerative processes. In Alzheimer's patients neuronal death is not an all-or-none phenomenon. Even in severely affected areas, studies have shown evidence of plastic changes in surviving neurons [20, 21]. rTMS can induce a partial recovery of language abilities [19, 22], which may be due to a strengthening of the synaptic activity of the surviving neurons in the stimulated network. Following the loss of a part of the neural population, a reduction of excitability of cortical neurons within the affected area might induce a depression\depotentiation of the cognitive circuit underling the function, resulting in an impaired function. TMS might induce a gradual readjustment of an intact but "functionally" suppressed area due to a steady reduction in synaptic strength. Therefore, these data supported the idea that brain stimulation-induced

changes in synaptic strength are an essential step toward recovery of function.

The potential for inducing a slowing down of the cognitive decline or even a behavioural improvement in AD patients, and the further possibility that these effects become long-lasting, are intriguing; and NIBS study's results could lead to the development of a new therapeutic approach.

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Transcranial Direct Current Stimulation (tDCS) and Cognitive Decline

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Neurologic disease, such as neurodegenerative disorders, stroke and traumatic brain injury, commonly leads to cognitive impairment. These problems persist despite pharmacotherapeutic and cognitive rehabilitative efforts [1].

In neurology, as in all branches of medicine, symptoms of disease and the resulting burden of illness and disability do not depend simply on the injury, inflammation or organ dysfunction, they also reflect the nervous system's attempt to adapt to the insult. The brain's plastic response includes compensatory changes that help the individual to adapt, as well as maladaptive changes that contribute to functional disability. In this context, brain stimulation techniques, tailored to modulate individual changes in brain plasticity associated with neurological diseases, might enhance clinical benefits and minimize adverse effects.

Transcranial direct current stimulation (tDCS), a non invasive neuromodulation technique that induces prolonged functional changes in the cerebral cortex, is now increasingly used experimentally for treating cognitive dysfunctions in various neurological diseases such as dementia, Parkinson's disease, and stroke, and has currently attracted growing attention [2].

tDCS consists of applying direct current over the scalp – usually delivered by a small battery-driven constant current stimulator – by attaching electrodes (anodal or cathodal DC) to the skin: the resulting constant electric field penetrates the skull and modulates cortical excitability.

The changes in cortical excitability (increase or decrease) induced by lead to corresponding changes in cortical function and activation. In general, whereas cathodal tDCS polarity has a suppressive effect, anodal tDCS polarity increases function in the underlying cortical areas [3]. For instance, anodal tDCS can improve cognitive and behavioral performance on tasks involving the stimulated area, whereas cathodal tDCS can improve cognitive performance by inhibiting underlying dysfunctional neuronal mechanisms. The prolonged cortical functional changes induced by tDCS probably depend on synaptic and non-synaptic mechanisms [4] and may be mediated by activity in sodium and calcium ion channels as well as by *N-Methyl-D-aspartate* receptor efficacy [5]. tDCS given according to current safety guidelines is considered a safe procedure [6]. The observed adverse effects are minor and consist of light itching beneath the electrodes or mild headache. Magnetic resonance imaging (MRI) scans showed no changes in the blood-brain barrier or cerebral tissue during tDCS [7]. Nor does tDCS alter serum neuron-specific enolase or *N-acetyl-aspartate* concentrates [8], sensitive indicators of neural damage.

Scientific literature has thoroughly described how tDCS modulates various cognitive functions, such as memory, attention, and language in the clinical population [2]. For instance, anodal tDCS applied in a single session to the dorsolateral prefrontal cortex in patients with stroke improved attention and memory versus sham stimulation suggesting that non-invasive cortical intervention could be used during rehabilitative training to improve attention [9] and working memory [10]. In these patients, currently available data indicate that tDCS can improve language skills and may help aphasic patients to recover language functions [11]. A study conducted by Boggio and colleagues showed that anodal tDCS also improved working memory in patients with Parkinson disease [12].

Increasing evidence over recent years shows that Alzheimer patients memory performance improves after they receive tDCS [13–15]. Recognition memory improves after they receive a single tDCS session and after a weekly treatment. In the first study Ferrucci and colleagues [13] (2008) tested the effects of temporo-parietal tDCS on a word recognition memory task and found that whereras cathodal tDCS worsened, anodal stimulation improved patients' memory performance. These initial results were later confirmed in a study by Boggio and colleagues [14].

More recently, Boggio and colleagues investigated how five consecutive sessions of anodal tDCS applied over the temporal cortex affected memory functions [15]. Their findings show that after patients receive anodal tDCS their visual recognition memory improves and the improvement persists for at least 4 weeks after therapy. These encouraging results provide additional support for continuing to investigate anodal tDCS as an adjuvant treatment for patients with Alzheimer disease.

These preliminary studies highlight the therapeutic potential of inducing long-term neuromodulatory

effects using a non invasive brain stimulation technique. They hold considerable promise, not only for advancing our understanding of brain plasticity mechanisms, but also for designing new rehabilitation strategies in patients with neurological disease.

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Liposomes Functionalized with GT1b Ganglioside with High Affinity for Amyloid β-peptide

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Abstract

Alzheimer's Disease (AD) is a neurodegenerative disorder that affects millions of individuals worldwide. Accumulation of amyloid-β peptide (Aβ) in the brain, and its aggregation into oligomers, fibrils and plaques, plays a central role in the onset and development of AD. Starting from this observation, the E.C. FP7 project "NAD" (Nanoparticles for therapy and diagnosis of Alzheimer's disease) is involved in the design of nanoparticles that recognize and remove brain Aβ. Previous investigations by NAD Consortium have already produced nanoparticles containing anionic phospholipids or curcumin-analogues able to bind Aβ with very high affinity, to inhibit fibril formation and to reduce Aβ toxicity *in-vitro*. Starting from the observation that ganglioside GT1b binds Aβ in vitro, we have synthesized liposomes, composed of sphingomyelin and cholesterol and containing GT1b ganglioside, and investigated their affinity towards Aβ peptide. Surface Plasmon Resonance experiments showed a good interaction of liposomes with Aβ fibrils, displaying Kd values between 125 and 150 nM. Moreover, Aβ aggregation into fibrils, measured by Thioflavin T and Congo Red binding assays, was reduced of about 50%, after two weeks of monomeric peptide incubation in the presence of GT1b-containing liposomes. The ability of GT1b-containing liposomes, and the other liposomes previously described by NAD research, to bind Aβ and to reduce fibrils formation, increases the interest in studying them as possible future diagnostic and therapeutic tools for the treatment of Alzheimer Disease.

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder affecting millions of individuals worldwide. The figures are expected to increase, as the elderly population proportionately increases [1]. The production and accumulation of amyloid-β peptide 1-42 (Aβ) plays a central role in the onset and development of AD. Aβ aggregates in the brain, forming oligomers, fibrils and plaques and inducing a progressive neurodegeneration [2]. Since treatment and diagnosis of the pathology are still a challenge, nanotechnology has been proposed as a promising approach to investigate this problem [3, 4]. The present study is part of the EC FP7 project "NAD" (Nanoparticles for therapy and diagnosis of Alzheimer's disease), involving 19 European partners and aimed to create nanoparticles (NPs) able to recognize and remove Aβ from the brain. A number of NPs have already been developed within the NAD Consortium, e.g. liposomes and solid-lipid NPs functionalized with anionic lipids or curcumin analogues, binding Aβ with very high affinity [6, 7], thanks to multivalency effect [8]. These NPs showed the ability to reduce Aβ fibril formation [9] and peptide toxicity *in vitro* [10]. Moreover, studies with NPs double-functionalized with Aβ ligands and molecules potentially enhancing the blood-brain barrier crossing gave promising results on an *in vitro* model [11, 12].

In the present investigation we started from the observation that gangliosides, and in particular trisialoganglioside GT1b, bind Aβ *in vitro*. Therefore, we synthesized liposomes functionalized with the ganglioside (GT1b-liposomes) and investigated their affinity for Aβ peptide, using Surface Plasmon Resonance. Moreover, we investigated the ability of NPs to inhibit the aggregation of Aβ using Thioflavin T and Congo Red assays.

Materials

Sphingomyelin (Sm), cholesterol (Chol) ThioflavinT (ThT), Congo Red (CR), recombinant human Aβ$_{1-42}$, HFIP and DMSO were purchased from Sigma Aldrich (Milano, Italy). Trisialoganglioside (GT1b) was extracted and purified from bovine brain as described in [13]. Mouse monoclonal anti-Aβ antibody mAb 6E10 was purchased from Signet (Dedham, MA). All other chemicals were reagent grade.

Methods

TLC immunostaining analysis of Aβ binding to gangliosides

The Thin Layer Chromatography (TLC) immunostaining technique previously described was utilized [6]. With this technique, equal amounts (0.5 nmoles) of different gangliosides are separated on a TLC plate.
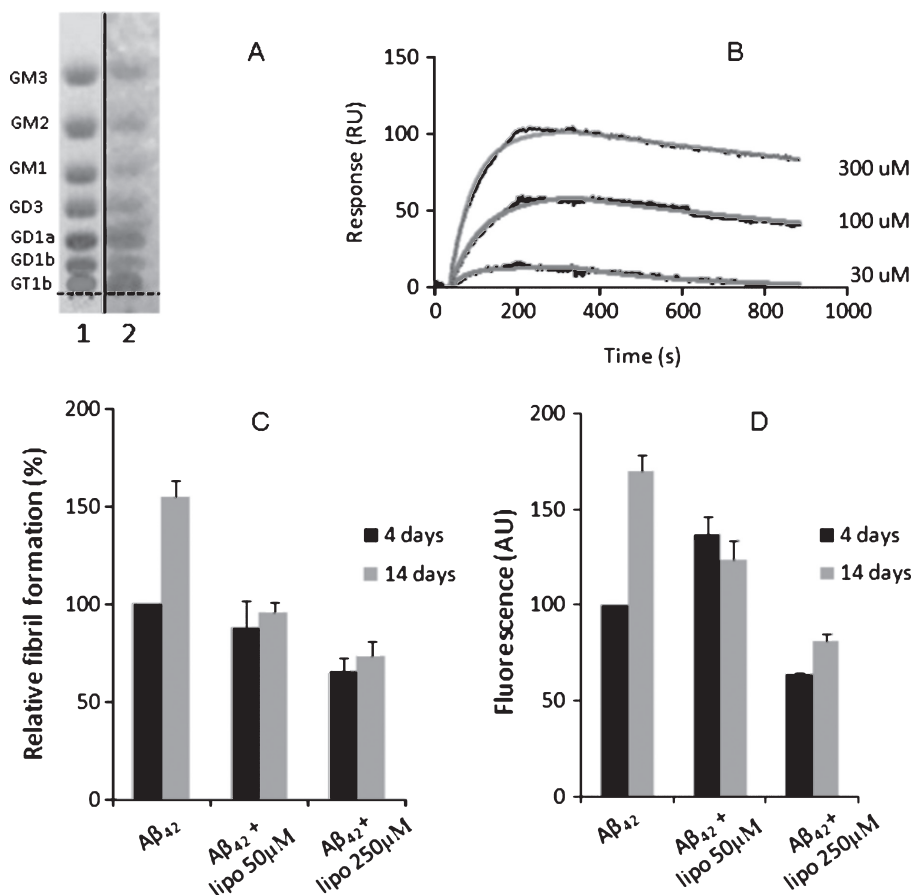
Fig. 1. (A) TLC immunostaining analysis of Aβ binding to gangliosides. 0.5 nmoles of different gangliosides were separated by TLC and re-vealed by iodine vapors (lane 1), or submitted to immunostaining with Aβ, followed by blotting with anti-Aβ antibody and ECL detection (lane 2). B) Liposomes composed of sphingomyelin/cholesterol (1:1, mol/mol) and containing 5% molar GT1b ganglioside, studied by SPR. Sensorgrams of GT1b-functionalized liposomes flowed at various concentrations of total lipids (30, 100, 300 μM) for 5 minutes onto Aβ fibrils immobilized on sensor surface. C–D) Effect of liposomes composed of sphingomyelin/cholesterol (1:1, mol/mol) and containing 5% molar GT1b ganglioside, on Aβ aggregation. Aβ fibril formation was evaluated after 4 and 14 days of incubation at 37°C in the presence or absence of GT1b-functionalized liposomes, as estimated from Congo Red (CR) (panel C) and Thioflavin T (ThT) (panel D) binding assay. For CR binding assay, values were calculated as the percent ratio of fibril concentration in the presence of GT1b liposomes to fibril concentration in the absence of liposomes, after 4 days. For ThT binding assay, fibril formation is estimated from fluorescence values expressed as arbitrary units. The graph represents the mean ± standard deviation of at least three independent experiments.

After fixation with polyisobutylmethacrylate, the plate is incubated with Aβ, then with the mAb 6E10 and finally with HRP-conjugated IgG anti-mouse followed by ECL detection.

Liposome preparation

Liposomes composed of Sm/Chol (1:1, mol/mol) and containing 5% molar GT1b were prepared by extrusion (Lipex Biomembranes extruder) through a 100-nm pore polycarbonate filter (Millipore). Lipid recovery, size, polydispersity and ζ-potential were determined as described [6].

Monomeric and fibrillar Aβ preparation

Different aggregation forms of the peptide were prepared and checked by Atomic Force Microscopy as previously described [6].

Aβ aggregation assay

Monomeric Aβ (25 μM) was incubated for 14 days in the dark at 37°C in TBS (pH 7.4) with or without GT1b-liposomes (50 μM or 250 μM total lipids). Aggregated Aβ was quantified after 4 and 14 days using CR and ThT binding assays. Each sample was assayed

in triplicate, and values were expressed as a mean of three individual results.

CR binding assay was performed following the procedure described [14]. Relative fibril content was calculated as the ratio of fibril concentration in the sample (liposomes plus Aβ) and in control (pure Aβ).

For ThT binding assay, fluorescence was measured after mixing 15 μL of 100 μM ThT, 50 μL of 100 mM glycine pH 8.5, 20 μL of samples and 65 μL water. Measurements were performed at excitation and emission wavelengths of 450 nm and 485 nm, respectively. Fluorescence intensity of GT1b-liposomes was subtracted from the intensity of samples.

Binding of GT1b-liposomes to Aβ studied by Surface Plasmon Resonance (SPR)

SensiQ semi-automatic apparatus with two parallel flow channels and a COOH5 sensor chip were employed (ICX Technologies). Fibrils were immobilized on one channel, while the other one was used as reference. After surface activation, the peptide (10 μM in acetate buffer pH 4.0) was injected for 5 min at a flow rate of 30 μL.min^{-1} and the remaining activated groups were blocked with ethanolamine, pH 8.0. The final immobilization levels were about 4000 Resonance Units (1 RU = 1 pg protein.mm^{-2}). The reference surface was prepared in parallel using the same immobilization procedure but without addition of the peptide. Preliminary injections with anti-Aβ antibody 6E10 were performed. Liposomes were injected at 30, 100, 300 μM in parallel in the channels, for 5 min at a flow rate of 30 μL min^{-1} at 25°C. Control liposomes (without GT1b) signal was subtracted from the final sensorgram. The fitted data were obtained using the Qdat Analysis Software (ICX Technologies).

Results and discussion

As first, the ability of GT1b to interact with Aβ was studied by a TLC-immunostaining technique previously utilized [6]. The results (Fig. 1A) suggest the ability of Aβ to preferentially bind GT1b, in comparison with other gangliosides, at least in this *in vitro* system, confirming previous data [6].

Succesively, GT1b-liposomes were synthesized. Liposomes have numerous advantages, such as biodegradability, low immunogenicity, lack of toxicity, high biocompatibility and high stability. Moreover, they offer the possibility of multi-functionalization, e.g. with contrast agents for diagnostic purposes and with ligands able to enhance the crossing of the blood-brain barrier [4].

The average diameter of GT1b-liposomes was 120 nm and the suspension resulted monodispersed (P.I. = 0,104). ζ-Potential was –66 mV due to the negative charge of sialic acid residues.

The ability of GT1b-liposomes to interact with Aβ fibrils was then investigated by SPR. As expected, a good interaction of liposomes with Aβ fibrils was observed and binding was concentration-dependent. The separate analysis of the three sensorgrams shown in Fig. 1B, according to the simplest equation modeling a Langmuir 1:1 interaction, resulted in Kd values in the micromolar range (5–6 μM total lipids). Assuming that the lipid components are equally distributed between the two leaflets of the NPs bilayer and that the interaction with the peptide is occurring only on the outer layer, the Kd value referred to exposed GT1b is 125–150 nM. This value is not far from the values previously obtained by NAD Consortium for acidic phospholipids and curcumin-analogue liposomes (5–50 nM) [6–7]. As mentioned before, each curve was fitted separately since, due to the complexity of the interaction, the global fitting could not be used. Thus, Kd values obtained should be considered as indicative of an apparent high affinity.

Finally, the capability of GT1b-liposomes to interfere with Aβ peptide aggregation process was evaluated using Congo Red (CR) or Thioflavin T (ThT) binding assays, that have been extensively used to characterize the presence of amyloid fibrils and their rates of formation [15–16].

The results of CR binding assay demonstrated that in the presence of GT1b-liposomes the aggregation process is attenuated. In particular, the aggregation of Aβ was reduced of about 12% and 38% (using 50 μM total lipids) and of 34% and 52% (250 μM total lipids), after 4 and 14 days, respectively (Fig. 1C).

Similar results were obtained utilizing ThT binding assay. GT1b-liposomes showed to reduce fibril formation of about 27% (50 uM lipids) and 52% (250 uM lipids) after 14 days, compared to the peptide alone (Fig. 1D).

The inhibitory effect of GT1b-liposomes on fibril formation is likely due to their affinity for Aβ peptide, as for other functionalized NPs [9]. Further experiments will be carried out to investigate the GT1b-liposomes binding affinity to the other Aβ aggregation forms, monomers and oligomers. Moreover, *in-vitro* assays will be performed to assess if they induce any modification in the cellular viability. Succesively, they could be multi-functionalized with

molecules to facilitate the passage through the blood-brain barrier.

In conclusion, GT1b-liposomes resulting from this study, together with other NPs prepared among the NAD Consortium, display interesting features as possible future diagnostic and therapeutic tools for the treatment of AD.

Acknowledgments

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Souvenaid® Improves Memory in Drug-Naïve Patients with Mild Alzheimer's Disease: Results from a Randomized, Controlled, Double-Blind Study (Souvenir II)

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Introduction

Souvenaid® (Medical Nutrition), containing the specific nutrient combination Fortasyn™ Connect, is designed to support synapse formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes, and increasing their dietary intake can promote the synthesis of new brain synapses (Cansev et al., Alzheimers Dement, 2008; Kamphuis and Scheltens, J Alzheimers Dis, 2010). A proof-of-concept study ('Souvenir I') in drug-naïve patients with mild AD (MMSE 20–26) showed that Souvenaid taken once per day was safe and improved memory (WMS-r, delayed verbal memory) after 12 weeks, the co-primary endpoint of the study (Scheltens et al., Alzheimers Dement, 6, 1–10, 2010). The 'Souvenir II' study was designed to confirm the effect of Souvenaid on memory in drug-naïve patients with mild AD, and also to extend the investigation through a longer intervention period of 24 weeks and through utilization of the whole memory domain z-score of a Neuropsychological Test Battery (NTB). The Souvenir II study was recently completed and first results will be presented.

Objectives

The Souvenir II study was designed to investigate the effect of Souvenaid on memory performance during 24 weeks intervention in drug-naïve patients with mild AD. Secondary objectives were to investigate safety and tolerance of the intervention, and to assess the effects on global cognition, functional abilities, and electroencephalography (EEG).

Materials and methods

The Souvenir II study was a randomized, controlled, double-blind study, conducted at 27 study centers in six European countries (the Netherlands, Germany, France, Belgium, Italy and Spain).

Drug-naïve patients with mild AD (MMSE scores ≥ 20) and diagnosis of probable AD according to the NINCDS-ADRDA criteria, were randomly assigned (1:1) to Souvenaid, a 125 mL once-a-day drink containing Fortasyn Connect, or an iso-caloric control product. The duration of intervention was 24 weeks. The memory domain score of a Neuropsychological Test Battery (NTB) was the primary outcome parameter. This memory composite score was derived from the Rey Auditory Verbal Learning Test (RAVLT: immediate recall, delayed recall and recognition performance) and the Wechsler Memory Scale (WMS) verbal paired associates test (immediate and delayed recall). Secondary outcomes resulting from the NTB were the executive function domain, total composite score and individual item scores. The other NTB items were WMS Digit Span, Trail Making Tests part A and B, Category Fluency, Controlled Word Association Test, the ADAS-cog orientation task and the Letter Digit Substitution Test. Other secondary outcome parameters were the Disability Assessment for Dementia (DAD) scale, EEG (basic frequency and functional connectivity analysis), product compliance, tolerance and safety. Main study parameters were assessed at baseline, week 12 and week 24. For the statistical analysis of the data, a repeated measures mixed model was used. The trial was registered with the ICMJE compliant www.trialregister.nl (NTR1975).

Results

A total of 259 drug-naïve subjects were randomized (2.6% screen failures). In the overall study population no differences in baseline characteristics were noted between the study groups. The mean age was 73.8 (±7.7) years, the mean screening MMSE was 25.0 (±2.8) and 51% were male. A pre-specified blinded interim analysis was conducted to check whether the calculated sample size was adequate and that no safety concerns had arisen, and the independent Data Monitoring Committee recommended continuation of the trial without modification. From the 259 subjects randomized, 238 subjects (91.9%) completed the study. Five subjects did not complete the study because of a (serious) adverse event ((S)AE); 3 in the Souvenaid group and 2 in the control group, and no differences between study groups were noted in the occurrence of (S)AEs. No clinically relevant differences in blood safety parameters were noted. The average compliance during 24 weeks was very high at 97% and not different between the groups. High compliance was confirmed by marked and significant changes in (nutritional) biomarkers of compliance, e.g. docosahexaenoic acid in erythrocyte membranes and plasma homocysteine. During 24 weeks, Souvenaid significantly improved the primary endpoint memory performance (composite memory domain z-score resulting from the NTB) compared to control product (repeated measures mixed model, $p = 0.025$). The significant effect on memory performance was confirmed by individual tasks of the NTB memory domain. No effect was found on the secondary parameters NTB executive function domain score and on the DAD. EEG analysis is ongoing.

Discussion

Based on the co-primary endpoint, the Souvenir I study showed that Souvenaid improved memory after 12 weeks in drug-naïve mild AD (mean MMSE score 23.9). The current Souvenir II study is the second study showing that the use of Souvenaid improves memory performance in drug-naïve patients with mild AD (mean MMSE score 25.0). This study also shows that use of Souvenaid in patients with mild AD for 24 weeks is safe: safety, tolerability and compliance in this study were consistent with findings from the Souvenir I study. The currently ongoing 24 weeks open label extension of the Souvenir II study will provide additional insights. The ongoing EU-funded[*] 'LipiDi-Diet' study in 300 subjects with prodromal AD (according to criteria in Dubois et al, Lancet Neurol, 2007) aims to assess the effect of Souvenaid on the memory domain of a NTB during 24 months. This will further extend insights regarding the effects on memory in a very early stage of AD. The EEG analysis in the Souvenir II study and the ongoing Magneto-encephalography (MEG) substudy of Souvenir II will provide further understanding of the effect of Souvenaid on functional connectivity, thus investigate the hypothesis that Souvenaid can support synapse formation and function in mild AD.

Conclusion

In conclusion, this study showed that 24-weeks of supplementation with Souvenaid is well-tolerated and improves memory in drug-naïve patients with mild AD.

Footnotes:

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Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia.

The Souvenir II study forms part of the Souvenaid Clinical Trials Program.

The Role of Physical Activity and Diet in Preventing Cognitive Decline

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Introduction

Clinical and epidemiological data strongly suggest that poor dietary practices and insufficient levels of exercise, lifestyles typical of our modern society, increase the risk for many neurodegenerative diseases such as Alzheimer's disease (AD) [1]. Here, we will discuss the clinical and experimental evidence showing how physical activity (PA) and diet may affect brain health and prevent neurodegenerative diseases such as AD.

Physical activity and brain health

Although with some exception, the results of cross-sectional, prospective and retrospective epidemiological studies support a relationship between the cognitive activity of older adults and physical activity. Colcombe and Kramer [2] conducted a meta-analysis to verify that physical activity has effects on the cognitive function of non-demented older adults. The authors observed a significant effect of aerobic exercise training.

Although the ability of PA in reducing the risk of cognitive decline is generally accepted, the biological mechanisms which result in such effect are only poorly understood. Movement has played a crucial role in the adaptability of the organism to the environment. Therefore, it is plausible to assume the presence of a retrograde flow of information with feedback functions to the CNS. The details of such a signaling system are still incomplete, but experimental observations suggest two fundamental mechanisms. Evidence indicates that events associated with energy balance can play a role in nervous functions. Brain metabolic responses to acute physical activity seems to extend beyond the regions specifically associated with skeletal motor, sensory, and cardiovascular autonomic control [3]. Lactate taken up from skeletal muscle seems to act as an intercellular energy shuttle within the brain during high-intensity exercise. Exercise increases pyruvate dehydrogenase kinase-4 (PDK-4) transcription in skeletal muscle, thus limiting the use of glucose by the muscle to assure sufficient amounts for the increased brain metabolic needs.

However, there is also clear evidence for effects of physical activity on nervous functions that are only indirectly dependent, or independent on energy metabolism. It was found that in the hippocampus, exercise significantly increases the levels of the uncoupling protein 2 (UCP2), a mitochondrial protein which uncouples substrate oxidation from ATP synthesis. Vaynman et al. [4] proposed a model in which the presence of UCP2 at the pre-synaptic and post-synaptic membranes could allow neuronal mitochondria to limit oxidative stress (OS), increase ATP production and modulate calcium levels. These modulations would subsequently influence vesicular release and transcription, by acting on vesicular release proteins, such as synapsin I, and signal transduction molecules, such as cAMP response element binding (CREB) protein, respectively. These results suggest the presence of fundamental mechanisms by which exercise affects key elements of energy metabolism that modulate substrates of synaptic plasticity underlying learning and memory. Finally, UCP2 could represent a mechanism linking the energy metabolism to the production of neurotrophic factors, such as brain-derived neurotrophic factor. Indeed, UCP2 seems to modulate the synthesis of brain-derived neurotrophic factor and its downstream molecular effectors such as CREB and CAMK-II [5].

A possible candidate for the role of reciprocal signaling systems between muscle and CNS may be interleukin-6 (IL-6), a cytokine with primarily immunomodulatory effects. During prolonged exercise, IL-6 is released both from the brain and active skeletal muscle. It was demonstrated that the level of circulating IL-6 increases dramatically in response to exercise.

A crucial role in the effect of PA on brain health seems to be played by growth factors such as brain-derived neurotrophic factor (BDNF). Neeper et al. [6] observed that the greatest effects of exercise on BDNF mRNA occurred in areas not directly related to the motor system but areas associated with cognitive function such as the hippocampus and caudal cortex. Voluntary exercise in rodents increases both mRNA and protein levels of BDNF in the hippocampus, cerebellum and frontal cortex. Blocking the binding of BDNF to its tyrosine kinaseB receptor (TrkB-R) abolishes the exercise induced performances benefits. Other trophic factors, including NGF and fibroblast growth factor 2 (FGF-2) were also induced in the hippocampus in response to exercise, but their upregulation was transient and less robust than that of BDNF, suggesting that BDNF is a better candidate for

mediating the long-term benefits of exercise on the brain.

Diet and brain health

Many evidences demonstrate effect of nutrients and/or diet on neuronal functions in particular high amount of cholesterol in neural membranes can regulate the level of β-amyloid (Aβ) in the brain [7]. Moreover, cholesterol-enriched high-fat diet seems to promote Aβ deposition [8]. Many nutrients such as policosanol, have a direct control on cholesterol levels and a hypocholesterolemic activity by downregulation of HMG-CoA reductase [9]. Some other nutraceutical, such as fiber, 9-cis-retinoic acid are involved in cholesterol transport, and promote cholesterol incorporation in HDL particles [10].

An alternative approach to regard the relationship between food and dementia is the evidence that neurodegenerative disorders such as AD may be delayed by cerebrovascular health caring. Docosahexaenoic acid (DHA), as well as low-salt diet and/or high dose folate associated with other strategies able to control hypertension could help in reducing risk for vascular dementia and AD [11]. Diet rich of anti-oxidant compound also could have relevant effect in decreasing risk of dementia due to the high contents of polynsatured fatty acids (PUFA) in neuronal membranes, while flavonors from fruits, cocoa beans and Ginko biloba was shown to reduce learning and memory impairment in rodents [12]. The effect of diet can be appreciated when this in enriched with products such as alpha lipoic acid (in spinach, broccoli, peas and yeast) and Vitamin E (in vegetable oils, nuts) which improves memory deficits and promotes neurological performances in murine AD model [13] and in human [14].

Conclusions

A growing body of animal and human studies suggest that PA and diet strongly influence brain functions, including learning and memory, and cognitive decline in aging. Nevertheless still a lots need to be clarified and perhaps understanding how PA and diet

influence brain functions or acting directly on brain structure and function could lead toward a better prevention of these disorders.

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Depression in Alzheimer Disease: What Treatment?

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Although the core diagnostic criterion of Alzheimer disease (AD) is cognitive impairment, neuropsychiatric phenomena frequently occur during the disease [1]. Depression is the second most frequent clinical neuropsychiatric manifestation in AD patients after apathy [2], and is particularly prevalent in the early phase of the illness [3, 4].

In reality, there are inconsistent data on how depression impact the clinical course of AD and on the effect of the antidepressant treatment on depressive symptoms and cognitive deterioration. There is evidence both in favor of, and contrary to, the hypothesis that antidepressant treatment may be efficacious in AD patients with comorbid depression [5, 6].

Critically, a very recent double-blind controlled study with the antidepressants sertraline or mirtazapine found no benefit compared with placebo and increased risk of adverse events [6]. The study was performed in a large patient sample ($n = 326$) with depression and AD and the negative results suggest different pathogenetic mechanisms between depression of AD and "psychiatric" depression, diagnosed in patients with primary unipolar mood disorder. Although authors of this study are not completely negative on the antidepressant usage in patients with AD and depression, these results indicate that their usage as first-line treatment is not recommended unless depression is severe. Thus, controlled trials on novel therapeutic approaches, such as non-pharmacological treatment, are urgently required for improving the management of depression in AD patients.

Since the pathogenesis of depression in AD may be peculiar, and sometime connected with that causing cognitive deterioration, also the treatment of depression should be specific for this type of patients. Indeed, depression improvement could be favored by drugs used to improve or stabilize cognitive deterioration. Unfortunately, little is known about the effects of acetyl-cholinesterase inhibitors (AchEIs) alone on depression [7], and negative results using antidepressant drug treatment make urgent new trial evaluating the AchEI effectiveness on depressive symptoms in AD.

In a 6-month open-label observational preliminary study we set out to determine whether the rivastigmine patch alone, at dosages comprised between 4.6 and 9.5 mg/24 h, was effective in treating AD patients, diagnosed according with the NINCDS-ARDRA criteria, with comorbid Major Depressive Episode (MDE), according with the modified DSM-IV diagnostic criteria for MDE in AD [8]. We included only patients undergoing their first diagnostic visit that confirmed the presence of AD who were not undergoing treatment with AChEI and who had not been treated with psychotropic drugs (i.e. antidepressants, antipsychotics or anxiolytics) in the last two years. Fifty patients completed all of the study evaluations. Results indicated that patients' MDE frequency reduced significantly from the first diagnostic visit ($n = 50$; 100%) to the 6-month follow-up ($n = 31$; 62%). CERAD dysphoria scores also reduced significantly from 6.2 to 4.9. Although this evidence is preliminary, and has a number of limitation, it suggests that treatment with the AchEI rivastigmine can improve the rate and severity of MDE in mild AD patients undergoing their first diagnostic assessment and encourage the design of further controlled studies that are needed to definitively confirm this preliminary but intriguing evidence.

In conclusion, nowadays the management of depression of AD is strongly debated because it is very common and has a devastating impact on patients and caregivers quality of life, because it may modify the course of cognitive deterioration and functional impairment and, last but not least, because it increases costs of care. After the initial enthusiasms, antidepressants efficacy is now under discussion and doubtful. Thus, new therapeutic approaches, either pharmacologic or nonpharmacologic, are needed. In the mean time, a revaluation of the effectiveness of AchEIs for the management of depression of AD, at least in the first phases of the disorder, could be proposed and further studied.

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ABSTRACTS

Abstracts

Clinical and Cognitive Correlates of White Matter Tract Damage in Progressive Supranuclear Palsy

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Background: Diffusion tensor imaging (DTI) measures might be useful as markers of disease severity and clinical symptoms in progressive supranuclear palsy (PSP).

Aim: To use DTI tractography to assess WM tract damage in PSP patients and to investigate correlations between tract integrity and clinical and cognitive measures.

Methods: Thirty-seven PSP and 42 healthy controls underwent clinical and cognitive testing and DTI scans. Probabilistic tractography was used to identify major WM tracts. Tract mean DTI metrics were compared between groups. Correlations between DTI metrics and disease severity, motor dysfunction, cognition, and behavioral changes were estimated.

Results: Patients showed a severe intrinsic damage to the superior cerebellar peduncles (SCP) and corpus callosum. Abnormal DTI measures were also found in the cingulum, inferior longitudinal (ILF), uncinate fasciculi, bilaterally. Damage to the SCP, corpus callosum (CC), uncinate, bilaterally, and right cingulum correlated with disease severity. CC mean diffusivity correlated with motor dysfunction. Damage to the CC, left superior longitudinal fasciculus (SLF), and bilateral uncinate was related to cognitive deficits. Left cingulum, uncinate, and SLF, and bilateral ILF involvement correlated with behavioral changes.

Conclusions: In PSP, the intrinsic damage to WM tracts likely plays a central role in clinical, cognitive and behavioral disturbances.

Diffusion Tensor MRI Contributes to Differentiate Richardson's Syndrome from PSP-Parkinsonism

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Background: PSP can occur with two main clinical presentations: Richardson's syndrome (PSP-RS) and progressive supranuclear palsy-parkinsonism (PSP-P). Clinicopathological studies showed that tau deposition as well as grey matter and white matter (WM) atrophy are significantly more distributed and severe in PSP-RS than in PSP-P cases.

Aim: This study investigated the regional distribution of white matter (WM) damage in PSP-RS and PSP-P using diffusion tensor imaging (DTI). The DTI classificatory ability in diagnosing PSP syndromes, when used in combination with infratentorial volumetry, was also quantified.

Methods: In 37 PSP (21 PSP-RS, 16 PSP-P) and 42 controls, the program Tract-Based Spatial Statistics (TBSS) was applied. DT MRI metrics were derived from supratentorial, thalamic, and infratentorial tracts. The MR parkinsonism index (MRPI) was calculated.

Results: All PSP harboured diffusivity abnormalities in the corpus callosum, fronto-parietal and fronto-temporo-occipital tracts. Infratentorial WM and thalamic radiations were severely affected in PSP-RS and relatively spared in PSP-P. When MRPI and DTI measures were combined, the discriminatory power increased for each comparison.

Conclusions: Distinct patterns of WM alterations occur in PSP-RS and PSP-P. Adding DTI measures to MRPI improves the diagnostic accuracy in differentiating each PSP syndrome from healthy individuals and each other.

Gait Analysis and Pattern Cognition in Parkinson's Disease

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Background: The relationship between cognition and gait in Parkinson's disease (PD) has received increase attention, however the specific connection between gait features and cognition is still not fully understood.

Aim: To find association between gait parameters and specific cognitive profiles in patients with PD.

Methods: Using motion analysis system, forty three PD patients during gait in normal conditions at on state were studied. We evaluated the following gait parameters: 1) step length; 2) stance phase; 3) swing phase; 4) single support/double support time ratio; 5) cadence; 6) velocity; 7) step length variability; 8) swing time variability. In order to reduce the larger number of gait variables to a smaller number of elements, a factor analysis was performed. Furthermore, we assessed all patients with an extensive neuropsychological battery and correlated the composite scores of three main cognitive domains, namely episodic memory, executive and visuospatial domains with the gait factors scores.

Results: Factor analysis revealed two independent factors, namely "pace" and "stability"**.** The "pace" factor was not correlated with cognitive or clinical variables. The "stability" factor was strongly and directly correlated with visuospatial domain.

Conclusions: Visuospatial impairment was strongly associated with the development of instability and the progression of disease.

Genetic Risk Factors in Neurodegenerative Diseases

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Background: The risk of developing Alzheimer's disease (AD) and frontotemporal dementia (FTD) could be associated to SNPs in specific genes.

Aim: To define a specific profile of risk for AD and FTD.

Population and methods: SNPs of APOE, Cyp46A1, ABCA1, PRNP, TOMM40, GAB2, NOS3 genes analyzed in 322 AD patients, 102 FTD patients and 366 controls. Statistics performed by χ^2 test.

Results: The APOE ε4 allele frequency was significantly different ($p = 0.000$) in AD (22.1%) and FTD (18.6%) subjects than controls (7.8%) with an OR of 3.36 and 2.71, respectively. Genotypic frequency of the GAB2 gene in FTD patients was different than controls ($p < 0.006$), with a frequency of TT genotype of 10% in subjects FTD vs. 2.8% in controls, and a T allele frequency was of 27% vs. 19% in controls ($p = 0.02$), with an OR of 1.52. Patients with TT and ε4 had an increased risk of developing FTD (OR7.28).

Conclusions: The association between APOE ε4 allele with AD and FTD is once again confirmed. T allele homozygosity of the GAB2 gene associated to ε4 increases the risk of developing FTD but further studies are needed to understand the role of this gene in the biochemical mechanisms underlying neurodegeneration.

Two Cases of Early Onset FTLD Due to the Chromosome 9 Hexanucleotide Repeats

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Background: A hexanucleotide repeat expansion in the first intron of *C9ORF72* has been shown to be responsible for a high number of familial cases of Amyotrophic Lateral Sclerosis or Frontotemporal Lobar Degeneration (FTLD) with or without concomitant Motor Neuron Disease (MND) phenotype and TDP-43 based pathology.

Aim: To describe two cases of FTLD carrying the hexanucleotide expansion.

Case report: Patient #1, a man having a positive family history for dementia (mother, aged 74, diagnosed with Alzheimer's disease) showed first symptoms at 51 years of age. He became apathetic and irritable and had perseverative stereotyped behaviuors. An year later he was diagnosed with Mild Cognitive Impairment. After few months, he started developing language impairment. He came to our attention at 53 years. At that time, language symptoms worsened, and he was apraxic. He underwent neuropsichological examination and scored 27/30 on MMSE. In addition, ADL were 6/6 and IADL 8/8. Brain magnetic resonance imaging (MRI) showed frontal cortical atrophy and brain PET scan showed hypometabolism in the basal-medium frontal lobe and in bilateral temporal lobes. Cerebrospinal fluid biomarkers, determined by ELISA, showed slightly increased Tau protein and normal Beta-Amyloid levels. Patient #2, a woman with positive family history for dementia (father diagnosed with Alzheimer's disease and dead at 61 years) developed behavioural dsturbances, aggressiveness and swearing at 57 years. She came to our attention at 60 and scored 15/30 on MMSE, 3/6 on ADL and 2/8 on IADL. The TC showed a marked frontal atrophy. Genetic analysis, carried out through Repeat-Primed PCR and sequencing, evidenced a hexanucleotide repeat expansion in the first intron of *C9ORF72*.

Conclusions: The hexanucleotide expansion in chromosome 9 is associated with early onset FTLD, characterized by multiple symptoms, including apathy, behavioural changes, language impairment and apraxia. Notably, the proband #1 mother developed dementia in her seventies and is at present still alive.

Isolated Hyperintensity of the Medial Cerebellar Peduncoli and Mild Cognitive Impairment

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Background: Hyperintensity of the medial cerebellar peduncoli is a rare features seldom found in the neuroradiological investigation.

Aim: To describe a case of mild ataxic gait impairment and areflexia.

Case report: G.C., 69 y.o., male, with prostatic hypertrophy. He developed a rapidly progressive gait instability and episodic falls. He was admitted to our departement after one episode of confusion followed by fall and doubtful loss of consciousness. The neurological examination showed partial spatial and temporal disorientation, axial incohordination, osteo-tendinal areflexia, tatto-punctorial hypoestesia of the lower limb. He underwent: basal and sleep deprivated EEG (normal), biochemical investigation (liquor examination, 14-3-3-protein, tau-p, ceruloplasmine dosage, normal), EMG (axonal sensitive polineuropathy), neuropsychological testing (MODA and MMSE score slight below normal range, executive and long term memory performance at lower normal limits). The MRI of the brain showed medial cerebellar pecuncoli hyperdensity.

Results: Clinical history and examination supported the hypothesis of c-MSA but they also were suggestive for X-Fragile premutation syndrome. This last diagnosis was excluded after genetic research.

Conclusions: Medial cerebellar peduncoli hyperintensity was unchanged after 4 months, and it was the only pathological finding. After one year there is not any sign of clinical or cognitive progression and the diagnosis still remains undefined.

Multidimensional Stimulation Therapy Improves Behavioral Status, Language and Attention Functions in Alzheimer's Disease Patients

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Background: The cognitive and behavioral status is not necessarily a mirror of pathological changes in the

brain, but there are cognitive and brain reserves for improvement. Multidimensional Stimulation Therapy (MST) leads to global benefits in Alzheimer's disease (AD).

Aim: To test the efficacy of MST and detect if specific behavioral and/or cognitive aspects might change more than others.

Population and methods: 48 AD patients were randomized in treated (tMST) and non-treated (ntMST) groups. MST sessions involved reality orientation, physical, recreational, and occupational activities. In all groups before and after rehabilitation –tMST groups- or observation period –ntMST groups- we evaluated neuropsychological and neurobehavioral assessments and collected functional MRI (fMRI) data with a language paradigm.

Results: Differences between the two groups after rehabilitation or observation period (group*factor interaction) were found in behavioral status (tMST>ntMST on NPI, $p=0.03$) and in language subscales of ADAS_Cog (tMST>ntMST, $p<0.05$). In concordance with behavioral data, fMRI results showed significant increase in brain activations only in tMST group (bilateral temporal, medial frontal and anterior cingulate cortex).

Conclusions: MST appears to have particular effects in promoting behavioral and cognitive functions (language). The fMRI results confirmed the attivation of language areas along with attentions ones.

Investigation of Colours in Semantic Dementia and Alzheimer's Disease

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Background: Many studies have investigated how semantic knowledge is organized, but most of them does not deal with colours. The present study is aimed to determine how colours are processed in the brain and what is their relationship with the general semantic knowledge.

Population and methods: An experimental neuropsychological test battery exploring colours involved perception, language and semantic tasks, was administered to 8 patients with Semantic Dementia (SD), and to 10 patients with Alzheimer Disease (AD). 18 normal subjects served as reference group.

Results: Colour perception was similar in the three groups studied. By contrast, SD patients showed prob-

lems in language and semantic association tasks. Their performance was significantly lower than the AD patient's performance. AD patients did not differ from the control subjects in tasks of language of colour or of semantic association.

Conclusions: SD patients show altered performance in processing the linguistic and semantic features of colours. The present data support the multimodal organization of semantic knowledge in the brain.

Verbal Fluency in Alzheimer's Disease, Frontotemporal Dementia and Vascular Dementia

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Background: There is agreement about the fact that patients with Frontotemporal Dementia (FTD), Alzheimer Disease (AD) and Vascular Dementia (VAD) make poor performance in verbal fluency tasks. By contrast the individuation of different profile that could contribute to differential diagnosis is still under debate.

Aim: To perform a quantitative and qualitative error analysis in fluency tasks.

Population and methods: Category and letter fluency tasks were administered to 142 patients with AD, 36 patients with FTD, and 63 patients with VAD. 114 healthy controls served as reference group. Quantitative score included number of words and errors produced. Qualitative error analysis was aimed to classify the errors on the basis of their nature (perseverations, breaking rules, intrusion).

Results: Category and letter fluency were poorer in each of the three groups compared to the reference group. AD patients made a number of errors significantly lower than FTD and VAD patients. Patients with FTD made more perseverations than other groups, while AD patients made more breaking rules. Intrusion were presented in AD and FTD.

Conclusions: Qualitative analysis of errors in fluency tasks reveals a different patter of error in the three dementia groups studied and can contribute to the differential diagnosis of dementia.

Event Related Evoked Potential as Possible Marker of Progression from MCI Toward Alzheimer's Disease: A 5 Years Longitudinal Study

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Background: N400 is cortical event related potential evoked by semantic incongruities. Longer N400 latencies have been described in patients with MCI and Alzheimer disease.

Aim: To assess if N400 neurophysiological parameters at baseline can predict clinical and neuropsychological progression towards Alzheimer's disease in subjects with MCI throughout 5 years.

Population and methods: 16 MCI patients and 21 healthy control (HC) subject were enrolled. At baseline N400 was evoked by a written verbal paradigm, evoking stimulus was a semantic incongruity in a short phrase. Target stimuli has been selected among words with high and low frequency of use in Italian language. All patients and subject underwent a neuropsychological evaluation including Mini Mental State Evaluation, tests exploring speed and attention, learning and memory, visuospatial abilities, language and executive functions. Patients then underwent a five years clinical and neuropsychological follow-up: end-point was conversion to dementia.

Results: At baseline N400 latency was significantly longer in MCI patients compared to healthy controls in the protocol involving high usage frequency words. After 5 years five MCI patients converted to Alzheimer disease, and 4 MCI patients converted to other dementia types. We analyzed baseline neurophysiological characteristic of N400 in subject who converted to AD, and we found that baseline latency longer of 525 ms had high Specificity (80%) and Sensitivity (80%) considering P4, T3 and T4 EEG channels, to predict conversion to dementia.

Conclusions: Our protocol, with specific linguistic characteristics, can distinguish among MCI and HC at baseline: MCI have a significant modification of N400 elicited by frequent usage stimuli, possibly caused by an impairment in semantic memory access, that could cause the loss of the frequent stimulus induced facilitation. Our longitudinal study suggests that ERP evaluation in patient with MCI may be helpful to determine which subject will convert to dementia with a good level of sensitivity and specificity.

Explorative Study on the Cognitive and Functional Predictors of Slow Versus Rapid Disease Progression in Alzheimer's Disease

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Background: Progression rates of Alzheimer's Disease (AD) are variable among patients. However, diagnostic tools of disease evolution are lacking.

Aim: To assess whether cognitive and functional tests can predict the progression of AD.

Population and methods: We retrospectively studied a preliminary sample of fifty-five AD patients (forty-two females and thirteen males; mean age 75.58, SD 7.56; mean education 6.11, SD 3.83). Mini-Mental State Examination (MMSE) mean total score was 20.09, SD 4.03. Patients were followed for three years to detect rapid disease progression, defined as a loss of at least 5 points on MMSE. Forty-eight patients had a slow disease progression, whereas seventeen patients had a rapid disease progression. We looked at the influence of the baseline performance on MMSE sub-items and daily functioning on the disease progression after three years as indicated by the MMSE total score in the two groups of slow and rapid decliners.

Results: Linear regression analyses showed that slow disease progression was predicted by low scores in temporal orientation and verbal recall while rapid disease progression was not associated with any baseline performance.

Conclusions: At variance with slow decliners, no apparent cognitive predictors emerged for fast decliner subjects.

Structural Brain Signature of FTLD Driven by Granulin Mutation

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Background: We have recently shown specific patterns of grey matter (GM) loss and functional MRI disconnection in patients with FTLD *carriers* of *GRN-Thr272fs* mutation (FTLD-GRN+).

Aim: To clarify, using diffusion MRI and GM volumetrics, the relationship between GM and white matter (WM) structural changes in determining the functional MRI and the clinical characteristics observed in FTLD-GRN+ patients.

Population and methods: Six patients with FTLD-GRN+, 17 patients with sporadic FTLD (FTLD-GRN–), and 12 healthy controls underwent MR scanning at 1.5T. T1-w volumes were used for voxel-based morphometry, while diffusion imaging data were used for the tractographic investigation of the corpus callosum (CC).

Results: FTLD-GRN+ compared to FTLD-GRN- patients, showed a more remarkable GM loss in the left medial prefrontal cortex, together with a more extensive microstructural damage in the left anterior CC. Post-hoc analysis revealed a strict association between these GM and WM abnormalities in FTLD-GRN+, but not in FTLD-GRN+ patients. Interestingly, a multivariate analysis indicated that this pattern of GM and WM damage accounts for some additional neuropsychological and behavioural abnormalities observed in FTLD-GRN+ patients.

Conclusions: These findings suggest an association between the presence of *GRN-Thr272fs* mutation, a peculiar pattern of brain damage, and the accrual of symptoms observed in FTLD-GRN+ patients.

Immunomediated Limbic Encephalitis Mimicking Fatal Insomnia: A Clinical and Neuropathological Case Report

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Background: Immunomediated encephalitis (paraneoplastic or not) can have heterogeneous presentations.

Aim: To describe clinical and neuropathological findings of immunomediated encephalitis mimicking Fatal Insomnia (FI).

Methods: Clinical, neuroimaging, genetic and neuropathological studies.

Case Report and results: A 69 year-old-woman presented rapidly progressive neurological symptoms: insomnia, fainting, and cognitive impairment (MMSE: 21/30). On neurological examination she had limb dyskinesia. Screening for immunological or neoplastic diseases was negative; onconeuronal autoantibodies, anti-VGKC and anti-NMDAR antibodies were not found. Total-body CT-FDGPET scan did not detect neoplastic lesions. Brain MRI was unremarkable. Polysomnography showed a profound disruption of sleep structure. CSF analysis was normal with negative 14-3-3. PRNP gene analysis showed no mutations (129M/V). Six months later the patient cognitively worsened (MMSE: 16/30). Heart dysautonomia and nocturnal central apnea were documented. A trial with Ig ev was unsuccessful. She died during sleep 6-months later.

Histopathology revealed a severe neuronal loss in the periaqueductal gray and thalamus, with sparse perivascular lymphocytic cuffing in the basal ganglia and thalamus. Western blot and immunohistochemistry analysis were negative for PrP. Serum indirect immunofluorescence assay detected anti-nuclear neuronal antibodies against an unknown intracellular antigen.

Conclusions: Immunomediated limbic encephalitis resembling FI raises the alert of accurate diagnosis of rapidly progressive cognitive impairment potentially reversible.

Quantitative Magnetization Transfer Imaging in Normal Aging, Amnestic MCI and AD

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Background: Quantitative-magnetization-transfer (qMT) is an MRI technique with the ability to detect subtle abnormalities in Alzheimer's disease (AD) brains, which exceed, and might precede, the occurrence of macroscopic atrophy.

Aim: To clarify, using MRI, the relationship between qMT changes and neurodegeneration in the brain tissue of patients with preclinical AD.

Methods: Thirty-four patients with AD, 18 with amnestic-mild-cognitive-impairment (MCI) single-domain, and 18 healthy controls underwent MRI at 3.0T, including T1-weighted volumes, used for brain volumetrics, and qMT to obtain the following parameters: RM_{0B}, F, and T_{2B}. A multimodal image analysis was run to assess between-group differences in the qMT parameters, controlling for grey matter (GM) atrophy.

Results: Consistent with previous findings, only RM_{0B} revealed significant between-group changes (not explained by local GM atrophy), with a reduction of this parameter in the temporal pole, thalamus, cingulate gyrus, parieto-occipital and insular cortex, of AD patients compared to both controls and amnestic-MCI patients.

Conclusions: Changes in RM_{0B} (which is likely to be a metabolic marker) might reflect early degenerative processes occurring over the transitional stage between preclinical and clinical AD. This interpretation, which still needs confirmation from longitudinal data, might support the hypothesis that mitochondrial dysfunction contributes to neurodegeneration in AD progression.

Posterior Cortical Atrophy as Expression of Damage of Multiple Large-Scale Brain Networks in Alzheimer's Disease: Neuropsychological and SPECT Evidence

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Background: Posterior cortical atrophy (PCA) is characterized by a progressive decline in "high-level" visual processing. Compared to dementia of Alzheimer's type (DAT), PCA has been described as a dorsal stream syndrome. On autopsy, PCA is commonly considered the posterior variant of Alzheimer's disease (AD) and the relationship between PCA and AD is under debate.

Aim: To identify in a group of 39 patients (24 PCA and 15 DAT, selected by standard criteria) subgroups with homogeneous cognitive profile and to describe the relative regional cerebral blood flow.

Methods: The patients underwent an extensive neuropsychological assessment and SPECT study. Twenty-six subtests were used as variables for the Principal Component Analysis; then, cluster analysis was applied. All images were converted to Analyze format using MRIcro software.

Results: Four clusters were derived; clusters 1 (69.2% DAT): prevalent memory deficit with left temporomesial and parietal hypoperfusion; cluster 2 (100% PCA): impairment in visuospatial domain and right parietal hypoperfusion; cluster 3 (80% PCA): prevalent visuopercetual deficit and hypoperfusion in bilateral temporomesial and right parietal areas; cluster 4 (50% DAT and PCA): diffuse cognitive impairment associated to bitemporal hyperfusion.

Conclusions: Our data support the conceptualization of AD as a disease of multiple large-scale brain networks.

Clinical and Cognitive Predictors of Post Stroke Dementia: One-Year Follow-Up Study

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Background: Stroke can have negative consequences in patients' cognitive abilities and in their daily functioning. Previous studies about cognitive disorders after stroke report vascular dementia as the main outcome.

Aim: The aim of this study is to examine if premorbid clinical and cognitive features can predict the development of post stroke dementia.

Methods: Premorbid clinical and cognitive features of 51 patients with a diagnosis of cerebrovascular pathology (ischemic or haemorrhagic stroke) were compared on the basis of the cognitive evolution (*Demented subjects* vs *Cognitively normal subjects*) at 12 months follow-up. Pre-existing cognitive decline was assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). At 12 months follow-up all the subjects underwent a standardized neuropsychological evaluation of global cognitive status, memory abilities and executive functions.

Results: *Demented subjects* were more compromised in premorbid cognitive and functional abilities than *Cognitively normal subjects;* moreover, *Demented subjects* have a higher number of cardiovascular risk factors. A higher degree of disability due to stroke (evaluated with the Rankin scale) was founded in *Demented subjects*. *Demented subjects* showed a greater atrophy in right medial temporal lobe than *cognitively normal subject*, when evaluated with CT scan.

Conclusions: Age, education, premorbid cognitive decline, functional abilities and presence of medial temporal lobe atrophy could be predictors of development of dementia after stroke at one year follow-up.

Inside the Spectrum of Tauopathies: Description of Three Cases of Corticobasal Degeneration

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Background: The clinical hallmark of corticobasal degeneration (CBD) is a combination of progressive cortical and extrapyramidal dysfunction, the latter being unilateral at onset and remaining very asymmetrical until death. Basal ganglia involvement manifests as asymmetric akinesia, rigidity, dystonia, myoclonus, tremor or any combination of the above; cortical features include alien limb phenomenon, ideomotor apraxia, cortical sensory loss or aphasia.

Aim: Describing three CBD patients showing a different clinical onset and disease evolution.

Methods: Neurological examination, neuropsychological evaluation, genetic, neuroimaging, PET and SPECT studies.

Results: In two cases the onset of disease mimic a primary progressive aphasia, the last case is characterized by bucco-facial apraxia. Comprehension was conserved in all case. PET and SPECT studies performed at the onset of disease showed different patterns.

Conclusions: These cases underlined the important overlap between CDB and other tauopathies (progressive supranuclear palsy and some forms of tau-positive frontotemporal lobar degeneration). Although different tauopathies have been considered for long to be separate diseases, this overlap suggests they may represent different phenotypes of a single disease process.

Colour Knowledge Impairment: An Unusual Presentation of Semantic Dementia? A Case Report

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Background: Semantic variant of primary progressive aphasia (SV) is characterized by progressive language and object identification impairments, and focal atrophy of the anterior temporal lobes. Colour knowledge impairments have been rarely reported with contrasting results.

Aim: We describe the case of a 55 years old chemistry expert, D.S., who presented with progressive colour knowledge impairments, associated with

behavioural modifications, language and object identification disorders.

Case report: D.S. performances were normal on colour perception, but impaired in colour (object) knowledge and naming. He also showed impaired recognition of fingers, shapes, symbols, and acalculia. Two years later, he presented a severe semantic knowledge decline spreading to all the investigated conceptual knowledge, as well as a prominent perseveration behaviour. Brain MRI and FDG-PET performed at the time of the first assessment highlighted a fronto-temporal damage, which progressively spread in the disease course.

Conclusions: Our case describes an unusual onset of the typical progressive deterioration of conceptual knowledge in SV. Apparent islands of relatively preserved/impaired conceptual ability in SV are of considerable theoretical significance, because they suggest that different "kinds" of conceptual knowledge might be differentially vulnerable in the disease. Disorders of colour naming and knowledge, with preserved colour perception, have been associated to occipito-temporal damage, and reported in posterior cerebral atrophy. Our case suggests that they can be observed also in SV, possibly related to an unusual posterior extension of pathology in the inferior temporal lobe.

Vascular Factors in Late and Early Onset AD and in a MCI

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Background: Neuropathology of Alzheimer disease (AD) includes vascular lesions and vascular factors seem to contribute significantly to its clinical appearance.

Aim: To evaluate them in Late Onset (LOAD) and Early Onset AD (EOAD) cases, and in aMCI subjects.

Population and methods: MRI scans of 374 LOAD, 68 EOAD and 70 aMCI patients, all diagnosed in our memory clinic, were evaluated through the Wahlund Scale and "pure Degenerative" cases were distinguished from "Mixed" and "vascular"cases. Vascular

risk factors (hypertension, diabetes, dyslipemia, smoking) and the disease progression were calculated in all groups.

Results: Within all groups two thirds of all cases were mixed forms. Vascular risk factors gradually increased from pure degenerative to pure vascular forms. Progression was more rapid in subjects showing the presence of associated vascular aspects.

Conclusions: Vascular risk factors characterize the majority of LOAD, EOAD and aMCI subjects and lead to worse disease progression. The synergistic effect of chronic cerebral hypoperfusion and amyloid beta toxicity, demonstrated in animal models, seems then crucial in our species also. A strong effort to prevent vascular factors is needed as it might significantly lower the global burden of dementia.

Slowly Progressive Anarthria: A Syndrome of the Frontotemporal Lobar Degeneration/amyotrophic Lateral Sclerosis Spectrum

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Background: Slowly progressive anarthria (SPA) is a rare neurodegenerative disorder, characterized by severe dysarthria, dysprosodia, phonetic/phonemic errors, and orofacial apraxia.

Aim: We report the case of a 63 years old woman with slowly progressive speech disorders and swallowing difficulties.

Methods: At onset, the patient presented with a selective impairment of speech articulation, with phonetic and phonemic errors, and a mild dysphagia, without any neurophysiological sign of lower motor neuron damage. Later on, neuropsychological testing indicated a progressive worsening of language, with defective performances in repetition, naming, reading and grammar comprehension tasks; in addition, there were signs of executive dysfunction, perseveration, orofacial and mild ideomotor apraxia. Brain MRI and [18F]FDG-PET showed marked involvement of the left frontal regions, spreading towards the left parieto-temporal regions with disease progression.

Results: Clinical findings support a diagnosis of SPA. The patient presented with a speech impairment without clear aphasic signs, that does not fit within the current criteria for primary progressive aphasias. In addition, the patient showed impaired swallowing without signs of motor neuron involvement. Functional neuroimaging revealed a significant hypometabolism in the left frontal regions.

Conclusions: SPA can be considered as a specific presentation of focal cortical degeneration within the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum of disorders.

Alzheimer-Type Dementia and Senile Myoclonic Epilepsy in a Patient with Down's Syndrome

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Background: Alzheimer's disease and Down's syndrome are often associated with senile myoclonic epilepsy. It is very frequent, although still under-recognized. De Simone et al have recently tried to outline its characteristics.

Case report: We describe the case of a man of 50yo with Down's Syndrome. At the age of 45yo he showed diffuse myoclonic jerks, and generalized tonic-clonic seizures with a weekly frequency. Seizures increased with CBZ and PB. Instead the seizures disappeared with VPA+LEV. By the age of 48yo a progressively and rapidly ingravescent dementia. A recent MRI showed widespread subcortical and cortical cerebral atrophy.

Conclusions: The association of these three entities is well known in the literature. Recently De Simone et al. have tried to indicate the salient features of this epilepsy. Probably it represents today the commonest form of progressive myoclonic epilepsy. Our patient has some peculiarities: onset of epilepsy before of the beginning of dementia and a rapid progression of dementia-Alzheimer's type with a benign course of epilepsy. Moreover, it is important to emphasize that this type of epilepsy is worsened with of CBZ and PB. In conclusion we believe that reporting similar cases is crucial to better define the clinical spectrum of this syndrome.

Decreased BDNF Production in Amyloid β 1-42 Treated Dendritic Cells from Alzheimer's Disease Patients

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Background: Chronic inflammation plays a pathogenic role in Alzheimer's Disease (AD). In particular, dendritic cells (DCs), main actors in immune responses and inflammation, seem to play a central role in AD. In fact, monocyte-derived DCs (MDDCs), generated *in vitro* with Amyloid β1-42 peptide (Aβ1-42), show a functional alteration and increased production of inflammatory molecules. Similarly, MDDCs from AD patients show a more pronounced pro-inflammatory profile than DCs obtained from control subjects.

Aim: To further investigate DC role in AD.

Methods: We analyzed *in vitro* the effect of Aβ1-42 treatment on differentiated DCs derived from AD.

Results: We found that, while Aβ1-42 triggering does not induce profound changes in the immune-related functional abilities of differentiated DCs in both AD and control subjects, interestingly, Aβ1-42 is able to cause a significant decrease in the expression of brain-derived neurotrophic factor (BDNF) specifically in cells derived from AD patients and not in controls.

Conclusions: These data suggest that DCs of AD patients could participate in brain damage by playing a part in Aβ-dependent neuronal toxicity.

Long Term Efficacy of Cholinesterase Inhibitors in Genetic vs Familial and Sporadic Naïve Alzheimer's Disease Patients: A Real Life Study

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Background: Few long-term and/or real-life studies exist on Cholinesterase-Inhibitors (ChEIs) in Alzheimer Disease (AD). No data in patients with genetic cause or familial trait.

Aim: To determine long-term, real-life ChEIs efficacy in patients with genetic, familial and sporadic AD and to evaluate predictors of drug response.

Population: Retrospective analysis of 608 AD patients (onset 67.7 ± 11.6): 13 Met1146LeuPS1-mutated, 126 with 1stdegree relative affected, 469 sporadic; donepezil 62.2%, rivastigmine 32%, galantamine 5.8%.

Methods: Comparing MMSE values (baseline,3, 9, 15, 21, 27, 33, 39, 45 months) to the expected decline (4.5 points/year). Investigating drug response among PS1-mutated, familial and sporadic patients. Correlating MMSE values with education, onset, progression rate, baseline MMSE, 3rd month response, ApolipoproteinE/ε4, CholineAcetyltransferase/SNPrs733722, CytochromeP-4502D6/SNPrs1080985 and Paraoxonase2/codon311Cys→Ser genotypes.

Results: At 3rd month 28.6% of patients gained ≥ 2 MMSE points (responders). At 9th there was 21.9% of responders. At 45th MMSE-score was statistically higher in all patients ($p = 0.000$). A lower baseline MMSE-score ($p = 0.000$) and 3rd month responsiveness ($p = 0.000$) predicted ChEI long-term efficacy. Examined genotypes didn't influence therapeutic response.

Conclusions: ChEI prevent cognitive worsening in real-life treated AD patients independently of their genetic status and from early pharmacological response. A lower MMSE-score at baseline and response at 3rdmonth can predict ChEI long-term treatment efficacy.

Perceptual Constancy are Respected in Alzheimer's Disease Patients

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Background: Narrative ambiguity in visual art, such as that of Vermeer's paintings, enhances interest and involvement in observers, allowing many plausible interpretations, differently from image ambiguity, as cubist Picasso's paintings. Visual brain neurobiology, specifically the "perceptual constancy" roles would account for difference.

Aim: To test if art appreciation follows "perceptual constancy" roles also in AD subjects.

Population and methods: 30 mild-moderate AD patients (16 females) were asked to comment and appreciate paintings: 20 narrative ambiguous, 20 no-ambiguous, and 20 images ambiguous (cubists).We had evaluated the time spent in the observation and comment of paintings and the aesthetical appreciation.

Results: Narrative ambiguity is associated with more time spent and more appreciation; images ambiguous (of cubists type) are usually not recognized and are poorly appreciated.

Conclusions: Cognitive decline due to AD does not modify the higher involvement and aesthetical appreciation associated with narrative ambiguity, suggesting that the general roles proposed by the neuroesthetic approach (Zeki, 2004) are long time preserved. The results may be useful in planning stimulation programs based on visual art for AD subjects.

Progressive Changes of Visual Art in a Professional Artist with Alzheimer's Disease

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Background: Previous studies have shown that dementia does not alter the affected patients' creative capacity. We report the case of F.G., a professional painter who suffers from Alzheimer's disease. When his cognitive disorders arose, his artistic production dramatically decreased.

Aim: The aim of our observational analysis was to evaluate how the patient's artistic production changed as his disease progressed.

Methods: The patient's artistic productions prior to or simultaneous with the onset of the disease were taken into account, and the assessment of the patient's artistic expression in a series of specific tasks performed on his admission (test) and discharge (retest) were also considered an important element of the analysis.

Results: The technique used by the artist before the disease is much different from that used at the onset of

Alzheimer disease. In his last works, the background is not evident, and few elements are represented, compared with the number of objects represented in the works he completed before the onset of his disease.

Conclusions: Our work is meant as a contribution to the idea that Alzheimer's disease does not destroy creativity but rather changes the cognitive instruments an artist can use to express himself, until the neuro-degenerative process makes them unavailable to him.

A Late Onset FTD/ALS Case Associated to a Mutation in CHMP2B Gene

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Background: Amyotrophic Lateral Sclerosis (ALS) may occur alone or associated with the behavioral variant of frontotemporal dementia (bvFTD). Mutations in CHMP2B gene have been described in familial and sporadic forms of FTD and ALS.

Aim: We report a late-onset, sporadic case of FTD/ALS who carried a variant in CHMP2B gene.

Methods: Clinical, neurophysiological, neuroradiological and genetic assessments were performed.

Results: The patient at 79 presented loss of muscle trophism of the hands, dysarthria, dysphagia and ideational-behavioral disorders. Clinically: fasciculating arms and pyramidalism; EMG: signs of active denervation associated with collateral reinnervation in more districts; CT scan: bilateral frontoparietal cortical atrophy. Diagnosis: patient with FTD/ALS. Molecular analysis: the variant I29V in CHMP2B gene, already described.

Conclusions: We identified the I29V substitution in a FTD/ALS late-onset patient. This variant has been previously associated to FTD or ALS with early-onset and reported as having a doubtful pathogenicity. However, *in vitro* and *in silico* data subsequently demonstrated that the variant alters the protein function involved in lysosomal degradation, a mechanism common to several neurodegenerative disorders. According to these data we hypothesized that I29V could be responsible for the patient's clinical picture suggesting to extend the genetic screening of CHMP2B in FTD/ALS cases even late-onset and sporadic.

Executive Dysfunction Affects the Serial Position Curve of Rey Auditory Verbal Learning Test

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Background: Word list learning deficits might be associated to both memory and/or executive function deficits.

Aim: To investigate the role of executive functions in the Rey Auditory Verbal Learning Test (RAVLT) in patients with neurodegenerative diseases associated with prevalent memory and/or executive dysfunctions.

Population and methods: We analysed the serial position curve of the RAVLT in 18 probable Alzheimer's disease (AD), 14 behavioural variant of frontotemporal dementia (bvFTD) patients, 14 cognitively-normal amyotrophic lateral sclerosis (ALScn), 14 ALS patients with mild executive dysfunction and/or behavioural impairment (ALSci/bi) and 48 healthy controls (HC).

Results: A severe short- and long-term memory impairment was present in both AD and bvFTD patients, with reduction of primacy and mid-list effects. BvFTD had also a reduced recency effect compared to all groups. Both ALS groups showed normal primacy and recency effects. Nevertheless, ALSci/bi displayed significantly lower scores in the mid-list part compared to HC, comparable to bvFTD and AD. The correlation analysis revealed a positive correlation between mid-list scores and executive measures in ALSci/bi and HC.

Conclusions: Our study provides evidence that executive functions contribute to controlled-strategic processing at encoding and retrieval of word-list, in particular in the case of mid-list items, even in the absence of memory dysfunction.

Cognitive Predictors and Correlations with Biomarkers and Functional Imaging in Patients with Primary Progressive Aphasia

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Background: Recently, a new classification of Primary Progressive Aphasia (PPA) has been reported. Three syndromes have been recognized: Primary Non Fluent Aphasia (PNFA), Semantic Dementia (SD) and logopenic aphasia.

Aim: To correlate neuropsychological testing with cerebrospinal fluid (CSF) Amyloid beta (Aβ), tau and hyperphosphorylated (P)tau levels and MRI in patients with PPA.

Methods: The clinical workup includes neurological examination, blood routine analyses, neuropsychological assessment (a battery of cognitive tests, including grammar, motor speech, picture description task, repetition, comprehension, reading, copy, writing under dictation, apraxia and spontaneous speech, lumbar puncture and MRI. Aβ, tau and Ptau were evaluated by ELISA. Statistical analysis is carried out by using Anova and Spearman test for correlations.

Results: At present, 16 patients have been consecutively recruited. Two had a clinical diagnosis of SD; remainders were diagnosed with PNFA. Two out of 14 patients with PNFA had an Alzheimer's disease-like CSF profile; 5 patients with PNFA and both patients with SD had a normal profile, whereas 7 patients had normal Aβ levels but increased tau concentration.

Discussion: These preliminary data on CSF profile suggest that there are different mechanisms at the basis of PPA pathogenesis.

Is Anxiety Trait a Common Factor in Subjects with Subjective Cognitive Decline? The Utility of an Anxiety Questionnaire in the Neuropsychological Assessment of Subjective Cognitive Impairment

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Background: A significant proportion of people with subjective cognitive impairment (SCI) suffer from mood disorders (anxious-depressive disorder).

Aim: To analyze how subjective memory disorder goes along with anxiety personality trait and to evaluate the utility of a specific anxiety questionnaire in the neuropsychological assessment.

Population and methods: Sixty-six SCI (age 69 ± 8.1, education 11.4 ± 4.6; female 53%, MMSE 28.4 ± 1.3) were assessed with a standard neuropsychological assessment together with the State-Trait Anxiety Inventory (STAI) and the Geriatric Depression Scale (GDS).

Results: An anxiety trait was found in about 60.6% of patients; about half of these patients also appeared to be depressed. Anxiety was slightly more frequent in women (χ^2 5.84, $p < 0.016$). More than a third of patients with SCI displayed neither anxiety nor depression.

Conclusions: People with subjective memory disorder frequently suffer from an anxiety disorder (often together with depression), while they are less likely to have an isolated depressed mood. The use of a dedicated questionnaire might help to detect an anxiety disorder that otherwise would be neglected and that could be an explanation for subjective cognitive complaints. Future studies are needed to clarify what's behind those cases who do not show any affective disorder.

Intrafamilial Clinical Variability in Pathologically-Proven Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 (FTDP-17) Caused by MAPT-P301L Mutation

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Background: Missense MAPT(tau) gene mutation P301L represents the most common mutation associated with Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Clinical and pathological heterogeneity in affected individuals has been recognized.

Aim: To outline the phenotypic features of a large FTDP-17 pedigree bearing MAPT-P301L mutation, focusing on a neuropathological case-report.

Methods: The family included 12 affected subjects in four generations. In a 61-years old woman affected by bvFTD and parkinsonism, histopathological study of brain and spinal cord was performed.

Results: Age of onset was 50 ± 3 years and disease duration was 5.3 ± 3 years. Clinical presentation was highly variable, with late epileptic seizures and parkinsonism in 4/14 patients. Neuropathological study showed marked atrophy, loss and shrinkage of cortical neurons in frontal and temporal lobes and depigmentation of substantia nigra. An inhomogeneous distribution of neuronal and glial inclusions immunoreactive for hyperphosphorylated tau associated with reactive astrocytic gliosis was present. Pyramidal layers of frontal and anterior temporal cortical areas, hippocampus, subcortical structures and spinal and cranial motoneurons were greatly involved, whereas parietal and occipital cortical areas and cerebellar hemispheres were spared.

Conclusions: Our findings confirm a marked intrafamilial variability in clinical presentation of pathologically-proven FTDP-17 caused by MAPT-P301L mutation, underlining the need of further genotype-phenotype correlation studies.

Identification of Famous Faces and Voices Discriminates Semantic Dementia from Alzheimer's Disease

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Background and aim: The present study aims to investigate the ability to identify celebrities from their faces and voices in two degenerative dementias (SD and AD).

Population and methods: 8 patients with SD, 12 patients with AD and 17 controls were enrolled. The following tests were applied:

1) Naming famous faces (98).
2) Recognition of famous faces (98): the subject was asked to match a photographs a proper name (two famous names were proposed).
3) Discrimination of famous faces: 108 stimuli were proposed and included 54 photographs of famous people and 54 photographs of normal people.
4) Recognition of famous voices: subjects were asked to listen a voice and match it to the target name from an array of 4 items.

Results: SD patients were profoundly impaired on both discrimination and recognition of famous faces and voices when compared with healthy controls and AD patients; by contrast AD patients did not differ from controls.

Conclusions: The present data confirm that SD patients show profound loss of semantic knowledge of famous people, regardless of the material access (faces or voices). The dissociation found between SD and AD, in naming and recognition of famous faces and voice could be of importance in the differential diagnosis between the two diseases.

Sound Production and Identification in Semantic Dementia and Alzheimer's Disease

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Background and aim: The ability to recognize the meaning of human and environmental sounds can be of crucial importance in day-to-day life. Until now, little attention has been drawn from research to the issue if sound recognition is impaired in SD and to what extent.

Population and methods: 9 patients with SD were enrolled and their performance compared to 17 normal controls and 12 patients with Alzheimer's Disease (AD), matched for age, sex and education.

The "sound battery" consisted of :

i) matching 70 sounds to pictures, ii) matching 70 sounds to written words. Subjects were asked to listen a sound and match it to the target stimulus (picture or written word) from an array of 4 items. For each item three distractors were provided: a visual, a semantic and an unrelated distractor.

iii) Subjects were asked to produce 35 sounds.

Results: SD patients were profoundly impaired in sound recognition and production when compared to patients with AD and controls. In matching tests involving sounds SD patients made significantly more semantic errors than AD patients.

Conclusions: It is demonstrated that SD patients show a profound loss of meaning of sounds (recognition and production). This issue can have important implications in patient's management and caregiver should be informed.

Lipid-Based Nanoparticles as a Potential Tool to Deplete Abeta. Toward New Therapeutic Strategies for Alzheimer's Disease?

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Background: The possibility to deplete beta-amyloid peptide from central nervous system represents one of the most promising approaches to prevent Abeta toxicity in Alzheimer's disease (AD). Nanoparticles (NPs) are an innovative vehicle to reach this aim.

Aim: To evaluate the capacity of different NPs classes to sequester Abeta from plasma and to reduce Abeta toxicity in a cellular model.

Methods: AD patients and controls were enrolled at San Gerardo Hospital, Monza, Italy. ELISA assay was used to evaluate Abeta plasma content both before and after NPs incubation. Fibroblast cultures were treated with Abeta and two different types of NPs for 24 hours and cell viability was evaluated by MTT assay.

Results: NPs can bind and sequester Abeta reducing its concentration in plasma both in AD and control subjects. NPs didn't affect cell viability when administered in fibroblast cultures from patients and controls. Abeta showed a cytotoxic effect depending on its concentration and this effect was partially recovered when fibroblast were incubated with NPs, depending on NPs class and concentration.

Conclusions: Lipid-based nanoparticles could represent a potential tool to sequester peripheral plasma Abeta amount, eventually reducing central levels by sink effect: furthermore they could prevent beta-amyloid induced citotoxicity *in vitro*.

Assessing the Risk of Cognitive Impairment in a Group of Elderly Travelers: The Validity of Informant Questionnaire on Cognitive Decline in the Elderly when Compared with Mini Mental State Examination

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Background: As the population ages, the need for identification of individuals at risk of dementia becomes increasingly important. Indeed, the effectiveness of pharmacological treatment is closely linked to early diagnosis. Hence the need to identify new tools for cognitive screening, in order to detect individuals with cognitive impairment, for including them in long-term preventive or therapeutic programs.

Aim: Assessing the risk of cognitive impairment by comparing the Mini-Mental State Examination (MMSE) and Informant Questionnaire on Cognitive Decline in the Elderly (IQ CODE).

Method: Fifty four couples were enrolled. One of the components was subjected to cognitive screening with MMSE. MMSE score and performance for each item were used to derive a "Dementia Global Risk" (DGR). All variables were statistically analyzed.

Results: DGR turns out to be statistically correlated with the risk of cognitive decline derived after IQ CODE administration ($p=0.000005$). MMSE score was found to be statistically correlated with the value of Body Mass Index (BMI) ($p=0.047$), with systolic ($p=0.00059$) and diastolic blood pressure ($p=0.006$). Spatial ($p=0.09$) and Temporal ($p=0.07$) Orientation were statistically correlated with hypercholesterolemia.

Conclusions: IQCODE is a reliable tool for screening of cognitive disorders in elderly.

Mini Mental State Examination in Patients with Atrial Fibrillation: Relationship between Cognitive Decline and Surrogate Markers of Atherosclerosis

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Background: Atrial fibrillation (AF) is the most common dysrhythmia encountered in clinical practice; its prevalence is closely associated with age. On the other hand, 15 to 30 percent of people aged 85 years and older are affected by dementia. Consistent evidence supports a possible role of AF and atherosclerosis in the development of cognitive impairment.

Aim: Aim of this study was to analyze the relationship between cognitive impairment, atherosclerotic disease and AF.

Methods: We examined 50 patients with AF aged over 65 years. Ankle brachial index (ABI) measurement and intima-media thickness (IMT), established subclinical atherosclerotic markers, have been evaluated as surrogate markers of atherosclerosis. A Global Geriatric Assessment was performed.

Results: In 48% of cases, AF patients had a pathological ABI value and IMT measurement. In 34% of cases, AF patients obtained a MMSE score under 24, indicating the presence of cognitive impairment. A pathological ABI value was significantly associated with the failure to recall test at Mini Mental State Examination (MMSE) ($p=0.037$) and MMSE scores inversely correlated with IMT values ($r=-0.2301$).

Conclusions: In AF patients, short term memory impairment correlates with atherosclerotic state, suggesting a possible role of AF and atherosclerosis in the pathogenesis of cognitive impairment and dementia.

Vascular Dementia or Early AD? A Case Report

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Background: Vascular dementia (VD) is a common form of cognitive decline, occurring either after a single major stroke (*post-stroke dementia*), or following a series of sub-clinic small-size infarcts *(multi-infarct dementia)*. In the latter case, the differential diagnosis with Alzheimer's disease (AD) may be challenging. White matter lesions are indeed frequently detected in AD brains, and VD may present with cognitive deficits similar those observed in AD.

Objectives: To present a single case of VD with a clinical presentation mimicking an early-AD.

Methods: An 86-year-old woman, suffering from high blood pressure and high cholesterol level, came to the clinic complaining of memory deficits, reduced interest in everyday activities, mood swings and personality changes. On the Mini Mental State Examination (MMSE), she scored 20/30, showing difficulties with solving problems. On the Geriatric Depression Scale (GDS) she scored 3/15.

Results: Neuropsychological testing (NPT) revealed a prominent impairment of short-term memory. Brain MRI scanning showed the presence of multiple lacunar infarcts in the basal ganglia/thalamus and in the right-hemisphere white matter. The diagnosis was *multi-infarct dementia*.

Conclusions: Symptoms of VD can vary, depending on the distribution of brain damage. MRI and NPT may provide convergent explanations for symptoms, and contribute in clarifying the diagnosis.

Clinical Validation of a Grid-Based SPM Web Tool for the Automatic Assessment of [¹⁸F]FDG PET Brain Metabolic Abnormalities in Single Subjects

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Background: [¹⁸F]FDG-PET imaging has been suggested to increase diagnostic accuracy in neurodegenerative disorders since the very early stages. At present, [¹⁸F]FDG-PET brain scans in single subjects are mostly evaluated through visual inspection, resulting in low sensitivity and specificity. Reports on voxel-based methods specifically designed to automatically perform single-case analysis are available in literature. Among these, Statistical Parametric Mapping (SPM) is the most used, and a Grid-SPM system is under development to provide a widely available tool to perform single-case analysis in clinical practice.

Aim: We assess the sensitivity and specificity of SPM analysis for early and differential diagnosis of neurodegenerative disorders (MCI, pAD, FTLD) at the single subject level.

Method: We recruited 113 healthy subjects (DIMI Project and European Alzheimer's Disease Consortium EADC) for comparison with 45 AD, 30 MCI and 25 FTLD cases. Visual ratings of resulting SPM maps of glucose hypometabolism were assessed by 9 neuroimaging experts.

Results: SPM analysis based on the comparison with 113 normal controls provided clusters of hypometabolism with conservative, FWE corrected statistical thresholds. Analysis of the expert raters' performances for diagnostic accuracy of [¹⁸F]FDG-PET indicated a specificity and sensitivity in detecting the typical metabolic patterns higher than 90%.

Conclusions: This voxel-based [¹⁸F]FDG-PET SPM approach, implemented in a Grid-system, is a very promising tool to be used by clinicians in specialized centers, enabling objective functional assessment to support early diagnosis of neurodegenerative disorders.

Improving Diagnostic Accuracy of DLB: An MRI Study

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Background: Alzheimer's disease (AD) and Lewy Body Dementia (LBD) are the most common neurodegenerative dementia. The accuracy of clinical diagnosis of LBD is insufficiently satisfactory due to poor sensitivity and specificity of some clinical features.

Aim: To use Magnetic Resonance (MR) as a potential tool to improve diagnostic accuracy of dementia subtypes.

Methods: Structural 3D T_1-W TFE and DWI-SE sequences were performed with Philips Achieva 3T scanner. 15 DLB, 15 AD, 11 controls were studied. Tract-based spatial statistics and voxel-based morphometry approaches were performed to assess White Matter (WM) integrity and grey mater (GM) atrophy. Shape and mean diffusivity analyses in connectivity-defined subregions were performed to provide macro- and micro-structural information at subcortical level.

Results: Cortical and subcortical GM and WM alterations were identified in AD and DLB, with

preservation of left medial temporal lobe in LBD vs. AD. Significant macro- and micro- structural thalamic changes were observed in dementia groups vs. controls. These changes were observed in antero- ventral and dorsal thalami and in pulvinar area projecting to occipital lobe . Micro-structural preservation of antero-dorsal thalami and pulvinar region projecting to temporal lobe were observed in LBD patients vs. AD.

Conclusions: MR techniques represent a tool to assess pathophysiological differences between AD and LBD.

Frontal Defects Contribute to the Genesis of Closing-in in Alzheimer's Disease Patients

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Background: In copying tasks, Alzheimer's disease (AD) patients may show the tendency to draw in proximity to or to overlap to the model. This behavior is labeled closing-in phenomenon (CIP). Owing to its complexity the CIP resists at a univocal interpretation; it has been suggested that frontal executive impairments could determine an attraction of the hand towards the focus of visual attention. Otherwise, CIP has been considered as a result of the attempt to overcome visuo-spatial defects.

Aim: The aim of the present study was to investigate cognitive mechanisms underlying the genesis of CIP in AD patients.

Methods: 44 patients with probable AD have been assessed. All patients underwent copying tasks and a neuropsychological assessment.

Results: CIP was found in 26 (59%) patients. Patients who demonstrated CIP showed more severe impairment on phonological verbal fluency and inhibition of automatic responses tasks than patients without CIP. Logistic regression revealed a significant association of executive defects (FAB: $p=0.008$; Stroop Test: $p=0.008$) with the occurrence of CIP.

Conclusions: Our results suggest that dysfunction of frontal monitoring processes and impaired inhibition of automatic responses could be considered critical factors for the occurrence of CIP in patients with AD.

Phenotypic Heterogeneity of Alzheimer's Disease: Towards the Identification of Molecular Determinants Underlying Distinct Clinico-Pathological Subgroups

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Background: Alzheimer's disease (AD) is usually sporadic (sAD), but a small fraction of cases is familial (fAD). fAD is characterized by a striking variety of clinical presentations, while sAD is commonly considered much less heterogeneous. Nevertheless, the finding of dissimilar phenotypes also among sAD patients is a very common experience among physicians facing with this type of dementia.

Aim: To detect different AD subgroups by defining the biochemical characteristics of Amyloid-beta (Abeta) species/assemblies and the neuropathological profile of AD cases, selected for having different clinical phenotypes.

Methods: Neuropathological assessment of selected AD cases by immunohistochemical studies with anti-Abeta antibodies. Biochemical analysis of CSF and brain fractions from AD patients with (i) ELISA to measure Abeta levels, (ii) immunoprecipitation to investigate Abeta oligomeric assemblies, (iii) SELDI-TOF MS to analyze the monomeric Abeta species and their distribution between CSF and brain tissue.

Results: Preliminary findings showed relevant differences in clinical and neuropathological expression of the disease which are associated with specific biochemical features regarding the composition of amyloid deposits, and distribution and relative abundance of Abeta species in brain tissue and CSF.

Conclusions: Overall these data suggest that AD exists in multiple forms characterized by specific phenotypes and distinctive molecular profiles.

Frontotemporal Dementia with Psychosis, Visuo-Spatial Dysfunction, Parkinsonism and Upper Motor Neuron Involvement Associated to Expansion of C9ORF72: A Peculiar Phenotype?

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Background: Recently it has been discovered that a hexanucleotide repeat expansion in *C9ORF72* gene is a major cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

Aim: To report the case of a 64-years-old man with FTD-parkinsonism-motor neuron disease (MND) associated to this intronic repeat expansion of the *C9ORF72* gene.

Case report and methods: The patient presented with a three years history of delusional mystic thoughts and multimodal hallucinations, followed by progressive cognitive decline and symmetric akinetic-rigid syndrome. Neuropsychological assessment demonstrated predominant frontal syndrome and marked constructional apraxia. A few months after, the patient rapidly developed a severe dementia and upper motor neuron involvement.

Results: Brain MRI documented frontotemporal atrophy but with consistent posterior regions involvement. Perfusion SPECT with ^{99}Tc-ethylene cystine dimer showed hypoperfusion in the frontotemporal and parietal regions bilaterally. The GGGGCC hexanucleotide repeat expansion in the first intron of *C9ORF72* gene was found.

Conclusions: Our patient developed a behavioural variant of FTD with some atypical features, like psychosis, constructional apraxia, atrophy and perfusional deficit extended to posterior cortical areas. It suggests that this hexanucleotide repeat expansion in C9ORF72 gene could be related to a distinctive phenotype of FTD-parkinsonism-MND.

Unilateral Ideomotor Apraxia Secondary to Left Parietal Stroke

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Background: Ideomotor apraxia has been thought to reflect a disturbance in programming the timing, sequencing and spatial organization of gestural movements. Unilateral lesions of the left hemisphere in right-handed patients produce bilateral deficits.

Aim: To describe a patient who developed unilateral ideomotor apraxia after a left parietal ischaemic stroke.

Case report: M., a right handed 71 year old Italian man, came to our attention complaining a 2 year-story of clumsiness of his left upper limb. The disturbance had an abrupt onset. Neurological examination and background neuropsychological examination were normal. He underwent a praxis battery able to analyze gesture comprehension and gesture production. Praxis'comprehension was normal. Gesture production revealed left arm clumsy and awkward movements with difficulties in performing meaningful and meaningless gestures both on command and on imitation. His CT scan showed a left parietal cortico-subcortical ischaemic lesion. DAT scan was normal.

Conclusions: The present case shows a selective left upper limb ideomotor apraxia following a left parietal focal lesion. It is in contrast with the traditional models of praxis where parietal lobe is assumed to be implicated in generating the motor program for right and left limbs.

Normal-Pressure Hydrocephalus: The Role of Apolipoprotein E Gene and the Surgical Outcome Assessment

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Background: Normal-pressure hydrocephalus (NPH) is a syndrome characterized by abnormal gait, dementia and urinary incontinence, associated with hydrocephalus and normal CSF pressure on lumbar puncture. The only treatment is shunting, although there is no evidence of its efficacy.

Aim: To assess whether the ε4 allele of the Apolipoprotein E (ApoE) gene is involved in NPH and to analyze the surgical outcome of ventriculo-peritoneal shunting and the correlations between ApoE genotype and clinical features.

Methods: The study group consisted of 87 subjects: 15 NPH patients enrolled from the Neurology Unit of the University of Florence, 12 surgical NPH patients from the Neurosurgery Unit and 60 controls. All subjects were genotyped for ApoE. The evaluation of the shunting effectiveness has been assessed by an extensive clinical protocol and a scale constructed ad-hoc.

Results: We found a significantly higher frequency of the ε4 allele of ApoE in NPH patients. The evaluation of surgical outcome only showed a slight improvement of gait. However carriers of the ε4 allele exhibited worse outcomes and worse scores on MMSE, Mac-Q, GDS and IADL.

Conclusions: ApoE gene may be involved in the pathogenesis and/or in increased susceptibility to cognitive impairment in NPH and also may correlate with surgical outcome.

Differences of Distributed Sources of Cortical EEG Rhythms in Dementia with Lewy Bodies (DLB) Respect to Alzheimer Disease (AD)

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Background: EEG abnormalities may be able to discriminate between dementia with Lewy bodies (LBD) and Alzheimer disease (AD).

Aim: To map the distributed sources of cortical EEG rhythms in LBD respect to AD.

Methods: We considered 51 DLB and 21 AD patients, who were assessed with a broad neuropsychological battery, including VOSP test for visuo-spatial abilities. Standard EEG was acquired and analyzed with sLoreta software.

Results: The two groups were matched for gender and age (years: LBD=75 ± 6; AD=74 ± 7). Global cognitive impairment was comparable between the two groups (MMSE. DLB=22.3 ± 5; AD=21.4 ± 5). LBD patients showed worse attentive functions ($p=0.02$ on TMT A) and visuo-spatial abilities (VOSP 1/8 = $p<0.01$, VOSP 6/7=$p<0.05$) respect to AD.

Upon EEG analysis, a cortical source of delta activity was detected in more than 75% of regional voxels in the primary and associative visual cortex (BA 17, 18), cingulate (BA 30, 23) and fusiform gyrus, respect to AD. In LBD VH+, the source of delta activity was significantly focused in the posterior cingulate cortex (BA23) respect to LBD VH–.

Conclusions: In LBD, the delta source of cortical EEG rhythms in parieto-occipital regions could be related to a "functional lesion" in regions processing visuo-spatial information.

Validation of a Dementia Screening Test for the General Practicioner

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Background: General practitioners rarely screen their patients routinely for dementia, mainly due to a lack of brief and valid instruments.

Aim: To compare the validity of two ultrashort cognitive screening tools, the General Practitioner assessment of Cognition (GP-COG) and the 3 Objects – 3 Places test (3O3P) with MMSE.

Population and methods: We enrolled 147 consecutive patients referred to our Neuropsychology Unit. They all underwent an extensive neuropsychological battery and the three screening test. MMSE score was disregarded when making diagnosis.

Results: Fifty-four patients were classified as having mild dementia, 65 as having MCI and 28 were cognitively normal. Known group validity analysis showed that all the instruments can discriminate between the three study groups. Concurrent validity in

identifying impaired patients was measured with ROC curves analysis: Area Under Curve (AUC) was 0.91 for MMSE, 0.93 for the GP-COG and 0.88 for the 3O3P. Sensitivity was 94% and 71%, respectively, for MMSE, and 90% and 75% for the GP-COG, and 81% and 79% for the 3O3P. Mean time of administration for the GP-COG was half as short as for MMSE, while the 30 min interval of the 3O3P test significantly increases its duration.

Conclusions: The 3O3P appears to be less valid and more time-consuming. The unique real advantage of using the GP-COG instead of MMSE appears to be its significant shorter time of administration.

Functional Network Connectivity in the Behavioral Variant of Frontotemporal Dementia

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Background: The most consistent resting state (RS) fMRI feature in the behavioral variant of frontotemporal dementia (bvFTD) is a reduced connectivity within the salience network.

Objective: To investigate, using RS fMRI, the functional connectivity within and among brain networks in bvFTD patients compared with healthy controls and patients with probable AD (pAD).

Methods: In 12 bvFTD, 18 pAD and 30 controls, functional connectivity within the salience, DMN, executive, attention/working memory, and dorsal attentional networks was assessed. The temporal associations among RS networks (RSN) were explored.

Results: A decreased dorsal salience network mean connectivity, mainly involving the anterior cingulate cortex, was observed in bvFTD compared with both controls and pAD. BvFTD was also characterized by a decreased ventral salience network connectivity of the basal ganglia, and divergent connectivity effects *vs.* controls in the dorsolateral prefrontal cortex (decreased) and precuneus (enhanced) within the right attention/working memory network. The dorsal attentional network had a decreased connectivity with the DMN and executive network in bvFTD *vs.* controls, and a decreased connectivity with the dorsal salience network *vs.* pAD patients.

Conclusion: RSN abnormalities occur in bvFTD, involving the salience, DMN and fronto-parietal networks. Regional connectivity changes differ from those seen in pAD.

Patterns of Microstructural White Matter damage in early and late age of onset Alzheimer's disease patients

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Background: Patients with early age of onset AD (EOAD) show a more severe brain atrophy and hypometabolism compared to the typical late-onset patients (LOAD) at a similar disease stage.

Objective: To investigate patterns of brain white matter (WM) integrity in EOAD and LOAD.

Methods: Structural and diffusion tensor imaging (DTI) were obtained from 19 EOAD and 19 LOAD patients (matched for demographics and dementia severity). Thirty-eight healthy controls (HC) were included. Tract-based spatial statistics and voxel-based morphometry were used.

Results: Compared to HC, EOAD showed WM damage to the corpus callosum (CC), whole cingulum, and major long associative WM tracts, bilaterally, and a distributed pattern of parieto-temporal and frontal GM atrophy. Compared to HC, LOAD showed WM damage to the CC and posterior cingulum, bilaterally, and left medial temporal GM atrophy. Compared to LOAD, EOAD showed a more severe damage to the splenium of the CC bilaterally, left posterior cingulum, and left superior longitudinal fasciculus, as well as a more severe GM atrophy in the posterior cingulate cortex.

Conclusions: WM damage is more distributed and severe in EOAD patients compared with typical LOAD, and is likely to contribute to the more generalized cognitive deficits in these patients.

Corticobasal Syndrome Presenting with an Atypical Clinical Picture: A Case Report

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Background: Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder characterized by distinctive clinical manifestations including cortical and basal ganglia signs. It is classified as a tauopathy. The most distinctive clinical feature is its markedly asymmetric presentation. The clinical picture of CBD considerably overlaps with a variety of other parkinsonian and dementing illnesses. Authors often prefer the term *corticobasal syndrome* (CBS), reserving the term *corticobasal degeneration* for post-mortem verified cases. Patients presenting as CBS have CBD as the underlying pathology only in about 55% of the cases.

Aim and case report: We report the case of a 71-years-old woman who at age 68 presented depression, with optimal response to SSRIs; two years later, she presented visual hallucinations. At age 71 years she showed clumsiness of the left hand. During the course of her illness, she suffered from progressive asymmetric clinical symptoms - rigidity, which was left side dominant, unilateral spatial neglect, imbalance with falls – and cognitive impairment. Cranial MRI and 18F-FDG PET were performed.

Conclusions: The patient described in this report had a clinical condition consistent with corticobasal syndrome, although there are no absolute markers for the clinical diagnosis. To our knowledge, however, there has been only one report of visual hallucinations associated with corticobasal syndrome.

Data Driven Analysis of Resting State fMRI in DLB with Fluctuating Cognition and AD Patients

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Background: Abnormalities of the Default mode network (DMN) evidenced by fMRI studies are described in Alzheimer disease (AD).

Aim: To assess whether patients with Lewy Body Dementia (LBD) with fluctuating cognition (fl-cog) and consistent resting state (RS) EEG abnormalities presented with different DMN activities pattern during RS than AD patients without fl-cog and EEG abnormalities.

Methods: 18 LBD patients with fl-cog and abnormal EEGs, 18-AD patients without fl-cog and normal EEG and 15 age matched controls were selected. Data driven functional connectivity (FC) assessed by Independent Component and additional Granger Causality analysis were used in order to establish areas involved during RS.

Results: DMN areas were identifiable in all groups. Reduced FC was found in AD/LBD vs controls ($p < 0.05$). Posterior cingulum activity was reduced in AD compared with LBD and controls ($p < 0.05$), right hemisphere FC was reduced in LBD vs AD/controls($p < 0.05$), also an involvement of right inferior-parietal-lobe was shown. In LBD was found a reduction of right hemisphere fronto-parietal connection and fl-cog($r = -0.69, p < 0.01$).

Conclusions: We suggest a probable role of the right hemisphere dysfunction in the occurrence of fl-cog. DMN areas during RS were identifiable in LBD also with sever fl-cog. This finding suggests that the role of DMN in different diseases cannot be distinguished by simple resting state protocols.

Frequency of Autosomal Dominant Mutations in an Italian Population of Patients with Frontotemporal Lobar Degeneration

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Background: Frontotemporal Lobar Degeneration (FTLD) recognizes high familial incidence. It has been shown that mutations in the genes encoding for Microtubule Associated Protein Tau (*MAPT*), progranulin (*GRN*), and more recently, a hexanucleotide repeat expansion in the first intron of *C9ORF72* are the most frequent causes of autosomal dominant familial forms of FTLD.

Aim: To describe the frequency of autosomal dominant mutations in patients with FTLD.

Methods: All patients underwent clinical and neuropsichological examination, as well as structural and functional brain imaging. Clinical diagnoses were done according to current criteria. *MAPT* and *GRN* mutations were detected by direct sequencing. The hexanucleotide expansion in *C9ORF72* was determined by repeated-primed PCR and subsequent sequencing.

Results: We screened 125 patients with FTLD patients (51 males and 74 females). Clinical diagnoses were: 96 behavioural variant Frontotemporal Dementia (bvFTD) and 29 Progressive Non Fluent Aphasia (PNFA). Six patients (4.8%) were carriers of *GRN* mutations leading to haploinsufficiency; one of them was diagnosed with PNFA, whereas remainders were diagnosed with bvFTD. One patient (0.8%), diagnosed with PNFA, was a carrier of a *MAPT* mutation, while 5 patients, all of which diagnosed with bvFTD, were carriers of the *C9ORF72* hexanucleotide expansion (4%). Patients with autosomal dominant mutations accounted for 9.6% of the total number of cases.

Conclusions: Our data suggest that the presence of an autosomal dominant mutation is a frequent cause of FTLD.

Frequency of the Chromosome 9 Hexanucleotide Repeats in Patients with Frontotemporal Lobar Degeneration

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Background: Aa hexanucleotide repeat expansion in the first intron of *C9ORF72* has been shown to be responsible for a high number of familial cases of amyotrophic lateral sclerosis or Frontotemporal Lobar Degeneration (FTLD) with or without concomitant Motor Neuron Disease (MND) phenotype and TDP-43 based pathology.

Aim: To analyze the frequency of the hexanucleotide expansion in a population of patients with FTLD (with or without MND)

Population and methods: DNA from 836 patients with FTLD (27 with concomitant MND) were collected. Analysis was done by Repeat-Primed PCR and sequencing.

Results: At present, 505 samples have been screened. Twenty six were carriers of the mutation (5.1%). Twenty of them were diagnosed clinically with behavioural variant Frontotemporal Dementia (bvFTD), 5 with bvFTD-MND (diagnosed initially with bvFTD and developing MND over time) and one with semantic dementia.

Conclusions: The hexanucleotide expansion in chromosome 9 is likely a common cause for FTLD, together with progranulin and tau mutations. Patients' follow up is ongoing to clarify whether the presence of this genetic defect is a prognostic biomarker predicting the development of MND in patients diagnosed with bvFTD.

Symptoms of Dementia Screener: Is it a Useful Questionnaire for Cognitive Impairment Screening?

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Background: Questionnaires on cognition can be useful to detect cognitive impairment.

Aim: To evaluate the Symptoms of Dementia Screener (SDS) (Mundt et al., 2000) as a valid tool for dementia screening**.**

Methods: We examined by a neuropsychological battery and daily living activity scales, 240 consecutive subjects who answered to SDS in a project for early screening for dementia. Criteria for MCI diagnosis were those of Petersen and for dementia were DSM IV and NINDCS-ADRDA criteria.

Results: 133 female and 107 male with mean age 69,44 yrs (±7.15), mean education: 7.61 yrs, (±3.51) were examined; 99 subjects received a diagnosis of MCI, 11 of dementia (D) and 130 of normal cognition (N). SDS showed significant worse result comparing D vs N and MCI and MCI vs. N. Discriminant analysis showed that in differentiating MCI vs. D, SDS had a discrete percentage of correct classification (76.4%); comparing D patients vs. N, SDS correctly classified all D patients and the 80.8% of N. On the contrary, comparing MCI and N the correct classifications were very low (58.1%).

Conclusions: SDS can be a useful tool in dementia screening, differentiating this condition both from normality and MCI; it is not completely useful in differentiating MCI from *N* subjects.

Methods of MCI Diagnosis: Which Differences?

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Background: Criteria for the diagnosis of Mild Cognitive Impairment (MCI) are debated in relation to the use of different methods.

Aim: To evaluate the percentage of the various subtypes of MCI, i.e., multiple domains (md) or single (sd) with amnesic (a) or not amnesic (na) impairment in relation to different diagnostic procedures.

Population and methods: We examined 260 consecutive MCI patients referred during a four years to our centres by an extensive neuropsychological battery.

Results: According to Petersen criteria based on 1.5 standard deviation (SD), we identified 38 MCI-a, 63 MCI-dm-a, 102 MCI-ds and 57 MCI-dm-na.. According to equivalent point (EP) criteria, we identified 26 MCI-a, 121 MCI-dm-a, 63 MCI-ds and 48 MCI-dm-na. Furthermore 2 patients did not show any deficit. Therefore, according to SD classification 38.8% MCI had memory impairment and 61.2% did had not, according to EP method, 57.0% had memory impairment and 43.0% did not; MCI-sd were 53.8% and MCI-md 46.2% by the first classification and by the second one 34.5% and 65.5% respectively. By chi-square the differences were highly significant ($p = 0.000$).

Conclusions: EP classification method increases diagnosis of MCI-md, especially of amnesic type. In both classifications MCI-a, represent a minority of the cases.

Neuroanatomical Correlates of Behavioral Disturbances in Frontotemporal Lobar Degeneration

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Background: Frontotemporal Dementia (FTD) is a neurodegenerative disorder characterized by behavioral disturbances and language impairment. At the onset, different combinations of behavioral changes may be present, as defined by clinical assessment (Frontal Behavioral Inventory, FBI).

Aim: To evaluate specific behavioral symptoms defined by FBI in a large FTD sample, and the correlation with perfusion pattern (rCBF).

Methods: 207 bvFTD patients entered the study. FBI was analyzed with a binomial model to group subitems into independent factors. In a subgroup of 102 patients a linear correlation analysis between

correlation coefficient for each factor and rCBF was performed.

Results: 4 independent factors, named "apathy", "disinhibition", "irritability" and "language" were identified. A significant relationship between apathy, euphoria and language and hypoperfusion in the frontal and temporal lobes was found ($p < 0.001$ uncorrected). Apathy correlated with hypoperfusion in right temporal lobe, limbic and anterior cingulate cortex, bilaterally; disinhibition involved left medial and superior frontal gyrus, while language correlated to hypoperfusion in left frontal and middle temporal gyrus. No significant correlation for irritability factor was found.

Conclusions: Different brain patterns of behavioral disturbances are present in FTD. The clinical evaluation could classify the different presentations, that are correlated with the involvement of specific brain regions.

A Case of Vanishing White Matter Disease due to the c.260C>T (p.Ala87Val) EIF2B3 mutation

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Background: Vanishing White Matter (VWM) is one of the most prevalent inherited childhood leukoencephalopathies. Initially described in children, the disease presents with cerebellar ataxia and less prominent spasticity. More recently it has became apparent that VWM has wider clinical spectrum than originally described, with age at onset inversely related to clinical severity. The initial clinical signs in adults consist of epileptic seizures, complicated migraine, presenile dementia and psychiatric symptoms. Many affected women experience a combination of leukoencephalopathy and primary amenorrhea or premature ovarian failure, a condition named ovarioleukodystrophy. Mutations in any of the genes encoding the 5 subunits of eucariotic initiation factor 2B (eIF2B1, 2, 3, 4 and 5) can independently cause VWM. More than 120 mutations have been reported to date; most reside in EIF2B5 and EIF2B2.

Aim: To describe a case of adult onset (VWM) disease due to the rare EIF2B3 mutation c.260C>T (p. Ala87Val).

Methods: Neurological examination, brain MRI, neuropsychological testing and DNA sequencing were performed.

Case report: The patient, a 66 years old woman, presented with progressive walking impairment associated with behavioural and cognitive disturbances, associated with primary ovarian failure (at 24 years of age). Neurological examination showed lower limbs hypertonia, spastic paraparesis, brisk reflexes, Babinski sign in the right foot, dysdiadochokinesia, and ideomotor apraxia. Mood deflexion was also present. Brain MRI T2-weighted images showed symmetric diffuse signal abnormality in the hemispheric white matter, sparing the U fibers; DWI images showed diffusion restriction; cortical subcortical atrophy was also reported. Neuropsychological testing showed planning, praxis and visuospatial memory deficits associated with less prominent abstraction and lexical retrieval impairment. DNA sequencing showed the presence of the EIF2B3 mutation c.260C>T (p.Ala87Val).

Conclusions: Here, we described the case of a 66 years old woman with a 5 years history of progressive walking impairment and cognitive decline associated with primary ovarian failure (at 24 years of age). The patient was a carrier of the rare EIF2B3 mutation c. 260C>T (p.Ala87Val.). This mutation was described only once before in literature in a childhood onset case. Our description enlarges the spectrum of phenotypic heterogeneity among patients with the same mutation.

Free and Cued Selective Reminding Test (FCSRT): A construct validity study

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Aim: To assess the construct validity of the Free and Cued Selective Reminding Test (FCSRT), an episodic memory task which controls for encoding and measures the sensitivity to cueing, proposed as a sensitive marker of the "hippocampal memory deficit" of early Alzheimer's Disease (AD) and as the core criterion for the diagnosis of "prodromal AD". We have developed an Italian version of the FCSRT.

Methods: The performance of 112 subjects with memory impairment (59 subjects with MCI) in FCS-RT measures (free and cued, immediate and delayed recall; index of sensitivity of cueing) was evaluated along with the results of other widely used memory tests (Rey auditory verbal learning test, story recall) and with other non-memory tools (Raven Coloured Progressive Matrices, semantic and phonemic fluencies, Rey complex figure copy, Stroop test, and trail making test).

Results and conclusions: Our results show that all FCSRT scores were correlated with the other memory tests scores (Pearson's $r \geq 0.45$ in all cases, $p < 0.0001$) and a high degree of correlation between free and delayed recall measures in all the memory tests used; a factor analysis identified three factors (memory, verbal fluency, executive functions) with all the FCSRT scores loading on the memory factor, independently from language and executive tasks.

Cortical Activation Correlates of Leuko-Araiosis. A fMRI and DTI Study

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Background: The term leuko-araiosis(LA) describes a common affection of the cerebral white matter(WM) of the elderly.

Objectives: We explored possible modifications of the cortical activation in 31 patients with LA of visually moderate or severe extension.

Methods: After measurement of the microstructural damage associated with LA, the patients were examined with functional-MRI during continuous tapping of the right dominant hand.

Results: After correction for behavioural variables, clusters of activation were observed in the left primary sensory-motor(SM1) cortex, bilateral supplementary motor area(SMA), left thalamus and vermis and cerebellar hemispheres. A single circumscribed area showing decreasing activation with increasing severity of the microstructural changes of the cerebral WM was observed in the left precentral gyrus. Conversely, multiple areas whose activation paralleled severity of the microstructural changes of the cerebral WM were present in the left and right precentral and postcentral gyrus, left proper and pre SMA and precuneus and in the right cerebellar hemisphere.

Conclusions: The combination of decreased or increased cerebralactivation in parallel with the severity of the microstructural damage indicates that differences in neuronal processing associated with LA is complex and entails both deafferentation and recruitment phenomenona. The predominance of the latter is consistent with an adaptive role for these changes.

Does Social Network Influence the Progression of MCI to Dementia?

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Aim: To examine the relationship between social network and the risk of progression of mild cognitive impairment (MCI) to dementia.

Methods: 176 MCI patients from the "Luigi Sacco" Hospital were included in the study and followed-up prospectively. Information on social network was obtained by personal interview at baseline. Specific elements of social network were assessed as follows: marital status was categorized as married versus single/widowed/divorced; living arrangement included living with someone or alone and social ties were categorized as close versus weak.

Results: During an average of 2.6 ± 1.9 years of follow-up, 92 (52.2%) out of 176 MCI subjects progressed to dementia. These subjects were older (75.7 ± 6.1 vs. 72.2 ± 8.2 years; $p = 0.001$) and more educated (8.5 ± 4.6 vs. 7.1 ± 3.6; $p = 0.03$) and had lower MMSE score (24.8 ± 2.6 vs. 26.0 ± 2.5; $p = 0.002$) and lower GDS score (8.4 ± 5.9 vs. 10.6 ± 6.3; $p = 0.02$) as compared to non-converters. Among patients who developed dementia APOEε4 genotype was more frequent (63.3% vs. 45.3%; $p = 0.045$). The multivariate analysis showed no association between each component of social network and the risk of progression to dementia.

Conclusions: To our knowledge, this is the first study specifically designed to assess if the richness of social network modifies the risk of progression to dementia in subjects with MCI attending a memory clinic. A poor social network does not increase the risk of progression from MCI to dementia.

GT1b-Liposomes and Amyloid β (1-42) Peptide: Studies of Binding and Effect on Fibril Formation

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Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that affects more than 15 million people worldwide. Accumulation of amyloid β peptide (1-42) ($A\beta_{1-42}$) in the brain to form oligomers, fibrils and plaques plays a central role in the onset and development of AD.

In the search of new diagnostic and therapeutic agents, it has been reported in our research group that gangliosides greatly bind $A\beta_{1-42}$. Moreover, some studies showed the reduction of CNS $A\beta_{1-42}$ after administration of gangliosides in the bloodstream.

Within this context, we prepared liposomes, that are biocompatible and non toxic nanoparticles, with GT1b ganglioside. The idea is that the binding affinity to the Aβ peptide would be higher relative to free GT1b, thanks to multivalency phenomena.

Binding experiments between $A\beta_{1-42}$ fibrils and liposomes performed using Surface Plasmon Resonance showed a good interaction, with Kd values of 125–150 nM, related to the exposed GT1b.

Moreover, GT1b-liposomes, at 250 μM, were found to inhibit fibril formation after 2 weeks by ThT and Congo red binding assay of 53% and 52%, respectively, compared to the peptide incubated alone.

The ability of GT1b-liposomes to bind $A\beta_{1-42}$ fibrils and to reduce their formation increases the interest on these nanoparticles as possible diagnostic and therapeutic agents.

Do Frontal Dysfunctions Play a Role in Visual Hallucinations in Alzheimer's as in Parkinson's Disease? A Comparative Study

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Background: Recent studies have demonstrated that non demented PD patients with Visual Hallucinations (VH) have lower frontal tasks score than those without VH.

Aim: To investigate whether also in AD patients the development of VH can be related to more severe frontal dysfunctions.

Population: 36 patients with AD (18 with VH) and 38 with idiopathic PD (19 with VH) were enrolled

Methods and Results: Statistic analysis performed for AD and PD patients, with presence of hallucinations (VH+, VH–) as a between-subject independent variable, showed that within the whole group of AD patients, the VH+ group scored significantly lower than the VH– group, whereas within PD patients VH+ and VH– did not show overall significant differences, but significantly differed on tests evaluating the frontal functions with lower scores for patients VH+.

Conclusions: These results demonstrate that in AD subjects an analogous neuronal cognitive mechanisms

is underlying hallucinations as in PD. A defective cholinergic circuitry of the prefrontal cortex is crucial to the genesis of hallucinations in PD, and this pathological condition should be also true for AD , where the cholinergic neurotransmission is the basic and very early defect.

Closing-in Phenomenon in Frontotemporal Dementia

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Background: Closing-in phenomenon (CIP) has been described as a tendency to draw in proximity to or to overlap to the model. This phenomenon has been usually described in dementia, especially in Alzheimer's disease. Recently, CIP has been reported also in fronto-temporal dementia (FTD) and interpreted as a primitive magnetic attraction of the hand towards salient visual stimuli.

Aim: In this study we investigated incidence and cognitive mechanisms of the CIP in FTD patients, by searching possible associations between CIP and other manual attraction behaviors.

Population and methods: We recruited 20 patients with diagnosis of FTD. After a comprehensive neuropsychological exam, all patients were required to perform a copying task and a special assessment to quantify manual approach behaviors (utilization and imitation behaviors).

Results: 13 (72%) patients showed evidence of CIP. Utilization behaviour was evident in 14 (70%) patients while imitation behaviour in 5 (25%) patients. The approach manual behaviors were associated to CIP in 3 (16%) patients.

Conclusions: Our results suggest that CIP in FTD patients is not strongly associated with other primate attraction behaviors. This would suggest that a defect of a specific motor control system is likely accountable for CIP in FTD patients.

Effects of Lexical-Semantic Treatment on Memory in Early Alzheimer Disease. An Observer-Blinded Randomized Controlled Trial

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Background: Episodic memory and semantic abilities deteriorate early in Alzheimer disease (AD). Since the cognitive system is made by interconnected neuronal networks, stimulation of semantic abilities may benefit semantically structured memory.

Aim: To investigate the effects of Lexical Semantic Stimulation (LSS) in patients with early AD. Unstructured Cognitive Stimulation (UCS) served as control condition.

Methods: Forty AD patients were randomized to receive LSS or UCS for 3 months, two sections a weak. The outcome measures were Mini Mental State Examination (MMSE), Boston Naming Test (BNT), Verbal Naming Test (VNT), Verbal Fluency, Story recall, Ray Auditory Verbal Learning (RAVL) and tests assessing executive functions, attention and visual-spatial abilities. A 6-month follow-up assessment was administered to the LSS group.

Results: LSS treatment yielded significant improvements of the MMSE, BNT, VNT, Story recall and RAVL delayed recall mean scores; working memory and the speed of a executive functions improved as well after LSS. UCS intervention did not improve any cognitive domain. Six months after LSS discontinuation, the MMSE mean score remains significantly higher than the baseline value.

Conclusions: LSS treatment may improve episodic memory in AD patients and may be regarded as a clinical option to counteract the cognitive decline of the disease.

Multidisciplinary Approach to MCI Help to Evaluate Risk of Convertion in AD

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Background: People with Mild Cognitive Impairment (MCI) could be considered at higher risk to convert to Alzheimer's disease (AD), but the progression rates are strongly variable and it is difficult to predict which patients will develop the disease.

Aim: We set up a prospective cohort study using a multidisciplinary approach (genetic, neuropsychological and functional neuroimaging) with the aim of identifying a pattern that results in clear risk of conversion. We evaluated ten MCI patients.

Methods: All subjects received Apolipoprotein E (ApoE) genotyping, a thorough neurological and neuropsychological examination and a (18)F-FDG PET, both at baseline and follow-up examination.

Results: After an average interval of 12 months, six patients head for a worsening of cognitive impairment and three of them, which developed AD, were considered as converters MCI. Four patients were classified as stable MCI. 60% (3/5) of amnesic mild cognitive impairment (a-MCI) went through a clinical decay. All (2/2) multidomain mild cognitive impairment (md-MCI) converted to AD. Only one of three non amnesic MCI (na-MCI) showed a cognitive decline, however without converting to AD. MCI patients showed a lower glucose metabolism in AD-typical regions such as precuneus/ posterior cingulate cortex. Converters MCI patients demonstrated an additional greater reduction of cortex glucose metabolic rate in left inferior parietal lobule and lower temporal lobe. Finally abnormalities in cortex glucose metabolism in the left precuneus are much more remarkable in MCI ApoE e4 carriers.

Conclusions: The classification of MCI patients by several point of view such as neuropsychological, genetic and functional neuroimaging seems to be the only method to obtain a reliable risk profile of conversion.

Different Patterns of Verbal Fluency Performance in Mild Cognitive Impairment and Alzheimer's Disease

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Background: Alzheimer Disease (AD) patients and subjects with Mild Cognitive Impairment (MCI) show significant deficits in verbal fluency with greater impairment on category (semantic) tasks. According to literature producing nouns and objects should be selectively impaired in these patients. Furthermore controversial results are present in literature and most of the studies examined only amnestic MCI (aMCI).

Aim: We investigated the different forms of verbal fluency (category, letter and grammatical) in a group of AD, aMCI, non-amnestic MCI (naMCI) and healthy controls.

Population and methods: Ten subjects affected by probable AD, 20 MCI (10 aMCI and 10 naMCI) and 10 healthy age and education matched controls were consecutively enrolled. The different forms of verbal fluency where examined administering phonemic, category and grammatical fluency tasks.

Results: AD patients performed significantly worse than controls in all the fluency tasks. A statistically significant difference was observed between controls and aMCI only in the category fluency tasks, sparing letter and grammatical fluency. No significant differences were observed between naMCI and controls.

Conclusions: Our study reveals an early decline of semantic memory in aMCI which could be of diagnostic and predictive value. However only the category fluency seems to be impaired.

Cortical Metabolic Deficits in a Rat Model of Cholinergic Basal Forebrain Degeneration

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Background: Evidences indicate that degeneration of the basal forebrain cholinergic system may represent an important factor underlying the progressive cognitive decline characterizing Alzheimer's Disease (AD). However, the nature of the relationship between

cholinergic depletion and AD symptoms is not yet fully elucidated.

Aim: To investigate the metabolic activity of several cortical areas in presence of cholinergic depletion in order to clarify the relation between deficits in cerebral energy metabolism and degeneration of cholinergic system.

Methods: In cholinergically depleted rats, we evaluated the neuronal metabolic activity assaying cytochrome oxidase activity in frontal, parietal and posterior parietal cortices at three different time-points from the lesion.

Results: Depletion of cholinergic cells in the basal forebrain induced a decrease of metabolic activity in all analyzed areas, even when the cholinergic degeneration was still incomplete.

Conclusions: These experimental findings support the link between metabolic deficit and cholinergic hypofunctionality which characterizes AD pathology. The present model of cholinergic hypofunctionality provides a useful means to study the complex mechanisms linking two fundamental and interrelated phenomena characterizing AD from the early stages.

Motor Deficits in Aphasia: Evidence from Knots

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Background: Patients with the nonfluent variant of Primary Progressive Aphasia (PNFA) have selective difficulties in producing and understanding syntactically complex sentences. Experimental evidence suggests that, besides grammatical analysis, frontal lobe's language areas play an important role in encoding human actions. According to this hypothesis, speech and hand actions might share similar syntactic structures.

Aim: Tying knots can be a task to test the ability of PNFA non-apraxic patients in organizing and understanding the particular pattern of manual actions with procedural rules.

Methods: We selected a group of 9 patients with aphasic disorders of neurodegenerative nature. Subjects (3 with PNFA, 3 with Semantic Dementia and 3 with Frontotemporal Dementia, according to the latest diagnostic criteria), as well as matched neurologically healthy controls, were asked to tie 8 knots after a previous demonstration and performances were compared among the 3 groups. *Results*. All and only PNFA patients had great difficulties in reproducing the "reef knot", a peculiar knot that commits both hands simultaneously and whose procedure is a misleading palindromic sequence of actions.

Conclusions: This result, yet to be confirmed by examining more patients, could indicate an impairment in PNFA in processing non-linguistic complex structures, suggesting a common neural basis for syntactic processing.

Neuropsychological Correlates of Right and Left Progressive Parietal Syndromes

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Background: "Progressive Parietal Syndromes" (PPS) are a neurodegenerative condition characterized by a gradual, prevalent impairment of visuo-spatial or praxic abilities. Some of these cases present with an asymmetric involvement of the left and right parietal lobes.

Aim: To compare the neuropsychological profile of patients with Left versus Right PPS.

Population and methods: We enrolled 14 consecutive patients with PPS (10 received a diagnosis of PCA, four of CBS and one of LBD), and with PET or SPECT evidence of predominantly Right ($n=7$) or Left ($n=9$) parietal dysfunction.

Results: The two groups showed a similar pattern of performance in non-parietal cognitive domains. The severity of visuo-perceptual deficits was also comparable. Controlesional visual neglect was present in 57% of Right patients and 22% of Left patients. Overall, limb apraxia was slightly less prevalent in Left (78%) than Right (86%) patients. The former group exhibited more frequently bilateral ideomotor apraxia, while in the latter group controlateral distal movements were more affected, possibly suggesting melokinetic apraxia.

Conclusions: This is the first formal comparison of the cognitive profile of left and right progressive parietal syndromes. While some finding was expected, some other (e.g. visuo-perceptual impairment) was unpredictable on the basis of current knowledge of cognitive topography.

A Case of Progressive Supranuclear Palsy

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Background: Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by mild dementia, postural instability and supranuclear ophthalmoplegia.

Case report: we describe a 59-year-old woman, suffering from diabetes and high blood pressure, referred to neurologist for worsening apathy and gait disturbance. She had an history of mood depression since 10 years, treated by psychiatrist with good response. In the last two years she developed walking instability with recurrent falls, during two of which she fractured an arm and a leg. Neurological examination showed hypomimia, gait slowness with short steps, slowness in vertical gaze and slight rigidity to the right arm. Neuropsychological evaluation showed deficits in attention, executive and visuospatial functions in addition to mild-to-moderate apathy and loss of drive. A lower glucose metabolism was detected by (18)F-FDG PET in both frontal and temporal-occipital lobes, as well as in the brainstem, mainly in the midbrain. RMN revealed normal imaging finding. Finally DAT SPECT indicated a decreased uptake of the radioligand in both putamen.

Conclusions: all of these findings match with the criteria for possible PSP even if the onset of disorder could be confused with a worsening of mood disturbance in a patient with history of depression.

Immunotherapy Clinical Trials in Alzheimer's Disease: Challenges Related to Recruitment and Retention of Patients

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Background: Beta amyloid (Aβ) is an opportune target for different therapeutic strategies in Alzheimer's disease (AD). Immunotherapy, that increase clearance of Aβ, became a promising therapy for AD and many clinical trials based on several vaccines are currently ongoing.

Aim: Our aim was to analyze critical aspects on enrolling patients in AD clinical trials based on immunotherapy.

Methods: Patients with mild to moderate AD were screened for the randomization in clinical trials aimed to investigate safety, tolerability and efficacy of some vaccines. All patients underwent a full revision of clinical criteria for AD, pre-existing conditions, comorbidity, concomitant medications, brain magnetic resonance (MRI) features.

Results: Of 43 screened patients, 4 were not included because of medical general conditions, 4 could not perform instrumental examination, 2 had revised diagnosis, 4 showed microhemorrages on MRI, and 2 patients revoked informed consent. Of 27 included patients, 1 had adverse events not compatible with study prosecution, 1 revoked informed consent after six months. One patient, after trial completion, could not be included in extension study.

Conclusions: In AD clinical trials based on immunotherapy a careful patient selection is a basic prerequisite for study prosecution and for restriction of study-related adverse events.

Validation of the Italian Addenbrooke's Cognitive Examination Revised (ACE-R) as a Screening Test

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Background: Mini Mental State Examination (MMSE) is currently the most frequently clinical instrument used to determine global cognitive state. The Addenbroke's Cognitive Examination Revised (ACE-R) offers the possibility to evaluate an increased number of cognitive domains involved in executive functions, visuo-spatial abilities and language, mainly altered in patients with Frontotemporal Lobar degeneration (FTLD). The Verbal fluency, Language,

Orientation and Memory (VLOM) Index is useful to obtain differential diagnosis between FTLD and Alzheimer's disease (AD) in the early stages.

Aim: To validate the Italian ACE-R, including VLOM index, in order to create an assessment instrument to distinguish between normal and pathological cognitive functioning. We aim to obtain normative data of ACE-R in a wide population of Italian subjects with age between 35 and 85, and schooling years between 0 and 18 years.

Methods: To administer the test and evaluate the independent effect of age and years of education on the average score in this population with a multiple linear regression model.

Results: Thirty subjects have been evaluated so far (15 males and 15 females; mean age 55, mean schooling: 13 years). Subjects aged 50 or less scored 95/100, whereas older individuals had borderline scores. Scores were correlated with schooling.

Discussion: Preliminary results show a correlation between performances and years of schooling and age. ACE-R results will be available after completing statistical analysis through linear regression model.

Brain Computer Interface and Eye-Tracking for Neuropsychological Assessment of Cognitive Functions in Amyotrophic Lateral Sclerosis

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Background: The cognitive assessment in Amyotrophic Lateral Sclerosis (ALS) patients still remains a critical issue, because of their severe physical disabilities, interfering with the outcome of traditional neuropsychological testing. No studies have been performed so far to evaluate Brain Computer Interface (BCI) and Eye-Tracking (ET) systems both as augmentative and alternative communication (AAC) devices and cognitive assessment tools in ALS.

Aim: The objective of the "eBrain: BCI-ET for ALS" project was to explore the possible development of a neuropsychological battery based on the integration of BCI and ET tools, also providing evidences for their effectiveness and usability.

Methods: Eight healthy volunteers subjects (4 females, 4 males) were assessed with a Verbal Fluency Test for both techniques. Moreover, AAC and usability of both instruments have been evaluated with an ad hoc questionnaire.

Results: Results showed a good usability of both instruments, better for ET, but promising for BCI too. As expected, BCI calibration was a critical issue. The average score obtained after the calibration process was 89.73%, leading to an accuracy of BCI system during the tests of 81.72% (i.e. 18.28% of errors).

Conclusions: These preliminary results may have interesting implications for both ALS patients clinical management and ethical issues.

Neuropsychological and Neuroimaging Correlates of Visuospatial Impairment in Mild Cognitive Impairment

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Background: Spatial abilities decline in normal aging and decrease faster and earlier in Alzheimer's disease (AD). Although episodic memory impairment was universally accepted as a core symptom in AD, spatial deficits were under investigated.

Aim: The main goal of this study was to assess visuospatial functions in the predementia stage of AD (MCI), in order to verify whether these tasks might be valid cognitive markers in subjects at risk to develop dementia. We also aimed to find a possible neuroimaging correlation of visuospatial deficits.

Population and Methods: Twenty MCI patients (ten females and ten males) and fourteen healthy controls

(ten females and four males) were included in this study. All participants underwent to an extensive neuropsychological assessment including standard and experimental spatial tests, and MRI brain scanning.

Results: MCI patients had significantly worse performance in almost all cognitive domains and visuospatial abilities specifically resulted to be impaired in MCI. Patients presented a different pattern of correlation between grey matter density and visuospatial performance, such as the involvement of more distributed areas of the frontal cortex for the execution of visuospatial tasks.

Conclusions: Visuospatial functions and brain networks implicated in their organization are impaired in MCI.

NeuroPsychological Training (TNP) in MCI Subjects: One Year Follow-up Study

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Background: Mild Cognitive Impairment (MCI) subjects have high risk of progressing to a dementia disorder and identifing early treatment is an important clinical objective. Few studies investigated benefits of neuropsychological training in MCI subjects.

Aim: The aim of this pilot study is to examine the efficacy and long term benefits at 1 year follow-up of NeuroPsychological Training (TNP) in subjects affected by MCI.

Methods: Neuropsychological features of 70 subjects with clinical diagnosis of MCI were analysed in oneyear retrospective comparison study: 45 subjects were randomized to receive TNP; 25 subjects did not receive treatment.All subjects without training underwent a multidimensional evaluation concerning neuropsychological, behavioral and functional features, at baseline and at one year follow-up. All TNP subjects underwent the same evaluation at baseline and after the training and twenty of these were also evaluated at one year follow-up.

Results: The two groupsdid not differ for demographic characteristics, cognitive functions and behavioural characteristics. MCI subjects without training maintained their cognitive, behavioral and functional status after one year follow-up. TNP subjects showed improvement in memory and in executive functions after training and this improvement remained evident at one year follow-up. After one year follow- up, TNP subjects showed also a significant reduction of anxiety and depressive symptoms.

Conclusions: TNP could determine a long-term positive effect on cognitive and mood disorders in patients affected by MCI.

Contribution of Neuropsychological Evaluation in Diagnosis of Tauopathies: A Single Case

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Background: Progressive Supranuclear Palsy (PSP) is the second most common form of parkinsonism after Parkinson's Disease. It pathologically belongs to tauopathies and it is clinically characterized by a severe atypical parkinsonism associated with typical neuropsychological involvement. Diagnosis of PSP is clinical, but usually neurologists make use of different exams, like morphologic or functional imaging, to dismiss similar pathologies.

Aim: To evaluate the contribution of neuropsychological assessment in diagnosis of PSP.

Methods. A 74 years old woman with clinical manifestation characteristic of PSP had a RMI of the brain showing severe diffuse cortical atrophy without a clear troncoencephalic involvement. Patient underwent to a complete neuropsychological battery.

Results: The most common abnormal behaviors are logopenia and apathy, both assessed by Frontal Behavioural Inventory. Neuropsychological assessment showed both slow motor responses and information processing speed, severe impairment of executive dysfunction. The combination of severely slowed information processing and marked executive dysfunction are characteristic of PSP and differentiates it from other dementias.

Conclusions: Neuropsychological evaluation could give a significant contribution in the diagnosis of PSP, particularly when clinical and imaging assessment are not in agreement. Neuropsychological tests should be part of neurological examination in PSP, to facilitate diagnosis and to quantify the deficit.

Mild Cognitive Impairment and Cognitive-motor Relationships in Newly Diagnosed Drug-naïve Parkinson's Disease Patients

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Aim: 1) to establish the prevalence of Mild Cognitive Impairment (MCI) in newly diagnosed drug-naive patients with Parkinson's disease adopting preliminary research criteria and 2) to investigate the relation between cognitive performances, MCI and motor dysfunction.

Population and methods: 121 consecutive newly diagnosed drug-naïve PD patients and 100 healthy controls (HC) underwent a neuropsychological evaluation. Moreover, on the basis of the UPDRS II, III, different motor scores were calculated and patients were classified in motor subtypes.

Results: MCI prevalence was higher in PD (14.8%) in comparison to HC (7.0%); PD reported lower cognitive performances in comparison to HC in several cognitive domains; MCI-PD patients presented a more severe bradykinesia score in comparison to non-MCI PD patients and patients mainly characterized by tremor had better performances in some cognitive domains and specific cognitive-motor relationships emerged.

Conclusions: Newly diagnosed drug-naive PD patients present a higher risk of MCI. Axial symptoms and bradykinesia represent a risk factor for MCI in PD patients and a classification of PD patients that highlights the presence/absence of tremor is probably be more tailored for the early stages of PD.

Circulating Lymphocytes as Possible Diagnostic Markers in Patients with Frontotemporal Dementia-Frontotemporal Lobe Degeneration

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Background: The clinical assessement identifies patients with frontotemporal dementia but frequently it is can not predict the type of frontotemporal lobe degeneration (FTLD) of individual patients. FTLD encompasses 3 groups based on the immunohisto-chemical profile: FTLD-tau, -TDP-43, -FUS. Biomarkers reflecting the specific neuropathologicalfeatures could be crucial for the prediction of FTLD type during life and for future targeted treatments. In patients with amyotrophic lateral sclerosis (ALS) the cytoplasmic location of TDP-43 protein from lymphocytes mirrors the specific motor neuron pathology. Also In FTLD-TDP type, TDP-43 protein accumulates in neuronal cytoplasm.

Aim: To determine whether the pattern of TDP-43 from lymphocytes of FTD patients points out the patients with FTDL-TDP, versus the other types of FTLD and other types of dementia.

Population and methods: TDP-43 was extracted from circulating lymphocyte of 10 patients with FTD; the subcellular distribution was analyzed by western immunoblot and immunocytochemistry. Ten healthy subjects and ten demented patients with non-FTD clinical diagnosis were the control groups.

Results: In lymphocytes of three FTD patients the TDP-43 protein was abnormally localized in the cytoplasm; in the other FTD patients, and in the control patients TDP-43 was normally localized in the nucleus.

Conclusions: It is possible that the abnormal cytoplasmic localization of TDP-43 of lymphocytes found in a subgroup of FTD patients mirrors the neuronal pathology and is a marker of FTLD type. Only the neuropathologicalassessementwill validate the diagnostic role of these results.

Neuropsychological Correlates of Behavioural Symptoms in Alzheimer's Disease, Frontotemporal, Vascular and Levy Body Dementias: A Comparative Study

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Background: Cerebral areas involved in Alzheimer's disease (AD), Frontotemporal (FTD), Lewy-body (LBD) and Vascular (VD) dementia are responsible of different cognitive impairment in these pathologies. Also different profiles of behavioural changes (BPSD) characterise these syndromes[2].

Aim: To investigate neuropsychological correlates of BPSD in these forms of dementia.

Methods: Subjects: Twenty-one frontal variant FTD, 21 LBD, 22 AD and 22 VD patients with a comparable dementia severity were included. *Neuropsychological evaluation*: Memory (Delayed recall of 15Word-list; Prose); praxis (Copy of drawings); reasoning (Raven's PM) executive functions (Phonemic Verbal Fluency; WCST- Criteria). *Behavioural assessment*: Neuropsychiatry Inventory (NPI; 10 items).

Results: Regression analyses in which behavioural disturbances were in turn the dependent variables and age, education, membership and the 6 neuropsychological scores were the independent variables, showed that the LBD membership predicted Delusions ($beta = 0.262, p = 0.02$) and Hallucinations ($beta = 0.555$, $p < 0.001$); the FTD membership predicted Euphoria ($beta = 0.35$, $p = 0.002$), Disinhibition ($beta = 0.625$, $p < 0.001$) and Aberrant Behaviours ($beta = 0.265$, $p = 0.02$); the FTD membership and WCST criteria predicted Apathy ($beta = 0.403$, $p < 0.001$ and $beta = -0.359$, $p = 0.001$ respectively). No variables predicted Depression, Agitation, Anxiety and Irritability.

Conclusions: Cognitive and behavioural symptoms are independent dimensions of the dementia syndromes. The syndrome of apathy follows to a damage of frontal cortical areas also implicated in set-shifting aptitude.

Influence of Controlled Encoding and Retrieval Facilitation on Memory Performance in Patients with Different Profiles of Mild Cognitive Impairment

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Background: Memory tests facilitating encoding and retrieval of memorandum differentiate deficits due to executive impairment, as in frontal circuits pathologies, from consolidation problems due to mesiotemporal structures involvement.

Aim: To evaluate the contribution of strategic and consolidation components to memory performance in patients with different profiles of Mild Cognitive Impairment (MCI).

Methods: *Subjects*: 8 non-amnesic MCI (naMCI), 16 amnesic single-domain MCI (aMCIsd), 9 amnesic multiple-domain MCI (aMCImd) and 20 normal subjects (NC). *Memory evaluation*: 15word-list: Delayed recall; Grober-Buschke procedure(GBp): Free and Cued delayed recall.

Results: At 15word-list and GBp Free recall naMCI and NCs performed similarly and better than aMCImd and aMCIsd ($p < 0.01$ in all comparisons) who did not differ one each other. At GBp Cued recall aMCImd, naMCI and NCs performed comparably and better than aMCIsd ($p < 0.01$ in all comparisons). NCs obtained an Index of cueing (IC) higher than aMCImd ($p = 0.03$) which in turn were better than aMCIsd ($p = 0.002$); naMCI did not differ either from NCs and aMCImd.

Conclusions: Both strategic and consolidation memory abilities are preserved in nmMCI; differently aMCIsd and aMCImd are impaired in both the strategic and consolidation memory aspects. aMCImd partially compensated memory deficit with assisted encoding and retrieval while aMCIsd did it very poorly.

Interplay Between Immunity, Neurodegeneration and Endothelial Perturbation in Alzheimer's Disease Patients

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Background: The interplay between innate immune response and protein misfolding may play a key role in neurodegenerative diseases. Deposition of amyloid beta (Abeta) in the walls of capillaries, arteries and arterioles, known as CAA, is an important factor in the severity of Alzheimer's disease (AD), as it provokes endothelial degeneration, affects cerebral blood flow, and enhances neuroinflammation. Thus, cerebral vessel endothelium could be considered as the critical locus of interaction between neuronal death and vascular perturbation in AD brain, wherein immunity

and endothelial damage may show functional overlaps. Focusing on these mechanisms became very crucial in order to decrease brain damage and determine neuroprotection not only in AD-related memory loss, but also in other diseases where a safely modulation of protein accumulation is fundamental, such as in CAA. Accordingly, we recently demonstrated that Tissue Factor Pathway Inhibitor (TFPI) should be a suitable marker of endothelial perturbation in AD, increasing up to 60% compared to healthy controls.

Aim and results: Since TFPI, like the naturally occurring antibodies against Abeta, has been found to be associated to senile plaques and activated microglia in AD brains, here we will show their relations with neurodegeneration and Abeta toxicity, and candidate their evaluation as future biomarkers during the ongoing disease modifying therapies in AD.

Prospective Memory in MCI, Alzheimer Disease and Subjective Cognitive Complaints Subjects

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Background: Prospective memory has been previously evaluated in Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) but not in Subjective Cognitive Complaints (SCC) patients.

Aim: To evaluate Prospective Memory (PM), by means of Memory-for-Intentions-Screening-Test (MIST) in SCC, MCI and AD patients.

Methods: We investigated neuropsychological function, affective-state and PM in 121 consecutive patients.

Results: We examined 31 AD, 55 MCI, 22 SCC, comparing them with a control group matched for sex, age and education. Evaluating PM by GLM multivariate with Bonferroni correction and using age and education as covariates, we found that AD group was significantly worse than the other groups in the main scores ($p < 0.00$). MCI group had significant worse results than controls, but not in respect to SCC, both in the Total-PM Score ($p < 0.02$) and in the 24-hours-PM Score ($p < 0.01$). AD group was significantly worse in respect to the other groups also in the Recognition PM Score ($p < 0.00$).

Conclusions: Our MCI group did not significantly differ from SCC in PM evaluation. The prospective component of PM is significantly impaired both in MCI and AD, while the retrospective component is significantly worse in the AD group than MCI.

Multidisciplinary Diagnostic Approach in a Case of Progressive Non Fluent Aphasia

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Background: Progressive nonfluent aphasia (PNFA) is one of three subtypes of primary progressive aphasia (PPA) with the semantic and logopenic variant. The PNFA can be the first manifestation of Frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), Corticalbasal degeneration (CBD) and Progressive supranuclear palsy (PSP).

Aim: To describe the diagnostic process in a case of NFPPA using neuropsycological assessment combined with CSF biomarkers, MRI and SPECT DAT-SCAN, to improve the ability to accurately predict the underlying neurodegenerative disease.

Methods: We used neuropsychological evaluation, SPECT DAT-SCAN, Perfusional SPECT, EEG, MRI, CSF biomarkers.

Results: The neuropsychological evaluation showed a PPA, apraxia of speech, ideomotor apraxia and mild memory impairment. Perfusional SPECT showed asymmetric ipoperfusion of left emisfhere of cortex (aspecific finding FTD, CBD or PSP). Negative SPECT DAT-SCAN excluded the CBD and PSP. CSF biomarkers (we are waiting for the result) will differentiate FTD from AD.

Conclusions: Multidisciplinar approch with neuropsycological investigation combined with CSF biomarkers and DAT SCAN SPECT can make to have a correct diagnostic framework of PPA *in vivo*.

Progranulin Plasma Levels and Alzheimer's Disease

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Background: Recent studies have demonstrated that some Progranulin (PGRN) allelic variants could be associated with Alzheimer's disease (AD). An influence of PGRN genetic variability on susceptibility to AD and on its expression levels in Peripheral Mononuclear Cells and in cells isolated from cerebrospinal fluid was observed, as well. Moreover, PGRN has been found to have implications in the sexual differentiation of the brain. In neonatal male mouse, androgen dependent up-regulation of PGRN expression in the hypothalamus is associated with the phenotypic biological development of the sexual differences.

Aim: To detect PGRN plasma concentrations in AD patients and healthy controls.

Population and Methods: The 214 subjects of this study included AD patients and relative controls. Plasma levels of PGRN were measured, using an ELISA kit according to manufacturer's instructions.

Results: A significant gender difference in plasma PGRN expression levels was observed in AD patients, with higher levels in females compared to males. Moreover, in an exploratory analysis performed on subgroups, by age and gender; PGRN levels increased in females with the age, in particular in AD group.

Conclusions: Our preliminary data suggest a possible influence of gender on PGRN expression in plasma of AD patients.

Risk and Determinants of Dementia in Patients with Mild Cognitive Impairment and Brain Subcortical Vascular Changes: A Study of Clinical, Neuro-Imaging and Biological Markers. The VMCI-Tuscany Study: Rationale, design and Methodology

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Background: Clinical expression of cerebral small vessel disease (SVD) is not fully explained by severity of lesions as depicted by conventional MRI. Advanced neuroimaging techniques might help to better understand the brain changes underlying SVD.

Aim: The VMCI-Tuscany Study is a multicenter, prospective, observational study aimed to: 1) estimate the role of clinical, neuro-imaging, and biological markers of SVD as independent predictors of the transition from vascular mild cognitive impairment (VMCI) to dementia; 2) assess the relative contribution and possible interaction of vascular and degenerative components; 3) generate a diagnostic algorithm able to determine the individual risk of transition.

Methods: Three-hundred-thirty patients affected by VMCI with SVD will be enrolled, assessed and followed-up for 2 years according to the study protocol: clinical, functional and neuropsychological assessment, MRI, laboratory. Data collected will be entered into an electronic database on the www.wmci-tuscany.it web site. Dementia and subtypes will be the main study outcome.

Results: Since February 2011, 88 patients (mean age 75.1 ± 7.1; 51 males) have been enrolled.

Conclusions: Knowledge about determinants of the transition to dementia in patients with VMCI and SVD is essential for the identification of preventive and therapeutic targets, contributing to reduce the burden of disability in the elderly.

Successful treatment of impulse control disorder in a patients with bvFTD using topiramate plus SSRI drug

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Background: Behavioural variant of Frontotemporal Dementia (bvFTD) may present with compulsive-ritualistic and abnormal eating behaviours.

Aim: To describe a case of bvFTD presenting with Compulsive Smoking (CS) followed by Binge-Eating Disorder (BED) responsive to low-dose topiramate.

Case description: A 64-year-old woman, admitted to our Memory Clinic for cognitive impairment and behavioural disorder characterized by impulsivity, apathy and anxiety, was used to smoke more than 60 cigarettes per-day. She had been treated with duloxetine (90 mg/die) and perfenazin (2 mg/die) without benefit. Neurological examination revealed axial rigidity and bradykinesia. Brain MRI showed no focal atrophy, while brain SPECT demonstrated a hypoperfusion in the anterior cingulate and left dorsolateral-frontal cortex. Deficits of attention and executive functions were detected, while verbal and visual memory was preserved. Drug therapy was changed to fluoxetine (60 mg/die) and bupropion (300mg/die), latter stopped for excessive sedation. Treatment with SSRI was successful in reverting CS. However, the patient developed BED with significant weight-gain (15 kg/2months). We added aripripazole (10 mg/die), later reduced and stopped for lack of benefit. Using low-dose topiramate (50 mg/day) we obtained rapid BED resolution.

Conclusions: Abnormal eating disorder, a feature of impulse-dyscontrol, is a distressing and resistant condition. Topiramate may represent a successful treatment of BED through a glutamate-antagonism mechanism.

A Case of Familiar Alzheimer Disease associated with the rare PSEN2 Mutation M239I

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Background: Mutations within PSEN2 represent the rarest cause of autosomal dominant Familiar Alzheimer Disease (FAD) with thirteen pathogenic mutations reported.

Aim: To describe a case of FAD carrying the PSEN2-mutation M239I.

Case Report: A 52-year-old woman was seen for cognitive deficits started at the age of 50 with forgetfulness and apathy. She had a familiar history for dementia (the father and three uncles). At neurological examination she had mild hands postural tremor with subtle myoclonic-like fingers jerking. Extensive blood tests were unremarkable. Cognitive impairment (MMSE: 24/30) with episodic memory, executive and visual-spatial abilities, and semantic fluency deficits was detected. Brain MRI showed no cortical or hippocampal atrophy, and SPECT revealed hypoperfusion of the right parieto-temporal lobe and frontal cortex bilaterally. Although on anti-dementia drugs, she had a rapid cognitive decline (MMSE 13/30 at age 55). After a follow-up of 10 years, the patient presents extrapyramidal rigidity, myoclonic jerks of the arms and mutacism. Pathogenic PSEN2 mutation was detected within exon7, leading to substitution from methionine-to-isoleucine at residue 239. No mutations in PSEN1, APP, PGRN and MAPT genes were found. She was homozygous for *ApoE*ε3 and PRNP-metionine-129.

Conclusions: This is the second report of FAD carrying the pathogenic M239I-PSEN2 mutation.

Nature Versus Nurture in Frontotemporal Lobar Degeneration: The Interaction of Genetic Background and Education on Brain Damage

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Background: Frontotemporal Lobar Degeneration (FTLD) is a progressive neurodegenerative disorder with a strong genetic background. It has been reported that modifiable factors, i.e. education might act as proxies for reserve capacity.

Aim: To evaluate the impact of genetic background (measured by a positive family history) on cognitive reserve measuring rCBF correlates in FTLD patients.

Population and methods: 145 FTD patients entered the study and underwent a clinical, neuropsychological and behavioral assessment, as well as a SPECT ECD study. The main effect of education and family

history on rCBF in FTLD was evaluated. To test the potential interaction between the two factor, a difference of slope analysis was made. Clinical Dementia Rating Scale (FTD-CDR) was considered as nuisance variable.

Results: A main effect of education (E+<E–) in frontal region bilaterally, was present in FTLD patients. High genetic loading in FTLD patients (FH+<FH–) was associated with a greater hypoperfusion in posterior and subcortical regions, bilaterally. By slope analysis, greater hypoperfusion of cingulated region in FH+ as compared to FH– was demonstrated.

Conclusions: Cognitive reserve mechanisms are available also in presence of an unfavorable genetic status. However, these compensative mechanisms were at least partially modulated by the interaction between environment and genetic profile.

Identification of the Causative Gene of FTLD in a Southern Italian Isolated Population

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Background: Patients with fronto-temporal lobe dementia (FTLD) show most frequently mutations in Microtubule Associated Tau Protein (MAPT) on chromosome 17q21.31, in the closeby Progranulin (PGNR) gene, in Charged Multivescicular Body Protein 2B (CHMP2B), Valosin-Containing Protein (VCP), WD Repeat Domain 40A (WDR40A) and Ubiquitin Associated Protein 1 (UBAP1).

Aim: To identify the causative gene of FTLD in a southern Italian isolated population.

Methods: We identified a geographic area in Southern Italy (Longobucco) with a strong enrichment of FTLD prevalence up to 10% in people over 65 years. Trough church and public archives we were able to reconstruct a seven generation pedigree in 11 affected subjects. After exclusion by mutation analysis of involvement of the already described causative genes, we performed a parametric and non paramertric linkage analysis by Merlin using data generated with Illumina 317 k SNPs bead-chip.

Results and conclusions: The results showed 9 loci that reached suggestive linkage. Massive sequencing of the exons of genes in these loci did not identify a causative mutation that would have explained the FTLD phenotype. Therefore, we have planned to sequence the exome of 5 pedigree patients in order to check for mutations in genes that are not in the identified loci and in genes that were not sufficiently covered by the previous sequencing efforts.

Insulin Sensitivity is Impaired in Frontotemporal Lobar Degeneration

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Background: Recent data demonstrate pivotal roles for brain insulin resistance and insulin deficiency as mediators of cognitive impairment and neurodegeneration. In literature, an impairment of central insulin signalling has been shown to play a key role in Alzheimer's disease (AD), while its involvement in frontotemporal lobar degeneration (FTLD) has not been deepened yet.

Aim: The purpose of this study was to investigate the role of insulin resistance in FTLD, and to compare insulin resistance/sensitivity indices among FTLD patients, AD patients, and healthy controls.

Population and methods: Twenty-two FTLD patients (10 men, 12 women, mean age ± SD = 62.3 ± 4.7 yrs) and twenty-five AD patients (14 men, 11 women, mean age ± SD = 66.5 ± 5.7 yrs) were selected for the study and compared with a group of 24 (12 men, 12 women, mean age ± SD = 65.3 ± 5.4 yrs) healthy subjects. Patients and controls underwent a standardized 75 g oral glucose tolerance test (OGTT). Several indices of insulin resistance/sensitivity were calculated.

Results: During OGTT, plasma glucose concentrations were significantly higher than controls in both FTLD and AD patients. Intriguingly, plasmatic insulin concentrations showed two different patterns in AD

and FTLD patients, with a delayed hyperinsulinemic response to glucose administration in FTLD. Indices of insulin resistance/sensitivity were significantly, though differently, altered in both group of patients.

Conclusions: Our preliminary data supports the hypothesis that, in addition to AD, insulin resistance plays a role also in FTLD pathogenesis. Additional studies in different populations are needed to confirm our findings.

Predicitve Value of CSF Biomarkers for Alzheimer's Disease in a Cohort of Patients with Mild Cognitive Impairment

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Background: There is a growing interest in identifying Alzheimer's disease (AD) at the early stages (mild cognitive impairment, MCI). Amnestic MCI patient presents a high risk of conversion to AD, while non-amnestic MCI may also convert to other forms of dementia.

Aim and methods: 88 patients (49 females and 39 males; mean age 68.3 ± 8.2 yrs) were recruited at the Department of Neuroscience, University of Torino. All patients were diagnosed with MCI, 42% amnestic MCI, 58% non-amnestic MCI. CSF Aβ-42, T-tau and P-tau concentrations were measured. AD CSF profile was calculated, as well as T-tau/Aβ-42, P-tau/Aβ-42 ratios.

Results: The initial diagnosis of MCI was re-evaluated at 2 years follow up: 4 patients had remained MCI, 28 had converted to AD, 27 to frontotemporal dementia, and 19 to other forms of dementia. Aβ-42 had an AUC of 0.88, a sensitivity of 86%, and a specificity of 79% (cut-off: 500 mg/mL). AD profile had an AUC of 0.97, a sensitivity of 97%, and a specificity of 96% (cut-off: 1).

Conclusions: CSF Aβ-42, T-tau, P-tau evaluation is extremely useful in patients with MCI, in order to assess the probability of progression to Alzheimer's disease. When evaluated together, these CSF biomarkers, show a sensitivity of 89%, a specificity of 77%, a PPV of 73%, and a VPN of 91% in highlighting a CSF alteration predicting AD. In particular, CSF AD profile seems to play an important role as predictive tool in MCI patients.

A Middle-Aged Man with Fluent (Semantic) Progressive Aphasia: Case Report and Review of the Literature

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Background: Primary progressive aphasia is a neurodegenerative disorder very recently classified into fluent (semantic), nonfluent, and logopenic . The semantic variant is closely related to frontotemporal dementia. Obsessive compulsive disorder as first symptom has been very rarely reported.

Aim: To describe the case of a middle-aged man who presented behavioural disturbance followed by the appearance of progressive aphasia and visual agnosia.

Methods: The patient was evaluated with clinical neurologic evaluation, Mri , Pet scan and with a careful neuropsychological assessment including MMSE, Clock drawing test, Language evaluation (ENPA, Token test), Vsuospatial abilities test (Constructional apraxia, Rey figure copy), Gnosic abilities (Pyramids and Palm test), Memory (Short story test , Rey 15 word test), Logic abstractive test (Raven PM 47) and the Frontal Assessment Battery. The global evaluation was consistent with the diagnosis of PPA, semantic variant.

Conclusions: The early symptoms of PPA , semantic variant, are subtle and require a high index of suspicion. Neurologists aware of this entity may, recruiting these patients, help improve our understanding of its pathophysiology that should guide one day to an effective treatment.

Quetiapine Dose-Sparing Effect with Addition of Memantine: Two Cases Report of Lewy Body Disease and Dementia Associated with Parkinson's Disease

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Background: Atypical antipsychotics are often employed to treat behavioral disturbances in patients with dementia but their adverse effects remain a significant concern. Memantine is an efficacious symptomatic treatment, other than of Alzheimer disease (AD), also of vascular dementia and Lewy Body Disease.

Aim: To describe the antipsychotic-sparing effect of add-on therapy with memantine in two patients affected by Lewy Body Disease (LBD) and Parkinson's disease dementia (PDD).

Case reports: A 65-year-old woman with LBD developed agitation and psychosis six years after the onset. She started quetiapine tapering the dose up to 400 mg/die, and a severe extrapyramidal syndrome progressively appeared. One year after memantine was started with improvement of behavioral symptoms and quetiapine was discontinued. A 69-year-old man with PDD developed hallucinations, sleep disorders and aberrant motor behaviors. Quetiapine was started up to 125 mg/die with motor disturbances worsening. When memantine was added to therapy, the patient showed an improvement in behavioural symptoms. This change in behavior allowed quetiapine dose reduction tapering to 25 mg/die.

Conclusions: Memantine seems to improve behavioural symptoms in DLB and PDD patients and it might be an option for treatment. Interventions allowing a discontinuation or a dose-sparing effect of antipsychotic medication must be considered.

Thalamic Stroke Mimicking Frontotemporal Dementia: A Case Report

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Background: The behavioral variant of frontotemporal dementia (bvFTD) is characterized by changes of personality, social behavior and cognition and relies on a neurodegenerative process. However, vascular lesions affecting subcortical structures may result in a clinical syndrome resembling bvFTD.

Aim: To describe a case of thalamic stroke resulting in frontal dementia.

Case report: A 58-year-old man was referred to our hospital because of behavioral and cognitive changes formerly diagnosed as bvFTD. In 2010, he suddenly presented loss of consciousness and in the next days he developed amnesia, apathy and personality changes. Toxicological exams, CSF analysis and CT scan were normal at admission. Neuropsychological tests showed an impairment of executive functions and amnesia. He was referred to our Center in 2011. Behavioral disturbances and cognitive dysfunctions were already improved since the onset, and at six-month follow-up neuropsychological test showed a further recovery of cognitive functions. Brain MRI showed a left thalamic infarct.

Conclusions: The sudden onset and the improvement of clinical signs suggest a vascular origin of the syndrome. The FTD-like picture is attributable to a disruption of the fronto-subcortical circuits at the level of the striatum or the anterior thalamic peduncle. Vascular dementia should be considered in differential diagnosis of bvFTD.

The Impact of Apathy on Suicide Ideation of Patients Affected by Dementia Due to Alzheimer's Disease

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Background: Suicide ideation and desire for death are important targets for risk identification in individuals affected by dementia. In particular, the early stage of Alzheimer Disease (AD) can be a period of heightened risk for suicide, frequently when patients have preserved insight. Geriatric Depression Scale 15-item (GDS) and the 5-item GDS subscale (GDS-SI) have been previously validated as effective screening tools for the assessment of suicide ideation among older patients.

Aim: To describe the cognitive, functional and psycho-behavioral profiles of a group of 206 individuals affected by dementia due to Alzheimer's Disease, highlighting differences between patients expressing (Ideators) or not expressing (Non-Ideators) suicide ideation.

Methods: We administered a multidimensional assessment, including Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) to a cohort of 206 individuals affected by dementia due to Alzheimer's Disease. GDS-SI cut score of ≥ 3 has been chosen to divide Ideators ($n = 42$) and Non-Ideators ($n = 164$) patients.

Results: In a logistic regression model, the variables independently associated with suicide ideation are apathy (evaluated as NPI sub-item, RR 1.3) and depressive symptoms (GDS, RR 2.8).

Conclusions: Suicide ideation in individuals affected by dementia due to AD is strongly associated with informant endorsed apathy and self-reported depressive symptoms.

SNRI-Induced Visual Hallucinations in Prodromal Lewy Bodies Disease: A Case Report

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Background: Visual hallucinations (VHs) may be induced by SSRI drugs in Lewy bodies disease (LBD). Association between SNRI drugs and VHs is not reported.

Aim: To describe a case of duloxetine-associated VHs in prodromal LBD.

Case report: A 78 year-old woman was admitted to Memory Clinic for mild cognitive impairment with isolated executive deficits. Two years earlier she was put on Duloxetine (30 mg/day) and Lorazepam (1 mg × 3/day) to treat anxiety. A few days later, she presented sleep alterations with nightmares and VHs described as seeing her face and arms covered in fur like a monkey. VHs persisted unchanged for more than 24 hours since discontinuation of both drugs. At first visit, neurological examination showed asymmetric extrapiramidal signs. Her MMSE was 30/30, with visual-perception deficits (VOSP battery) and attention deficits (TMTB). A DaT-scan showed decreased tracer uptake in the left putamen; brain MRI was normal. For the persistence of depression and anxiety Citalopram (20 mg/day) was started with improvement of symptoms without recurrence of VHs. In the following year cognitive and neurological conditions were stable.

Conclusions: Duloxetine may induce VHs in association with benzodiazepines, which could decrease the gate for the emergence of "internal" images, in the background of LBD with visual-perception deficits.

The Attentional Impairment in Multiple System Atrophy

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Background: Several studies have reported cognitive impairment in the Parkinsonian and Cerebellar variants of MSA, particularly in executive functions, attributed to a dysfunction of the cognitive loop linking the prefrontal cortex to basal ganglia. A few studies investigated attentional functions in MSA patients.

Aim: To assess cognitive dysfunction and attention in MSA patients.

Population and methods: 17 patients underwent a cognitive assessment of verbal/visual memory, language, visuo-spatial abilities and executive functions. Patients and 32 matched-controls were presented with an experimental attentional task designed on Posner's Attention Network Test. The task provided three cue conditions (no-cue/temporal-cue/spatial-cue), two target conditions (congruent/incongruent) and two cue validity manipulations (valid/invalid-cue). Comparing RTs in experimental conditions allowed assessing the efficiency of the attentional components: Alerting, Orienting and Executive Control.

Results: MSA-P patients were impaired in executivemfunctions, verbal memory and visuo-spatial abilities; MSA-C in space and object perception. MSA patients performed significantly worse than controls in attentional tasks with MSA-C patients showing more errors and longer RTs in incongruent target conditions.

Conclusions: MSA patients mshow specific cognitive impairments. MSA-C patients are impaired in the attentional tasks. The greater impairment of Executive Control in these patients may be attributed to the widespread degeneration of cerebellum and cerebello-ponto-thalamo fibres projecting to medial areas of prefrontal cortex.

Cognitive Testing in Subjects with MCI: Prediction of Conversion to AD and Correlation with Cerebrospinal Fluid Biomarker Levels

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Background: The most common diagnostic test to define global cognitive state is the Mini Mental State Examination (MMSE). However, cognitive domains that best predict progression from MCI to AD are episodic memory and executive functioning. Were selected two neuropsychological tests for both domains: Story Recall Test (SRT) and Paired-Associate Learning (PAL) to examine episodic verbal memory, and Coloured Progressive Matrices of Raven (CPMR) and Clock Drawing Test (CDT) to investigate executive functioning.

Aim: To find out the best neuropsychological test able to predict conversion to Alzheimer's disease (AD) in subject with Mild Cognitive Impairment. To correlate neuropsychological testing with cerebrospinal fluid (CSF) Amyloid beta ($A\beta$), tau and Ptau levels.

Methods: Forty subjects with MCI were recruited. All of them underwent naurological exam, neuropsychological testing and lumbar puncture at time of diagnosis. Cognition were explored by MMSE (global cognitive functioning), CPMR and CDT (executive functions), SRT and PAL (episodic verbal memory). Statistical analysis was carried out by using *t*-test and Spearman test for correlations.

Results: At time of MCI diagnosis, no significant correlation between cognitive and biological markers evaluated was observed. After a one-year follow up, 18 subjects converted to dementia. Among these, 13 were diagnosed with AD and 12 out of 13 had decreased CSF $A\beta$ levels. MMSE at time of MCI diagnosis was lower in converters as compared with stable MCI (26.4 versus 27.6 $P = 0.066$). Moreover, CDT and PAL were significantly lower in converters versus non-converters (3 versus 5, $P = 0.003$ and 5.85 versus 8.32, $P = 0.03$, respectively).

Conclusions: According to these results, PAL and CDT are the most useful tests to predict conversion from MCI to AD. Larger studies are needed to define reference values.

SQSTM1 Gene Mutations in the Frontotemporal Lobar Degeneration/ Amyotrophic Lateral Sclerosis Spectrum

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Background: Over the past decade, there has been a growing body of clinical, pathological and genetic evidences suggesting the idea that frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) belong to the same clinico-pathological spectrum of disease. Lately, mutations in SQSTM1 gene have been reported in ALS patients.

Objective: To evaluate the frequency of *SQSTM1* gene mutations in a dataset of unrelated FTLD and ALS Italian patients in comparison with Paget disease of bone (PDB) patients and healthy controls.

Methods: Promoter region and all exons of the SQSTM1 gene were sequenced in a group of 727 subjects, including FTLD, ALS, PDB patients and controls. Clinical data of FTLD/ALS patients with gene mutations were examined.

Results: Seven novel heterozygous missense mutations and four new genetic variants in the promoter region of the *SQSTM1* gene have been identified in 11 patients belonging to the FTLD/ALS spectrum. None of these mutations was found in PDB patients. In *silico* analysis suggested a pathogenetic role for these mutations.

Conclusions: *SQSTM1* gene mutations are present in patients belonging to the FTLD/ALS spectrum and have a prevalence of 2.3% in FTLD and 2.4% in ALS.

The pathogenicity of these mutations deserves additional experimental and clinical studies.

Impact of Cognitive Tasks on Kinematic Gait Parameters in FTD Patients

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Background: Patients with Alzheimer's disease (AD) present impairment of kinematic gait parameters and a consequent greater risk of falls. Relationship between gait parameters and cognitive decline was never evaluated in patients affected by frontotemporal dementia (FTD).

Aim: To investigate the effect of a dual task paradigm on gait parameters in FTD patients.

Methods: Patients with clinical, neuropsychological and instrumental diagnosis of FTD have been enrolled. They were classified as strongly (MMSE <25 but >20) or lightly (MMSE >25) compromised. A three-dimensional motion analysis was performed. We analyzed kinematic gait parameters in normal conditions and while a motor or cognitive task was performed. The following gait parameters were analyzed: 1) stride width; 2) stride length; 3) cycle time; 4) double limb support time; 5) single limb support time; 6) double limb support time/ single limb support time ratio.

Results: Relevant difference in double limb support time/single limb support time ratio was observed in patients more cognitively compromised when they performed cognitive dual task as compared to motor dual task.

Conclusions: Our preliminary data show that in FTD patients cognitive dual tasks impairs gait efficiency as compared to a motor dual task.

IL-18 Pathway is Altered in Mild Cognitive Impairment Subjects

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Background: Progressive neurodegeneration characterizes Alzheimer's Disease (AD) and is accompanied by inflammation and cytokine release. Among them, IL-18 was suggested to have an important role in AD.

Aim: To evaluate IL-18 system in the early stage of AD, in subjects with mild cognitive impairment (MCI).

Population and methods: Sixty-nine aged- and gender-matched subjects (34 with MCI, 22 healthy controls (HC) and 13 AD) were recruited for this study. Serum was collected and peripheral blood mononuclear cells (PBMC) from all donors were isolated and cultured in the presence or absence of lypopolysaccharide (LPS). IL-18Rα and β chains expression was analysed by flow cytometry and IL-18 and IFN-γ production was measured by ELISA.

Results: No differences in serum levels and PBMC production of IL-18 were found between MCI and HC subjects. Flow cytometry analysis showed no changes in IL-18Rα expression between all groups. On the contrary, IL-18Rβ chain was highly induced by LPS in both MCI and AD, but not in HC cells. Interestingly, LPS-induced cell production of IFN-γ was decreased slightly in AD and significantly in MCI as compared to controls.

Conclusions. These data confirm that the IL-18 pathway is dysregulated in AD and in its earliest stages.

Development of a Neuropsychological Battery for Vascular Mild Cognitive Impairment, the Experience of the VMCI-Tuscany Study. Automation and Standardization of the Scoring Procedures: From Tables to Equations

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Background: The VMCI-Tuscany Study is a multicenter, prospective, observational study aimed to evaluate risk and determinants of dementia in patients with vascular mild cognitive impairment and small vessel disease.

Aim: For the study's aims, we developed a test battery thought to: 1) be sensitive to vascular cognitive decline; 2) allow automation and standardization of the scoring procedures; 3) obtain a cognitive profile for each patient.

Methods: Test selection was based on the availability of correction and evaluation norms for healthy Italian adult samples and ES methodology, that allows to obtain a cognitive profile for each patient. To automate and standardize the scoring procedures, regression equations have been extracted by normative studies.

Results: The final version of the battery includes 11 tests. Data collected are entered into an electronic database on the www.wmci-tuscany.it web site. Starting from demographic variables and raw scores, and using the regression equations, the database automatically calculates corrected and equivalent scores.

Conclusions: The VMCI-Tuscany neuropsychological battery is a comprehensive but not too long instrument, administrable on a single visit. The automation and standardization of the scoring procedures allow to avoid errors, save time, optimize the agreement between operators and centers, and improve the quality of data collected.

Cognitive Profile of Parkinsonisms at Onset

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Background: Parkinsonisms at onset can be associated to non motor symptoms such as cognitive impairment.

Aim: To describe the cognitive characteristics of patients with parkinsonism at onset.

Methods: We consecutively selected patients with parkinsonism and disease duration up to three years. Each patient was evaluated by a neuropsychologist, blinded to the diagnosis, by means of the Brief Mental Deterioration Battery, the Stroop Test and the Semantic Fluency Task.

Results: We recruited 26 patients: 21 affected by Parkinson Disease (PD),1 by Progressive Supranuclear Palsy (PSP), 1 by Multiple System Atrophy (MSA) and 3 by Parkinsonian Syndromes not otherwise specified (PS).

In these patients we observed 7 different patterns of cognitive deficits: executive deficits (ED) in 7 PD and 1 PS; ED plus praxis deficits in 2 PD; ED plus fluency deficits in 2 PD; ED plus visuospatial deficits in 1 MSA; verbal memory deficits in 1 PD; global cognitive deterioration in 2 PD and 1 PSP. Finally, no cognitive deficits were found in 7 PD and 2 PS patients.

Conclusions: Cognitive impairment at onset in parkinsonian patients may be heterogeneous. Global cognitive deterioration can be present at onset and with similar features independently from diagnosis.

A Case of Early Primary Progressive Aphasia in Sjögren Syndrome

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Background: Neurologic involvement in Sjögren Syndrome (SS) occurs in approximately 25% of patients. Manifestations are different and may affect the peripheral nervous system and the central nervous system (CSN). Neurological complications often precede or reveal SS. Cognitive dysfunctions seem to be frequent in SS. Two patterns have been described: disorders mimicking Alzheimer's disease and subcortical disorders.

Aim: To describe a case of early Primary Progressive Aphasia (PPA) in SS.

Case report: A 56 years old woman was admitted to our Department for cognitive decline. The symptoms started three years before with progressive difficulties of speech, subjective memory deficit, behavioural abnormalities, disphagia and progressive difficulty in writing. Neurological examination showed bucco-facial and ideomotor apraxia. The neuropsychological assessment revealed an impairment of praxis, attentional and executive functions, a speech articulation deficit and dysgraphia. General blood tests were normal. SSA-Ro and SSB-La antibody titles were positive. Brain MRI and SPECT of cerebral perfusion documented the involvement of frontal and temporal area.

Conclusions: CNS involvement in SS is probably underestimated and the diagnosis is often delayed. SS should be suspected in patients presenting atypical clinical and radiologic CNS manifestations. To our knowledge, this is the first case of PPA in SS.

The Savvy Caregiver Program: A Probe, Multicenter, Controlled Trial

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Background: Caregivers (CGs) of Alzheimer's Disease (AD) patients carry a great burden and are at a greater risk of depression, anxiety disorders and physical problems. The Savvy Caregiver program (SCgP) is a psychoeducation program which reported success in reducing CGs' distress.

Aim: To evaulate the efficacy of the SCgP in modifying coping strategies in CGs of AD patients and reducing their burden; effects on behavioural and functioning in daily living of patients were evaluated as well.

Methods: CGs of AD patients were consecutively enrolled from ten Memory Clinics and randomly assigned to treatment or control group. All CGs and patients underwent evaluation scales (Cope, CBI, CES-D, STAIY1-Y2, SF12, NPI, CIRS,MMSE, IADL, ADL) at baseline, after treatment and after 3 months

Results: 164 CGs were enrolled (80 treated - 84 control). The groups were comparable for all variable but sex. Treated CGs showed increased score at Social Sustain item of Cope ($p = 0.038$) and reduction in Transcendet Orienting score ($p = 0.039$) as well as reduction in CES-D ($p = 0.047$), CBI ($p = 0.085$) and STAIY1 ($p = 0.057$); in patients the treatment reduced NPI total score ($p = 0.012$), especially for apathy ($p = 0.001$).

Conclusions: The SCgP showed efficacy in modyfing cope strategies, reducing CGs burden and behavioral symptoms of AD patients.

The APOE Chromosomal Region in Primary Progressive Aphasia and in the Behavioral Variant of Frontotemporal Dementia

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Background: Apolipoprotein E (APOE) gene locus (19q13.31) has been associated to frontotemporal lobar degeneration (FTLD), in particular to the behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) subtypes.

Aim: To investigate the APOE chromosomal region in bvFTD and PPA.

Population and methods: We investigated three single nucleotide polymorphisms rs2075650, rs157590 (TOMM40 locus at 19q13), rs429358 and rs7412 (APOE at 19q13.21) and rs1064725 (APOC1 locus at 19q13.2), representative of the linkage disequilibrium blocks at 19q13-q13. 282 patients with clinical diagnosis of FTLD, namely 207 bvFTD and 75 PPA, and 296 cognitively healthy controls were investigated in blinded fashion.

Results: Linkage disequilibrium between rs2075650 and rs1064725 (D'>0.71) was observed in PPA and controls, but not in bvFTD. Inside this region of 21kb, linkage disequilibrium between rs2075650 and rs429358 (D'>0.74) was observed in bvFTD but not PPA and in controls. Inside this region of 16.3kb, linkage disequilibrium between the rs157590 and rs429358 (D'=0.84) was observed in PPA and controls but not in bvFTD. Accordingly to this LD pattern, significant differences ($p < 0.01$) in haplotype distribution between bvFTD, PPA and controls were detected.

Conclusions: These results strongly suggested an association of the 19q13-q13.2 chromosomal region with FTLD, and in particular with bvFTD and PPA subtypes.

Cytochrome P450 2D6 Allele 4 (CYP2D6*4) in the Response to Donepezil-based Treatment of Alzheimer's Disease

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Background: Cytochrome P450(CYP)2D6 isozyme is the major responsible of donepezil metabolism. Functional polymorphisms in the CYP2D6 gene may affect enzyme activity and donepezil metabolism. Allele CYP2D6*4 represents the most common variant in Caucasians, affecting CYP2D6 enzyme activity.

Aim: To evaluate the effect of the CYP2D6*4 on the clinical response to donepezil-based treatment of mild-to-moderate AD.

Population and methods: In this study we evaluated 222 unrelated Caucasians clinically diagnosed as sporadic AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Work Group (NINCDS-ADRDA) criteria. Patients were treated with donepezil (5-10 mg/daily) for 6 months. Response to treatment was evaluated at 6-month follow-up according to the National Institute for Health and Clinical Excellence (NICE) requirements. The identification of CYP2D6*4 was performed by standard methods.

Results: 144 of 222 patients (65%) were responders and 78 patients (35%) were non-responders to donepezil-based treatment. No significant differences were observed in the distribution of CYD2D6*4 genotypes or alleles between responder and non-responder patients.

Conclusions: Whereas functional polymorphisms in the CYP2D6 gene can influence the clinical efficacy of donepezil, more studies on highly selected AD patients are needed to clarify the role of CYP2D6*4 in the treatment of AD.

TMEM106B Genetic Variability in Patients with Alzheimer's Disease

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Background: Recently, the uncharacterized Transmembrane protein 106B gene (*TMEM106B)* on chromosome 7p21.3, has been identified as a novel risk factor for Frontotemporal Lobar Degeneration (FTLD) with TDP pathology, acting by modulating the levels of secreted progranulin.

Objectives: To test whether *TMEM106B* genetic variability is associated with AD and to determine its possible influence on plasma progranulin levels.

Methods: An association analysis of *TMEM106B* Single Nucleotide Polymorphisms (SNPs) rs1020004, rs6966915 and rs1990622, covering the whole genetic variability of the gene, was carried out in a population of 300 patients with Alzheimer's disease (AD) compared with 323 age-matched controls. In addition, plasma progranulin levels were analyzed in 80 AD patients.

Results: Considering *TMEM106B* variants, no differences were found both in allelic and genotypic frequencies in patients compared with controls. Stratifying according to age at onset or gender no differences were found as well. No differences in progranulin plasma levels were found after stratification according to rs1990622 status (A carriers: $130 \pm 3,2$ ng/ml vs G carriers: $135 \pm 4,1$ ng/ml).

Conclusions: According to these preliminary results, *TMEM106B* does not appear to act as susceptibility factor for AD. Moreover, rs1990622 does not seem to exert an influence on circulating progranulin levels, in contrast with data previously described in patients with FTLD.

Mild Cognitive Impairment: The same Identity for Different Entities. A Voxel-Based Morphometry Study

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Background: It is becoming increasingly clearer that mild-cognitive-impairment (MCI) represents an heterogeneous condition.

Aim: To assess whether different patterns of regional grey matter (GM) atrophy allow to discriminate between different MCI categories, and may help in predicting patients' clinical outcome.

Population and methods: Fifteen patients with amnestic-MCI-single-domain, 12 with amnestic-MCI-multiple-domain, 13 patients with non-amnestic-MCI (showing executive dysfunctions), and 28 matched controls, underwent MRI for GM volumetrics, and were clinically followed-up for 1 year.

Results: All amnestic-MCI- single-domain patients remained stable. The 40% of amnestic-MCI-multiple-domain patients converted to AD, while the 60% remained stable. The 24% of non-amnesic-MCI patients converted to fronto-temporal dementia, while the 50% remained stable, and the 25% reverted back to normality. At baseline, voxel-based morphometry revealed distinct patterns of GM loss across groups. In amnestic-MCI-single-domain patients, GM atrophy was limited to the entorhinal cortex , while it extended to the supramarginal gyrus in those with amnestic-MCI-multiple-domain. Conversely, non-amnestic MCI patients had a well localized GM reduction in the orbitofrontal cortex.

Conclusions: This study provides evidence, based on GM volumetrics, that patients with amnestic-MCI (either single or multiple-domain) and those with non-amnestic-MCI belong to different pathways of neurodegeneration. VBM contributes in reducing the heterogeneity observed in MCI populations.

Theory of Mind abilities in early stage of Dementia

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Background: Theory of Mind (ToM) abilities guide people in social interactions, including cognitive perspective taking (cognitive ToM) and understanding emotions (affective ToM).

Aim: to evaluate whether a deficit in cognitive and/or affective ToM could explain the behavioural and emotional deficit found in patients at early stage of dementia.

Methods: We compared 7 patients with initial Frontotenporal Dementia-FTD (mean MMSE=24.9), 8 patients with initial Alzheimer Disease-AD (mean MMSE=25.8) with 15 healthy subjects. Cognitive ToM abilities were tested using the Faux Pas Test. To evaluate affective ToM, we tested the abilities to infer complex mental states from eye gaze and prosody. In addition, the recognition of facial and prosodic expressions of basic emotions was tested.

Results: FTD were impaired in the Faux Pas Test, in the auditory test of affective ToM, and in several subtests of the emotional batteries. AD showed defective performances in the Faux Pas Test and in the emotional tasks requiring memory abilities.

Conclusions: FTD patients were impaired in processing complex and simple emotional states: this could explain the behavioural impairment detectable even at the early stage of the disease. On the contrary, impaired performances of AD patients could be attributed to a non-emotional deficit.

Structural Brain Disconnection has a Different Anatomical Distribution in Alzheimer's Disease and Dementia with Lewy Bodies

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Background: The clinical symptoms of Alzheimer's disease (AD) and Lewy bodies dementia (LBD) partially overlap, thus often making a differential diagnosis challenging. It is recognized that clinical manifestations of these diseases are partially associated with abnormal integration of different brain regions by disconnection mechanism. Approaches based on diffusion-MRI-tractography can be used to investigate brain connectivity non-invasively.

Aim: To assess whether different patterns of brain disconnection exist in AD and LBD.

Population and methods: Twelve LBD and 12 AD patients had MRI at 3T, including volumetric and diffusion-weighted scans. Probabilistic tractography was used to initiate streamlines from all parenchymal voxels, and anatomical connectivity maps (ACMs) were obtained by counting, among the total number of streamlines initiated, the fraction passing through each brain voxel. After image normalization, ACMs were used to test for between-group differences.

Results: LBD patients had reduced ACM in the occipital and cerebellar areas, while AD patients showed an anterior pattern of reduced connectivity.

Conclusions: These results support on an "anatomical connectivity" basis the role of different patterns of brain disconnection in determining different clinical aspects of AD and LBD. In particular, the occipital disconnection observed in LBD might account for the typical visual hallucinations that characterize this condition.

No evidence of Association Between EXOC3L2 Gene and Italian Late-Onset Alzheimer's Disease

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Background: Genome wide association studies (GWAS) have recently identified different genes probably candidate for late-onset Alzheimer's disease (LOAD). In particular, the rs597668 SNP, near to *EXOC3L2* gene (exocyst complex component 3-like 2), was also considered, but because of its proximity to APOE, was examined in less detail.

Objectives: In order to better clarify the possible role of this SNP, we performed a case-control study in a dataset of LOAD patients.

Methods: The study group consisted of 554 Italian subjects: 282 sporadic LOAD patients and 278 controls enrolled from the outpatient clinics connected with the Neurology Department at the University of Florence. DNA was extracted from white blood cells using the phenol-chloroform procedure and all of the genotyping was performed by KBioscience (http://www.kbioscience.co.uk).

Results: We found no statistical difference in rs597668 SNP in the *EXOC3L2* gene (allele/genotype frequency) between AD patients and controls. Similarly, no significant difference was observed when our sample was stratified by gender or ApoE E4 allele presence.

Conclusions: Our data, obtained from analysis in rs597668 SNP in the *EXOC3L2* gene, replicated the Lambert's study in a large European dataset, suggesting that this polymorphism do not contribute to an increased risk of developing AD in Italian patients.

Common Disease-Causing Genes Link Amyotrophic Lateral Sclerosis and Fronto-Temporal Dementia

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Background: Emerging evidence suggests that amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTLD) belong to the same disease spectrum: 1) the two phenotypes are often seen in the same patient; 2) TDP-43 immunoreactive inclusion, the neuropathological hallmark of ALS, are also observed in ~50% of all FTLD cases; 3) causative mutations in ALS-related genes have been described in FTLD patients.

Aim: To screen for mutations the *TARDBP*, *FUS, UBQLN2*, and *C9ORF72* genes in a large cohort of ALS and ALS-FTLD Italian patients.

Methods: Amplification by PCR and direct sequencing of exon 6 of *TARDBP*, exons 13–15 of *FUS*, and of the PXX repeat region of *UBQLN2*. A fluorescent repeat-primed PCR method has been used to detect the hexanucleotide GGGGCC-repeat expansion in the first intron of *C9ORF72*.

Results: The combined mutational frequency of *TARDBP*, *FUS* and *UBQLN2* in ALS-FTD cases is ~2%. Conversely, a pathological *C9ORF72* expansion was observed in ~25% of familiar ALS and ALS-FTD cases.

Conclusions: These data strengthen the original hypothesis that ALS-related genes, mainly *C9ORF72*, have an important role also in the pathogenesis of FTLD.

Immune Response Against Beta-Amyloid is Modulated by Acetyl-cholinesterase Inhibitors

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Background: Acetyl-cholinesterase inhibitors (AChEI) are approved for the treatment of mild-to-moderate Alzheimer's disease (AD). We previously demonstrated that AD patients receiving AChEI display a specific increase of anti-Abeta 1–42 antibodies in plasma with respect to untreated patients and controls.

Aim: To further investigating this influence of AChEI on the endogenous immune response against Abeta.

Methods: *Ex vivo* lymphomocytes (PBMC) were obtained from AD patients treated with different AChEI. *In vitro* lymphocytes cultures were prepared as well. mRNA levels of GATA-3 and T-bet, transcription factors involved in Th2/Th1 differentiation, were assessed by real-time RT-PCR.

Results: PBMC obtained from AD patients treated with donepezil showed a significant increase in GATA3-mRNA with respect to AD patients treated with rivastigmine, untreatred AD and healthy controls. Concomitantly, we stimulated lymphocytes cultures with donepezil (20 ng/ml for 7 days) to verify this hypothesis in a controlled system. Preliminary data suggest that GATA-3 mRNA levels are modestly increased in donepezil-stimulated cultures respect to unstimulated ones.

Conclusions: In conclusion, AChEI induce a Th2 response, increasing anti-Abeta antibody production. Finding a way of further reinforcing the endogenous response against Abeta might represent a putative novel strategy for controlling disease progression in AD.

Cerebrospinal Fluid Biomarkers in Preclinical Dementia: Early Diagnosis in Clinical Practice

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Introduction: It is well known that cerebrospinal fluid (CSF) levels assessment of $A\beta1\text{-}42$ and Tau protein helps discriminating preclinical AD from age-associated memory impairment, depression and other forms of dementia.

Aim: To explore if CSF biomarkers ($A\beta1\text{-}42$, t-Tau, p-Tau) in our cohort of MCI patients are helpful to identify patients at risk to develop AD and other forms of dementia after a 2-year-long follow-up.

Population and methods: A group of 61 MCI patients were recruited from our Memory Clinic according to clinical criteria. At baseline, all patients underwent neurological assessment, complete neuropsychological evaluation, routine blood tests, ApoE determination, and lumbar puncture to dose t-Tau, p-Tau, $A\beta1\text{-}42$. We investigated baseline CSF biomar-

kers patterns between groups of MCI patients stratified by later diagnoses of conversion to AD or other dementia.

Results: MCI patients who went on to convert to AD show at baseline lower Aβ1-42 and higher t-Tau and p-Tau compared to patients who did not convert to AD. Logistic regression analysis with the diagnostic status (MCI-AD vs MCI-notAD) as the dependent variable shows significant *p*-value for Aβ1-42.

Conclusions: Our results are in agreement with previous reports, suggesting a possible role of these CSF biomarkers in clinical setting and not only in research or experimental studies.

Exploring Limits of Neuropsychological Screening for Frontal Lobe Dysfunction in ALS Patients

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Background: Cognitive dysfunction has been recently recognized as a consistent part of the clinical phenotype of amyotrophic lateral sclerosis (ALS). Major problems in the assessment of these patients consist in marked dysarthria or upper limbs strength deficits which impair the execution of most tests.

Aim: Comparing the feasibility of two brief tests for the screening of frontal lobe dysfunction in ALS patients in follow-up at our dedicated centre.

Methods: 10 clinically definite ALS patients (4 bulbar/6 spinal; mean ALSFRS_R: 25.8 ± 6.7; age 67.4 ± 10.9) were screened with the Frontal Assessment Battery (FAB) and the Weigl's sorting test (WST).

Results: For the FAB, incomplete testing due to the above cited problems was observed in half of the patients, in whom mean completion rate was 85%. Bulbar patients could complete the tasks in 75% of the cases, while spinal patients only in 33%. By contrast, all patients could undergo the WST.

Conclusions: Albeit preliminary, our data confirm that, with respect to FAB, the WST is consistently less affected by those deficits that strongly characterize this category of patients. The need for ALS dedicated neuropsychological tests still remains an unsolved issue of high practical importance.

Mild Cognitive Impairment: Follow-up Study and Neuropsychological and Neuroimaging Characterization of the Vascular Subtype

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Background: Mild cognitive impairment (MCI) may precede dementia and MCI subtypes are recognizable based on clinical and neuroimaging aspects.

Aim: To better characterize MCI of vascular origin (V-MCI).

Methods: We reviewed the neuropsychological and neuroimaging data of 106 MCI patients: 30 degenerative-MCI (D-MCI), 53 V-MCI, and 23 mixed MCI (M-MCI).

Results: After a mean of 1.8 ± 1.1 years, out of 72 followed-up patients, deterioration occurred in 38.8% patients (35.3% D-MCI, 28.2% V-MCI, and 68.8% M-MCI), a stable status was recorded in 52.7 % MCI patients (47.1% D-MCI, 64.1% V-MCI, and 31.3% M-MCI). In V-MCI patients, the underlying vascular lesions were strategic infarcts (50.9%), multiple lacunar infarcts with leukoaraiosis (41.5%). Extensive neuropsychological evaluation was performed in a subgroup (*n*=27) of V-MCI patients.

Conclusions: With the limitation of the small sample, our study reinforces the hypothesis that small vessel disease (SVD) represents the main substrate of V-MCI and that SVD-related forms of V-MCI cause progression to dementia through lesions accumulation. In this setting, V-MCI is characterized by an initial impairment of attentive capacity of the higher level. In our sample, cognitive decline seems to occur less frequently in V-MCI than in other forms of MCI.

Delusional Misidentification Syndromes in Neurodegenerative Dementia: Report of a Clinical Case

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Background: Delusional misidentification syndromes such as Capgras syndrome occur in several

neurodegenerative diseases, in particular Alzheimer's Disease (AD) and Lewy Body dementia (LBD).

Objectives: To describe a clinical case of a patient with memory impairment and subsequent delusional symptoms, whose clinical and imaging results suggest a possible overlap between different neurodegenerative pathologies.

Methods and results: M.B. is a 82 years-old female referred to our Memory Clinic because of memory disturbances developed one year before. No other cognitive symptoms were detected and neurological examination was negative. Six months later, the patient developed delusional misidentification symptoms characterized by recurrent and transient belief that her husband has been replaced by an imposter. Neuropsychological evaluation showed verbal and spatial memory impairment and visuo-constructive dysfunction. Cerebral MRI showed diffuse subcortical vascular damage and cortical atrophy in the right parieto-occipital region and in fronto-temporal region bilaterally. Lumbar puncture showed lower level of amyloid $A\beta_{1-42}$. Cerebral PET detected a glucose metabolism reduction in visual and occipital cortex and DAT-SCAN SPECT showed dopaminergic activity reduction in bilateral striatal regions. Acetylcholinesterase inhibitor treatment and antipsychotic therapy didn't show any improvement of symptoms.

Discussion: Neuroimaging and neuropsychological findings suggested a diagnosis of LBD, whereas cerebro-spinal fluid analysis and clinical history were more suggestive of AD. Probably, co-association between AD and LBD pathology is present in M.B.

Immune Gene Expression is Different in Alzheimer Disease Patients with Comorbid Depression vs. Psychogeriatric Depression

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Background: Alzheimer Disease (AD) is frequently complicated by depression (DP). Both conditions are characterized by a peripherally reflected chronic neuroinflammation that contributes to neuronal damage by means of a pletora of mechanisms, many of them are still unclear.

Aim and methods: This study investigates whether DP affects the inflammatory gene expression in 10 HC, 9 AD patients, 10 DP geriatric patients and 7 AD/DP patients. Groups were age and gender-matched. All subjects were drug free and at their first clinical examination. The expression of IL-4, IL-18, IL-18BP, IL-10, IL-1beta, IL-37, IL-1R2, IFN-gamma, IL-1-RN, TNF-alpha genes was evaluated by real-time PCR in blood mononuclear cells.

Results: Compared to HC (100%), DP patients showed a significant up-regulation in the expression of IFN-gamma (181%; $p=0.0355$), TNF-alpha (313%; $p=0.0288$) and IL-1R2 (170%; $p=0.014$), while a down-regulation of IL-1β (34%; $p=0.025$) was observed in AD/DP. This confirms that the expression of immune related genes is altered both in DP and AD/DP patients, while unchanged in AD subjects. Notably, the dysregulated gene expression pattern in DP remarkably differs from that in AD/DP.

Conclusions: These results clarify how the occurrence of depression in AD vs. non-AD subjects is associated with different immune mechanisms, indicating depression as a peculiar phenomenon in AD.

Genetics and Expression Analysis of the Transcription Factor Sp4 in Patients with Alzheimer's Disease and Frontotemporal Lobar Degeneration

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Background: Transcription factor Sp4 (Specificity protein 4) levels are increased in the brain of patients with Alzheimer's disease (AD), and Sp4 colocalizes with neurofibrillary tangles. Moreover, Sp4 is a

susceptibility gene for Bipolar disorder and Schizophrenia which share many clinical features with Frontotemporal Lobar Degeneration (FTLD).

Populations and methods: The distribution of three tagging Single Nucleotide Polymorphisms (SNPs), covering 100% gene variability, has been determined in a population of 352 patients diagnosed clinically with AD, 290 patients with FTLD and 341 age-matched controls. Expression analysis of Sp4 was performed in Peripheral Blood Mononuclear Cells (PBMC).

Results: No significant differences in either allelic or genotypic frequency of the three SNPs were found ($P > 0.05$). Stratifying according to gender, a trend towards to a decreased frequency of the Sp4 rs9639379 *T* allele was observed in male AD patients as compared with male controls (27.9 versus 32.5%; $P = 0.057$, OR: 0.60, CI: 0.37–0.98). A significant increased Sp4 relative expression levels in PBMC was observed in patients with AD (7.652 ± 1.405 versus 3.960 ± 0.991, $P = 0.050$) and a similar trend was seen in patients with FTLD, as compared with controls (7.816 ± 2.002 versus 3.960 ± 0.991, $P = 0.084$).

Conclusions: According to these results, Sp4 gene does not act as susceptibility factor for either AD or for FTLD. However, the increased production of Sp4 mRNA may result in aberrant expression of downstream target genes, possibly contributing to the pathogenesis of both diseases.

Vascular Disorder and Oxidative Stress in Mild Cognitive Impairment

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Background: Up to 40% of the patients with amnestic mild cognitive impairment (aMCI) convert to Alzheimer's disease (AD) after 3 years. Many researchers are trying to identify markers that may increase the diagnostic specificity allowing to identify the dementia in a pre-clinical stage and to anticipate the start of treatment to delay the onset of the disease.

Aim: To identify new markers and the possible pathogenetic mechanisms of aMCI.

Methods: By means of near-infrared spectroscopy (NIRS) we measured tissue oxygen saturation of cerebral cortex (TOI) in 21 patients with aMCI (10M and 11F, 70.2 ± 7.3 years) and 10 age matched healthy controls on frontal, parietal, temporal and occipital cortex.

Results: Cerebrovascular risk factors (CVR) were present in 81% of patients with aMCI. In these patients we found a significant decrease of TOI –36%, $p < 0.001$ compared to the controls on the frontal, temporal and parietal cortex of both side, suggestive of chronic hypoperfusion.

Conclusions: In the aMCI patients with CVR the TOI reduction (tissue oxygen deficiency /hypoperfusion) may be the priming (or initiating) factor in the development and maturation of AD suggesting neuronal oxidative stress. The reduction of TOI below a threshold may be considered a new marker of MCI.

The Presence of Carotid Stenosis and Cerebrovascular Reactivity Impairment is Related to Poor Cognitive Performance in Asymptomatic Subjects

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Background: Increasing evidences highlight that cerebral vascular impairment is associated with cognitive deterioration pathogenesis, but there are no specific data about the relationship between cognitive performances and vascular parameters in asymptomatic subjects.

Objectives: To investigate the correlation between cerebral vascular status, particularly extracranial carotid disease and cerebrovascular reactivity, and global cognitive performances.

Population and Methods: 420 consecutive asymptomatic subjects with multiple vascular risk factors were enrolled and submitted to a neuropsychological evaluation, carotid ultrasound estimate and cerebral vasoreactivity evaluation with the breath-holding-index (BHI) method. An ordinal regression model was set up using MMSE as dependent variable and carotid stenosis and BHI as independent variables. Age, sex and cardiovascular risk factors were also included in the model as covariates.

Results: Subjects with intra or extracranial vascular impairment had a higher risk of low MMSE scores: the ones affected by bilateral carotid stenosis had a risk increased of 9.24 [95% IC: 2.62–32.64; $p < 0.05$] while a pathologic BHI was associated to an odds ratio of 6.49 [95% IC: 2.51–16.77; $p < 0.05$].

Conclusions: A bilateral carotid stenosis or a pathologic BHI value increase the probability of a cognitive impairment even in an asymptomatic subjects. This result, if confirmed, could help for a better clinical management of cognitive impaired patients.

Functional Profile Differences in Mild Cognitive Impairment and Subjective Memory Impairment

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Background: To date, recent studies suggest that functional activities decline may occur early in mild cognitive impairment (MCI).

Aim: To examine whether patients with MCI have impaired activities of daily living (ADL) and which items of ADL are particularly useful to distinguish between MCI and subjective cognitive impairment (SCI).

Subjects and methods: ADCS-ADL scale and an extensive neuropsychological battery were administered to 26 patients with MCI (20 a-MCI, 4 na-MCI and 2 md-MCI) and 24 patients with SCI, age and education-matched; patients with MCI also completed the Memory Functioning Questionnaire.

Results: The overall score on the ADCS-ADL MCI scale was significantly lower in the MCI group, compared to SCI. The two groups differed particularly in the items assessing memory, problem-solving and initiative. After the 1-2 years follow-up period, 4 patients developed a mild form of dementia; if considering the functional profile, no differences were observed in ADCS global score, nor in the single items scores.

Conclusions: These results suggest that an accurate evaluation of daily functions often reveals a subtle restriction in complex activities in patients with MCI. Items involving memory, problem-solving and initiative may be useful, in clinical practice, to detect early manifestations of disease.

Resting and Task-Related Functional MRI in Mild Cognitive Impairment and Alzheimer's Disease

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Background: Functional MRI can detect abnormalities in patients with MCI and AD. These abnormalities are thought to occur with different timecourses along the progression from MCI to AD: resting state default mode network (DMN) connectivity decreases in both MCI and AD, whereas hippocampal activation during memory tasks increases in MCI and decreases in AD. We aimed to better characterize the functional abnormalities occurring in MCI and AD.

Population and methods: Thirty AD patients, 24 MCI patients, and 23 controls underwent both resting fMRI and task-related (visuo-spatial paired association learning) fMRI. Analyses were performed with FSL tools. Atrophy and cognitive performance were taken into account.

Results: During resting fMRI, increased activation within the DMN was found bilaterally in hippocampus and posterior cingulate in controls relative to MCI and AD. During task-related fMRI, increased activation in the hippocampi was found in MCI patients relative to controls and AD. However, when comparing successful relative to unsuccessful performance of task, the control group was the one with greater hippocampal activation for successful relative to unsuccessful performance.

Conclusions: Hippocampal DMN activation decreases across different phases of AD progression. Efficient task-related hippocampal fMRI activation also decreases across phases of AD progression. This suggests that the task-related hippocampal hyperactivation frequently observed in MCI represents maladaptive compensation.

Performing Prototype Distortion Tasks does not Require any Contribution from the Explicit Memory System: Evidence from Amnesic MCI on a New Experimental Paradigm

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Background: Amnesic patients can learn to categorise new exemplars drawn from the same prototype as previously encountered items. Whether this ability relies on a spared implicit learning system or on residual explicit memory resources is still a matter of debate.

Aim: In the present study we aimed at providing a strong test for the independence of prototype based category learning from explicit memory.

Methods: Patients suffering from amnesic MCI and Normal Controls were enrolled in a prototype learning task. In the study phase subjects had to judge, on a 4 point scale, how pleasant morphed faces, drawn from a single prototype, seemed to them. In the test phase, subjects had to judge the regularity of faces they had never seen before on a 4 point scale. We reasoned that implicit learning of the category boundaries would lead to a category-specific increase of perceived regularity.

Results: Results confirmed our predictions: subjects which were exposed to a series of category members in the study phase, gave higher regularity scores to new faces drawn from the same prototype as compared to subjects which did not perform the study phase. This effect was superposable across subjects' groups.

Conclusions: Our results argue in favour of separable neural systems for explicit memory and category learning.

Physicochemical Properties of Aβ Peptides in Cerebrospinal Fluid of Alzheimer Disease Patients

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Background: Cerebrospinal fluid (CSF) biomarkers are currently included among supportive criteria for Alzheimer disease diagnosis (AD). In particular, a decrease of CSF levels of amyloid beta peptide 1-42 (Aβ42) coupled with an increase of tau and phospho-tau$_{181}$ protein levels support AD diagnosis.

Objectives: In this study, we evaluated in CSF samples from 40 patients with diagnosis of probable AD and from 10 age matched controls, the diagnostic value of ELISA and Western blot analysis in determining Aβ40 and Aβ42 levels.

Methods and results: CSF samples were tested by using two different ELISA kits one from Innogenetics (Ghent, Belgium) and the other from Wako (Osaka, Japan), which provided different results as to the levels of Aβ40 and Aβ42 peptides. Spurred by these discrepancies, we determined the Aβ40 andd Aβ42 levels by Western Blot analysis. While in CSF samples from AD patients, Aβ40 values overlapped those obtained by ELISA, Western blot analysis showed Aβ42 values significantly higher, indicating that ELISA detects only partially Aβ42.

Conclusions: These findings indicate that part of Aβ42 peptides in the CSF of AD patients exist under oligomeric/polimeric forms or in combination with other proteins, thus masking reactive epitopes under the ELISA assay.

Dementia with Lewy Bodies (DLB) Presenting with Epilepsy-like Syndrome

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Aim: To report a case of Lewy Body Dementia (LBD) with severe and prolonged fluctuations of alertness as presenting condition for a few years, misinterpreted at first as non convulsive seizures.

Case report: A 69 year-old-man presented with confusional state and paroxysmal right-side limb paraesthesiae. Neurological and cognitive examination was unremarkable. EEG evidenced bouffèes of diffuse slow waves. Brain MRI with gadolinium detected

chronic ischemic lesions of the white matter. A diagnosis of partial-onset seizures was made and antiepileptic treatment was started. At 72 years, he was admitted for a prolonged decreased vigilance (48 hours) followed by confusional state. Neurological examination showed mild strength deficit of the right arms. Generalized slowing of the EEG rhythms, not modified by benzodiazepine infusion, was detected. CSF tau protein level was 980 pg/ml, with positive 14.3.3. Search for anti-neuron antibodies was negative and total-body PET was normal. Six months later he developed cognitive impairment (MMSE 21/30) with fluctuating executive and visual-spatial deficits. A second MRI was unchanged, the CSF 14.3.3 protein was negative, the level of tau protein was reduced (380 pg/ml). At age 73 the patient's wife reported RBD and episodes of psychosis (Capgras syndrome). A brain TC-PET showed left parietal-occipital hypometabolism and a decreased DaTSCAN tracer uptake in the right striatum. Finally, a diagnosis of probable LBD was made.

Conclusions: This case shows how fluctuations of alertness may be the presenting symptom of LBD and be so severe and prolonged to mimic other neurological conditions and leading to misdiagnosis.

Quantitative Magnetization Transfer in Alzheimer's Disease, mild Cognitive Impairment and Subjective Memory Complaints

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Background: Quantitative magnetization transfer (qMT) provides complementary information to conventional magnetic resonance imaging (MRI) in the characterization of Alzheimer's Disease (AD).

Aim: To extend these findings to the analysis of Mild Cognitive Impairment (MCI) and Subjective Memory Complaints (SMC).

Population and methods: 86 subjects complaining of memory deficit and 15 controls underwent a comprehensive clinical history, neurological examination, and extensive neuropsychological investigation. Patients were classified as AD ($n=21$), MCI ($n=31$), and SMC ($n=34$). All subjects had an MRI acquisition at 1.5T including a T1-and a MT-weighted sequence for qMT. The T1-weighted images were processed to grey matter volumetric maps of the whole brain by using voxel based morphometry (VBM). Mean qMT values were calculated bilaterally in hippocampus, thalamus, caudate, putamen, pallidum and subsequently compared between groups.

Results: qMT significantly differed between AD and SMC patients ($p=0.026$) in the hippocampus. VBM analysis showed significant differences between AD and SMC patients in the hippocampus, parahippocampal regions, precuneus and posterior cingulate.

Conclusions: Our data indicate that qMT, although sensitive to AD pathology, fails to identify MCI. Furthermore, metabolic and structural parameters do not differ in SMC and healthy subjects, insofar confirming the necessity of further studies on this population, which clinical meaning remains vague.

When Semantics Intrudes into the Calculation System: Evidence from Early Semantic Dementia

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Background and purpose: The issue whether arithmetical knowledge is invariably spared or impaired in Semantic Dementia is still under debate.

Aim: To explore arithmetical knowledge in a group of 8 patients affected by early Semantic Dementia (SD).

Materials and methods: Eight patients (7 men, 1 woman) affected by early Semantic Dementia (SD) were enrolled in the study. A group of 9 healthy subjects, matched with the patients for demographical characteristics, served as reference group.

An extensive neuropsychological battery exploring arithmetical knowledge was applied. The battery included tasks of arithmetical signs recognition (presented in visual or auditory modality), written and mental calculation (addition, subtraction and multiplication sums).

Results: A significantly lower performance of SD patients was found in the following tasks: identification of arithmetical signs, written addition, written

subtraction, written multiplication, mental addition, mental multiplication.

The qualitative analysis of errors revealed that patients made prevalent procedural errors mostly in carrying, omission and integration errors; in mental calculation errors were equally distributed in frequency between subtractions and multiplications (36.5%), and, in the latter case, operand, carrying and non-table errors were the most frequent errors.

Conclusions: the present data show impairment of arithmetical knowledge in early SD.

Randomized Clinical Trial of a Computer-Based Cognitive Treatment for Healthy Elderly, Clinical and Preclincal Alzheimer's Disease. The SOCIABLE Project

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Background: Cognitive training has been successfully applied to Alzheimer Disease (AD) patients and to mild cognitive impairment (MCI) patients considered the preclinical stage of AD.

Aim: aim of this randomized crossover design study is to obtain evidences of the efficacy and its long-lasting maintenance of a cognitive training implemented on a state-of-the-art technological support in healthy subjects, MCI and AD patients. This study is part of an ICT project called 'SOCIABLE' funded by the European Commission.

Methods: Separately for each group, AD patients, MCI patients and Healthy elderly were randomly assigned to two different arms of the study: half participants received first the cognitive training and after three months of no-training, whereas half participants received first three months of no-training and after the cognitive training. The cognitive training was 24 sessions long (twice a week), administered through a touch screen horizontal Microsoft surface. The surface was used from 3 users together and the cognitive training tapped 7 different cognitive functions. Outcomes of the treatment were measured through an extended neuropsychological battery tapping cognitive, functional, behavioural and social aspects.

Results: Preliminary ANOVA analysis showed significant effects of the treatment encouraging to enlarge the sample of participants.

Can control of hypertension (HT) in Alzheimer Disease (AD) modify the progression of cognitive impairment?

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Background: Likely dementia, HT increases with advancing age. Many studies reported that long-standing HT may lead to impaired cerebrovascular autoregulation, atherosclerosis and dementia, which in turn are thought to correlate with dementia. HT is considered a modifiable risk factor for AD and dementia. Controlling blood pressure with specific antihypertensive agents may alter disease progression.

Aim: To examine the effects of different antihypertensive medication on cognitive function in AD and MCI patients (pts).

Methods: 31 pts with probable AD, 7 pts with MCI and 35 matched controls were evaluated. Risk factors beside hypertension and pharmacological treatment were registered and analyzed. There were a total of 19 AD/MCI pts on anti-hypertensive treatment (HT).

Results: The mean MMSE at T0 and after 6 months (T6) (21.7 ± 3.07 and 22.0 ± 3.7) in AD pts with HT and without HT (20.8 ± 5.1 and 19 ± 5.4) did not show significant difference ($p = 0.4$).

Cognitive functions in a subgroup of five AD pts with HT taking ARBs did not show statistical difference over time (T0 MMSE: 22.4 ± 3.7; T6 MMSE: 23.0 ± 4.6 $p = 0.77$). Multivariate analysis is ongoing.

Conclusions: accordingly to our preliminary data we can not support recent evidences of the literature hypothesizing that ARBs may represent the first choice antihypertensive agents for AD.

Usefulness of cerebrospinal fluid (CSF) biomarker in the diagnosis of AD

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Background: The new proposed diagnostic criteria for early diagnosis of AD underline the value of CSF biomarkers.

Abstracts

Aim: To analyse CSF beta amyloid $A\beta_{1-42}$, Tau and p-Tau$_{181}$ concentrations and IATI (Innotest Amyloid Tau Index) to differentiate AD from healthy subjects and MCI. IATI score cut off was one. Sensitivity and specificity of IATI index was calculated.

Methods: We studied 71 CSF samples: 31 AD (age 71.1 ± 6.7), 7 MCI (73.5 ± 4.4) and 33 controls (mainly motor neuron disease and peripheral neuropathy) (age 71.3 ± 8.1). Elisa by Innogenetics was performed to determine the concentration of the three biomarkers, then combined in IATI [(measured Ab1–42)⁄(240 + 1.18*measured Tau)].

Results: $A\beta_{1-42}$, Tau and p-Tau$_{181}$ concentration showed statistically significant differences between AD and CO (341.8 ± 141.4 and 648.4 ± 258.3; 531.1 ± 370 and 318.5 ± 237.8 and 69.2 ± 47.2 and 44.9 ± 26.1 respectively, $p < 0.05$); while the difference between AD and MCI was statistically different only for $A\beta_{1-42}$ ($p < 0.05$). The IATI index was 0.5 ± 0.3 in AD, 0.7 ± 0.2 in MCI and 1.25 ± 0.7 in CO. The sensitivity and specificity of the IATI index in discriminate AD from CO was 87% and 57% respectively.

Conclusions: IATI, as expected, shown a good sensitivity whereas its low specificity is probably due to the absence of healthy controls.

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