VI Sindem MEETING

Italian Association for the Study of Dementia
linked to the Italian Neurological Society (SIN)

Milan, Centro Congressi della Provincia di Milano –
Via Corridoni, 16
March 17–19, 2011

PROCEEDINGS

Scientific Committee

Vincenzo Bonavita
Carlo Caltagirone
Claudio Mariani
Alessandro Padovani
Elio Scarpini
Sandro Sorbi

SINdem

INVITED SPEAKERS

Journal of Alzheimer's Disease 23 (2011) S5–S41
DOI 10.3233/JAD-2011-001433
IOS Press

Invited Speakers

The Progressive Aphasias

Stefano F. Cappa
Vita-Salute University and San Raffaele Scientific Institute, Milan, Italy

Prevalent production disorders

Several clinical presentations are characterised by the disproportionate impairment of language production in comparison to other aspects of language performance. These include a form with prevalent articulation impairment, in the absence of an apparent clinical language disorders. The typical motor speech impairment is apraxia of speech, which in most cases is accompanied by some degree of dysarthria. The underlying site of prevalent cortical involvement is the rolandic operculum, anterior insula and possibly the opercular portion of Broca's area [1]. Some patients can show isolated speech impairments for years, but the disorder most often evolves to a more classical "aphasic" clinical picture when patients develop language symptoms, typically a lexical retrieval deficit and agrammatism. Patients then present with a mild production deficit, dropping articles and proposition, while they show clear syntactic comprehension problems in tasks such as sentence-to-picture matching. When the grammatical impairment is prevalent, or becomes apparent during the course of the disease progression, the clinical picture is usually labelled as "progressive non-fluent aphasia" (PNFA). Patients with these kind of production deficits often also develop more generalized motor impairments involving the trunk and limbs and some evolve to a clear corticobasal or progressive supranuclear palsy syndrome. The most common pathological correlate in patients with progressive production deficit is a tauopathy, either corticobasal degeneration or progressive sopranuclear palsy [2]. Less commonly patients can have Pick's disease, ubiquitin positive TDP43-related inclusions (FTLD-U).

Prevalent semantic disorders

Other patients present with prevalent anomia, single-word comprehension and non-verbal semantic impairments. In the early stage, patients may present with a prominent word-finding impairment in spontaneous speech and severe anomia in confrontation naming tasks, with apparently preserved non-verbal semantics. A non-verbal semantic deficit is almost invariably present if tested with items that are sufficiently low-familiarity. The non-verbal deficits include object, people and environmental sound identification deficits but word comprehension problems usually prevail. This is the typical syndrome of "semantic dementia" (SD), associated to left anterior temporal lobe (ATL) atrophy [3, 4]. While prevalent left ATL damage is clearly linked to the classical presentation of SD, atypical clinical syndromes may arise when the right ATL is the most affected. Patients with greater right than left atrophy also show a more prominent behavioural syndrome, with severe loss of empathy, emotional processing deficits, personality changes and compulsive behaviours (see above). Pathologically, SD has been consistently associated with FTLD-U pathological, although cases of Pick's disease and AD are less commonly identified [5].

Prevalent phonological/short-term memory disorders

Another clinical presentation is characterised by prominent anomia and repetititon impairment. Gorno Tempini and colleagues [1] described ten patients whose clinical presentation was characterized by slow speech (without articulation deficits) and impaired sentence comprehension and naming, but spared single word comprehension and semantics. On voxel-based morphometry analysis (VBM) this group was characterized by a distinctive pattern of atrophy involving the left posterior temporal cortex and inferior parietal lobule. A further analysis of this clinical phenotype was conducted in six new cases, based on an extensive neuropsychological evaluation including an experimental

ISSN 1387-2877/11/$27.50

study of phonological loop functions (auditory and visual span tasks with digits, letters, and words) [7]. The study indicated that speech rate was slow, with long word-finding pauses. Grammar and articulation were preserved, although phonological paraphasias could be present. Repetition and comprehension were impaired for sentences but preserved for single words, and naming was moderately affected. Investigation of phonological loop functions showed that patients were severely impaired in digit, letter, and word span tasks. Performance did not improve with pointing, was influenced by word length, and did not show the normal phonological similarity effect. For each patient, a voxel-wise, automated analysis of MRI or SPECT data were conducted. Atrophy or decreased blood flow was consistently found in the posterior portion of the left superior and middle temporal gyri and inferior parietal lobule. These findings support the idea that logopenic progressive aphasia (LPA) is a distinctive variant of primary progressive aphasia. Cognitive and neuroimaging data indicate that a deficit in phonological loop functions may be the core mechanism underlying the LPA clinical syndrome. The LPA clinical picture is consistent and in most patients is characterised by anomia, hesitations and slow language production and severely defective repetition, especially evident for low-probability sentences. However, some cases also show prominent phonological errors in production and possibly greater white matter involvement of the arcuate fasciculus. The differential diagnosis with PNFA becomes problematic in these cases because phonological paraphasias can easily be mistaken for motor speech errors, especially in the contest of decreased speech rate. A careful evaluation of all domains of speech and language is mandatory in these cases, since early correct diagnosis can have important clinical and therapeutical implications. LPA is most often caused by Alzheimer's disease, and these patients could therefore be candidates for experimental AD therapies.

Conclusions

To summarise, in the case of progressive aphasias, the phenotype is a predictor of the brain location of pathology, which bears a probabilistic relation with the type of pathology. Progressive production impairments have been associated with tau pathology, in particular if associated with apraxia of speech. Prominent semantic disorders appear to be associated with ubiquitin-positive pathology, compatible with a TDP-43 proteinopathy. The phonological/short-term memory forms, on the other hand, appear to be often associated with evidence of cortical amyloid on PET and Alzheimer pathology at autopsy. It is thus clinically relevant to be able to identify the existence of consistent associations between a set of relatively common clinical presentations and the underlying neuropathology.

References

[1] Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, Johnson JK, Weiner MW, Miller BL (2004) Cognition and anatomy in three variants of Primary Progressive Aphasia. *Ann Neurol* **55**, 335-346.

[2] Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, Parisi JE, Hauser MF, Witte RJ, Boeve BF, Knopman DS, Dickson DW, Jack CR Jr, Petersen RC (2006) Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain* **129**, 1385-1398.

[3] Hodges JR, Patterson K, Oxbury S, Funnell E (1992) Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain* **115**, 1783-1806.

[4] Snowden JS, Goulding PJ, Neary D (1989) Semantic dementia: a form of circumscribed cerebral atrophy. *Behavioural Neurol* **2**, 167-182.

[5] Knibb JA, Xuereb JH, Patterson K, Hodges JR (2006) Clinical and pathological characterization of progressive aphasia. *Ann Neurol* **59**, 156-165.

[6] Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, Perani D, Garibotto V, Cappa SF, Miller BL (2008) The logopenic/phonological variant of primary progressive aphasia. *Neurology* **71**, 1227-1234.

Corticobasal Degeneration and Corticobasal Syndrome: Lumping Versus Splitting

Barbara Borroni
Centre for Ageing Brain and Neurodegenerative Disorders, University of Brescia, Brescia, Italy

Abstract

Current clinical criteria for Corticobasal Syndrome (CBS) describe this disorder as an asymmetric, akinetic-rigid syndrome, levodopa-resistant, associated with prominent apraxia, cortical sensory loss, focal reflex myoclonus, dystonia, alien limb phenomena, and without early dementia. Conversely, Corticobasal Degeneration (CBD) defines autopsy findings characterized by cortical degeneration with swollen 'achromatic' neurons, neuronal loss in the substantia nigra and extensive neuronal and glial cytoplasmic tau-positive inclusions. Patients with clinically classic CBS have a wide spectrum of pathologies, ranging from CBD to Alzheimer's disease (AD).

Recently, predictors of neuropathological features in patients with CBS have been studied. By retrospective, autopsy-confirmed studied, it has been demonstrated that early episodic memory impairment versus early behavioral abnormalities appear to best differentiate AD and CBD, respectively. Moreover, temporoparietal atrophy suggests AD, whilst, more focal atrophy predominantly involving the premotor and supplemental motor areas suggests CBD or Progressive Supranuclear Palsy pathology. As increased cerebrospinal (CSF) fluid Tau and decreased CSF Abeta are reliable markers of AD, it has been suggested that these might be used in clinical practice to identify AD pathology in CBS patients.

In the present review, the overlap between CBD and CBS will be reported, and the predictors of neuropathological hallmarks in CBS discussed. Identifying markers of pathology and the associated clinical and biological features is of crucial importance for therapeutic choices in CBS patients.

Text

Current clinical criteria for Corticobasal Syndrome (CBS) describe this disorder as an asymmetric, akinetic-rigid syndrome, levodopa-resistant, associated with prominent apraxia, cortical sensory loss, focal reflex myoclonus, dystonia, alien limb phenomena, and without early dementia [1]. As originally conceived, neuropathology of the disease was considered as a specific disorder, namely Corticobasal Degeneration (CBD), characterized by cortical degeneration with swollen 'achromatic' neurons, neuronal loss in the substantia nigra and extensive neuronal and glial cytoplasmic tau-positive inclusions [1]. Unfortunately, the predictive value of this syndrome for underlying pathology is poor [2], and there is growing evidence that patients with clinically classic CBS have a wide spectrum of pathologies, ranging from CBD to Alzheimer's disease (AD). Moreover, in the recent years, frontotemporal lobar degeneration with tau-negative and TDP-43 immunoreactive inclusions (FTLD-TDP) has been found at autopsy of sporadic CBS cases [3].

Moreover, by a genetic point of view, patients with classical CBS might bear pathogenetic mutations within *Microtuble Associated Protein Tau (MAPT)* [4, 5] and within *Progranulin* [6–8], thus leading to either tau-positive or TDP-43 positive inclusions, respectively.

These observations open a new chapter in the field of CBS-CBD, in light of future therapeutic interventions aimed at targeting tau pathology or other neuropathological abnormalities. The identification of CBS patients who have really tau-positive inclusions, and which type, and those with TDP43 inclusions or other neuropathological features is mandatory.

A recent interesting workof autopsy cases at Queen Square Brain Bank for Neurological Disorders [9] has reviewed the cases with either clinical diagnosis of CBS or neuropathological diagnosis of CBD. The authors reported that only almost 25% of CBS cases had CBD pathology. These patients had unilateral presentation, clumsy useless limb, limb apraxia and myoclonus. However, the others CBS patients had AD or Progressive Supranuclear Palsy pathology. Conversely, CBD neuropathology can present very commonly with clinical picture closely resembling Progressive Supranuclear Palsy. These patients, termed as CBD-Richardson's syndrome, had delayed onset of vertical supranuclear palsy (more than 3 years after symptom onset) and predominantly downgaze abnormalities [9].

Interestingly, the pathological prediction of primary tauopathy is more accurate, and the clinical presentation of CBS or Progressive Supranuclear Palsy-like syndrome was 100% specific for a primary tauopathy, as the neuropathological hallmarks will be those of

CBD or Progressive Supranuclear Palsy (i.e. 4-repeat tauopathies) or frontotemporal dementia/Pick's disease (i.e. 3-repeat tauopathy) [9].

In clinical grounds, there is a urgent need of biological and neuroimaging markers able to identify neuropathological correlates in CBS patients. Only recently, predictors of neuropathological features in patients with CBS have been considered. By retrospective, autopsy-confirmed studied, patients presenting as CBS and having either CBD (CBS-CBD) or AD (CBS-AD) pathology have been compared. One study did not find any differences in regard to neuropsychological profile, although CBS-AD were younger at onset, more likely to have myoclonus and less likely to have tremor [10]. Another work demonstrated that early episodic memory impairment versus early behavioral abnormalities appear to best differentiate CBS-AD and CBS-CBD, respectively [11].

Moreover, imaging patterns of atrophy in CBS vary according to pathologic diagnosis, and might be of help in identifying AD and CBD during life. Using automated and unbiased voxel-based morphometry (VBM) techniques, Josephs and colleagues reported that CBS-AD showed greater loss in both inferior and parietal cortices than CBS-CBD [2]. These findings suggest that in subjects presenting CBS prominent temporoparietal atrophy may be a clue to the presence of AD pathology. Conversely, more focal loss predominantly in the posterior frontal lobes is a signature of CBS-CBD.

From the same group, it has been reported that imaging patterns of atrophy in CBS vary according to the presence of either tau or TDP43 pathology [12]. Widespread atrophy pointed towards a pathological diagnosis of AD or frontotemporal dementia with TDP43 inclusions. On the contrary, more focal atrophy predominantly involving the premotor and supplemental motor area suggested CBD or Progressive Supranuclear Palsy [12]. Moreover, among those with TDP43 inclusions, CBS patients always presented type 3 according to MacKenzie criteria [13, 14].

Along with neuroimaging, biological markers hold the premises to be of help in differentiating neuropathologcal hallmarks in CBS. Up to now, the most worldwide recognized biological markers are cerebrospinal fluid (CSF) Tau and Abeta measurements. A few studies on CSF markers in CBS are already available, reporting conflicting results. In two studies, CSF Tau protein dosage was significantly higher in CBS than healthy controls [15, 16], whereas other studies showed no significant differences between CBS and patients affected by neurodegenerative diseases with distinct tau-related pathology [17, 18].

As increased cerebrospinal (CSF) fluid Tau and decreased CSF Abeta are reliable markers of AD (i.e. Tau/Abeta > 1) [19, 20], it might be suggested that these biological markers might be used in clinical practice to identify AD pathology in CBS patients.

In a recent work [21], it has been reported that patients with classical CBS have two distinct profiles of CSF Tau/Abeta ratio, twenty percent presenting with an AD-like (increased CSF Tau, decreased CSF Abeta, with CSF Tau/Abeta > 1) pattern and the others presenting a non-AD pattern (nAD-like). No differences in demographic characteristics were detected between groups, and apraxia scores were comparable. Compared to nAD-like CBS, AD-like patients reported earlier memory impairment as well as worse psychomotor speed and language dysfunctions. Conversely, nAD-like patients had a more severe akinetic extrapyramidal syndrome. Finally, in AD-like CBS patients, CSF and neuropsychological profiles were corroborated by greater hypoperfusion in those areas typically affected by AD, namely hippocampus, parahyppocampal region, precuneus and posterior cingulate, bilaterally [21].

The findings described above represent the starting point of future studies, prompted at identifying markers of pathology and the associated clinical and biological features in CBS patients. The identification of the underlying pathological abnormalities is mandatory for a correct therapeutic approach.

References

[1] Litvan I, Bathia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, Quinn N, Sethi KD, Shults C, Wenning GK; Movement Disorders Society Scientific Issues Committee (2003) Movement disorders society scientific issues committee report: SIC task force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Mov Disord* **18**, 467-486.

[2] Josephs KA, Whitwell JL, Boeve BF, Knopman DS, Petersen RC, Hu WT, Parisi JE, Dickson DW, Jack CR Jr (2010) Anatomical differences between CBS-corticobasal degeneration and CBS-Alzheimer's disease. *Mov Disord* **25**, 1246-1252.

[3] Tartaglia MC, Sidhu M, Laluz V, Racine C, Rabinovici GD, Creighton K, Karydas A, Rademakers R, Huang EJ, Miller BL, Dearmond SJ, Seeley WW (2010) Sporadic corticobasal syndrome due to FTLD-TDP. *Acta Neuropathol* **119**, 365-374.

[4] Rossi G, Marelli C, Farina L, Laurà M, Maria Basile A, Ciano C, Tagliavini F, Pareyson D (2008) The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. *Mov Disord* **23**, 892-895.

[5] Spillantini MG, Van Swieten JC, Goedert M (2000) Tau gene mutations in frontotemporal dementia and parkinson-

ism linked to chromosome 17 (FTDP-17). *Neurogenetics* **2**, 193-205.

[6] Masellis M, Momeni P, Meschino W, Heffner R Jr, Elder J, Sato C, Liang Y, St George-Hyslop P, Hardy J, Bilbao J, Black S, Rogaeva E (2006) Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain* **129**(Pt11), 3115-3123.

[7] Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, Spina S, Coppola G, Karydas AM, Stewart H, Johnson N, Hsiung GY, Kelley B, Kuntz K, Steinbart E, Wood EM, Yu CE, Josephs K, Sorenson E, Womack KB, Weintraub S, Pickering-Brown SM, Schofield PR, Brooks WS, Van Deerlin VM, Snowden J, Clark CM, Kertesz A, Boylan K, Ghetti B, Neary D, Schellenberg GD, Beach TG, Mesulam M, Mann D, Grafman J, Mackenzie IR, Feldman H, Bird T, Petersen R, Knopman D, Boeve B, Geschwind DH, Miller B, Wszolek Z, Lippa C, Bigio EH, Dickson D, Graff-Radford N, Hutton M (2007) Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C–>T (Arg493X) mutation: an international initiative. *Lancet Neurol* **6**, 857-868.

[8] Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, de la Sayette V, Belliard S, Vercelletto M, Meyrignac C, van Broeckhoven C, Lambert JC, Verpillat P, Campion D, Habert MO, Dubois B, Brice A; French research network on FTD/FTD-MND (2007) Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* **131**(Pt3), 732-746.

[9] Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, Paviour DC, Lees AJ (2010) Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* **133**(Pt7), 2045-2057.

[10] Hu WT, Rippon GW, Boeve BF, Knopman DS, Petersen RC, Parisi JE, Josephs KA (2010) Alzheimer's disease and corticobasal degeneration presenting as corticobasal syndrome. *Mov Disord* **24**, 1375-1379.

[11] Shelley BP, Hodges JR, Kipps CM, Xuereb JH, Bak TH, Hu WT (2009) Is the pathology of corticobasal syndrome predictable in life? *Mov Disord* **24**, 1593-1599.

[12] Whitwell JL, Jack CR Jr, Boeve BF, Parisi JE, Shelley BP, Ahlskog JE, Drubach DA, Senjem ML, Knopman DS, Petersen RC, Dickson DW, Josephs KA (2010) Imaging correlates of pathology in corticobasal syndrome. *Neurology* **75**, 1879-1887.

[13] Mackenzie IR, Munoz DG, Kusaka H, Yokota O, Ishihara K, Roeber S, Kretzschmar HA, Cairns NJ, Neumann M (2010) Distinct pathological subtypes of FTLD-FUS. *Acta Neuropathol*, in press.

[14] Rohrer JD, Geser F, Zhou J, Gennatas ED, Sidhu M, Trojanowski JQ, Dearmond SJ, Miller BL, Seeley WW (2010) TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia. *Neurology* **75**, 2204-2211.

[15] Urakami K, Wada K, Arai H, Sasaki H, Kanai M, Shoji M, Ishizu H, Kashihara K, Yamamoto M, Tsuchiya-Ikemoto K, Morimatsu M, Takashima H, Nakagawa M, Kurokawa K, Maruyama H, Kaseda Y, Nakamura S, Hasegawa K, Oono H, Hikasa C, Ikeda K, Yamagata K, Wakutani Y, Takeshima T, Nakashima K (2001) Diagnostic significance of tau protein in cerebrospinal fluid from patients with corticobasal degeneration or progressive supranuclear palsy. *J Neurol Sci* **183**, 95-98.

[16] Paraskevas GP, Kapaki E, Liappas I, Theotoka I, Mamali I, Zournas C, Lykouras L (2005) The diagnostic value of cerebrospinal fluid tau protein in dementing and nondementing neuropsychiatric disorders. *J Geriatr Psychiatry Neurol* **18**, 163-173.

[17] Borroni B, Malinverno M, Gardoni F, Alberici A, Parnetti L, Premi E, Bonuccelli U, Grassi M, Perani D, Calabresi P, Di Luca M, Padovani A (2008) Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. *Neurology* **71**, 1796-1803.

[18] Noguchi M, Yoshita M, Matsumoto Y, Ono K, Iwasa K, Yamada M (2005) Decreased beta-amyloid peptide42 in cerebrospinal fluid of patients with progressive supranuclear palsy and corticobasal degeneration. *J Neurol Sci* **237**, 61-65.

[19] Bian H, van Swieten JC, Leight S, Massimo L, Wood E, Forman M, Moore P, de Koning I, Clark CM, Rosso S, Trojanowski J, Lee VM, Grossman M (2008) CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* **70**(19 Pt 2), 1827-1835.

[20] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* **6**, 734-746.

[21] Borroni B, Premi E, Agosti C, Alberici A, Cerini C, Archetti A, Lanari A, Paghera L, Lucchini S, Caimi L, Padovani A (2011) Cerebrospinal fluid AD-like pattern in Corticobasal Syndrome: evidence for a distinct disorder. *J Neurol Neurosurg Psychiatry*, in press.

Amyotrophic Lateral Sclerosis and Dementia: The Borders

Lucio Tremolizzo, Emanuela Susani, Matteo De Rosa, Michela Strozzi, Laura Marzorati, Ildebrando Appollonio and Carlo Ferrarese
Department of Neurology, ALS clinic, S. Gerardo Hospital, Monza and Department of Neuroscience and Biomedical Technology, University of Milano-Bicocca, Milan, Italy

Amyotrophic lateral sclerosis (ALS) is the most frequent adult-onset motoneuron disease, defined by the coexistent progressive degeneration of the first and the second motoneuron. This disease is known since the second half of 1800 and, over time, several concepts related to its clinical phenotype, progression, etiology and pathology have been repeatedly revised. In particular, the ideas that cognitive dysfunction might be a consistent part of the clinical phenotype and that a continuum between ALS and frontotemporal dementia (FTD) might exist, are among the most revolutionary changes observed in the field. Moreover, the evidence of such an association leads necessarily to the need of rethinking about the modalities by which support and end-life procedures are proposed to these patients.

The concept of selective motoneuron involvement had already been challenged some years ago, especially by neuropathologists, who reported more widespread degeneration with respect to the original descriptions. However, the "classical" clinical picture was still not encompassing cognitive impairment in 1994, with the first edition of the El Escorial diagnostic criteria for ALS: in fact, cognitive dysfunction specifically excluded a diagnosis of ALS at the moment [1]. Such limit was subsequently removed in 1998, with the first revision of these diagnostic criteria, due to the increasing evidence of an association between dementia and ALS [2]. As a matter of fact, searching the literature, this association has been reported since the beginning of the last century [3], but these cases were invariably regarded as anecdotal and atypical, hence implicitly denying the possibility of a frequent relationship. Until about 2003, these accounts recurred regularly during the years, enriching the picture by adding new confirmatory findings due to the application of novel techniques, such as, for example, imaging [4–8]. After 2003, this phenomenon rapidly attenuates and then disappears: indeed, FTD in ALS was not any more regarded as a rarity worth of an *ad hoc* report, but was felt as one possible expression of the clinical phenotype generated by the disease.

Collecting data over the years, the researchers arrived to hypothesize that ALS and FTD spectrum might not only overlap but even share same of the pathological mechanisms, belonging, therefore, to the same nosological entity. A major advancement in the field was obtained when Lomen-Hoerth and colleagues demonstrated that, if adequately tested, up to half of ALS patients might fulfill the Neary criteria for FTD diagnosis [9]. Nevertheless, there is still considerable variability regarding the frequency of cognitive impairment in patients affected by ALS, possibly due to limited samples and power, difficulties in collecting and interpreting data, limited follow-up due to the fast progression of the underlying disease, and to the presence of confounding factors during test administration (dysarthria, upper limb weakness). On the other hand, investigating the phenomenon by inverting the factors, the demonstration that about 15% of FTD patients might present clinical and/or EMG evidence compatible with motoneuron disease appears [10]. Besides, even basic research suggests that an ALS-FTD continuum might exist (see Fig. 1). For example, voxel based morphometry MR data allowed to demonstrate *in vivo* the presence of frontotemporal atrophy in ALS patients, even when they express classical motoneuron phenotypes in the absence of overt cognitive deterioration [11]. SPECT and PET studies repeatedly demonstrated in the same brain areas metabolic anomalies that were more pronounced in the presence of cognitive dysfunction. Then, even when clinically silent, frontotemporal dysfunction might be evidenced in ALS patients early in the course of the disease: preliminary longitudinal studies show that this phenomenon might worsen over time, sometimes leading to the surfacing of a full-blown dementia, although the literature is not clear on this issue [12]. Neuropathology also confirms this ALS-FTD overlap, arriving to the definition of a disease, in which the recently recog-

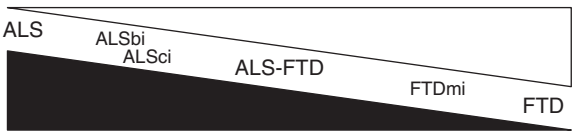

Fig. 1. The existence of a phenotypic continuum might be hypothesized between ALS and FTD. Motor (black) and cognitive (white) symptoms might considerably overlap in the clinical phenotype determining in few cases a real full-blown coexistence. Since EMG and/or clinical motor impairment might be expressed in FTD patients, we might suggest the term FTDmi (FTD with motor impairment) for indicating them.

nized TDP-43-based pathology often expresses itself within the entire fronto-temporal lobes and beyond. Again, FTD cases expressing spinal cord motoneuron alterations typical of ALS might be observed in the absence of motor dysfunction [13].

Approaching to a diagnosis

A recent workshop held in London, Canada, established the consensus criteria for diagnosing FTD in ALS [14]. Indeed, this intent goes beyond few nosological minutiae, since cognitive dysfunction, besides arising several important issues in the relationship with the patient, might be also an indicator of a poor prognosis. According to the consensus participants, axis II evaluation focuses on cognitive and behavioural characterization, essentially arriving to define five categories of ALS patients: "pure" ALS (no evidence of cognitive impairment) – ALSci (ALS with cognitive impairment) – ALSbi (ALS with behavioural impairment) – ALS-FTD, with the possible presence of either one of the three different FTD phenotypes (behavioural FTD, non fluent progressive aphasia, semantic dementia) – ALS in comorbidity with dementias other than FTD. ALSbi can be diagnosed in presence of two of the support characteristics among Neary criteria [15], as evidenced from by at least two sources among patient colloquium/observation, caregiver reports, and structured interview. On the other hand, ALSci can be diagnosed if a value lower than the fifth percentile is scored by the patients in at least two different tests of executive functions, taking into consideration the premorbid level. In both cases, concomitant psychiatric or other disorders must be excluded, as they might act as confounders. Apathy and depression might lead to overdiagnose cognitive dysfunction, although the physician should be aware of the possibility that this sometimes might appear later during the course of the disease. Furthermore, pseudo-bulbar impairment, respiratory insufficiency, sleep disturbances, delirium, generalized asthenia, drug effects should be considered as potential variables, and current recommendations stress the necessity of minimizing the effects of these disease-related confounders when preparing neuropsychological test batteries.

Conclusions

In conclusion, although ALS is known since more than 100 years the array of the possible nuances of the clinical phenotype are only now surfacing in a structured manner to the attention of the clinician. It is also important to note that, although the presence of an ALS-FTD continuum can not be denied any more, the wide spectrum of clinical phenotypes expressed by ALS patients, in addition to common mechanisms, might underlie a certain degree of diversity in the involved pathological processes. A more deep comprehension of this complex relationship might therefore be auspicated, since it might reveal, for example, to play a critical role in the future attempts of optimizing therapeutic trials for ALS.

References

[1] Brooks BR (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. *J Neurol Sci* **124**, 96-107.

[2] Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* **1**, 293-299.

[3] Ziegler LH (1930) Psychotic and emotional phenomena associated with amyotrophic lateral sclerosis. *Arch Neurol Psychiatry* **24**, 930-936.

[4] Mitsuyama Y, Takamiya S (1979) Presenile dementia with motor neuron disease in Japan. A new entity? *Arch Neurol* **36**, 592-593.

[5] Wikstrom J, Paetau A, Palo J, Sulkava R, Haltia M (1982) Classic amyotrophic lateral sclerosis with dementia. *Arch Neurol* **39**, 681-683.

[6] Neary D, Snowden JS, Mann DM, Northen B, Goulding PJ, Macdermott N (1990) Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiatry* **53**, 23-32.

[7] Gentileschi V, Muggia S, Poloni M, Spinnler H (1999) Fronto-temporal dementia and motor neuron disease: a neuropsychological study. *Acta Neurol Scand* **100**, 341-349.

[8] Marquard R, Bergida R, Muller R, Becker I, Wada M, Kurz A (2003) Dementia accompanying motor neuron disease – 7 cases. *Dement Geriatr Cogn Disord* **16**, 98-102.

[9] Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B (2003) Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* **60**, 1094-1097.

[10] Lomen-Hoerth C, Anderson T, Miller B (2002) The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* **59**, 1077-1079.

[11] van der Graaff MM, de Jong JM, Baas F, de Visser M (2009) Upper motor neuron and extra-motor neuron involvement in amyotrophic lateral sclerosis: a clinical and brain imaging review. *Neuromuscul Disord* **19**, 53-58.

[12] Talbot PR, Goulding PJ, Lloyd JJ, Snowden JS, Neary D, Testa HJ (1995) Inter-relation between "classic" motor neuron disease and frontotemporal dementia: neuropsychological and single photon emission computed tomography study. *J Neurol Neurosurg Psychiatry* **58**, 541-547.

[13] Nakano I (2000) Frontotemporal dementia with motor neuron disease (amyotrophic lateral sclerosis with dementia). *Neuropathology* **20**, 68-75.

[14] Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, Murphy J, Shoesmith C, Rosenfeld J, Leigh PN, Bruijn L, Ince P, Figlewicz D (2009) Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* **10**, 131-46.

[15] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**, 1546-1554.

Diagnostic Flow Chart for the Atypical Variants of Dementia

Paolo Caffarra[a,b,c], Simona Gardini[a] and Letizia Concari[a]
[a]*Department of Neuroscience, University of Parma, Parma, Italy*
[b]*Department of Psychology, University of Hull, Hull, UK*
[c]*Consultorio Disturbi Cognitivi, AUSL, Parma, Italy*

Diagnostic flow chart for the atypical variants of dementia

The differential diagnosis in dementia represents a fundamental clinical step and it is essential to dispose of effective screening tools for this process. Cognitive, neuroimaging, genetic and bioumoral markers are the main instruments used in the assessment of degenerative diseases, able to differentiate the variants of dementia. Although this process is nowadays complex and the evolution of dementia might follow a non linear progress, the use of these instruments in clinical practice is of primary importance and their validity has to be supported by experimental evidences. A number of information about diagnostic criteria for the principal forms of dementia, such as Alzheimer's and Parkinson's diseases are ready for use, while less procedural diagnostic information are available regarding the atypical forms of dementia. The principal aim of this paper is the to provide some practical guidelines which might help in the differential diagnosis of atypical variants of degenerative diseases. A comprehensive diagnostic flow chart for the atypical forms of dementia is shown in Fig. 1.

Posterior Cortical Atrophy (PCA)

Diagnostic criteria indicated that PCA has an insidious onset and gradual progression, presents a cognitive profile characterized by disabling visual deficits in the absence of any ocular disease, preserved anterograde memory, insight and awareness of illness in the absence of tumor, stroke, parkinsonism or visual hallucinations [1]. Other features that might be found are visuoconstructive apraxia, topographical disorientation, and

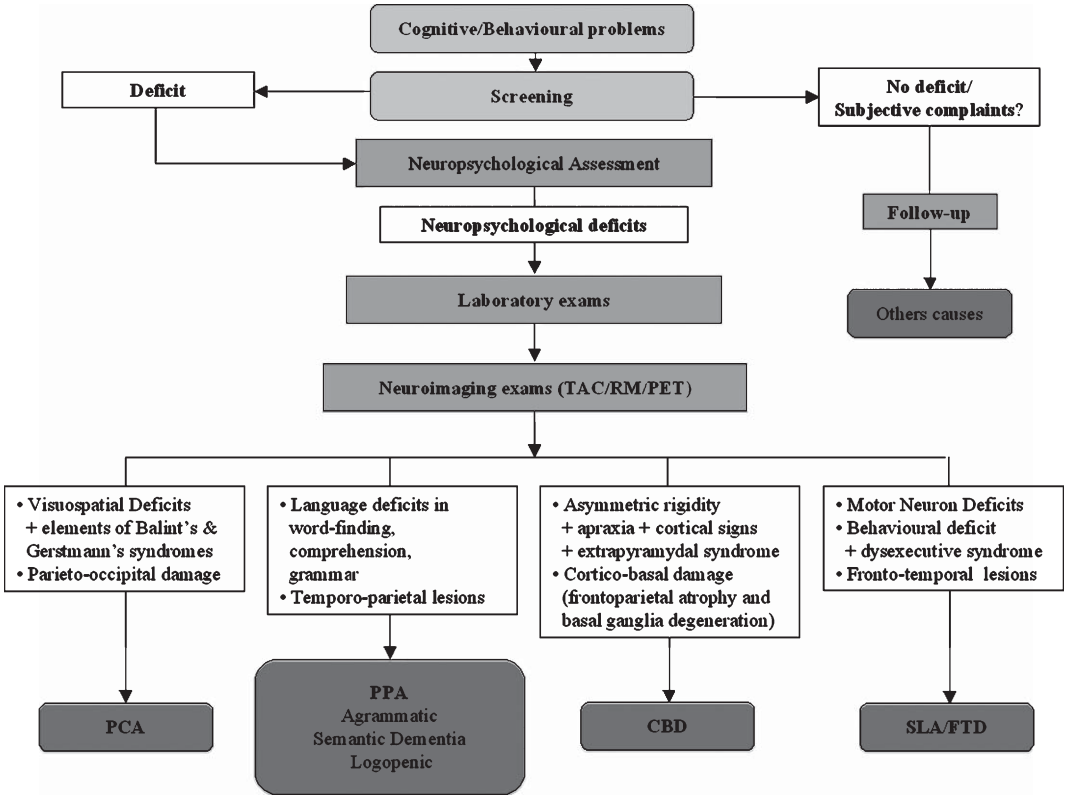

Fig. 1. Diagnostic flow chart for the atypical variants of dementia.

some elements of the Gerstmann's and Balint's syndromes. PCA showed deficit of visual imagery, spatial representation and episodic-autobiographical memory [2]. Further features might be pre-senile onset, alexia, ideomotor or dressing apraxia, and prosopoagnosia. These clinical characteristics should be associated with structural and/or functional brain dysfunction in parieto-occipital regions (Brodmann areas 17 and 18) involved in visual processing [1]. In these areas typical AD neuropathological features, such as neurofibrillary tangles and neuritic plaques, are usually found [3]. Genetic pathway showed similar findings to typical Alzheimer's Disease (AD), with homogeneous proportion of APOE $\varepsilon 4$ and tau haplotypes.

Primary Progressive Aphasia (PPA)

Primary progressive aphasia presents with degeneration of language process without generalized dementia, usually associated with damage of the language dominant network. Different variants of PPA have been described [4, 5]. Agrammatic or nonfluent subtype is characterized by abnormality in syntax or other aspects of grammar, preserved single word comprehension and poor fluency, corresponding to a deficit mainly in left inferior frontal regions. Semantic dementia shows abnormality in single word comprehension, impaired naming, circumlocutions and paraphasia in the output and relatively conserved grammar and fluency, caused by atrophy of bilateral anterior and inferior temporal regions, with a larger extensively in the left hemisphere. Logopenic progressive aphasia featured with word-finding difficulties, phonemic paraphasias, slow speech, impaired naming, preserved grammar and articulation, corresponding to left temporo-parietal degeneration. Automated methods of analysis combining both neuroimaging and linguistic features could help in the differential diagnosis of PPA variants [4]. APOE $\varepsilon 4$ allele frequency is different in the different variants: 50–60% in the logopenic aphasia, and 20% in the semantic dementia and non fluent aphasia [6].

Corticobasal Degeneration (CBD)

When CBD was described for the first time, it was believed to be essentially a movement disorder. More recently CBD has been considered as a neurodegenerative disease of late middle age, generally associated with a clinical presentation known as corticobasal syndrome (CBS), whose core clinical features are progressive asymmetric rigidity and apraxia, accompanied by signs of cortical (alien limb phenomena, cortical sensory loss, myoclonus) and extrapyramidal dysfunction (dystonia, bradykinesia and tremor) [7]. Recently more attention has been given to speech deficits and frontal symptoms as possible early clinical signs of CBD [8]. The involvement of frontal structures is supported by neuropsychological evaluation showing deficits of attention, concentration, executive function, praxis, language and visuospatial domains [9]. Structural (CT, MRI) and functional (PET, SPECT) neuroimaging also supports the clinical diagnosis, with evidence of asymmetric fronto-parietal atrophy, as well as a common involvement of basal ganglia, lateral ventricles and cerebral peduncles [10]. CBD is generally described as a tauopathy, pathologically characterized by neuronal loss, gliosis and tau deposition in grey and white neocortex, basal ganglia and brainstem [11]. Thus, the criteria for suspecting a clinical diagnosis of CBD focuses on clinical and radiological typical features.

Frontotemporal Dementia-Motor Neuron Disease (MND-FTD)

Frontotemporal dementia (FTD) is one of the most common early-onset dementia (average age at onset around 50–60 years, although approximately 10% have an age of over 70 years) and is clinically characterised by progressive behavioural changes and frontal executive deficits and/or selective language difficulties, evolving into a severe dementia, accompanied by progressive cerebral hypometabolism and atrophy of frontal and temporal lobes [12]. The clinical spectrum of FTD includes several syndromes: the behavioural variant of FTD (bvFTD) and the language variants semantic dementia (SD) and progressive non-fluent aphasia (PNFA). In the last years more interest has been attributed to the well documented overlap of FTD with motor neuron disease (MND-FTD) [13]. Motor neuron disease (MND) has long been defined a pure motor system disease, but recent evidence has led to consider it as a multisystemic disease, as up to 50% of patients with MND have cognitive impairment that in 10–15% of cases fulfils the criteria for frontotemporal dementia (FTD), thus designated as MND-FTD. Furthermore, a similar proportion of patients with FTD develop MND. Although all the subtypes of FTD can occur with MND, this association is most commonly seen with bvFTD, occasionally with PNFA and in rare cases with SD. Pathological findings also support this overlap: MND patients and a subset of FTD

cases have demonstrable TAR DNA binding protein 43 (TDP-43) inclusions, typically found in bvFTD. As demonstrated by structural and functional neuroimaging techniques, the degree of neuronal loss affects primarily the anterior cingulate gyrus, substantia nigra and amygdala, as well as middle and inferior frontal gyri, more commonly in the right hemisphere [14]. Less frequently neuronal cytoplasmic and intra-nuclear inclusions immunoreactive for FUS/TLS (fused in sarcoma/translated into liposarcoma) have been found in pathological cases of FTLD-U without TDP-43 inclusions [15]. Patients with FTD-MND have the shortest survival, amongst all patients with a diagnosis of FTD, with a mean of 3 years. The pattern of cognitive deficits is characterized by personality disorders, mental rigidity, disinhibition, impulsivity, loss of insight, lack of foresight and planning, distractibility, irritability and deficits on frontal-executive tests. Apathy, which is reported in 50% of patients, can alternate with irritability and sometimes aggression. Psychotic features and bizarre behaviour may also be present and can resolve within a few months leaving the patients placid. When performed, the neuropsychological examination in non-demented individuals with ALS, is characterized by deficits in a frontotemporal pattern, with posterior association cortices relatively spared. Language difficulties may also appear with isolated anomia becoming more severe during the time course of the disease. Severe progressive non-fluent aphasia is a frequent feature and written language tends to be involved later.

References

[1] Tang-Wai DF, Graff-Radford NR, Boeve BF, Dickson DW, Parisi JE, Crook R, Caselli RJ, Knopman DS, Petersen RC (2004) Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology* **63**, 1168-1174.

[2] Gardini S, Concari L, Pagliara S, Ghetti C, Venneri A, Caffarra P (2011) Visuo-spatial imagery impairment in posterior cortical atrophy: a cognitive and SPECT study. Accepted for publication in *Behavioural Neurology*.

[3] Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR (2007) Focal cortical presentations of Alzheimer's disease. *Brain* **130**, 2636-2645.

[4] Wilson SM, Ogar JM, Laluz V, Growdon M, Jang J, Glenn S, Miller BL, Weiner MW, Gorno-Tempini ML (2009) Automated MRI-based classification of primary progressive aphasia variants. *NeuroImage* **47**, 1558-1567.

[5] Mesulam MM, Wieneke C, Rogalski E, Cobia D, Thompson C, Weintraub S (2009) Quantitative template for subtyping primary progressive aphasia. *Arch Neurol* **66**, 1545-1551.

[6] Cummings J (2008) Primary progressive aphasia and the growing role of biomarkers in neurological diagnosis. *Annals of Neurology* **64**, 361-364.

[7] Boeve BF, Lang AE, Litvan I (2003) Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol* **54**, S15-S19.

[8] Lladó A, Sánchez-Valle R, Rey MJ, Ezquerra M, Tolosa E, Ferrer I, Molinuevo JL, Catalan collaborative Study Group for FTLD (2008) Clinicopathological and genetic correlates of frontotemporal lobar degeneration and corticobasal degeneration. *J Neurol* **255**, 488-494.

[9] Pillon B, Blin J, Viadailet M, Deweer B, Sirigu A, Dubois B, Agid Y (1995) The neuropsychological pattern of corticobasal degeneration. *Neurology* **45**, 1477-1483.

[10] Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, Parisi JE, Dickson DW (2006) Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology* **66**, 41-48.

[11] Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, Jellinger K, Lantos PL, Lippa CF, Mirra SS, Tabaton M, Vonsattel JP, Wakabayashi K, Litvan I; Office of Rare Diseases of the National Institutes of Health (2002) Office of rare diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol* **61**, 935-946.

[12] Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC (2010) Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. Accepted for publication in *J Neurol Neurosurg Psychiatry*, 2010 Oct. 22 [Epub ahead of print].

[13] Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG (2005) The evolution and pathology of frontotemporal dementia. *Brain* **128**, 1996-2005.

[14] Lillo P, Hodges JR (2010) Cognition and behaviour in motor neurone disease. *Current Opinion in Neurology* **23**, 638-642.

[15] Neumann M, Rademakers R, Roeber S, Baker M, Kretzschmar HA, Mackenzie IR (2009) A new subtype of frontotemporal lobar degeneration with FUS pathology. Brain **132**, 2922-2931.

Predictors of Successful Ageing: Epidemiological Evidence

Laura Fratiglioni
Aging Research Center, Karolinska Institutet, Stockholm, Sweden

It is the first time in the history of mankind that so many people are surviving up to 85 years or longer. The aging of the population is a relatively new phenomenon that started in the industrialized countries and has now also reached less developed areas of the world. We are living longer on all the continents and this positive phenomenon has focused attention on all the chronic disorders that are strongly related to age, such as cognitive impairment, dementia and multimorbidity. This increasing focus on the negative aspects of aging has already led to deleterious consequences for individuals who are frightened, for example, at the appearance of the first signs of memory decline which are immediately related to the development of a dramatic disease such as Alzheimer's disease. We need to implement a more scientific attitude in our approach to health and illness in old age. Aging covers a long period of our lives, and is not necessarily linked to disease and disability, and most importantly aging is ongoing for the whole of life.

During recent decades population-based studies on health in aging have made tremendous progress. The risk of disease and disability in late life is considered to be a result of the complex interaction of genetic susceptibility, biological factors, and environmental exposure, experienced over the whole life span. Different factors associated with an increased risk of mortality, morbidity and disability will be discussed taking into account their different biological mechanisms and grades of epidemiological evidence. Several factors affect the health of elderly people, but current evidence strongly supports the potential role of midlife vascular risk factors, nutrition and psychosocial factors in the pathogenetic process and clinical manifestation of several age-related diseases such as dementia and multimorbidity. It is expected that interventions leading towards the optimal control of vascular risk factors; the maintenance of a socially-integrated lifestyle and mentally-stimulating activities may lead to a healthier life after the age of 70.

Lifestyle and Rate of Progression of Cognitive Decline: Results of the SINDEM Cohort Study

Massimo Musicco
Consiglio nazionale delle Ricerche, Istituto di Tecnologie Biomediche, Segrate (Milan), IRCCS Fondazione Santa Lucia Rome, Italy

In Alzheimer disease (AD) early deterioration in memory is followed by progressive impairment of other cognitive domains, and is accompanied by a large spectrum of behavioral and psychological symptoms occurring during the entire course of the disease [1, 2]. In individual patients, the time of appearance of clinically relevant events such as severe cognitive impairment or severe BPSD, loss of autonomy, institutionalization and death are difficult to predict [2–6]. This heterogeneity might result from differences in the localization and severity of brain damage, or variations in patients' personalities, life history and risk factors [7]. Studies suggest that presence of extrapyramidal signs and psychosis [8, 9], level of disease severity [5, 10, 11] and education [12, 13]. However, current knowledge is limited due to differences in study populations, factors examined, instruments used for evaluation, and definitions of outcomes. In AD patients, memory impairment represents the prominent and early disturbance and is caused, with any likelihood, by the early and preferential involvement of temporal cerebral areas devoted to memory processes (entorhinal cortex and hippocampus). In contrast, the severity and timing of the involvement of other cognitive domains is heterogeneous, varying from patient to patient.

Authors used different instruments and methodologies to investigate the rate of AD progression but most based the estimate on the general cognitive performance of patients generally measured with the Mini Mental Status Examination (MMSE). However no evidence exists on the capacity of these measures of catching the progression of the pathological process of AD and it is possible that reductions at MMSE might be largely determined by factors only indirectly related to the progression of AD. The use of standardized and agreed measures of progression remains one of the key points for the study of prognostic predictors of AD.

The cohort study promoted by the Italian Association for the Study of Dementias (SINDEM) is aimed at evaluating the natural history of dementias. The idea supporting the study is that a better knowledge of prognostic predictors of AD and of other dementias might give new insight into the pathogenic mechanisms of these diseases besides to be useful for clinicians caring for patients. As of November 2010, 20 neurological centers enrolled 238 newly diagnosed patients with AD. Diagnosis of AD was based on clinical diagnostic criteria (NINCDS-ADRDA criteria). All the enrolled patients were carefully investigated about presence of comorbidities, and on life habits. The neuropsycholgical profile of each patient was characterized according to an extensive battery of test that investigated different cognitive domains. Of the enrolled patients with AD 153 had at least one follow-up visit and could be analyzed and investigated on prognostic predictors. A decrease of 5 points or more in MMSE score in the first 24 months following enrolment was considered as an indicator of disease progression. A 5-point decrease is considered to be a clinically relevant worsening, and is too large a change to be attributed to the intrinsic limits of test reliability. The date of the visit when the 5-point reduction was recorded marked the time of occurrence of the progression. Data were analysed with survival analysis considering the time of occurrence of 5 point decrease at MMSE as the end point. The studied patients had a mean age of 74 year and women represented the 64% of the entire cohort. The mean disease duration since first symptoms was about two years and at enrollment the mean score at MMSE was 18. One fourth of the patients had a decrease of 5 points or more at MMSE during a follow-up period of 24 months.

Preliminary results suggest that more educated patients had more rapid progressions, that more severe involvement of cognitive functions and reduced social and physical activities are negative prognostic factors and that diabetic patients had slower progression rates as compared to non diabetic patients. Albeit preliminary these results support the idea that relevant knowledge on AD can be derived by the study of the natural history of the disease.

References

[1] Burns A, Iliffe S (2009) Alzheimer's disease. *BMJ* **338**, b158.
[2] Marin DB, Green CR, Schmeidler J, Harvey PD, Lawlor BA, Ryan TM, Aryan M, Davis KL, Mohs RC (1997) Noncognitive disturbances in Alzheimer's disease: frequency, longitudinal course, and relationship to cognitive symptoms. *J Am Geriatr Soc* **45**,1331-1338.
[3] Cortes F, Nourhashémi F, Guérin O, Cantet C, Gillette-Guyonnet S, Andrieu S, Ousset PJ, Vellas B, Group R-F

(2008) Prognosis of Alzheimer's disease today: a two-year prospective study in 686 patients from the REAL-FR Study. *Alzheimers Dement* **4**, 22-29.

[4] Holtzer R, Tang MX, Devanand DP, Albert SM, Wegesin DJ, Marder K, Bell K, Albert M, Brandt J, Stern Y (2003) Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* **51**, 953-960.

[5] Morris JC, Edland S, Clark C, Galasko D, Koss E, Mohs R, van Belle G, Fillenbaum G, Heyman A (1993) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part 4. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology* **43**, 2457-2465.

[6] Spalletta G, Baldinetti F, Buccione I, Fadda L, Perri R, Scalmana S, Serra L, Caltagirone C (2004) Cognition and behaviour are independent and heterogeneous dimensions in Alzheimer's disease. *J Neurol* **251**, 688-695.

[7] Snowden JS, Stopford CL, Julien CL, Thompson JC, Davidson Y, Gibbons L, Pritchard A, Lendon CL, Richardson AM, Varma A, Neary D, Mann D (2007) Cognitive phenotypes in Alzheimer's disease and genetic risk. *Cortex* **43**, 835-845.

[8] Stern Y, Mayeux R, Sano M, Hauser WA, Bush T (1987) Predictors of disease course in patients with probable Alzheimer's disease. *Neurology* **37**, 1649-1653.

[9] Scarmeas N, Brandt J, Albert M (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* **62**, 1601-1608.

[10] Drachman DA, O'Donnell BF, Lew RA, Swearer JM (1990) The prognosis in Alzheimer's disease: 'how far' rather than 'how fast' best predicts the course. *Arch Neurol* **47**, 851-856.

[11] Stern RG, Mohs RC, Davidson M, Schmeidler J, Silverman J, Kramer-Ginsberg E, Searcey T, Bierer L, Davis KL (1994) A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *Am J Psychiatry* **151**, 390-396.

[12] Musicco M, Palmer K, Salamone G, Lupo F, Perri R, Mosti S, Spalletta G, di Iulio F, Pettenati C, Cravello L, Caltagirone C (2009) Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. *J Neurol* **256**, 1288-1295.

[13] Scarmeas N, Albert SM, Manly JJ, Stern Y (2006) Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **77**, 308-316.

Vascular Risk Factors and Leukoaraiosis: Results from the LADIS Study

Domenico Inzitari
Department of Neurological and Psichiatric Siences, University of Florence, Florence, Italy

Cerebral white matter changes, also called leukoaraiosis (LA) [1], are frequently observed on computed tomography or magnetic resonance imaging (MRI) in the brains of elderly subjects, particularly in those with vascular risk factors [2]. Since age represents the strongest factor associated with LA, its prevalence is expected to increase in the forthcoming years as a consequence of the progressive aging of the world population. From the clinical point of view, LA has been found associated with motor and gait disturbances, urinary dysfunctions, mood disorders, and cognitive impairment [2]. All these factors notoriously contribute to disability in the elderly.

During the last 10 years, clinical and functional outcomes in 639 elderly patients with LA have been investigated through the European multicenter collaboration called LADIS (Leukoaraiosis And DISability) Study [3], which was started in 2001, supported by the European Union, with the main aim of assessing LA as independent predictor of the transition from an independent functional status to disability in elderly subjects. Final results have shown that the risk of transition or death was more than twofold higher in patients with severe white matter changes compared to those with mild degrees [4]. The LADIS study has also provided evidence that LA has an effect on cognitive decline and dementia, independently of the presence of other types of cerebral lesions, such as infarcts, mainly of the lacunar type, atrophy and medial temporal lobe atrophy (MTA).

The pathogenesis of LA is still a matter of investigation, althoughit is nowadays recognized as one of the ischemic manifestation related to small vessel disease on the brain parenchyma [5]. The vessel lumen restriction is thought to lead to a state of chronic hypoperfusion of the white matter, eventually resulting in degeneration of myelinated fibres as a consequence of repeated selective oligodendrocyte death. This kind of white matter damage is thought to be a form of incomplete infarct or selective necrosis. Alternatively, acute occlusion of a small vessel is hypothesised to occur, leading to focal and acute ischaemia and complete tissue necrosis (pannecrosis): this is the putative mechanism of lacunar infarcts. Other mechanisms such as blood–brain barrier damage, local subclinical inflammation, and oligodendrocytes apoptosis could be involved in small vessel disease and contribute to the final pathological picture [5]. In the neurovascular unit, vessels and cells, including neurons, closely interact, pointing to endothelial dysfunction as a key element [6]. The strong epidemiological association that exists between white matter lesions and vascular risk factors support ischemia as a main contributing factor. Apart from ageing, the most common risk factor for LA is arterial hypertension, followed by diabetes mellitus [7]. All these conditions share a common substrate in the type of alterations induced on the small penetrating arteries and arterioles of the white matter. Moreover, recent findings provide evidence for a remarkable susceptibility of the cerebral circulation to the deleterious effects of Angiotensin-II, raising the possibility that cerebrovascular dysfunction is an early event also in human hypertension [8]. Cerebrovascular impairment can be present in patients who, based on the magnitude of blood pressure elevation, do not yet meet the criteria for hypertension, and although the relevance of these experimental data to human hypertension remains uncertain, they support early preventive interventions in patients with prehypertension, especially in high-risk individuals with other cardiovascular risk factors [8].

Concerning the association of vascular risk factors with LA, LADIS data have confirmed the trend in the association between increasing age, increasing frequency of hypertension, and increasing LA severity, as well as the association of smoked cigarettes with the most severe LA degree [9]. Considering vascular co-morbidities, only frequency of stroke increased along with increasing LA severity. Combining risk factors and comorbidities in the same regression model, history of stroke remained independently associated with LA severity, while history of hypertension did not. However, stratifying for stroke history, the trend in the association between increasing prevalence of hypertension and increasing LA severity was apparent only among subjects without a history of stroke and not among subjects with stroke history. In a multinomial logistic regression model entering with all the other risk factors and comorbidities the variable stroke split into the 2 stroke types, lacunar and non-lacunar stroke, increasing prevalence of lacunar stroke proved the strongest independent factor associated with LA severity. In this model the effect of hypertension was weaker, although still showing an incremental effect, while non-lacunar stroke remained

associated with the most severe degree of LA only [9].

The LADIS Study has also offered the opportunity to study the natural course of LA and lacunes over the 3-year follow-up and to evaluate possible predictors, among which vascular risk factors, for their development [10]. LA progressed in 74% of the subjects, mainly in the subcortical white matter, where LA was also most prevalent at baseline. The majority of new lacunes, which were found in 19% of the subjects, also appeared in the subcortical white matter, mainly of the frontal lobes, whereas most baseline lacunes were located in the basal ganglia. Baseline LA and lacunes predicted both LA progression and new lacunes. Furthermore, previous stroke, diabetes, and blood glucose were risk factors for LA progression. Male sex, hypertension, systolic blood pressure, previous stroke, body mass index, high-density lipoprotein, and triglyceride levels were risk factors for new lacunes [10].

LADIS cross sectional analyses have shown that severe LA was associated with worse cognitive performances, and that among risk factors and comorbidities, diabetes, arterial hypertension and stroke interfered with different cognitive domains [11]. The effect of these vascular risk factors was independent of LA severity, age and education, thus stressing the need to control vascular risk factors in order to prevent cognitive decline in the elderly. Finally, predictors of cognitive decline and dementia have been investigated. LA severity was confirmed as one of the main independent predictors of cognitive decline even when controlling for medial temporal lobe atrophy. LA severity and history of previous stroke were predictors of vascular dementia [12]. Among all vascular risk factors studied, diabetes was the only independent predictor of cognitive decline in the LADIS sample. This effect was independent of LA severity and medial temporal lobe atrophy, suggesting an effect mediated not only by vascular damage or white matter disease, but probably through direct neuronal metabolic damage [12].

In conclusion, the LADIS study has documented a specific role of LA in many aging-related processes, confirming LA as a marker of poor prognosis in terms of cognitive, mood and gait disturbances, and as a predictor of fast transition to a disable status. The understanding of the complex relationship between LA and vascular risk factors is also essential for the identification of potential preventive and therapeutic targets, contributing to reduce the burden of disability and cognitive decline. Preliminary studies indicate that treating hypertension may slow the progression of age-related white matter changes [13]. Now, future research is needed to implement all possible measures able to slow or halt progression of LA and the related disability.

References

[1] Hachinski VC, Potter P, Merskey H (1987) Leukoaraiosis. *Arch Neurol* **44**, 21-23.

[2] Pantoni L, Garcia JH (1995) The significance of cerebral white matter abnormalities 100 years after Binswanger's report: a review. *Stroke* **26**, 1293-1301.

[3] Pantoni L, Basile AM, Pracucci G, Asplund K, Bogousslavsky J, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D (2005) Impact of age-related cerebral white matter changes on the transition to disability – the LADIS study: rationale, design and methodology. *Neuroepidemiology* **24**, 51-62.

[4] Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, Langhorne P, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Pantoni L; LADIS Study Group (2009) Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ* **6**, b2477.

[5] Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* **9**, 689-701.

[6] Iadecola C (2010) The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol* **120**, 287-296.

[7] Pantoni L, Garcia JH (1997) Pathogenesis of leukoaraiosis: a review. *Stroke* **28**, 652-659.

[8] Capone C, Faraco G, Park L, Cao X, Davisson RL, Iadecola C (2010) The cerebrovascular dysfunction induced by slow pressor doses of angiotensin-II precedes the development of hypertension. *Am J Physiol Heart Circ Physiol*, 2010 Oct. 22. [Epub ahead of print]

[9] Basile AM, Pantoni L, Pracucci G, Asplund K, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D; LADIS Study Group (2006) Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. The LADIS (Leukoaraiosis and Disability in the Elderly) Study. *Cerebrovasc Dis* **21**, 315-322.

[10] Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Scheltens P, Barkhof F; LADIS Study Group (2008) Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. *Stroke* **39**, 1414-1420.

[11] Verdelho A, Madureira S, Ferro JM, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'Brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D; LADIS Study (2007) Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. *J Neurol Neurosurg Psychiatry* **78**, 1325-1330.

[12] Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D; LADIS Study (2010) White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology* **13**, 160-167.

[13] Dufouil C, Chalmers J, Coskun O, Besançon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C; PROGRESS MRI Substudy Investigators (2005) Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation* **13**, 1644-1650.

Dual Tasking and Memory Binding in Alzheimer's Disease

Sergio Della Sala, Jennifer A. Foley, Mario A. Parra and Robert H. Logie
Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

The ideal assessment of AD

Early and accurate diagnosis of Alzheimer's disease (AD) has important prognostic and therapeutic implications. It is also crucial that the patients involved in treatment trials have the correct initial diagnosis and can be followed up over time [1].

Physiological biomarkers are available. However, they are often invasive (e.g. lumbar punctures), expensive, not widely available and require specialist facilities and staff. Even the promising morphometric analysis of hippocampal volume based on MRI requires a great deal of specialised expertise, and automatized versions have yet to be validated [2]. Therefore, cognitive tests that could reliably discriminate between AD, normal ageing, chronic depression and non-AD dementias would represent the ideal assessment.

They should also be theoretically and psychometrically sound, ensuring that the results are reliable and valid, and are both sensitive and specific to AD.

Limitation of current cognitive assessment

Memory disorder is the cognitive hallmark of AD. However, memory problems also occur in many other disorders, including depression and even healthy normal aging, leading to diagnostic uncertainty. So, memory tests are sensitive but not specific to the disease. Moreover, performance on such tests reaches floor very early in the disease making them a poor marker of disease severity and progression.

Dementia severity scales are useful to assess overall severity, but like episodic memory tests, they are not specific to AD and have poor sensitivity for testing cognitive impairment in well educated individuals.

The available test batteries involve several tests that require extended testing times, and extensive training to administer and score. They also tend to be constructed from tests chosen to assess a wide range of different cognitive abilities. This maximises the chances that one or more tests will show an impairment. However, a major disadvantage is that this kind of broad test battery may detect cognitive impairments that could reflect any of a range of underlying neuropathologies. This is of very limited help in diagnosing the specific underlying pathology in a particular patient. In recent years, there has been significant advancement in published scientific evidence for specific cognitive impairments that can identify the early stages of AD, but do not appear in other conditions that can be mistaken for AD such as chronic depression or even healthy ageing. This has led to the possibility of using short, objective cognitive assessments that are targeted as diagnostic aids for AD. Here, we describe the evidence for this form of targeted cognitive assessment.

Dual tasking

Our previous work over two decades [e.g. 3–7] has shown that in addition to the well-established memory disorder, people with AD demonstrate impairment in the ability to do two things at once, or 'dual tasking'. These findings have been replicated by other researchers [8]. Importantly, when individual performance levels on single tasks are equated across groups, dual task is not affected by age [4, 6, 9].

In contrast, people with AD always show a striking impairment in dual tasking ability, in computer based laboratory tasks [4, 5, 7, 10], in paper and pencil versions [6, 10] and in everyday tasks [e.g., 11, 12]. This impairment appears to be specific to AD and not present in people with other disorders that can be confused with AD, such as chronic depression, even when severity of episodic memory disorder is equated between groups [13]. Crucially, unlike memory measures, the dual task did not discriminate between the group with depression and the healthy controls.

Unlike many other cognitive tests, the dual task measure does not show practice-based improvements with repeated testing. It is also an objective performance measure, so is not prone to biases in response that can affect questionnaire based measures. It has high internal consistency, as evidenced by the large number of studies reporting the same findings with different task combinations [6]. Moreover, it has been shown that it is the ability to perform two tasks at the same time that is a problem for AD, not an effect of overall demand of a difficult task on their damaged cognitive system [5]. Unlike many memory tests, it has no ceiling and, as the assessment is adjusted to individual level

of ability, it can be used to assess patients with AD for longer. Moreover, the dual task measure is brief, non-invasive, inexpensive, easily portable and usable by primary health care staff with a minimal amount of training.

Dual tasking proves to be a very specific measure of the cognitive deficits associated with AD. However, in the clinical versions of the tasks its sensitivity was not ideal [6], and this led to a refinement of the procedure.

Short-term memory binding

To increase the sensitivity, while maintaining high specificity for AD we have developed a version of dual task performance based on short-term feature binding in memory, which has the further advantage of not being dependent on language.

Short-term memory (STM) binding is the memory function that enables the integration and temporary retention of the multiple features of objects, such as their shape and colour [14]. Our version of this paradigm assesses memory for single features (e.g., shape or colour only) and for the binding of these features (coloured shapes) (Fig. 1A) and there is no learning involved.

STM binding of colour and shape does not decline as people age [15] and is not affected by chronic depression [16], but it shows a clear and specific effect in sporadic AD [17]. Moreover, a selective deficit of bindings held in visual STM was also observed in carriers of the mutation E280A of the Presenilin-1 gene who will subsequently develop familial AD in 100% of cases [18]. Of note, these carriers were otherwise completely asymptomatic based on standard neuropsychological measures (Fig. 1B). Finally, the impairment was not found in fronto-temporal dementia, Parkinson's disease, vascular dementia, or dementia with Lewy bodies, all of which showed equivalent performance in memory for binding and memory for individual features, demonstrating that the STM binding impairment is specific to AD. Hence, STM binding appears to be a promising candidate as a preclinical as well as a clinical marker that is specific to AD and could be used to aid diagnosis as well as to assess disease progression.

Conclusion

Both the classic dual tasking and the STM binding paradigm specifically differentiate between the cognitive deficits associated with AD, and those deficits associated with both healthy aging and a variety of other dementias. These specifically refined tests take into account 'floor-effects' as the disease progresses and age-related and intergroup differences in cognitive impairments. They also provide for an internal control in the testing protocol, and do not show evidence of learning or improvement with practice, giving them high reliability.

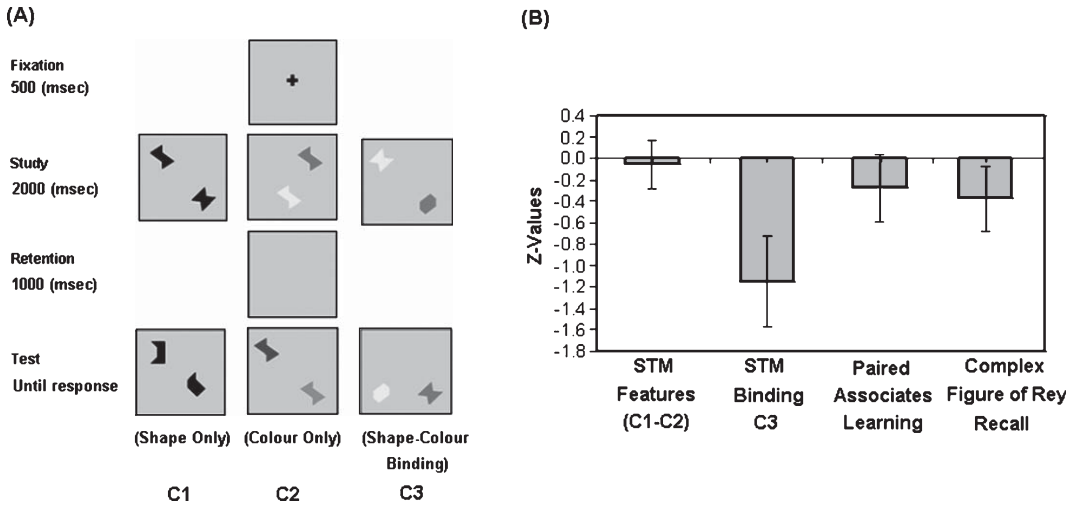

Fig. 1. (A) STM binding paradigm: two conditions assessed STM for single features (C1 and C2) and one assessed STM for bound features (C3). The participants detected changes between the Study and Test display. Changes were in the Test display and consisted of new features replacing studied features (C1 and C2) or features swapping between objects (C3). (B) Data collected from asymptomatic carriers of the E280A-PS1 mutation. The condition assessing STM binding was the only task that showed impaired performance in carriers.

References

[1] Tarawneh R, Holtzman DM (2010) Biomarkers in translational research of Alzheimer's disease. *Neuropharmachology* **59**, 310-322.

[2] De Meyer G, Shapiro F, Vanderstichele H, Vanmechelen E, Engelborghs S, de Deyn PP, Coart E, Hansson O, Minthon L, Zetterberg H, Blennow K, Shaw L, Trojanowski JQ (2010) Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Arch Neurol* **67**, 949-956.

[3] Baddeley AD, Logie R, Bressi S, Della Sala S, Spinnler H (1986) Dementia and working memory. *Q J Exp Psychol* **38**, 603-618.

[4] Baddeley AD, Bressi S, Della Sala S, Logie RH, Spinnler H (1991) The decline of working memory in Alzheimer's disease: a longitudinal study. *Brain* **114**, 2521-2542.

[5] Logie RH, Cocchini G, Della Sala S, Baddeley A (2004) Is there a specific executive capacity for dual task coordination? Evidence from Alzheimer's disease. *Neuropsychology* **18**, 504-513.

[6] Della Sala S, Foley JA, Beschin N, Allerhand M, Logie RH (2010) Assessing dual task performance using a paper-and-pencil test: normative data. *Arch Clin Neuropsychol* **25**, 410-419.

[7] Della Sala S, Cocchini G, Logie RH, MacPherson SE (2010) Dual task during encoding, maintenance and retrieval in Alzheimer disease and healthy ageing. *J Alzheimers Dis* **19**, 503-515.

[8] Sebastian MV, Menor J, Elosua MR (2006) Attentional dysfunction of the central executive in AD: Evidence from dual task and perseveration errors. *Cortex* **42**, 1015-1020.

[9] Della Sala S, Baddeley A, Papagno C, Spinnler H (1995) Dual-task paradigm: a means to examine the central executive. *Annals of the New York Academy of Sciences* **769**, 161-171.

[10] MacPherson SE, Della Sala S, Logie RH, Wilcock GK (2007) Specific AD impairment in concurrent performance of two memory tasks. *Cortex* **43**, 858-865.

[11] Alberoni M, Baddeley A, Della Sala S, Logie R, Spinnler H (1992) Keeping track of a conversation: impairments in Alzheimer's disease. *Int J Geriatr Psychiatry* **7**, 639-646.

[12] Cocchini G, Della Sala S, Logie RH, Pagani R, Sacci L, Spinnler H (2004) Dual task effects of walking whilst talking in Alzheimer's disease. *Rev Neurol* **160**, 74-80.

[13] Kaschel R, Logie RH, Kazén M, Della Sala S (2009) Alzheimer's Disease, but not ageing or depression, affects dual-tasking. *J Neurol* **256**, 1860-1868.

[14] Zimmer HD, Mecklinger A, Lindenberger U (2006) Levels of binding: types, mechanisms, and functions of binding. In *Handbook of binding and memory, perspective from cognitive neuroscience*, Zimmer HD, Mecklinger A, Lindenberger U, eds., Oxford University Press, New York, pp. 3-25.

[15] Brockmole JR, Parra MA, Della Sala S, Logie R (2008) Do binding deficits account for age-related decline in visual working memory? *Psychon Bull & Rev* **15**, 543-547.

[16] Parra MA, Abrahams S, Logie RH, Della Sala S (2010) Visual short-term memory binding in Alzheimer's disease and depression. *J Neurol* **257**, 1160-1169.

[17] Parra MA, Abrahams S, Fabi K, Logie R, Luzzi S, Della Sala S (2009) Short-term memory binding deficits in Alzheimer's Disease. *Brain* **132**, 1057-1066.

[18] Parra MA, Abrahams S, Logie R, Mendez LG, Lopera F, Della Sala S (2010) Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain* **133**, 2702-2713.

Cognitive Neuroscience of Decision Making: Clinical Implications

Stefano F. Cappa
Vita-Salute University and San Raffaele Scientific Institute, Milan, Italy

The neuropsychology of reasoning and decision-making is an interdisciplinary sector of research devoted to build a neurobiological model of inferential and decisional-processes, by means of the integration of methods from several disciplines (psychology, economics and neuroscience). The interest of this sector has initially focused on the neural correlates of reasoning. A new interdisciplinary field has recently developed, which specifically aims at investigating how inferences and decisions are made by the brain in several domains.

The implications of this area of research for clinical neurology are multiple, and involve several diseases, such as Parkinson's disease, motor neuron disease and fronto-temporal dementia. In particular, the behavioural variant of frontotemporal dementia is characterized by a clinical picture, in which the main components of social cognition and decision making are involved. The presentation is dominated by changes in personality and social conduct, reflecting in its early stages by the involvement of ventromedial limbic structures, responsible for social-emotional intelligence. The patients can be euphoric, highly distractible, logorrhoic and restless. In contrast, they can also be apathetic and lacking initiative. They may show dishinibition in alimentary and sexual behaviour. They tend to be inflexible, and not to adapt to environmental requests. They show defective empathy, as manifested by shallow, tactless and rude behaviours. The socially inadequate actions and verbal responses may lead to violation of moral norms and legal infringements. Overall, these clinical features can be interpreted theoretically within the framework of contemporary social cognitive neuroscience [1].

In the early stages, social cognition impairment can be observed in the absence of other cognitive dysfunction. This is important to note clinically, because it means that the profile of neuropsychological performance on cognitive tests, including "frontal lobe" and "executive function" can be totally unremarkable. This is due to the fact that these tests typically evaluate dorsolateral, rather than ventromedial frontal functions. The following aspects needs to be carefully considered, on the basis of detailed history taking as well as of experimental tests.

Empathy

Loss of empathy is frequently reported by relatives and friends as a "personality change". The *Interpersonal Reactivity Index* can be used for a formal assessment [2]. The questionnaire evaluated both cognitive (perspective taking and fantasy) and emotional (personal distress and emotional concern) aspects of empathy. Bv-FTD patients show a selective impairment in *perspective taking,* while a more global dysfunction was present in patients with a diagnosis of semantic dementia (SD, see below). The patients are totally unaware of these personality changes.

Emotion recognition

The ability to recognize emotional facial expression can be considered as a pre-requisite for understanding and sharing emotional states. Many studies have shown defective recognition, in particular of negative emotions, by FTD patients [3]. It is noteworthy, however, that when the task involves more ecologically valid stimuli (short videoclips), and evaluates subjective ratings, behavioural and autonomic responses to basic emotional situations, the FTD patients do not appear to be impaired in comparison to controls [4]. In contrast, in a more complex context, using *The Awareness of Social Inference Test* (TASIT), bvFTD showed a defective comprehension of sarcasm [5].

Theory of mind

The ability to attribute mental states to others, and to understand them, has been linked to frontomedial cortex function, and has been found to be defective in FTD [6]. This impairment has been connected to defective comprehension of social situations [7].

Moral reasoning

The violation of social norms is a frequent reason for the early suspicion of a diagnosis of FTD. These include violation of traffic norms, theft, sexual aggression, etc. It has been suggested that these manifestations reflect the acquired loss of moral sense, as a sort of "moral agnosia". This does not seem to be

the case, as Bv-FTD patients are usually fully aware of the norms if questioned directly. They appear to solve moral dilemmas in a deliberate, purely cognitive way, without emotional colouring. This may lead to "utilitarian" responses, which reflect the lack of empathy and appropriate emotional responses [8].

A recent challenge in the field has been the identification of a subgroup of patients fulfilling the clinical criteria for Bv-FTD, who fail to show disease progression [9]. Long-term follow-up studies are needed to clarify the status of what has been called the "phenocopy" of Bv-FTD.

Similar disorders can be found in other disease conditions, which are characterised by the pathological involvement of the decision-making-social cognition networks. This is of course not limited to neurological disorders, but also to many psychiatric conditions, in which the same structures can be involved by different mechanisms, such as anatomical disconnection or neurochemical dysfunction.

References

[1] Adolphs R (2009) The social brain: neural basis of social knowledge. *Annu Rev Psychol* **60**, 693-716.

[2] Rankin KP, Kramer JH, Miller BL (2005) Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cogn Behav Neurol* **18**, 28-36.

[3] Rosen HJ, Pace-Savitsky K, Perry RJ, Kramer JH, Miller BL, Levenson RW (2004) Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. *Dement Geriatr Cogn Disord* **17**, 277-281.

[4] Werner KH, Roberts NA, Rosen HJ, Dean DL, Kramer JH, Weiner MW, Miller BL, Levenson RW (2007) Emotional reactivity and emotion recognition in frontotemporal lobar degeneration. *Neurology* **69**, 148-155.

[5] Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR (2009) Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. *Brain* **132**, 592-603.

[6] Gregory C, Lough S, Stone V, Erzinclioglu S, Martin L, Baron-Cohen S, Hodges JR (2002) Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* **125**, 752-764.

[7] Eslinger PJ, Moore P, Troiani V, Antani S, Cross K, Kwok S, Grossman M (2007) Oops! Resolving social dilemmas in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* **78**, 457-460.

[8] Mendez MF, Anderson E, Shapira JS (2005) An investigation of moral judgement in frontotemporal dementia. *Cogn Behav Neurol* **18**, 193-197.

[9] Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR (2006) Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* **63**, 1627-1631.

The Role of Emotions in Decisional Processes: How Neuroscience can Impact Evaluation of Patients' Ability to will and to Act

Paolo Nichelli[a], Mariangela Molinari[b] and Francesca Benuzzi[a]
[a]*Department of Neurosciences, University of Modena e Reggio Emilia, Modena, Italy*
[b]*Servizio di Neuropsicologia Clinica, Ausl di Modena, Modena, Italy*

When we think about emotions we often refer to our conscious experience of them, the internal state of mind that is associated with complex physiological activities in our brain and in our body.

However, within an evolutionary perspective, those physiological activities that are connected with what we call emotions are nothing more than shortcuts to provide living organisms with adaptive reactions to complex challenges of the environment.

Within this framework, emotions can be seen as tools that humans share with animals to provide fast decisions. Sometimes we tend to oppose emotional to "logical" decision, the latter being based on rationale methods of contrasting choices using the principle of utility, whereby assigning weighted criteria assesses the value of each option. However, emotions can be hardly excluded by decision-making processes. Indeed, it can be argued than when this happens decisional ability is seriously impaired.

This is the case of patients with acquired brain damage to brain areas involved in emotional processing (i.e., prefrontal cortex) and that appear to fail in everyday life social relationship due to their difficulty in making decisions. In recent decades, neuroscience is providing a robust evidence of the role of the prefrontal cortex in cognition, emotion regulation, control of impulsive behavior, and moral reasoning. These findings converge in demonstrating that there are individuals that, due to their brain pathology, are capable of differentiating right from wrong but are, nonetheless, incapable of appropriately regulating their behavior.

Demonstrating the strong link between brain pathology, emotion regulation, and decision-making poses completely new perspectives to the criminal justice system as long as individuals might not always be considered fully responsible of their acts based on the rationale knowledge of the legal rules.

Assessment of Capacity

Andrea Stracciari
Neurology Unit, S. Orsola-Malpighi University Hospital, Bologna, Italy

Definition of capacity

Capacity is has been defined as "*something that distinguishes between a person who is capable of making a decision and whose choice must therefore be respected [irrespective of the 'reasonableness' of that decision] from one who requires others to make decisions for him/her*" [1].

Conversely, lack of capacity constitutes a status that is defined by functional deficits (due to mental or cognitive impairment) judged to be sufficiently severe as to make the person currently unable to meet the demands of a specific decision-making situation weighed in the light of its potential consequences [2, 3].

The term capacity – *capacity to act* in Italy, *competence* or *mental capacity* elsewhere [2–6] – is common in legal arenas, and should be distinguished from the terms "*decision-making capacity*" and "*clinical competence*", often adopted in health-related literature. Capacity mainly refers to a legal concept, which implies the capacity to decide or undertake actions that may have legal implications. Only a judge can declare the lack of capacity, whereas a physician assesses whether someone has sufficient capacity to make a decision – *decision-making capacity*. This assessment is based on a broad spectrum of individual abilities related to cognitive, functional, emotional and social competences, which allow a person to perform different actions ranging from simple daily activities to complex choices like voting, making medical decisions, testifying, managing financial resources, marrying, living alone, etc., based both on the patients' decisional autonomy and *ad hoc* cognitive skills. Assessment of these '*capacities*' is the concern of the clinician and is the basis of relevant information which will permit a legal decision. The distinction between *legal capacity* and *clinical capacity* lies in the role of the person making the judgment. Judges have sole jurisdiction to declare a person as having lost legal capacity, therefore meaning the person needs someone else to make decisions for him/her. Physicians do the same in their daily practice, e.g., stating that a patient is not competent to decide whether to undergo surgery. In short, the terms *capacity* and *decision-making capacity* distinguish between legal and medical judgments, but their outcomes are similar: a person can no longer choose for himself.

This gives rise to the question of whether capacity is a monolithic attribute or whether it can be divided into specific subtypes?

Viewing incapacity as a global rather than a situation-specific deficit has long been a given for clinicians, but this is now questionable [3–5, 7, 8]. There are many clear-cut cognitive processes supporting capacity as a whole, such as the ability to process information, reason, make a decision, and articulate that decision. However there is emerging evidence that specific competencies are governed by distinct rules and that the type and level of ability needed to be competent to make one type of decision may be different from those needed to make another. For example, the criteria for determining financial or testamentary capacities are reasonably different from those used in medical decisions. This new approach has implications for assessments in this area. From a legal point of view, capacity is now mostly defined in terms of specific competencies. Current theories of decision-making capacity recognize this specificity when determining whether a patient still has the capacity to make that decision and courts have begun to accept that competency is situation-specific and that the determination that a person lacks the capacity to do something – e.g., economic management – does not mean that the patient lacks capacity for any other purpose.

Clinicians involved in capacity assessment thus have a duty to identify the specific capacity at issue and to tailor the assessment using methods and procedures designed to assess that particular capacity.

Assessment of capacity

There is widespread agreement that a capacity assessment is a clinical assessment, but issues such as who should do it, how the assessment should be performed, and what level of mental/cognitive impairment defines lack of capacity remain largely unresolved and there are no gold-standard measuring instruments. In any case, clinicians must have a clear understanding of the complex concept of decision-making capacity and awareness that capacity may be fluctuating, intermittent and situation-specific.

Different models of decision-making capacity has been proposed, all identifying four key conditions [8, 9]: the ability to state and express a decision (*expressing*), the ability to comprehend the meaning of in-

formation relevant to choice (*understanding*), the ability to recognize how information applies to a person, such as risks and benefits of the choice (*appreciation*), and the ability to compare options and logically infer the consequences of choices (*reasoning*). These key conditions concern how the choice is made, not its nature: capacity does not depend on the fact that the subject makes a decision which seems "reasonable" to most people, and conversely a bizarre choice must not be considered an index of incapacity *per se* [9, 10]. However, this does not imply that the quality of the decision should be neglected in capacity judgement, since the consequences of the choice have to be considered. Contextually, the examiner must be sure that the subject is absolutely autonomous and aware in his decision-making.

Clinical capacity assessment should reasonably follow a multistep and multidimensional process, incorporating clinical and neuropsychological examinations designed to test both general cognitive status and those cognitive domains underlying the decision-making key conditions, as well as assessment of knowledge specific to the type of capacity being investigated. The ideal assessment of capacity should include:

a) detailed history-taking with the patient and other informants (relatives, caregivers, friends, general practitioner, etc.) and a neuropsychiatric examination;
b) a battery of neuropsychological tests exploring both general cognition and specific domains involved in abilities for which the assessment of capacity is requested. The decision-making neurocognitive substrate is mainly represented by supramodal functions – attention, esecutive functions, memory – and these must constitute the core of capacity assessment [5, 7];
c) assessment of abilities related to single capacities needs ecological evaluations and functional ability measuring tools including "*purpose-built*" tests, scales, questionnaires and vignettes. Many *ad hoc* scales have been proposed [5, 11] but may prove unreliable in the absence of a careful and competent clinical and neuropsychological assessment;
d) interpretation of test results on the basis of the patient's disease (clinical features, course of illness) and the complexity of the choice, grading them in relation to known legal standards;
e) identification and recommendation of adapting strategies and environment supports aimed to improve subjects' decisional capacities, and cognitive training of domains involved in decision-making capacity.

Ethical issues

Determination of incompetence is one of the most extreme infringements of a citizen's rights [3], because legal revocation of capacity may result in loss of basic individual freedoms. For this reason, capacity must be presumed until one has proof to the contrary.

Clinicians involved in the assessment of capacity must be aware of the professional controversies and ethical challenges inherent in the assessment of capacity, including the current lack of methodological and procedural guidelines.

Ethical challenges include balancing the need to respect an individual's freedom of choice and self-determination (ethical principle of *autonomy*) with the need to promote the individual's safety and protection (principles of *beneficence* and *non maleficence*), attaining professional competence and selecting, using and interpreting assessment methods appropriately [7, 11, 12].

Conclusions

Capacity assessment requires the utmost responsibility. It also requires a high degree of professional competence as well as adherence to biomedical ethics, balancing respect for patients' self-determination and the need to protect them. Continuing medical education and improvement of the assessment tools in this field are essential for a more appropriate approach to the human rights of cognitively impaired patients.

References

[1] Wong JG, Clare CH, Gunn MJ, Holland AJ (1999) Capacity to make health care decisions: its importance in clinical practice. *Psychol Med* **29**, 437-446.
[2] Grisso T (1994) Clinical assessment for legal competency of older adults. In *Neuropsychological Assessment of Dementia and Depression in Older Adults: A Clinicians Guide*, Storandt M, VandenBos, GR, eds. American Psychological Association, Washington, DC, pp. 119-139.
[3] Grisso T, Appelbaum (1998) *Assessing Competence to Consent to Treatment*. Oxford University Press, New York.
[4] Karlawish J (2008) Measuring decision-making capacity in cognitively impaired individuals. *Neurosignals* **16**, 91-98.
[5] Sullivan K (2004) Neuropsychological assessment of mental capacity. *Neuropsychol Rev* **14**, 131-142.
[6] Mental Capacity Act (2005) www.opsi.gov.uk/-acts/acts 2005/20050009.htm

[7] Moye J, Marson DC (2007) Assessment of decision-making capacity in older adults: an emerging area of practice and research. *J Gerontol B Psychol Sci Soc Sci* **62**, P3-P11.

[8] Ganzini L, Volicer L, Nelson W, Derse A (2003) Pitfalls in assessment of decision-making capacity. *Psychosomatics* **44**, 237-243.

[9] Defanti CA, Tiezzi A, Gasparini M, Gasperini M, Congedo M, Tiraboschi P, Tarquini D, Pucci E, Porteri C, Bonito V, Sacco L, Stefanini S, Borghi L, Colombi L, Marcello N, Zanetti O, Causarano R, Primavera A (2007) Ethical questions in the treatment of subjects with dementia. Part I. Respecting autonomy: awareness, competence and behavioural disorders. *Neurol Sci* **28**, 216-231.

[10] Stracciari A, Bianchi A, Sartori G (2010) *Neuropsicologia Forense*. Il Mulino, Bologna.

[11] Moberg PJ, Kniele K (2006) Evaluation of competency: ethical considerations for neuropsychologists. *Appl Neuropsychol* **13**, 101-114.

[12] Beauchamp TL, Childress JF (2001) *Principles of Biomedical Ethics*. Oxford University Press, UK.

Using Biology to Untie the Gordian Knot of Alzheimer's Disease

George Perry[a,b], Mark A. Smith[b], Gemma Casadesus[c], Hyoung-gon Lee[b], Paula I. Moreira[d], Rudy J. Castellani[e] and Xiongwei Zhu[b]
[a] *UTSA Neuroscience Institute, University of Texas at San Antonio, San Antonio, TX, USA*
[b] *Departments of Pathology, Case Western Reserve University, Cleveland, OH, USA*
[c] *Department of Neurosciences, Case Western Reserve University, Cleveland, OH, USA*
[d] *University of Coimbra, Coimbra, Portugal*
[e] *University of Maryland, Baltimore, MD, USA*

Alzheimer's disease (AD) is marked by a multitude of structural and biochemical changes that played a major role in the definition of the disease more than a century ago by Alois Alzheimer [1]. Intraneuronal neurofibrillary tangles composed of highly phosphorylated cytoskeletal proteins and extracellular amyloid-β surrounded by neuronal and glial responses define the complex senile plaques [2] (Fig. 1). With a vast array of changes, sorting out the initial changes from subsequent changes has been like untying a Gordian knot. Every pathway examined is fundamentally altered to establish what appear to be *de novo* relationships between systems. The past 30 years of pulling apart pleotrophic changes has only advanced a better understanding of the pathways, not the system. As Alexander did for the knot, cutting complexity is required. Biology is the sword, the elegant simplicity of evolution, natural selection and biological self organization is as much a guide for the properties of chronic pathology as they are for normal physiology. Biological properties are based on selective advantage for offspring survival. Biology confers emergent properties based on selective advantage, not self-destruction. We argue that the emergent properties of AD are based on responses of the brain to injury, amyloid-β is upregulated with injury [3], and it is not a surprise that it is upregulated during the greatest insult that we all face, aging [4]. The apparent pathology of AD may play a protective role [5] responsible for the survival of neurons for years following onset of AD [6]. That amyloid-β, tau, oxidative stress, and altered signal transduction are also seen in brain injury supports the view of these changes as responses to the disease that are essential to maintain normal function, and their removal can be detrimental [7]. This view moves the argument from pathology, end stage or incipient, molecular biology or genetic, to the biology driving disease years prior to any apparent abnormality. Biology is driven by responses that favor survival not self-destruction. In contrast, the amyloid cascade fundamentally favors the brain that destroys itself, for no apparent selective advantage.

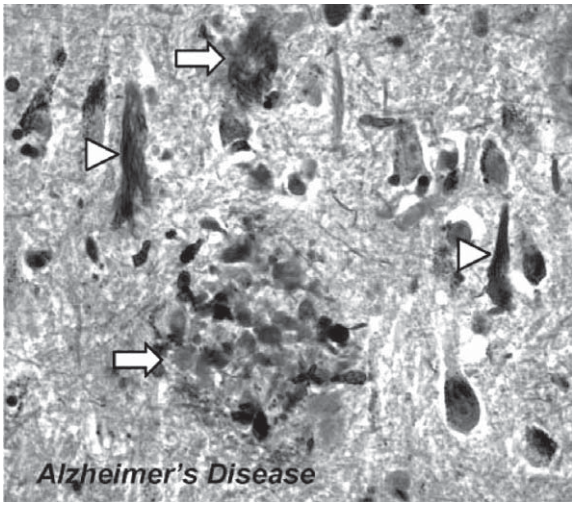

Fig. 1. In Alzheimer's disease, the brain develops numerous abnormal pathological structures that contribute to the loss of cognitive function. Extracellular senile plaques composed of amyloid-β (arrows) and intraneuronal formation of neurofibrillary tangles (arrowheads) result in a Gorgian knot of tissue disruption.

Understanding the biology of normal as well as pathological aging (AD) opens the field to new therapeutic avenues that focus on promoting successful responses of the brain to maintain normal function. And while that might be to remove amyloid-β from some compartments, it might also be to promote its accumulation in others. Instead of focusing on cures, which so far have been ineffective for age-related chronic conditions, the interest should be on therapeutics to increase the number of high-quality years. This change in focus in AD research is already happening and offers the hope of a greater understanding of what we can do to patients in our lifetime.

References

[1] Perry G, Avila J, Kinoshita J, Smith MA (2006) *Alzheimer's Disease: A Century of Scientific and Clinical Research*, IOS Press, Amsterdam.
[2] Castellani RJ, Rolston RK, Smith MA (2010) Alzheimer disease. *Dis Mon* **56**, 484-546.
[3] Cochran E, Bacci B, Chen Y, Patton A, Gambetti P, Autilio-Gambetti L (1991) Amyloid precursor protein and ubiquitin immunoreactivity in dystrophic axons is not unique to Alzheimer's disease. *Am J Pathol* **139**, 485-489.
[4] Davies L, Wolska B, Hilbich C, Multhaup G, Martins R, Simms G, Beyreuther K, Masters CL (1988) A4 amyloid protein depo-

sition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. *Neurology* **38**, 1688-1693.

[5] Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, Smith MA (2001) Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* **60**, 759-767.

[6] Morsch R, Simon W, Coleman PD (1999) Neurons may live for decades with neurofibrillary tangles. *J Neuropathol Exp Neurol* **58**, 188-197.

[7] Perry G, Nunomura A, Raina AK, Smith MA (2000) Amyloid-beta junkies. *Lancet* **355**, 757.

The Genetics of Alzheimer's Disease and Other Tauopathies

John Hardy[a], Rita Guerreiro[a], Selina Wray[a], Raffaele Ferrari[a,b] and Parastoo Momeni[b]
[a]*Rita Lilla Weston Laboratory, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK*
[b]*Department of Internal Medicine 4C127 Texas Tech University Health Sciences Center, Lubbock, TX, USA*

Abstract

In this review, we detail the genetics of those diseases which have tangle pathology. These include Alzheimer's disease (AD), frontotemporal dementia with tau pathology (FTD-T), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's dementia complex of Guam (and related diseases: PDC) and myotonic dystrophy. Our intention is not to reiterate the well established, but rather, in the case of mendelian disease, to discuss new findings and also to discuss the new findings from genome wide association studies.

Introduction

Genetic analysis has led to enormous progress in our understanding of the tangle diseases. With respect to mendelian forms of the tangle diseases we now know that all cases of autosomal dominant Alzheimer's disease have mutations in the APP or presenilin 1 and 2 genes (reviewed in [1]) and that most, if not all autosomal dominant tangle disease have mutations in the MAPT gene (reviewed in [2]). In this review, with respect to mendelian forms of the disease, we highlight unusual mutations and discuss their general mechanisms and then discuss genetic analysis of the non-mendelian forms of the illnesses.

Mendelian disease

Autosomal Alzheimer's disease

Dominant disease. All cases of autosomal dominant Alzheimer cases are caused by mutations in APP and presenilin 1 and 2 [1]. All mutations are missense mutations with a couple of exceptions: duplications of the APP gene can cause Alzheimer's disease [3] and some mutations in the presenilin 1 gene result from in frame deletions which do not disrupt the overall structure of the protein, most notably the Δexon9 mutation [4]. While there have been reports of presenilin 1 mutations causing frontotemporal dementia (and thus implying that there was a route PSEN1 – >MAPT which did not involve APP), most of these reports were misleading and involved (probably harmless) polymorphisms in the presenilin 1 gene in patients with dementia who had pathogenic mutations in other genes (see refs [5–8]).

The presenilins are the major component of γ-secretase, together with nicastrin, APH-1 and PEN2 [9]. Recently, loss of function mutations (nonsense, frameshift etc.) in presenilin and the other γ-secretase components has been shown to cause *acne inversa* with no hint of a dementing illness [10]. This phenotype appears to be due to a problem with the cleavage of Notch by γ-secretase. Indirectly this observation of the phenotypic effects of clear loss of function mutations, together with the fact that clear simple loss of function mutations do not occur in Alzheimer's disease strongly suggests that Alzheimer causing mutations are not simple loss of function changes. However, it remains possible, even probable, that loss of function of γ-secretase is part of the mechanism. Clearly, Alzheimer causing mutations have in common that they increase Aβ42 [11]. Several lines of evidence suggest that this is mediated though a dominant negative loss of function of greater than 50% with respect to APP as a substrate. First, knockdown of presenilin 1 to <20% residual level leads to increases in Aβ42 of the same order as pathogenic mutations [12]. Second, the known loss of function mutation, which causes the notch phenotype in *C. elegans, sel12*, is an Alzheimer causing mutation [13, 14], and third, some Alzheimer pathogenic mutations have been directly shown to be loss of function changes (e.g. [15]). Thus the most parsimonious current view is that Alzheimer causing mutations lead to a greater than 50% decrease in γ-secretase activity with regards to APP as a substrate, leading to an increase in Aβ42 and a decrease in Aβ40 production. Quite why these mutations do not appear to lead to *acne inversa* is not clear, but presumably relates to differences in the specificity of the complex to different substrates.

The major hypothesis concerning Alzheimer's pathogenesis, especially as it relates to the autosomal dominant forms has been that it is the increase in the process of Aβ deposition that is key to pathogenesis [16]. An alternative is that it is the loss of activity in γ-secretase activity towards its multiple substrates that is in fact the key (with mutant APP acting as a competitive inhibitor in APP mutation families) [17, 18]. This hypothesis is a logical formal possibility, although

the findings with *acne inversa* and the analogy with Worster Drought syndrome (another plaque and tangle disease) [19], both point towards the Aβ hypothesis being the more plausible.

Recessive Alzheimer's disease?

All the above comments relate to autosomal dominant disease. No loci for autosomal recessive disease have been identified, although two homozygous pathogenic mutations in the APP gene have been reported [20, 21]. Technically, this would have been very difficult because recessive early onset disease would usually appear merely as sporadic and the challenges of identifying recessive disease loci, if they exist, was extremely challenging. Whole genome genotyping arrays now make this challenge tractable and there have been two reports of potentially recessive disease in inbred populations. If there are such loci, they should be identified in the near future [22, 23].

Frontotemporal dementia with tau pathology

Mutations in the MAPT mutations are either the major or the only cause of autosomal dominant frontotemporal dementia with tangles. Mutations are of three types: point mutations in exons 1, 9, 10, 11, 12 and 13 [23, 24], mutations which alter the splicing of exon 10 such that more of this exon is incorporated in to the final protein [25, 26] and thirdly, structural mutations at the locus [28, 29]. A recent review has discussed the former two groups of mutations and so these will not be further discussed [30]. PGRN, VCP and CHMP2B mutations are other causes of FTD, but these cause the clinical phenotype but without the occurrence of tangles and so are outside the scope of this review (see [31]).

The report of a duplication of the MAPT locus in a case of FTD with parkinsonism is of great interest, although not definitive [28]. It is of interest because it fits with the general pattern in the protein deposition diseases, of gene duplications being pathogenic, like SNCA and APP duplications [32, 33]. This seems to be a general phenomenon in neurodegenerative protein deposition disorders [34]. It is not definitive however, because it was not possible to assess segregation in the kindred meaning that it remains possible that this was just a chance finding: assessment of other FTD cases should eventually resolve this uncertainty. The duplication, which has also been reported in two young children with developmental delay [35, 36] is the inverse of the deletion of the locus which causes a mental retardation syndrome. The deletion is caused by the fact that the locus is inverted on ∼20% of European chromosomes [37, 38].

The internal MAPT deletion is also interesting [29]. The deletion takes out exons 7 and 9 from the full length protein (the deletion encompasses exons 6–9 but 6 and 8 are not brain expressed). As with the duplication, there was not the possibility of assessing segregation though there was a clear family history of disease. The resultant protein, like many of those with point mutations, is less effective at stabilising microtubules [39]. Unfortunately, there was no autopsy available from the patient and so we do not know whether only the mutant protein was deposited.

Genetic analysis of complex tangle diseases: association studies, including genome wide association studies

Genetic analysis of diseases with complex modes of transmission has not had great success until 2008 with the advent of genome wide association studies. Before that time, candidate gene association studies were the only approach that was possible, and these had limited success. For Alzheimer's disease, the identification of apolipoprotein E as a risk locus was an early success [40] (see the Alzgene website for summary statistics for all association studies in Alzheimer's disease [41]) and for progressive supranuclear palsy and corticobasal degeneration, the MAPT locus was a clear candidate gene which showed a strong association [42–44].

Late onset Alzheimer's disease

Beyond apolipoprotein E, no other reported associations with Alzheimer's disease had been identified [39]. However, in whole genome analysis, a number of loci have been identified including CLU [45, 46], CR1 [46], PICALM [45], BIN1 [47], ABCA7, CD2AP, CD33, EPHA1 and MS4A4/MS4A6E [48, 49]. The number of loci identified simply reflect the numbers of samples analysed, and it is likely that the number of established loci will increase considerably over the next year. The loci identified so far fit into three broad pathways: the complement cascade (which had been previously proposed to be important in Alzheimer's disease based on pathologic studies [50, 51], endosomal vesicle recycling and cholesterol metabolism (which, of course, is the classical role of apolipopro-

tein E) [52]. Thus, the genes involved in late onset Alzheimer's disease are involved in a defined number of pathways. It is not yet clear how the pathways identified by this analysis relate to APP metabolism or function.

Progressive supranuclear palsy and corticobasal degeneration

PSP and CBD are the most common sporadic tauopathies. MAPT associations for both diseases have been established for many years [42–44]. The associated MAPT haplotype is also related to increased expression of the 4-repeat isoform of the tau protein [53]. A whole genome association has additionally identified associations with STX6, a protein thought to be involved in vesicle fusion and in MOBP, a myelin protein. Additionally other genes involved in both the innate immune system and the endoplasmic stress response also seemed to have a role in PSP [54]. The association study for CBD was underpowered but proffered evidence for the same loci as for PSP. This study was, because of the comparative rarity of the diseases, of necessity, rather small and again, as for Alzheimer's disease, undoubtedly more loci will be found as additional samples are assessed.

Other disease with tangles

Tangles are found in many other diseases. These include some autosomal prion diseases [55] and Worster Drought syndrome (British Dementia) [19]. These, like Alzheimer's disease are diseases in which there is an extracellular amyloid and intracellular tangles. The occurrence of tangles in these diseases suggests by analogy that tangle formation is somehow a general response to the amyloid deposition process. Tangle formation also occurs in the CNS in myotonic dystrophy [56]. The reason for this occurrence is not clear and deserves further study, but may relate to disregulation of tau splicing indirectly induced by the CUG expansions in DMPK mRNA that define DM1. The CUG expansions sequester the RNA binding protein MBNL1, leading to a reduction in cellular levels of the protein and widespread pre-mRNA splicing defects (reviewed in [57]). The splicing of MBNL1 is also affected, although it is thought that changes to MAPT splicing are a result of reduced levels of functional MBNL1 rather than changes in MBNL1 expression [59]. DM1 seems to be distinct from other tangle disorders with aberrant splicing of tau in that it is altered splicing of exons 2 and 3 of MAPT that is observed, rather than altered exon 10 splicing as seen in FTD, PSP and CBD [60]. The functional significance of this is not known and warrants further investigation. Finally, it is worth noting that splicing of exons 2 and 3 can also differ between the two major tau haplotypes, with H1 showing reduced exon 2 and 3 inclusion [61].

Tangles have been a feature of three epidemic diseases: Von Economo's disease (the sleepy sickness) [62], Subacute Sclerosing Panencephalitic Encephalitis [63] and Parkinson Dementia/Motor Neuron Disease complex of Guam (*lytico-bodig*) [62–64]. The first of these was a prevalent parkinsonian disorder possibly related to the ∼1920 influenza pandemic [63] and the second is a rare complication of measles infection [64] and the last was the prevalent and phenotypically varied, idiopathic disease found on Guam after the Second World War [65]. While the cause of the latter has never been determined, it seems that it, like PSP and CBD shows a MAPT association [66].

A note about Parkinson's disease

Parkinson's disease is defined pathologically by the presence of Lewy Bodies composed of alpha-synuclein rather than the presence of tau tangles. However, there are several reports of tangle pathology in PD, and the association of mutations in MAPT with the clinical syndrome of parkinsonism prompted several candidate gene studies reporting an association of the H1 haplotype with PD (see [67]). This association was confirmed by a recent GWAS that variation at the MAPT locus is a major factor influencing PD risk [68]. The disease associated H1 haplotype can be further dissected into several sub-haplotypes, and, interestingly, the haplotype associated with PD is distinct from the haplotype associated with PSP and CBD [67, 69]. Increased 4R tau levels are found in PD brain with the disease haplotype, suggesting some common functional mechanisms [70].

General principles

It is clear from the above discussion that tangle formation and cell death can be initiated by very disparate events: from APP mutations, to measles virus exposure. Our aim to draw commonalities between these initiating events and this is clearly still a difficult challenge. A conventional separation has been between primary tauopathies, where tau is the only deposited protein, and secondary tauopathies, where

there is some deposition of extracellular amyloids. This separation seems to have merit in that in all the cases where it has been possible to assess, the occurrence of the primary tauopathy diseases is influenced by the splicing and expression of the tau protein. This is not true of the secondary tauopathies where the autosomal dominant genes simply relate to the production of the amyloid deposits. So far, none of the same risk genes, or indeed none of the same pathways have been implicated both in Alzheimer's disease and in PSP. As more genes are identified for both diseases, this may, of course, change, but currently, the most parsimonious explanation is that the aetiologies of the different diseases are not related to each other and that factors which influence the production of tangles, have little influence on the occurrence of Alzheimer's disease.

References

[1] Rogaeva E (2002) The solved and unsolved mysteries of the genetics of early-onset Alzheimer's disease. *Neuromolecular Med* **2**, 1-10.

[2] Rademakers R, Cruts M, van Broeckhoven C (2004) The role of tau (MAPT) in frontotemporal dementia and related tauopathies. *Hum Mutat* **24**, 277-295.

[3] Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D (2006) APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* **38**, 24-26.

[4] Perez-Tur J, Froelich S, Prihar G, Crook R, Baker M, Duff K, Wragg M, Busfield F, Lendon C, Clark RF, et al. (1995) A mutation in Alzheimer's disease destroying a splice acceptor site in the presenilin-1 gene. *Neuroreport* **7**, 297-301.

[5] Tang-Wai D, Lewis P, Boeve B, Hutton M, Golde T, Baker M, Hardy J, Michels V, Ivnik R, Jack C, Petersen R (2002) Familial frontotemporal dementia associated with a novel presenilin-1 mutation. *Dement Geriatr Cogn Disord* **14**, 13-21.

[6] Dermaut B, Kumar-Singh S, Engelborghs S, Theuns J, Rademakers R, Saerens J, Pickut BA, Peeters K, van den Broeck M, Vennekens K, Claes S, Cruts M, Cras P, Martin JJ, Van Broeckhoven C, de Deyn PP (2004) A novel presenilin 1 mutation associated with Pick's disease but not beta-amyloid plaques. *Ann Neurol* **55**, 617-626.

[7] Pickering-Brown SM, Baker M, Gass J, Boeve BF, Loy CT, Brooks WS, Mackenzie IR, Martins RN, Kwok JB, Halliday GM, Kril J, Schofield PR, Mann DM, Hutton M (2006) Mutations in progranulin explain atypical phenotypes with variants in MAPT. *Brain* **129**(Pt11), 3124-3126.

[8] Hutton M (2004) Presenilin mutations associated with frontotemporal dementia. *Ann Neurol* **55**, 604-606.

[9] Sato T, Diehl TS, Narayanan S, Funamoto S, Ihara Y, De Strooper B, Steiner H, Haass C, Wolfe MS (2007) Active gamma-secretase complexes contain only one of each component. *J Biol Chem* **282**, 33985-33993

[10] Wang B, Yang W, Wen W, Sun J, Su B, Liu B, Ma D, Lv D, Wen Y, Qu T, Chen M, Sun M, Shen Y, Zhang X (2010) Gamma-secretase gene mutations in familial acne inversa. *Science* **330**, 1065.

[11] Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird TD, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Viitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D, Younkin S (1996) Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased *in vivo* by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med* **2**, 864-870.

[12] Refolo LM, Eckman C, Prada CM, Yager D, Sambamurti K, Mehta N, Hardy J, Younkin SG (1999) Antisense-induced reduction of presenilin 1 expression selectively increases the production of amyloid beta42 in transfected cells. *J Neurochem* **73**, 2383-2388.

[13] Lewis PA, Perez-Tur J, Golde TE, Hardy J (2000) The presenilin 1 C92S mutation increases abeta 42 production. *Biochem Biophys Res Commun* **277**, 261-263.

[14] Levitan D, Doyle TG, Brousseau D, Lee MK, Thinakaran G, Slunt HH, Sisodia SS, Greenwald I (1996) Assessment of normal and mutant human presenilin function in Caenorhabditis elegans. *Proc Natl Acad Sci U S A* **93**, 14940-14944.

[15] Heilig EA, Xia W, Shen J, Kelleher RJ 3rd (2010) A presenilin-1 mutation identified in familial Alzheimer disease with cotton wool plaques causes a nearly complete loss of gamma-secretase activity. *J Biol Chem* **285**, 22350-22359.

[16] Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **297**, 353-356.

[17] Sambamurti K, Suram A, Venugopal C, Prakasam A, Zhou Y, Lahiri DK, Greig NH (2006) A partial failure of membrane protein turnover may cause Alzheimer's disease: a new hypothesis. *Curr Alzheimer Res* **3**, 81-90.

[18] Shen J, Kelleher RJ 3rd (2007) The presenilin hypothesis of Alzheimer's disease: evidence for a loss-of-function pathogenic mechanism. *Proc Natl Acad Sci U S A* **104**, 403-409.

[19] Plant GT, Révész T, Barnard RO, Harding AE, Gautier-Smith PC (1990) Familial cerebral amyloid angiopathy with nonneuritic amyloid plaque formation. *Brain* **113**(Pt3), 721-747.

[20] Tomiyama T, Nagata T, Shimada H, Teraoka R, Fukushima A, Kanemitsu H, Takuma H, Kuwano R, Imagawa M, Ataka S, Wada Y, Yoshioka E, Nishizaki T, Watanabe Y, Mori H (2008) A new amyloid beta variant favoring oligomerization in Alzheimer's-type dementia. *Ann Neurol* **63**, 377-387.

[21] Di Fede G, Catania M, Morbin M, Rossi G, Suardi S, Mazzoleni G, Merlin M, Giovagnoli AR, Prioni S, Erbetta A, Falcone C, Gobbi M, Colombo L, Bastone A, Beeg M, Manzoni C, Francescucci B, Spagnoli A, Cantù L, Del Favero E, Levy E, Salmona M, Tagliavini F (2009) A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science* **323**, 1473-1477.

[22] Clarimón J, Djaldetti R, Lleó A, Guerreiro RJ, Molinuevo JL, Paisán-Ruiz C, Gómez-Isla T, Blesa R, Singleton A, Hardy J (2009) Whole genome analysis in a consanguineous family with early onset Alzheimer's disease. *Neurobiol Aging* **30**, 1986-1991.

[23] Sherva R, Baldwin CT, Inzelberg R, Vardarajan B, Cupples LA, Lunetta K, Bowirrat A, Naj A, Pericak-Vance M, Friedland RP, Farrer LA (2010) Identification of Novel Candidate Genes for Alzheimer's Disease by Autozygosity Mapping using Genome Wide SNP Data from an Israeli-Arab Community. *J Alzheimers Dis*, 2010 Nov. 23. [Epub ahead of print]

[24] Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P (1998) Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702-705.

[25] Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD (1998) Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* **43**, 815-825. Erratum in: *Ann Neurol* 1998, **44**, 428.

[26] Malkani R, D'Souza I, Gwinn-Hardy K, Schellenberg GD, Hardy J, Momeni P (2006) A MAPT mutation in a regulatory element upstream of exon 10 causes frontotemporal dementia. *Neurobiol Dis* **22**, 401-403.

[27] Spillantini MG, Bird TD, Ghetti B (1998) Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies. *Brain Pathol* **8**, 387-402.

[28] Rovelet-Lecrux A, Hannequin D, Guillin O, Legallic S, Jurici S, Wallon D, Frebourg T, Campion D (2010) Frontotemporal dementia phenotype associated with MAPT gene duplication. *J Alzheimers Dis* **21**, 897-902.

[29] Rovelet-Lecrux A, Lecourtois M, Thomas-Anterion C, Le Ber I, Brice A, Frebourg T, Hannequin D, Campion D (2009) Partial deletion of the MAPT gene: a novel mechanism of FTDP-17. *Hum Mutat* **30**, E591-E602.

[30] Goedert M (2005) Tau gene mutations and their effects. *Mov Disord* **20**(Suppl. 12), S45-S52.

[31] Sleegers K, Cruts M, van Broeckhoven C (2010) Molecular pathways of frontotemporal lobar degeneration. *Annu Rev Neurosci* **33**, 71-88.

[32] Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J (2003) Gwinn-Hardy K/alpha-Synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841.

[33] Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D (2006) APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* **38**, 24-26.

[34] Singleton A, Myers A, Hardy J (2004) The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases. *Hum Mol Genet* **13**(Spec No. 1), R123-R126.

[35] Kirchhoff M, Bisgaard AM, Duno M, Hansen FJ, Schwartz M (2007) A 17q21.31 microduplication, reciprocal to the newly described 17q21.31 microdeletion, in a girl with severe psychomotor developmental delay and dysmorphic craniofacial features. *Eur J Med Genet* **50**, 256-263.

[36] Grisart B, Willatt L, Destrée A, Fryns JP, Rack K, de Ravel T, Rosenfeld J, Vermeesch JR, Verellen-Dumoulin C, Sandford R (2009) 17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction. *J Med Genet* **46**, 524-530.

[37] Evans W, Fung HC, Steele J, Eerola J, Tienari P, Pittman A, Silva R, Myers A, Vrieze FW, Singleton A, Hardy J (2004) The tau H2 haplotype is almost exclusively Caucasian in origin. *Neurosci Lett* **369**, 183-185.

[38] Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A, Gudnadottir VG, Desnica N, Hicks A, Gylfason A, Gudbjartsson DF, Jonsdottir GM, Sainz J, Agnarsson K, Birgisdottir B, Ghosh S, Olafsdottir A, Cazier JB, Kristjansson K, Frigge ML, Thorgeirsson TE, Gulcher JR, Kong A, Stefansson K (2005) A common inversion under selection in Europeans. *Nat Genet* **37**, 129-137.

[39] Hong M, Zhukareva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed L, Miller BI, Geschwind DH, Bird TD, McKeel D, Goate A, Morris JC, Wilhelmsen KC, Schellenberg GD, Trojanowski JQ, Lee VM (1998) Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. *Science* **282**, 1914-1917.

[40] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[41] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Mat Genet* **39**, 17-23.

[42] Conrad C, Andreadis A, Trojanowski JQ, Dickson DW, Kang D, Chen X, Wiederholt W, Hansen L, Masliah E, Thal LJ, Katzman R, Xia Y, Saitoh T (1997) Genetic evidence for the involvement of tau in progressive supranuclear palsy. *Ann Neurol* **41**, 277-281.

[43] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M (1999) Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* **8**, 711-715.

[44] Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, Lees AJ, Rossor MN, Quinn NP, Kertesz A, Khan MN, Hardy J, Lantos PL, St George-Hyslop P, Munoz DG, Mann D, Lang AE, Bergeron C, Bigio EH, Litvan I, Bhatia KP, Dickson D, Wood NW, Hutton M (2001) Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology* **56**, 1702-1706.

[45] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* **41**, 1088-1089.

[46] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F,

Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O; European Alzheimer's Disease Initiative Investigators, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanché H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alpérovitch A, Lathrop M, Amouyel P (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* **41**, 1094-1099.

[47] Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth WT Jr, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, Harris TB, Petersen RC, Berr C, Owen MJ, Lopez-Arrieta J, Varadarajan BN, Becker JT, Rivadeneira F, Nalls MA, Graff-Radford NR, Campion D, Auerbach S, Rice K, Hofman A, Jonsson PV, Schmidt H, Lathrop M, Mosley TH, Au R, Psaty BM, Uitterlinden AG, Farrer LA, Lumley T, Ruiz A, Williams J, Amouyel P, Younkin SG, Wolf PA, Launer LJ, Lopez OL, van Duijn CM, Breteler MM; CHARGE Consortium; GERAD1 Consortium; EADI1 Consortium (2010) Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* **303**, 1832-1840.

[48] UK/French study.

[49] USA study.

[50] Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, Pocklington A, Abraham R, Hollingworth P, Sims R, Gerrish A, Pahwa JS, Jones N, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, van den Bussche H, Heuser I, Peters O, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Rüther E, Carrasquillo MM, Pankratz VS, Younkin SG, Hardy J, O'Donovan MC, Owen MJ, Williams J (2010) Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PLoS One* **5**, e13950.

[51] McGeer PL, McGeer EG (2002) The possible role of complement activation in Alzheimer disease. *Trends Mol Med* **8**, 519-523.

[52] Guerreiro RJ, Gustafson DR, Hardy J (2010) The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. *Neurobiol Aging*, 2010 Jun. 29. [Epub ahead of print]

[53] Myers AJ, Pittman AM, Zhao AS, Rohrer K, Kaleem M, Marlowe L, Lees A, Leung D, McKeith IG, Perry RH, Morris CM, Trojanowski JQ, Clark C, Karlawish J, Arnold S, Forman MS, Van Deerlin V, de Silva R, Hardy J (2007) Rhe MAPT H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. *Neurobiol Dis* **25**, 561-570.

[54] PSP GWAS.

[55] Hsiao K, Dlouhy SR, Farlow MR, Cass C, Da Costa M, Conneally PM, Hodes ME, Ghetti B, Prusiner SB (1992) Mutant prion proteins in Gerstmann-Sträussler-Scheinker disease with neurofibrillary tangles. *Nat Genet* **1**, 68-71.

[56] Maurage CA, Udd B, Ruchoux MM, Vermersch P, Kalimo H, Krahe R, Delacourte A, Sergeant N (2005) Similar brain tau pathology in DM2/PROMM and DM1/Steinert disease. *Neurology* **65**, 1636-1638.

[57] Cooper TA, Wan L, Dreyfuss G (2009) RNA and disease. *Cell* **136**, 777-793.

[58] McCall S, Henry JM, Reid AH, Taubenberger JK (2001) Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases. *J Neuropathol Exp Neurol* **60**, 696-704.

[59] Dhaenens CM, Schraen-Maschke S, Tran H, Vingtdeux V, Ghanem D, Leroy O, Delplanque J, Vanbrussel E, Delacourte A, Vermersch P, Maurage CA, Gruffat H, Sergeant A, Mahadevan MS, Ishiura S, Buée L, Cooper TA, Caillet-Boudin ML, Charlet-Berguerand N, Sablonnière B, Sergeant N (2008) Overexpression of MBNL1 fetal isoforms and modified splicing of Tau in the DM1 brain: two individual consequences of CUG trinucleotide repeats. *Exp Neurol* **210**, 467-478.

[60] Leroy O, Wang J, Maurage CA, Parent M, Cooper T, Buée L, Sergeant N, Andreadis A, Caillet-Boudin ML (2006) Brain-specific change in alternative splicing of Tau exon 6 in myotonic dystrophy type 1. *Biochim Biophys Acta* **1762**, 460-467.

[61] Caffrey TM, Joachim C, Wade-Martins R (2008) Haplotype-specific expression of the N-terminal exons 2 and 3 at the human MAPT locus. *Neurobiol Aging* **29**, 1923-1929.

[62] Geddes JF, Hughes AJ, Lees AJ, Daniel SE (1993) Pathological overlap in cases of Parkinsonism associated with neurofibrillary tangles. A study of recent cases of postencephalitic parkinsonism and comparison with progressive supranuclear palsy and Guamanian parkinsonism-dementia complex. *Brain* **116**(Pt 1), 281-302.

[63] Bancher C, Leitner H, Jellinger K, Eder H, Setinek U, Fischer P, Wegiel J, Wisniewski HM (1996) On the relationship between measles virus and Alzheimer neurofibrillary tangles in subacute sclerosing panencephalitis. *Neurobiol Aging* **17**, 527-533.

[64] Hudson AJ, Rice GP (1990) Similarities of guamanian ALS/PD to post-encephalitic parkinsonism/ALS: possible viral cause. *Can J Neurol Sci* **17**, 427-433.

[65] Steele JC (2005) Parkinsonism-dementia complex of Guam. *Mov Disord* **20**(Suppl. 12), S99-S107.

[66] Sundar PD, Yu CE, Sieh W, Steinbart E, Garruto RM, Oyanagi K, Craig UK, Bird TD, Wijsman EM, Galasko DR, Schellenberg GD (2007) Two sites in the MAPT region confer genetic risk for Guam ALS/PDC and dementia. *Hum Mol Genet* **16**, 295-306.

[67] Vandrovcova J, Pittman AM, Malzer E, Abou-Sleiman PM, Lees AJ, Wood NW, de Silva R (2009) Association of MAPT haplotype-tagging SNPs with sporadic Parkinson's disease. *Neurobiol Aging* **30**, 1477-1482.

[68] Simón-Sánchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Krüger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T (2009)

enome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet* **41**, 1308-1312.

[69] UK Parkinson's Disease Consortium; Wellcome Trust Case Control Consortium 2, Spencer CC, Plagnol V, Strange A, Gardner M, Paisan-Ruiz C, Band G, Barker RA, Bellenguez C, Bhatia K, Blackburn H, Blackwell JM, Bramon E, Brown MA, Brown MA, Burn D, Casas JP, Chinnery PF, Clarke CE, Corvin A, Craddock N, Deloukas P, Edkins S, Evans J, Freeman C, Gray E, Hardy J, Hudson G, Hunt S, Jankowski J, Langford C, Lees AJ, Markus HS, Mathew CG, McCarthy MI, Morrison KE, Palmer CN, Pearson JP, Peltonen L, Pirinen M, Plomin R, Potter S, Rautanen A, Sawcer SJ, Su Z, Trembath RC, Viswanathan AC, Williams NW, Morris HR, Donnelly P, Wood NW (2011) Dissection of the genetics of Parkinson's disease identifies an additional association 5′ of SNCA and multiple associated haplotypes at 17q21. *Hum Mol Genet* **20**, 345-353.

[70] Tobin JE, Latourelle JC, Lew MF, Klein C, Suchowersky O, Shill HA, Golbe LI, Mark MH, Growdon JH, Wooten GF, Racette BA, Perlmutter JS, Watts R, Guttman M, Baker KB, Goldwurm S, Pezzoli G, Singer C, Saint-Hilaire MH, Hendricks AE, Williamson S, Nagle MW, Wilk JB, Massood T, Laramie JM, DeStefano AL, Litvan I, Nicholson G, Corbett A, Isaacson S, Burn DJ, Chinnery PF, Pramstaller PP, Sherman S, Al-hinti J, Drasby E, Nance M, Moller AT, Ostergaard K, Roxburgh R, Snow B, Slevin JT, Cambi F, Gusella JF, Myers RH (2008) Haplotypes and gene expression implicate the MAPT region for Parkinson disease: the GenePD Study. *Neurology* **71**, 28-34.

Molecular Basis of Immune Response in the Central Nervous System

Maria Teresa Giordana and Silvia Grifoni
Department of Neuroosciences, Univerity of Turin, Turin, Italy

Immune responses are the major active defense mechanisms of the body. Antigens are the molecules against which an immune response can be directed; antigens are foreign or self-component. Any immune response is accompanied by inflammation. Inflammation is a complex process which commences with a primary reaction and is followed by a secondary reaction which involves supplementation by blood borne elements. Both primary and secondary reactions may be either successful or have lethal consequences; factors determining the responses of the nervous system are the route of entry of the antigens, the type of antigen (proteins, organisms, type of organisms), the competence of the host to mount an immune response, and the unique features of the human central nervous tissue, namely the blood–brain barrier.

The immune system operates by means of the secretion of single antigen-specific antibodies (humoral arm of immunity); this implies the recognition of the antigen (epitope) by B lymphocytes containing specific surface-bound immunoglobulins. After binding an epitope to their surface IgM, B cells proliferate and mature within the lymph nodes, become plasma cells and secrete antibodies (IgG); IgG antibodies to a specific epitope have higher affinity than their IgM progenitors.

Antigen-antibody binding permits either activation of complement, or binding of the complex to phagocytes, or to other effectors of the inflammatory responses. Most sustained antibody responses necessitate collaboration between B cells and T cells (helper T cells, CD4+).

T cells of lymph nodes operate by themselves (cellular arm of immunity) or as helpers of B cells. By means of the T cell receptor (TCR), T cells recognize the epitopes presented to them by the antigen presenting cells (APC). Monocytes, macrophages, dendritic cells, as well as B cells, may function as APC. A major role in foreign antigen presentation, as well as in self-recognition, is played by mayor histocompatibility complex (MHC) proteins expressed on the surface.

Activated T cells secrete interferon gamma, which favours antigen presentation, while APC and CD4 cells release IL-1 and -2 respectively, providing mitogenic signals. As a consequence, activated CD4 cells expand, leave the lymph nodes and home to target tissue, in which antigen presentation is amplified.

The effector phases of the cell-mediated immune response is represented by delayed-type hypersensitivity response and cytotoxycity. An example of the first is experimental allergic encephalitis (EAE) in Lewis rats. EAE is produced by immunizing with a peptide that cross-reacts with aminoacid sequences within myelin constituents. In EAE, activated CD4 cells release lymphotoxin, and macrophages, driven by lymphokines, release IL-1 and TNF. TNF is toxic to oligodendrocytes, causing them to retract their processes and to close their K+ channels. TNF can cause demyelination and possibly oligodendrocyte killing; IL-1 and lymphotoxin may potentiate the TNF effects. Antigen presentation is effected by astrocytes and microglia; the oliogodendrocytes provide the antigen, i.e. myelin basic protein (MBP), but do not present it. A similar pathogenic sequence of events may occur in multiple sclerosis, Guillain-Barrè syndrome and postinfectius or post-immunization encephalitis.

Cell-mediated cytotoxicity involves CD8 cell proliferation, and is facilitated by IL-2 produced by CD4 cells within the lymph nodes. Expanded T cell clones enter the target organ; target cells present antigen via their class I MHC molecules, and cytotoxic cells adhere to their target, release perforin and other cytolitic products. Brain cells do not express class I MHC alleles, but IFN-gamma secreted by CD4 and CD8 cells may induce the expression on astrocytes and oligodendrocytes.

The setting in motion of humoral and cellular immune response requires the existence of lymph nodes and free access to the target organ; the recognition of self requires the expression of class I MHC alleles. Class I MHC alleles are expressed on the surface of cells in most body tissue, with the notable exception of healthy brain, which is thought to be a major reason why grafts of brain tissue to brain are rejected indolently.

However, the concept of immunologic privilege of the brain needs to be revisited, taking into account that lymphocytes re-circulate in the normal brain, intrathecal production of immunoglobulin is reported in pathological conditions (multiple sclerosis, viral encephalitis), and antibodies and peptides, amyloid beta included, are transported between the brain and the blood [1].

In addition, dendritic cells (DC) are normally present in the CSF compartment, including leptomeninges and choroid plexus, and additional DCs

are recruited from blood and, possibly, from brain microglia in case of brain or CSF inflammation.

A connection between central nervous system (CNS) and deep cervical lymph nodes exists, potentially allowing mature DCs to migrate out of the CNS and induce a T cell response against foreign antigens present in the intratecal compartment. In chronic inflammation, some DCs may interact with T cells directly in the meninges; in chronic EAE, T cells of the meningeal infiltrates express TCRVbeta8.2, i.e. are directed against MBP, and proliferate in situ, contributing to and maintaining lesion activity with features of chronicity and autoimmunity [2]. A key questions is why chronic inflammation and autoimmunity do not develop in the neurological diseases associated with tissue damage and release of myelin antigens, such as stroke.

A typical feature of the CNS, and an additional issue of confusion when analyzing the effects of systemic modifiers of immunity and inflammation in Alzheimer patients, is microglia. Microglia are resident macrophages in the CNS; they derive from myeloid precursor cells and enter the developing CNS during embryogenesis. The resting microglia, identified by ramified morphology, change phenotype to an activated morphology characterized by hypertrophy and extensive branching as a consequence of disease or injury. Activated microglia upregulate receptors and cytoplasmic molecules, but the active status does not clarify the role of microglia in disease pathogenesis and whether it acerbates pathology or aids in tissue repair. After an acute brain injury, activation of microglia is accompanied by the synthesis of proinflammatory cytokines and inflammatory mediators and results in additional detrimental tissue damage. In slow degeneration, such as Wallerian degeneration within the CNS, activated microglia is associated with an anti-inflammatory phenotype [3].

Microglia was originally considered as the major player of not specific innate immune defense in CNS, which respond immediately to all provocations to the host; nevertheless, microglia do not phagocyte amyloid beta in normal conditions. In neurodegenerative diseases, activated microglia is present; its role as contributor or consequence of the pathology is not fully understood. Apparently, neither extracellular misfolded proteins nor chronic neuronal loss are able to induce a strong proinflammatory response.

References

[1] Stolp HB, Dziegielewska KM (2009) Role of developmental inflammation and blood-brain barrier dysfunction in neurodevelopmental and neurodegenerative diseases. *Neuropathol Appl Neurobiol* **35**, 132-146.

[2] Pashenkov M, Teleshova N, Link H (2003) Inflammation in the central nervous system: the role for dendritic cells. *Brain Pathol* **13**, 23-33.

[3] Hugh Perry V, Nicoll JAR, Holmes C (2010) Microglia and neurodegenerative disease. *Nat Rev Neurol* **6**, 193-201.

ABSTRACTS

Journal of Alzheimer's Disease 23 (2011) S45–S81
DOI 10.3233/JAD-2011-001434
IOS Press

Abstracts

Resting State Network Abnormalities in Alzheimer's disease: Beyond the Default Mode Network

Federica Agosta[a], Michela Pievani[a], Cristina Geroldi[b], Massimiliano Copetti[c], Giancarlo Comi[a], Giovanni Frisoni[b] and Massimo Filippi[a]
[a]*Scientific Institute and University Hospital San Raffaele, Milan, Italy*
[b]*IRCCS Centro San Giovanni di Dio – Fatebenefratelli, Brescia, Italy*
[c]*IRCCS-Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*

Aims and methods: Using resting state (RS) functional MRI (fMRI), the connectivity patterns of the default mode network (DMN), as well as the fronto-parietal, executive, and salience networks were explored in 13 patients with Alzheimer's disease (AD) and 12 patients with amnestic mild cognitive impairment (aMCI) relative to 13 healthy controls.

Results: Compared with healthy controls and aMCI, AD was associated with opposing connectivity effects in the DMN (decreased) and frontal networks (enhanced). The only RS abnormality found in aMCI patients compared with controls was a precuneus connectivity reduction in the DMN. RS fMRI group differences were only partly related to grey matter atrophy. Cognitive impairment correlated with enhanced executive network connectivity in aMCI, and with a reduced connectivity of the same network in AD.

Conclusions: This study shows that AD is associated with an alteration of large-scale functional brain networks, which extends well beyond the DMN. The limited resources of the parieto-temporal cortex of AD patients may be paralleled, in an attempt to maintain cognitive efficiency, by an increased prefrontal connectivity. A medial parietal RS fMRI signal change seems to be present since the early phase of AD.

Brain Leptin Signature of Hyperphagia in Frontotemporal Lobar Degeneration

Antonella Alberici[a], Barbara Borroni[a], Carmelo Iacobello[b], Silvana Archetti[b], Enrico Premi[a], Carlo Cerini[a], Alessandra Valerio[a], Luigi Caimi[a] and Alessandro Padovani[a]
[a]*University of Brescia, Brescia, Italy*
[b]*Spedali Civili, Brescia, Italy*

Background: Frontotemporal lobar degeneration (FTLD) is characterized by abnormal eating behaviour. We demonstrated a selective gender differences in leptin levels between females in FTLD, as compared to Alzheimer disease (AD) patients, providing a evidence of an involvement of leptin in the regulation of hyperphagia of FTLD.

Aims: To understand the brain frameworks associated with leptin in FTLD.

Methods: FTLD patiens were recruited, and extensively assessed for their cognitive and behavioral profiles. Serum leptin levels were measured using a human leptin enzyme linked immunoasorbent assay (ELISA) kit according to manufacturer's instructions (Diagnostic Biochem Canada Inc. Version 6). Magnetic resonance imaging (MRI) was performed, and Voxel Based Morphometry (VBM) analyses were implemented in the SPM8 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5.1 (MathWorks, Natick, MA).

Results: Leptin levels correlated with gender, BMI, and hyperphagia. Higher leptin levels were specifically associated with greater atrophy in Brodmann area 6.

Conclusions: We provided a novel biochemical and structural framework to FTLD, and its relationship with the control of body weight and energy homeostasis.

Gait Assesment and Cognition in Parkinson's Disease

Marianna Amboni[a], Paolo Barone[b], Alfonso Fasano[c], Luigi Iuppariello[b], Ilaria Lista[a], Riccardo Tranfaglia[b], Simona Nicolosi[d] and Giuseppe Sorrentino[a]

ISSN 1387-2877/11/$27.50

[a] *University of Naples Parthenope, Naples, Italy*
[b] *University of Naples Federico II, Naples, Italy*
[c] *Catholic University of Sacred Heart, Rome, Italy*
[d] *University of Enna Kore, Enna, Italy*

Background: Increasing evidences support a strong association between gait and cognition. Originally the construct of Mild Cognitive Impairment (MCI) was conceptualized as the transitional state between normal aging and Alzheimer's disease (AD), recently, this concept has been applied to cognition in patients with Parkinson's disease (PD).

Aims: To perform a quantitative gait assessment in PD patients with or without MCI.

Methods: Forty-three PD patients were investigated. All patients were assessed both clinically and cognitively. Quantitative gait analysis was performed in the following conditions both at off and on state: 1) normal gait (Gait-off an, Gait-on); 2) motor dual task (Mot-off, Mot-on); 3) cognitive dual task (Cog-off, Cog-on).

Results: Based on neuropsychological testing, nineteen subjects were classified as patients with MCI (MCI+) and twenty-four subjects without (MCI−). The two groups didn't differ on clinical features. MCI+ vs MCI− showed: 1) reduced single/double support time ratio in Mot-off ($p = 0.044$), Cog-off ($p = 0.011$); 2) increased step length variability in Gait-off ($p = 0.030$); 3) reduced gait stride in Cog-on ($p = 0.046$).

Conclusions: MCI+ vs MCI− PD patients displayed specific gait features: impairment of dynamic stability, increased variability and reduced gait stride.

A Methodological Approach for an Early Identification and Diagnose of Cognitive Disorders of Patients Seen in the UVA n°1 of the Neurologic Clinic of the AOU of Sassari

Caterina F. Bagella, Rossella Cherchi, Dario Zanetti, Raimonda Piu and Maria R. Piras
Azienda Ospedaliero-Universitaria, Sassari, Italy

Background: During the last ten years, the Alzheimer's Evaluation Units (UVA) have obtained an important role in the diagnosis, follow-up and management of patients with cognitive disorders and are an important support for family and care-givers.

Aims: Based on our clinical experience and on the state of art, we elaborated a data survey form (SRD) for each patient seen for the first time in our unit. The SRD contains patient-specific information; information regarding risk factors (environmental and non); age and modality of outbreak of the cognitive disorder; neuropsychological information; and the pharmacological therapy.

Results: The observation time was of one year. We've diagnosed 68 new cases: 29 with Alzheimer (AD), 5 with Frontotemporal, 1 with Lewy Body, 9 with Vascular Dementia (VaD), 1 with Multisistemic Atrophy (MSA), 1 with dementia caused from hydrocephalus, 23 with Mild Cognitive Impairment (MCI) (15 EOMCI and 8 LOMCI). From our study emerged that there isn't a significant numerical difference between familial and sporadic AD form (14 FAD and 15 SAD), women are noticeably more predisposed for AD (EOAD 6 : 1, LOAD 14 : 8) and school attendance is generally very low (5.6 ± 1.2). Within MCI we've 15 EO (13 women on 15) and 8 LO (6 women on 8) and school attendance is higher (8.15 ± 4.7). From a first analysis of the more significant risk factors (hypertension, hypercholesteremia, diabetes) emerged that of 22 ADLO 13 are hypertensive, 3 hypercholesterolemic and 5 diabetic; and of 7 ADEO patients 4 are hypertensive, 2 hypercholesterolemic and 1 diabetic. Things change when we analyse VaD patients, i.e. 7 are hypertensive, 3 hypercholesterolemic and 2 diabetic. Particular attention has to be given to MCI, i.e. of 23 new cases, 9 are hypertensive, 6 are hypercholesterolemic, none has diabetes, and 8 have a familiarity for dementia.

Conclusions: The SRD has not only allowed us to elaborate a more accurate method to diagnose patients affected by a cognitive deficit, but also to notice how risk factors, co-morbidity, age, school attendance and gender are modified in accordance with the variation of the clinical phenotype. In the future management of our unit the SRD will not only have the function to create an accurate and specific database in order to lay the foundations for a systematic epidemiological study of the patients seen in our unit, but also to give a dynamic overview of a considerable part of the North Sardinian cognitive impaired population.

fMRI, Tractography and EEG Analysis Integrated into Neurological Diagnosis of Corticobasal Degeneration. A Case Study

Francesca Baglio[a], Maria G. Preti[b], Ludovica Griffanti[b], Luigi Pugnetti[a], Elisabetta Farina[a], Massimo Garegnani[a], Maria M. Laganà[a], Pietro Cecconi[a], Giuseppe Baselli[b] and Raffaello Nemni[a,c]

[a] *Fondazione Don Gnocchi, Milan, Italy*
[b] *Politecnico, Milan, Italy*
[c] *University of Milan, Milan, Italy*

Background: The phenotypes of Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy(PSP) are closely related and frequently overlap at the onset.

Aims: We report a case of early atypical Parkinsonism prevalent on the left side, introducing the use of advanced neurophisiological and neuroimaging techniques in order to further support the clinical diagnosis of CBD.

Methods: A single patient was examined with advanced MRI techniques-fMRI with passive motor task and DTI- and EEG source mapping. Tractography of the cortico-spinal tract (CST) was performed and fMRI-based tractography was also applied.

Results: Although conventional MRI does not reveal asymmetric brain damage, fMRI and EEG during hand motor passive task confirmed that the left hand movement was less effective than the right, and displayed asymmetric activation patterns in pre- and postcentral gyri (right > left). fMRI-guided tractography also found asymmetric recruitment of CST, whereas the conventional CST tractography showed a considerable difference between the number of right and left reconstructed tracts.

Conclusions: The combination of tractography, fMRI and EEG confirms the clinical asymmetric parkinsonism by mapping the specific bundles involved in the functional activation consequent to the hands passive motion. Taking together, these findings supports the clinical diagnosis of CBD excluding other closely related diseases, such as PSP.

The Efficacy of Multidimensional Stimulation Therapy in Mild to Moderate Alzheimer's Disease Patients: a Randomized Controlled Trial with fMRI

Francesca Baglio[a], Ludovica Griffanti[b], Maria G. Preti[b], Maria M. Laganà[a], Margherita Alberoni[a], Fabiana Villanelli[a], Laura Carelli[a], Francesca Saibene[a], Raffaella Critelli[a], Pietro Cecconi[a], Giuseppe Baselli[b], Raffaello Nemni[a,c] and Elisabetta Farina[a]
[a] *Fondazione Don Gnocchi, Milan, Italy*
[b] *Politecnico, Milan, Italy*
[c] *University of Milan, Milan, Italy*

Background: There is good evidence that group Multidimensional Stimulation Therapy (MST) leads to generalised cognitive benefits in Alzheimer's disease (AD). However, few literature illustrates whether some aspects of cognition might change more than others.

Aims and methods: Thirty-six 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 paced-overt verbal fluency paradigm.

Results: The tMST and ntMST groups were comparable at the baseline regarding MMSE values and fMRI activations pattern. Direct comparison (paired *t*-test; $p < 0.005$) of fMRI results before and after rehabilitation or observation period showed: 1. in tMST groups greater activation after MST in bilateral temporal cortex, basal ganglia and right hippocampus; 2. in ntMST groups no significant changes in brain activation patterns after the observation period.

Conclusions: Increased fMRI activations only in tMST groups support that MST appears to have particular effects in promoting cognitive functions (language function, response inhibition, motor preparation and sustained attention). Particularly, the efficacy on language may be explained through generating opinions and creating new semantic links.

Cognitive Training in Outpatients Affected by Mild Cognitive Impairment: a Longitudinal Study with fMRI

Francesca Baglio[a], Ludovica Griffanti[b], Maria G. Preti[b], Maria M. Laganà[a], Margherita Alberoni[a], Raffaella Critelli[a], Alessandra D'Amico[a], Alessandra Pini[a], Pietro Cecconi[a], Giuseppe Baselli[b], Raffaello Nemni[a,c] and Elisabetta Farina[a]
[a] *Fondazione Don Gnocchi, Milan, Italy*
[b] *Politecnico, Milan, Italy*
[c] *University of Milan, Milan, Italy*

Aims: The aim of this study was to evaluate the impact of a 3 months cognitive training (CT) on the clinical, neuropsychological, neurobehavioral and neuroimaging evolution of Mild Cognitive Impairment (MCI) patients.

Methods: Thirty MCI patients were evaluated with neuropsychological and neurobehavioral assessments at the study inclusion and after 6 and 12 months. Fifty percent were randomized to a 12 weeks CT consisting of 2 individual sessions/week. fMRI with verbal flu-

ency paradigm was performed in CT group before and after rehabilitation.

Results: The CT group did not differ from the group without CT in MMSE value at the baseline ($p = 0.36$) and after six months ($p = 0.61$). Despite a statistical comparable performance on correct responses during the task (92% before versus 93% after CT; $p = 0.7$), direct comparison of fMRI results before and after rehabilitation showed: before CT, greater activation in bilateral frontal areas and anterior cingulate cortex ($p < 0.005$); after CT, in right temporal cortex and parahippocampal gyri ($p < 0.005$).

Conclusions: Increased fMRI activations on frontal areas before CT could be related to a higher cognitive load required to complete the verbal fluency task. Our fMRI results showed that CT is a useful non-pharmacological treatment to improve response inhibition, motor preparation and sustained attention.

Multidisciplinary study in FTD Italian patients

Silvia Bagnoli, Irene Piaceri, Andrea Tedde, Benedetta Nacmias, Laura Bracco, Alberto Pupi and Sandro Sorbi
University of Florence, Florence, Italy

Background: The frontotemporal dementia (FTD) is an heterogeneous disease both in terms of clinical, genetics and neuropathology.

Aims: In this study, a group of 171 Italian patients with FTD was analyzed with a multidisciplinary approach including a thorough clinical evaluation, an extensive genetic analysis and functional neuroimaging with FDG-PET. The aim was to define markers of disease to improve diagnostic protocols.

Methods: Genetic analysis was performed in all the patients in the genes associated in FTD (PGRN, MAPT, TDP-43) and in Presenilin1 gene (PS1) recently involved in FTD.

Results: We identified the presence of five mutations: one mutation (V363I) in the MAPT gene, three mutations (T272fsX10, R493X, C139R) in the PGRN gene and 1 mutation (L171P) in the PS1 gene. The FDG-PET showed hypometabolism pattern compatible with a diagnosis of FTD and differential characteristics with respect to the forms of Alzhimer's disease.

Conclusions: The extension on a larger scale of this multidisciplinary study will provide a powerful route to understanding the mechanisms underlying the disease and could provide evidence to future therapeutic treatments.

Early-onset Dementia with Presenilin-1 Mutation and Motor Abnormalities in an Italian Patient: a Case Report

Pierluigi Bertora[a], Elisa Capiluppi[a], Carlo Lovati[b], Giuliana Cislaghi[b], Raffaele Maletta[c], Daniela Galimberti[a,d] and Claudio Mariani[a]
[a] *University of Milan, Milan, Italy*
[b] *Azienda Ospedaliera L. Sacco, Milan, Italy*
[c] *A.S.P. Catanzaro, Lamezia Terme, Italy*
[d] *Fondazione Cà Granda, IRCSS Ospedale Policlinico, Milan, Italy*

Case report: A 37-yr old, previously healthy woman developed progressive impairment of memory, orientation, and speech over a period of 2 years. No family history of dementing illnesses was present. Neurological examination showed temporal and spatial disorientation, nonfluent aphasia, defects in sustained attention and order comprehension. Mild limb ataxia, myoclonic jerks of upper limbs with a consistent EMG pattern, and psychomotor apraxia were also present. Brain magnetic resonance imaging showed diffuse cortical and deep atrophy and nonspecific minute T2-hyperintense lesions in supratentorial white matter. Routine cerebrospinal fluid (CSF) examination was normal. Low levels of CSF Aβ1-42 (184 pg/ml, normal > 600), elevated total Tau protein (1030 pg/ml, normal <300) and phosphorylated Tau (1030 pg/ml, normal <40) were found. 14-3-3 protein was slightly elevated. No mutations of prion protein gene were found. Brain SPECT showed mild left parieto-temporal hypoperfusion. An EEG evidenced moderate and diffuse slowing of cerebral rhythms. Mutation of the presenilin-1 gene (exon 7, met233Thr) was found.

Conclusions: The clinical presentation and the results of instrumental and laboratory tests make a diagnosis of early-onset Alzheimer disease likely. The peculiar clinical presentation, which adds motor signs (myoclonus) to the cognitive impairment warrant further investigation about the clinico-pathological features of neurodegeneration in this patient.

EEG and Mild Cognitive Impairment (MCI): Possible Predictive Value for Progression to Lewy Body Dementia

Stefania Bifolchetti, Laura Bonanni, Elisa Mancino, Leopoldo Ricciardi, Francesca Anzellotti, Fausta Ciccocioppo, Daniela Monaco, Maria C. D'Amico, Iole Borrelli, Holta Zhuzhuni, Astrid Thomas and Marco Onofrj

G. D'Annunzio Chieti-Pescara University, Chieti, Italy

Aims: The aim of this study is to investigate whether q-EEG can identify specific patterns that have predictive value for progression from MCI to dementia.

Methods: In the study were enrolled non-demented subjects ($n = 21$) who meet Petersen's criteria for MCI – called isolated MCI (i-MCI) – and 28 Parkinson's disease patients with MCI (p-MCI) matched on age and years of education. All patient underwent to quantitative EEGs (QEEG) from 21 scalp derivations: power spectra measurements or CSA, including the four variables, Dominant Frequency-DF, DF Variability-DFV, Frequency Prevalence-FP and Band Inscription-BI, and the resulting categorization in 5 patterns observed in anterior (F3, F4, Fz) and posterior (P3, P4, O1, O2) pooled derivations were analysed for the purpose of the present study. The neuropsychological battery includes: executive functions, memory, language, attention, visuospatial/constructive skills and evaluation of anxiety and depression.

Results: In the i-MCI group 80.9% of the patients showed pattern CSA-1, whereas the most part of PD patients (92.8%) with MCI showed patterns CSA > 1.

Conclusions: qEEG could be used as a reliable and sensitive biomarker(s) of different subtypes of MCI.

Joint Analysis of Structural and Quantitative Magnetization Transfer MRI for Classification of Alzheimer's Disease and normal aging

Marco Bozzali[a], Giovanni Giulietti[a], Viviana Figura[a], Roberta Perri[a], Camillo Marra[b], Franco Giubilei[c] and Mara Cercignani[a]
[a]*Santa Lucia Foundation, Rome, Italy*
[b]*Cattolica University, Rome, Italy*
[c]*Sapienza University, Rome, Italy*

Background: Quantitative magnetization transfer (qMT) is an MRI able to detect biological changes of brain tissues due to modifications of sub-cellular components.

Aims: To determine the joint contribution of gray matter (GM) atrophy and qMT parameters for the classification of AD patients.

Methods: We recruited overall 30 subjects (19 AD; 11 healthy controls [HC]), who underwent neuropsychological examination and MRI at 3.0T : T1-weighted volumes were used for GM volumetrics, while qMT sequences were used to assess RM0B, F, and T2B parameters. A logistic regression analysis was carried out to assess the contribution of GM atrophy and qMT parameters to the classification in AD or HS categories.

Results: GM atrophy in putamen, pallidus and thalamus, and reduced RM0B in areas belonging to the so-called default-mode network (i.e., posterior cingulate, parietal cortex) and in hippocampus/parahippocampus were found to be predictive of AD. RM0B resulted as the qMT parameter most sensitive to AD pathology.

Conclusions: QMT seems promising for the diagnosis of AD. The anatomical distribution of RM0B changes (which overlap the typical pattern observed by PET scans), indicate qMT as a technique able to reflect both, structural and metabolic information *in vivo* and non-invasively.

Profound Semantic Impairment in Corticobasal Degeneration: a New Phenotypic Variant of Tauopathies

Viviana Cafazzo, S. Baldinelli, L. Vella, L. Provinciali and S. Luzzi
Polytechnic University of Marche, Ancona, Italy

Background: It is generally assumed that semantic knowledge is relatively preserved in CBD; however, no longitudinal studies have deeply investigated this cognitive domain.

Case report: Mrs MG, a right-handed 69-year-old woman with 5 years of education, came to our attention complaining a 3-year history of involuntary movements of her left upper limb. The neurological examination revealed a left akinetic-rigid extrapyramidal syndrome and dystonia of left upper limb. Background neuropsychological evaluation revealed ideomotor apraxia of MG's left upper limb, a dysexecutive syndrome and anomias. A deep assessment of language confirmed moderate naming impairment with semantic paraphasias, errors in semantic matching tests, difficulty in single word comprehension with tendency to choice semantic distractors. Indeed the patient showed problems in recognition of famous faces and in detecting silhouettes. Brain MRI scan showed an asymmetrical atrophy (>left) of the right parietal lobe and bilateral atrophy of the temporal pole lobes. The 123-I-FP-DAT SCAN was abnormal. A 18 month-follow-up confirmed the clinical and neuropsychological picture revealing a worse performance mainly in the domains of praxis and semantics.

Conclusions: The present case provides evidence that semantic knowledge can be damaged in CBD

and reinforces the view that tauopathies do have an high phenotypic variability.

Cognitive Rehabilitation in Patients with Mild Cognitive Impairment

Sergio Cammarata, Cristina Novello, Valeria Pollero and Monica Colucci
E.O. Galliera, Genoa, Italy

Background: Mild cognitive impairment (MCI) patients are at increase risk of developing dementia. To date it remains controversial if cognitive training intervention can improve cognitive and functional performances and delay the development of dementia.

Aims: To explore the benefits of a computer-based cognitive training (CT) in patients affected by MCI of the amnestic type (a-MCI) according to Petersen criteria, compared with not treated a-MCI patients in a longitudinal follow-up study.

Methods: Eighteen a-MCI patients were randomised to receive CT programme consisted in 20 individual sessions of 45 minutes two days a week for ten weeks and sixteen a-MCI received no intervention. All the a-MCI patients underwent a multidimensional assessment concerning neuropsychological and functional characteristics, at baseline and after 9 months follow-up. The neuropsychological performances were compared.

Results: a-MCI patients treated with CT showed significant improvements (pre- and post-intervention difference) on verbal and nonverbal episodic memory and attention. In contrast a-MCI patients without treatment, showed no significant difference between baseline and follow-up cognitive performances.

Conclusions: These results suggest that computer-based cognitive training can improve a-MCI patients cognitive performances.

Cognitive Decline and Extrapyramidal Features in a Sporadic case of Frontotemporal Dementia-Parkinsonism caused by a Novel Progranulin Mutation

Miryam Carecchio[a], Daniela Galimberti[b], Francesca Cortini[b], Claudia Cantoni[b], Elio Scarpini[b], Francesco Monaco[a] and Emanuela Terazzi[a]
[a]*University of Eastern Piedmont, Novara, Italy*
[b]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*

Background: Mutations in Progranulin (GRN) have been reported in autosomal dominant and sporadic FTLD cases.

Case report: We report on a 54 years old male presenting at age 51 with an asymmetric rest tremor in his right hand; one year later, he started complaining of short-term memory deficits, poor concentration, word finding difficulty with apathy and echolalia. There was no significant family history and he had a major depressive episode at age 18. On examination, he showed camptocormia; on the right side, he had reduced arm swings and a rest, postural and intention tremor with mild bradykinesia on finger tapping and cogwheel rigidity in the elbow. His MMSE score was 24/30. A brain MRI scan showed marked, slightly asymmetric (L > R) frontotemporal cortical atrophy with periventricular hyperintensity on FLAIR sequences. CSF biomarkers were normal (Aβ1-42 637 pg/ml, Tau 264 pg/ml, P181-Tau 16 pg/ml) and GRN plasma levels were markedly decreased (13 pg/ml; ref > 70). GRN sequencing revealed a novel mutation in exon 10 [Gly387fs25X (g.11654delG)] resulting in a premature stop codon.

Conclusions: Our case underlines the importance of assessing GRN plasma levels also in sporadic patients with cognitive decline and extrapyramidal features and confirms a normal CSF profile in these subjects as previously observed.

Neuropsychological Evaluation and CSF Markers of Neurodegeneration in Amyotrophic Lateral Sclerosis Patients

Cecilia Carlesi, Cristina Pagni, Leda Volpi, Elena Caldarazzo Ienco, Livia Pasquali, Lucia Petrozzi, Gabriele Siciliano and Gloria Tognoni
University of Pisa, Pisa, Italy

Background: Amyotrophic Lateral Sclerosis (ALS) should be regarded as a multisystem disorder with cortical involvement beyond the confines of the primary motor areas.

Aims: To evaluate neuropsychological profile in ALS patients as compared to healthy controls matched for age, sex, education and to correlate neuropsychological measures to cerebrospinal fluid value of t-TAU, p-TAU and β-amiloid.

Methods: Ten patients with sporadic ALS and 6 controls, were studied. The neuropsychological assessment consisted of standardized tests for executive and memory functions. We evaluated also cerebrospinal fluid value of t-TAU, p-TAU and β-amiloid.

Results: The data analysis showed in ALS patients as compared to healthy controls a poorer performance in a test of verbal memory (RAVLT immediate recall). Moreover data obtained showed in ALS patients the presence of positive correlation between t-TAU and p-TAU value and number of errors in Stoop test and a negative correlation between p-TAU value and MMSE.

Conclusions: These results support the presence of extra-motor neuronal involvement, in particularly of executive functions in ALS patients. Even for the t-TAU and p-TAU data are in some way conflicting, they could be markers related to frontal cortex degeneration also in sporadic ALS patients with normal cognition.

Fractal Analysis of Retinal Vessels Reveals Reduced Complexity in CADASIL

Michele Cavallari[a], Teresa Falco[a], Marina Frontali[b], Silvia Romano[a], Francesca Bagnato[c] and Francesco Orzi[a]
[a]*Sapienza University, Rome, Italy*
[b]*CNR, Rome, Italy*
[c]*3NIH, Bethesda, USA*

Background: The cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) affects middle-aged adults and leads to disability and dementia. Animal models provide compelling evidence for the crucial pathogenetic role of a specific arteriopathy affecting mainly the small cerebral arteries, through an early dysfunction of the neurovascular unit. It is uncertain, however, whether, and at which stage, the small vessels undergo morphological changes in humans. *In vivo*, direct imaging of small vessels in the brain is still lacking. Ophtalmoscopic examination is a simple and accessible technique that is thought to represent a window into cerebral microcirculation.

Aims: We sought to test the hypothesis that subjects with CADASIL present changes in the retinal vessels, as compared to a group of control persons. In order to test the hypothesis we carried out a fractal analysis of the vascular tree in digital retinal photographs.

Subjects: Ten subjects with genetically confirmed diagnosis of CADASIL and ten gender and age-matched control subjects.

Methods: Fractal analysis of retinal digital images was performed using the computer-based program ImageJ and the FracLac plugin. Brain MRI lesional load assessment in FLAIR and T1-weighted DICOM images was perormed using MIPAV software. The analysis was carried out on a single parameter, the mean fractal dimension (mean-D). We used Student's *t*-test in order to detect differences in fractal dimension between CADASIL and control group. Linear regression was performed to test for a correlation between mean D and lesional load in the CADASIL group.

Results: Both the mean age and the prevalence of cerebrovascular risk factors did not differ between the groups. There was a marked difference in the mean-D, the value being significantly lower in the subjects with CADASIL (1.42 ± 0.05) than in control (1.50 ± 0.04; $p < 0.001$; figure). Linear regression analysis revealed no correlation between mean-D and MRI lesional load.

Conclusions: Fractal dimension is an index of the complexity or density of the retinal vessel branching. The reduced fractal dimension likely reflects early abnormalities of the brain microvessels, associated with the chronic progression and poor vessel remodelling of the disease.

Sociocultural Construction of Dementia in Two Eastern Societies

Gabriele Cipriani and Gemma Borin
University of Pisa, Pisa, Italy

Background: Western and non-Western cultures differ significantly in disease construction.

Aims: To report the perception of disease in two eastern communities.

Results: In China dementia is seen as a normal part of aging. There the family, rather than the individual, is the most important unit of social organization. Furthermore, cognitive domain is not taken to be the total sum of the person: greater emphasis is placed on the affective dimension. Traditional Confucian ethical values specifically mandate that the eldest son cares for his parents in their old age. So, Chinese elderly with dementia are not particularly vulnerable to stigma. Boke is a very important folk concept that describes early stages of dementia in Japan. Traditionally, it is very important for Japanese to be socially involved and boke is viewed as a preventable of frailty arising from inactivity and insufficient involvement in social settings. Boke suggests some degrees of moral lacking: this is related to the problem of Japanese people to be unable to carry out reciprocal obligations in daily social networks. To become boke is considered a kind of anti-social behavior.

Conclusions: Anthropological perspective shows the need to extend dementia models beyond the biomedical for providing care in a contextualized way.

Reversible Dementia and Corticosteroid Therapy

Gabriele Cipriani[a], Lucia Picchi[b], Angelo Nuti[b] and Ubaldo Bonuccelli[b]
[a]*University of Pisa, Pisa, Italy*
[b]*ASL12, Viareggio, Italy*

Background: Excessive circulating corticosteroids' levels are associated with cognitive impairment. We report the case of a patient who developed a reversible dementia-like syndrome receiving a long-term corticosteroid therapy.

Case report: EC, a 75-year-old woman, suffering from giant cell arteritis, was treated with prednisone 60 mg per day. After seven months of treatment she developed insomnia and impaired memory. The month later she presented defective temporal orientation and was unable to care for herself. Neurologic examination was normal. Neuropsychological testing confirmed grossly cognitive deficits. Brain gadolinium-enhanced NMR showed mild temporal atrophy. SPECT demonstrated a non-diagnostic pattern of mild diffuse hypoperfusion. The diagnosis of neurodegenerative disease (AD, LBD, FTD) was improbable considering that cognitive deficits were rapidly progressive; in the absence of cancer and of any concurrent inflammatory, infectious, ischemic, toxic-metabolic cause the working diagnosis was "steroid induced organic brain syndrome". Prednisone dosage was discontinued. Cognitive deficits improved in 15 days. Two months after withdrawal of the corticosteroid therapy the patient was asymptomatic. Neuro-psychological tests showed great improvement in all functions.

Conclusions: Neuro-psychiatric adverse effects during systemic corticosteroid therapy occur frequently. Cognitive deficits, have been documented during both long and short term therapy.

Two Cases of Sporadic Creutzfeldt-Jakob Disease (sCJD): Clinical, Molecular and MRI Findings

Monica Colucci, Andrea Assini, Daniela Audenino, Daria Bianchini, Giovanni Ajmar, Sandro Ratto, Maria P. Fondelli, Nunzio P. Nuzzi, Maria C. Novello, Valeria Pollero and Sergio Cammarata
E.O. Ospedali Galliera, Genoa, Italy

Aims and methods: We describe two cases of sCJD admitted to our Neurological Unit that underwent to serial EEG recordings, quantification of tau protein in CSF and 14-3-3 analysis; the prion protein gene (PRNP) codon 129 genotype was determined and for each patient two MRI study were performed.

Results: One patient was homozygous for methionine at codon 129; he died after 6 months and post-mortem examination was conducted. The MRI showed in diffusion-weighted imaging (DWI) a cortical and basal ganglia involvment. The other patient was heterozygous (MV) at codon 129 and is still alive after one year from the disease onset. Initially, DWI demonstrated an isolated cortical involvment, but during the follow-up the MRI pattern was modified, showing basal ganglia lesions in addition to the cortical hyperintensities.

Conclusions: Some authors postulated that an isolated cortical pattern is seen more often in patients with slow disease progression. Our findings suggest that MRI lesion profile can change during the course of the disease. In particular, we hypothesize that an isolated cortical hyperintensity in DWI could represent an early sign of CJD and might be found in the earlier stage of the disease; therefore, it will be easier to see in sCJD with slow disease progression.

Cerebrospinal Fluid Levels of Tissue Inhibitor of Metalloproteinase 1 are Increased in Subjects with Mild Cognitive Impairment

Cristoforo Comi[a], E. Boggio[a], Miryam Carecchio[a], Daniela Galimberti[b], Annalisa Chiocchetti[a], Sara Buttini[a], Elio Scarpini[b], Francesco Monaco[a] and Umberto Dianzani[a]
[a]*University of Eastern Piedmont, Novara, Italy*
[b]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*

Background: Tissue inhibitors of metalloproteinases (TIMPs) have been shown to be increased in post-mortem brain tissue from AD patients and have been localized to neuritic senile plaques. TIMPs have been investigated in both plasma and CSF of patients with AD compared to controls, but no statistically significant difference was found. Moreover, TIMP-1 plasma levels have been studied in MCI subjects compared to controls and again no difference was found.

Aims and methods: In the present study we aimed at assessing TIMP-1 levels in the CSF of MCI subjects compared to AD patients and healthy controls. We enrolled 20 patients with AD, 15 patients with MCI and a CSF biomarker profile suggestive for AD, and 35 controls.

Results: We found that TIMP-1 levels were significantly increased in MCI subjects (median value

65 ng/ml) compared to both AD patients (22 ng/ml) and controls (25 ng/ml). On the contrary, no difference was found between AD patients and controls.

Conclusions: Our data support *in vivo* the hypothesis that TIMP-1 up-regulation represents a self-defensive attempt to eliminate amyloid deposition from AD brains.

Sleep Disorders in Different Subgroups of Mild Cognitive Impaired Patients

Marta Z. Conti, Salvatore Caratozzolo, Barbara Vicini Chilovi, Marina Zanetti, Maddalena Riva, Luca Rozzini and Alessandro Padovani
Spedali Civili, University of Brescia, Brescia, Italy

Background: Despite literature suggests that sleep disturbance is an important psycobehavioral symptom in neurodegenerative disease, few studies have examined this disorder in subjects affected by mild cognitive impairment (MCI).

Aims: To investigate the sleep disturbances in different subtypes of MCI.

Methods: Thirty one subjects affected by amnestic MCI (aMCI), 16 subjects affected by non amnestic MCI (naMCI) and 58 healthy control subjects underwent a comprehensive neuropsychological evaluation. We compared the proportion of patients with MCI between groups using standard diagnostic criteria. Sleep disorders were evaluated using two different scale: Pittsburgh Quality Index-PSQI measuring the quality of sleep and Epwort Sleepiness Scale measuring the sleepiness.

Results: Data show that naMCI patients have more behavioral disturbances when compared with aMCI (mean score PSQI 8.3 ± 5.8 vs $5.3 + 3.4$: $p = 0.004$) and compared with controls (mean score PSQI $8.3 + 5.8$ vs 4.5 ± 2.9; $p = 0.02$). No difference was found in the scores measuring sleepiness between groups.

Conclusions: The preliminary analysis of the data suggests that the sleep disturbances are more present in naMCI patients and that this disorders could be (associated with non memory neuropsychological disturbances) a clinical non biological predictor of dementia, non Alzheimer type.

Oligodendrocyte Lineage Transcription Factor 2 Role in Alzheimer's Disease: Association and Expression Analysis

Francesca Cortini[a], Chiara Fenoglio[a], Francesca Clerici[b], Luisa Benussi[c], Roberta Ghidoni[c], Salvatore Gallone[d], Alessandra Marcone[e], Chiara Villa[a], Maria Serpente[a], Claudia Cantoni[a], Elisa Ridolfi[a], Massimo Franceschi[f], Giuliano Binetti[c], Innocenzo Rainero[d], Stefano Cappa[e], Claudio Mariani[b], Nereo Bresolin[a], Elio Scarpini[a] and Daniela Galimberti[a]
[a]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*
[b]*University of Milan, Ospedale Sacco, Milan, Italy*
[c]*IRCCS Centro S. Giovanni di Dio-FBF, Brescia, Italy*
[d]*University of Turin, Turin, Italy*
[e]*Ospedale San Raffaele Turro, San Raffaele Scientific Institute, Milan, Italy*
[f]*Clinica Neurologica, Casa di cura Santa Maria di Castellanza, Varese, Italy*

Background: Oligodendrocyte Lineage Transcription Factor 2 (OLIG2) is a helix-loop-helix transcriptional factor. It is expressed both in the developing and in the mature vertebrate central nervous system. Recently studies identified OLIG2 as a candidate gene for schizophrenia and psychotic symptoms, which can occur also in patients with Alzheimer's disease (AD).

Aims and methods: To carry out an association study of OLIG2 rs1005573 (T/C) and rs2834072 (A/G) by allelic discrimination in a population of 348 patients with AD and 326 age-matched controls. To perform an expression study of OLIG2 in Peripheral Blood Mononuclear Cells (PBMC).

Results: The frequency of the rs1005573 C allele was significantly increased in patients as compared with controls (40% versus 31%; $p = 0.015$; OR: 1.48; CI 95%: 1.09–2.02). Stratifying according to gender, a statistically significant difference was observed in female patients as compared with female controls (42% versus 33%: $p = 0.007$; OR: 1.76; CI 95%: 1.19–2.62), but not in males ($p > 0.05$). Conversely, we didn't observe any differences stratifying according to age at onset (early/late). No differences in the distribution of rs2834072 between cases and controls were found. Significantly decreased relative expression levels of OLIG2 in PBMC was observed in patients versus controls. Patients carrying the rs1005573 C allele displayed an even lower expression rate than non-carriers (0.101 ± 0.067 vs 0.911 ± 0.203; $p = 0.001$).

Conclusions: rs1005573 variant is a risk factor for Alzheimer, and acts by regulating OLIG2 mRNA levels.

Free and Cued Selective Recall Reminding Test (FCSRT): from Subjective Memory Complaints to Alzheimer Disease

Valentina Cucumo[a], Paola Frasson[b], Roberta Ghiretti[a], Laura Parisi[c], Simone Pomati[a], Alessandra Marcone[b], Francesca Clerici[a], Stefano Cappa[b] and Claudio Mariani[a]
[a] *University of Milan, Ospedale Sacco, Milan, Italy*
[b] *Vita-Salute San Raffaele University, Milan, Italy*
[c] *Campus Biomedico University, Rome, Italy*

Background: The Free and Cued Selective Recall Reminding Test (FCSRT) is an episodic verbal memory test with semantic cueing that permits to isolate the patient's storage capacities.

Aims: To analyze the performance of subjects with subjective memory complaint (SMC) at FCSRT, assuming a continuum from SMC to MCI to AD.

Methods: One hundred sixty seven healthy controls, 31 SMC, 36 amnestic MCI and 25 mild AD subjects underwent the FCSRT. The following FCSRT subitems were analyzed: index of cueing (IC), delayed free recall (DR-F), delayed total recall (DR-T), number of intrusions. A complete neuropsychological assessment and an evaluation of functional impairment completed the study protocol.

Results: A statistically significant difference was observed among the performances of the four groups for all the variables studied. A logistic regression analysis with group (SMC and Ctrls) as a dependent variable and a stepwise approach identified a final model with DR-F differentiating the two groups. No differences in IC and number of intrusions were found.

Conclusions: These preliminary results suggest that the FCSRT could be useful in detecting early memory difficulties in SMC.

Reduced Striatal Dopamine Transporter Binding in Posterior Cortical Atrophy

Chiara Cupidi, Valentina Arnao, Sabrina Realmuto, Antonio Cinturino, Renato Costa and Tommaso Piccoli
University of Palermo, Palermo, Italy

Background: Posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome characterized by cognitive decline with visuospatial and visuoperceptive dysfunction, but relatively preserved memory, insight and judgement. The neuropathologic correlates of PCA remain poorly defined. Pathological findings have been often revealed Alzheimer's Disease (AD), even if Lewy Bodies Disease (LBD) has also reported. The evaluation of striatal dopamine transporter (DAT) using functional imaging with dopaminergic presynaptic ligand (ioflupane or DAT-scan) has been recently demonstrated to enhance the accuracy of diagnosis of DLB *in vivo*.

Aims: The study was aimed at evaluating the presence of nigrostriatal dopaminergic dysfunction in patients affected by PCA, using single photon emission computed tomography (SPECT) with a dopaminergic presynaptic ligand.

Methods: Five patients (4 male and 1 female, mean age 64.2 ± 5.54 years, mean age at onset of 59 ± 5.6 years) fulfilling clinical criteria for PCA were selected. Standardized diagnostic protocol with extensive neuropsychological assessment and brain MRI or CT was conducted. A SPECT scan with ioflupane was carried out for each patients. Quantitative analyses of SPECTs were performed using ROIs placed in the caudate, putamen and occipital cortex. An abnormal scan was defined by a posterior putamen binding value lower than 2 SD respect to mean in normal subjects.

Results: The patients presented with progressive visual agnosia and constructional apraxia, which were associated to transcortical sensorial aphasia with alexia and agraphia in two patients. Other cognitive domains such as verbal memory and executive functions were normal. Neurological examination did not reveal parkinsonian signs. Brain imaging ruled out basal ganglia lesions. Probable or possible LBD diagnosis was not supported by clinical features, in accord to international standardized criteria. Three patients showed abnormal DaT-scan in both posterior putamens, while in 2 patients the DaT uptake was decreased in putamen and/or in caudatum.

Conclusions: We observed a reduced DaT uptake in striatum of PCA patients, suggestive for a dysfunction of nigrostiatal dopaminergic system. These findings could suggest PCA as a possible cognitive variant of LBD. In this perspective, neuroimaging with presynaptic dopaminergic ligand could be proposed as biological marker *in vivo* for this rare condition.

A 3 years follow-up of a MCI cohort

Sabrina Curcio, Nicoletta Smirne, Rosanna Colao, Francesca Frangipane, Gianfranco Puccio, Maria Mirabelli, Raffaele Maletta, Alessandra Clodomiro, Raffaele Di Lorenzo and Amalia C. Bruni
Centro Regionale di Neurogenetica, Azienda Sanitaria Provinciale di Catanzaro, Lamezia Terme, Italy

Introduction: Predictive role of neuropsychological tests in dementia is of interest for clinicians. Aims of this work were to calcolate MCI progression rate in dementia and to assess the possible predictive value of neuropsychological tests.

Aims and methods: Two hundred and eighty seven subjects, 126M; 161F, average age 71.9 ± 7.8 years. Mental Deterioration Battery was used to assess cognitive functions; correlation test, *t*-Student, logistic regression for statistical analysis.

Results: The patients had a MMSE of 24.4 ± 3.4 and an onset of 69.1 ± 8.5 yrs. After a 3 years follow-up period the progression rate was 12.3% per year. 75.5% of converters was diagnosed as Alzheimer's disease. Converters had a lower score in neurocognitive tests and later age of onset than non-converters. Patients with highest conversion rate had at baseline a multidomain cognitive impairment with amnesia (48%). Predictive tests were: Rey's words recall test (p-value = 0.000); categorical verbal fluency (p-value = 0.032); drawings copy with allmarks (p-value = 0.005); attentive matrices (p-value = 0.002).

Conclusions: Our study confirms that progression rate of MCI in dementia is nearly 12% per year. Subjects with multidomain cognitive impairment with amnesia, deficits in delayed recall, in visual-spatial and attention, with a later onset have a greatest risk to convert in dementia.

Neuropsychological and Behavioral Features of Elderly with Cancer After Rehabilitation Interventions

Fulvia Di Iulio, Silvia Zabberoni, Mirella Multari, Giovanni Morone, Jacob Shofany, Stefano Paolucci, Massimo Musicco and Carlo Caltagirone e Luca Cravello

Tor Vergata University, Foundation Santa Lucia, Rome, Italy

Background: Elderly patients with cancer often need rehabilitation but frequently suffer from cognitive disturbances and depression that might reduce the efficacy of interventions.

Aims: To assess, in patients with a history of cancer admitted to a rehabilitation hospital, the prevalence of cognitive disturbances and of depression and to evaluate the efficacy, on functional recovery, of an intensive cognitive and anti-depression intervention.

Methods: We studied 148 patients with a history of cancer that were randomly assigned to receive an intensive or a standard treatment. At inclusion patients were evaluated with an extensive neuropsychogical battery and were investigated on the presence and severity of depression.

Results: Almost all showed abnormal scores at one or more neuropsychological tests and half of them had symptoms of depression. Patients randomized for the intensive cognitive treatment performed a cognitive rehabilitation, while those randomized to the intensive antidepressive treatment were treated with serotonin reuptake inhibitor drugs according to a standardized protocol. The standard intervention consisted in a treatment according to caring physiscian preferences. A follow-up visit including all the neuropsychological and behavioural evaluations of the baseline was performed at hospital discharge. Patients assigned to intensive treatment showed better functional recovery than those assigned standard treatment.

Lifestyle and Rate of Progression of Cognitive Decline: Results of the SINDEM Cohort Study

Simona Di Santo and Massimo Musicco for the SINDEM Cohort Study Group

Consiglio Nazionale delle Ricerche, Istituto di Tecnologie Biomediche, Segrate (Milano), IRCCS Fondazione Santa Lucia, Rome, Italy

Background: In Alzheimer disease (AD) early deterioration in memory is followed by progressive impairment of other cognitive domains, and is accompanied by a large spectrum of behavioral and psychological symptoms occurring during the entire course of the disease. In individual patients, the time of appearance of clinically relevant events such as severe cognitive impairment or severe BPSD, loss of autonomy, institutionalization and death are difficult to predict. This heterogeneity might result from differences in the localization and severity of brain damage, or variations in patients' personalities, life history and risk factors. Studies suggest that presence of extrapyramidal signs and psychosis, level of disease severity and education. However, current knowledge is limited due to differences in study populations, factors examined, instruments used for evaluation, and definitions of outcomes. In AD patients, memory impairment represents the prominent and early disturbance and is caused, with any likelihood, by the early and preferential involvement of temporal cerebral areas devoted to memory processes (entorhinal cortex and hippocampus). In contrast, the severity and timing of the involvement of other cognitive domainsis heterogeneous, varying from patient to patient. Authors used different instru-

ments and methodologies to investigate the rate of AD progression but most based the estimate on the general cognitive performance of patients generally measured with the Mini Mental Status Examination (MMSE). However no evidence exists on the capacity of these measures of catching the progression of the pathological process of AD and it is possible that reductions at MMSE might be largely determined by factors only indirectly related to the progression of AD. The use of standardized and agreed measures of progression remains one of the key points for the study of prognostic predictors of AD.

Aims and methods: The cohort study promoted by the Italian Association for the Study of Dementias (SINDEM) is aimed at evaluating the natural history of dementias. The idea supporting the study is that a better knowledge of prognostic predictors of AD and of other dementias might give new insight into the pathogenic mechanisms of these diseases besides to be useful for clinicians caring for patients. As of November 2010, 20 neurological centers enrolled 238 newly diagnosed patients with AD. Diagnosis of AD was based on clinical diagnostic criteria (NINCDS-ADRDA criteria). All the enrolled patients were carefully investigated about presence of comorbidities, and on life habits. The neuropsycholgical profile of each patient was characterized according to an extensive battery of test that investigated different cognitive domains.

Results: Of the enrolled patients with AD 153 had at least one follow-up visit and could be analyzed and investigated on prognostic predictors. A decrease of 5 points or more in MMSE score in the first 24 months following enrolment was considered as an indicator of disease progression. A 5-point decrease is considered to be a clinically relevant worsening, and is too large a change to be attributed to the intrinsic limits of test reliability. The date of the visit when the 5-point reduction was recorded marked the time of occurrence of the progression. Data were analysed with survival analysis considering the time of occurrence of 5 point decrease at MMSE as the end point. The studied patients had a mean age of 74 year and women represented the 64% of the entire cohort. The mean disease duration since first symptoms was about two years and at enrollment the mean score at MMSE was 18. One fourth of the patients had a decrease of 5 points or more at MMSE during a follow-up period of 24 months.

Conclusions: Preliminary results suggest that more educated patients had more rapid progressions, that more severe involvement of cognitive functions and reduced social and physical activities are negative prognostic factors and that diabetic patients had slower progression rates as compared to non diabetic patients. Albeit preliminary these results support the idea that relevant knowledge on AD can be derived by the study of the natural history of the disease.

Applause Sign in Alzheimer's Disease

Katia Fabi, Martina Pesallaccia, Mauro Silvestrini, Leandro Provinciali and Simona Luzzi
Università Politecnica delle Marche, Ancona, Italy

Introduction: Originally, the applause sign has been considered highly specific for Parkinsonian disorders. Recently, we were able to provides evidence for presence of the applause sign in cortical dementias such as AD and FTD.

Aims: The present study aims to analyse if the severity of cognitive impairment can play a role in the generation of the applause sign.

Methods: Eighty one patients with AD were enrolled and stratified on the basis of the severity of disease: 32 patients with mild AD (MMSE 21–30); 35 patients with moderate AD (MMSE 11–20) and 14 patients with severe AD (MMSE 0–10). The applause sign was detected using the three clap test: the subjects was asked "to clap three times as quickly as possible after demonstration of the examiner". The subject's performance was considered normal when he/she clapped three times (score = 3), abnormal when the subject clapped more than three times (2 = four times, 1 = five to ten times, 0 = more than ten times).

Results: The Kruskal-Wallis test and the Mann-Whitney test did not show a significant difference in the presence of the applause sign in the three subgroups.

Conclusions: The present study excludes any potential influence of the severity of disease with the generation of the applause sign.

MRI Multimodal Investigation on a Small Cohort of Patients Affected by Amnetsic Mild Cognitive Impairment

Fabrizio Fasano, Chiara Ganazzoli, Simona Gardini, Fabio Sambataro, Letizia Concari and Paolo Caffarra
University of Parma, Parma, Italy

Aims: In the present study we push the envelope of the MRI multimodal methodology to investigate a small cohort of patients affected by amnestic mild cognitive impairment.

Methods: The intra-subject inter-modality variability, and the inter-subject variability are challenged

by the use of the novel Symmetric Normalization (SyN) method. Abnormal iron content, as revealed by transverse relaxometry, and gray matter atrophy were assessed in a group of 10 patients in comparison to a group of 10 healthy subjects. The acquisition protocol was performed on a GE MR750 3T scanner equipped with an 8 channel Head Coil, and consisted in a T1 weighted high resolution image, and in a couple of EPI acquisitions (SE and GRE) both acquired 6 times with different TE. Statistical analysis was implemented through non-parametric permutation statistics.

Results: The morphometric investigation revealed differences between groups in the right hippocampus and medial parahippocampal gyrus, and in the anterior part of the parahippocampal and fusiform gyrus bilaterally. Iron content analysis didn't reveal any difference between the two groups, neither in a voxel based approach nor in the analysis performed on 90 labeled areas.

Clinical and Neurophysiological Correlates of Visual Hallucinations in LBD

Silvia Favaretto, Francesca Gnoato, Nela Jelcic, Viviana Lunardelli, Sara Pompanin, Marina Saladini, Mario Ermani and Annachiara Cagnin
Ospedale Universitario di Padova, Padova, Italy

Aims: To study clinical, neuropsychological and neuropsysiological correlates of visual hallucination (VH) in DLB.

Methods: LBD patients were assessed with NPI, UPDRS, and questionnaires for fluctuations and RBD. A broad neuropsychological battery was administered, including VOSP test for visuo-spatial abilities. Standard EEG was analyzed with the software sLoreta to detect mapping of distributed sources of electrical activity.

Results: Among 61 LBD patients, 33 (54%) had VH. DLB VH+ were older respect to VH- (mean age VH+: 77 ± 6, VH−: 71 ± 6, $p < 0.001$). There were no differences on UPDRS score, RBD or fluctuations frequency. VH+ had a lower MMSE score (VH+: 20.9/30, VH−: 24/30, $p = 0.01$) and performed worse on attention ($p < 0.001$) and VOSP. In VH+ EEG analysis showed a source of delta activity in the parieto-occipital area (BA 30) and of theta activity in the frontal region (BA 24).

Conclusions: In LBD, VH are associated with older age, greater cognitive impairment with worse attention and visuo-spatial abilities. We hypothesized that the source of theta activity in frontal regions could be the correlate of attentional deficits, while the independent delta source in the parieto-occipital regions could be the correlate of a "functional lesion" in regions processing visuo-spatial information.

Sociocognitive Functions Decline During Normal Aging: Facial Expression Recognition

Francesca Federico[a], Nicola Polizzotto[b], Valentina Bianchetti[a] and Fiorenzo Laghi[a]
[a]*Sapienza University, Rome, Italy*
[b]*University of Siena, Siena, Italy*

Background: Sociocognitive functions involved the processing of emotions and the regulation of social behavior. Some neuropsychological evidence showed that sociocognitive function are related to frontal lobes and in particular ventromedial frontal areas. It is well known that frontal areas activity declines with normal aging.

Aims: We investigate the facial expression recognition in three groups of subjects: young adults, adults and old adults.

Methods: We used a self-reported test battery that comprises Roman Alexithimia Scale; Self-efficacy in managing negative affect; Self-efficacy in expressing positive emotions, and a computerized task. The task use a software that enables images of faces to be modified quantitatively so as to gradually change their expression (morphing). The subject was invited to report when he/she recognizes a new expression. Transitions between all six basic emotions are shown in a continuous, random manner. By analyzing the accuracy of emotion recognition and factors from behavioral scales we founded a decline on facial expression recognition not accompanied by difficulty in sympathizing with others.

Conclusions: This pattern could reflect a dissociation between the neuropsychological decline of frontal functions that support the explicit facial expression recognition and the behavioral preserved social function.

Study of Amnesia in Three Variants of Alzheimer's Disease

Laura Ferigo, Valeria Valbusa, Francesca Sala, Elisabetta Broggio, Giuseppe Moretto and Giuseppe Gambina
Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

Background: The heterogeneity of Alzheimer's disease (AD) is demonstrated in many of its aspects: clinical manifestations, types and patterns of neurological and neuropsychological symptoms; the memory impairment may presents heterogeneity too.

Aims: To describe the heterogeneities of memory impairment in atypical presentation of AD.

Methods: We describe and analyze the performance at the Rey Auditory Verbal Learning Test of 7 patients with diagnosis of three variants (v.) of AD: 1 case (posterior v.) with progressive visual-spatial dysfunction, 2 cases (aphasic v.) with progressive aphasia, 4 cases (frontal v.) with predominant behavioural disorders. All patients were submitted to neurological and neuropsychological examination, morphology and functional neuroimaging.

Results: Our data show different patterns of memory impairment in AD. The Rey Auditory Verbal Learning Test highlights the following patterns: frontal with false recognitions and verbal intrusions; aphasic with low learning and phonemic and semantic paraphasias; posterior with good learning and few missed recognitions.

White Matter Damage in Frontotemporal Lobar Degeneration Spectrum

Massimo Filippi, Federica Agosta, Elisa Scola, Elisa Canu, Alessandra Marcone, Giuseppe Magnani, Lidia Sarro, Giancarlo Comi, Stefano F. Cappa and Andrea Falini

Scientific Institute and University Ospedale San Raffaele, Milan, Italy

Aims and methods: We used diffusion tensor (DT) MRI to assess white matter (WM) damage in behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) variants. Thirteen bvFTD and 20 PPA (9 nonfluent, 7 semantic, and 4 logopenic) patients were studied. Grey matter (GM) and WM atrophy was assessed using voxel-based morphometry.

Results: bvFTD patients showed widespread patterns of DT MRI abnormalities affecting the most of the WM, bilaterally. In PPA patients, WM damage was more focal and varied by variant, with predominant left fronto-temporo-parietal abnormalities in nonfluent, left frontotemporal in semantic, and the least extensive WM damage involving the left frontoparietal network in logopenic. Although WM abnormalities mirrored the patterns of GM atrophy, DT MRI changes extended beyond the topography of GM loss. Left uncinate was the best predictor of patient diagnosis in each group, followed by anterior corpus callosum in bvFTD, left superior longitudinal fasciculus in nonfluent, and left inferior longitudinal fasciculus in semantic.

Conclusions: DT MRI metrics may be early markers of WM integrity loss in bvFTD and PPA variants that only at a later stage will be detectable by volumetric measures. DT MRI may be an additional tool in the diagnostic workup of these patients.

The Topographical Distribution of White Matter Damage in Progressive Supranuclear Palsy Syndromes

Massimo Filippi[a], Federica Agosta[a], Michela Pievani[a], Sebastiano Galantucci[a], Tanja Stojkovic[b], Giancarlo Comi[a] and Vladimir S. Kostic[b]

[a]*Scientific Institute and University Ospedale San Raffaele, Milan, Italy*

[b]*University of Belgrade, Belgrade, Serbia*

Aims and methods: We investigated the pattern of microstructural changes of white matter (WM) in patients with different progressive supranuclear palsy (PSP) syndromes using diffusion tensor (DT) MRI and tract-based spatial statistics approach. Thirty-seven PSP patients and 34 age- and sex-matched healthy subjects were studied. PSP patients were classified as Richardson's syndrome (PSP-RS, 21 patients) or PSP-Parkinsonism (PSP-P, 16 patients) based on clinical criteria.

Results: Compared with controls, PSP-RS patients showed areas of WM damage in the superior cerebellar peduncle (SCP), cerebral peduncles, and multiple supratentorial areas including corpus callosum, cingulum, corona radiata, internal capsulae, and fronto-parietal WM. On the contrary, in PSP-P patients relative to controls the pattern of WM damage was restricted to the corpus callosum, with a relative sparing of the SCP. When patient groups were contrasted directly, PSP-RS patients showed a more marked damage to the SCP, bilaterally than those with PSP-P. No difference was found when comparing PSP-P vs. PSP-RS patients.

Conclusions: This study suggests an impaired structural integrity of WM tracts in PSP patients. In keeping with pathological data, WM damage was more pronounced in PSP-RS vs. PSP-P patients. The less prominent involvement of WM in PSP-P patients might be associated to their favorable clinical status.

Closing-in behaviour in Mild Cognitive Impairment

Sara Finotto[a], Elisabetta Ambron[b,c], Robert D. McIntosh[b], Francesca Clerici[a], Claudio Mariani[a] and Sergio Della Sala[b]
[a]*Ospedale Luigi Sacco, University of Milan, Milan, Italy*
[b]*University of Edinburgh, Edinburgh, UK*
[c]*Suor Orsola Benincasa University, Naples, Italy*

Background: "Closing-in behaviour" (CIB) is the tendency in figure copying to draw very close to or on top of the model. CIB has never been explored in people with Mild Cognitive Impairment (MCI).

Aims and methods: The files of 313 people diagnosed with MCI were reviewed and CIB was found in 74 people. Then, two approaches were used to explore CIB. First, we assessed the cognitive correlates of CIB, by selecting two groups of MCI – with ($n = 35$) and without CIB ($n = 133$) – who underwent executive, visuo-constructional and memory tasks. Second, we capitalised on the cognitive profiles of the MCI, subdividing the overall sample into MCI with and without memory deficits.

Results: MCI people with CIB showed lower performance in visuo-constructional ($z = -2.54$, $p < 0.05$) and executive tasks ($z = -3.64$, $p < 0.001$) than those without CIB, but the two subgroups did not differ in severity or memory performance. Moreover, the frequency of CIB was higher in Multidomains non-Amnestic MCI (33%) than in Amnestic MCI (9%).

Conclusions: The findings suggest a stronger association of CIB with impairment of executive functions rather than memory. This is consistent with the hypothesis that CIB is a primitive default behaviour, released under conditions of reduced executive resources.

Effects of Linguistic Training in Primary Progressive Aphasia

C. Fonti[a], I. Cristofori[b], L. Cretella[a] and A. Stracciari[a]
[a]*S.Orsola-Malpighi University Hospital, Bologna, Italy*
[b]*University of Lyon, Lyon, France*

Background: Primary progressive aphasia (PPA) is a degenerative syndrome characterized in its early stage by deterioration of language without dementia. At present, there are no effective drugs for PPA. A treatment option may be language therapy, which is used to explore and improve alternative communication strategies; however, literature on this topic is very poor.

Aims and methods: In our study, two PPA patients underwent linguistic training three times a week for six months. Training consisted of one-hour sessions which included exercises involving language, executive functions and memory (i.e. reading, writing, and summarizing stories). Patients were evaluated via Aachener Aphasie Test (AAT) before and after the treatment.

Results: Patient 1 exhibited an improvement in understanding and repetition subtests of the AAT. Patient 2 showed a decreased score on the denomination subtest, while performances on the other subtests remained stable. Qualitatively, both patients showed improved capabilities in communication behavior, syntactic structure, and (only in patient 1) semantic structure. At functional imaging patient 1 had a normal cerebral PET, whereas patient 2 presented a left frontoparietal hypoperfusion on SPECT.

Conclusions: Notwithstanding these differences, these data suggest that language rehabilitation in PPA may produce beneficial effects on general linguistic competence.

CSF Markers in the Differential Diagnosis of Alzheimer's Disease from Frontal Variant of Frontotemporal Dementia

Massimo Franceschi[a], Giuseppe Magnani[b], Francesca de Rino[a], Francesca Caso[b], Elisabetta Coppi[b], Gabriella Passerini[b], Matteo Zabeo[a] and Filippo Martinelli Boneschi[b]
[a]*IRCCS Multimedica, Castellanza (Varese), Italy*
[b]*IRCCS S. Raffaele Scientific Institute, Milan, Italy*

Background: The early differentiation between Alzheimer's disease (AD) and frontal variant of frontotemporal dementia (fvFTD) is often difficult.

Aims and methods: We evaluated the usefulness of baseline CSF beta-amyloid 1-42 (bA), tau (t) and Th131-phosphorilated tau (Pt) in the early differentiation of AD from fvFTD, following up the patients for one to five years to confirm the initial diagnoses.

Results: Seventy-two patients with AD and 42 patients with fvFTD showed baseline different CSF levels of Pt (increased in AD, $p = 0.001$), bA (reduced in AD, $p = 0.012$), and ratio Pt/bA ($p = 0.003$). A multivariate logistic regression model has been implemented with the diagnosis as dependent variable and gender, education, age at onset, basal MMSE and

levels of CSF metabolites as independent variables. Only bA and Pt were predictors of the model, and a higher index of the ratio Pt/bA was associated with a higher risk of AD versus fvFTD ($p = 0.005$; OR: 58.7). ROC analyses suggest that the ratio Pt/bA is able to predict diagnosis with an AUC of 0.73 (optimal level being 0.156 = sensitivity 79.7% and specificity 68.3%).

Conclusions: Our findings suggest that CSF metabolites may be only further tools in the early differentiation of AD from vfFTD.

Pharmacogenomics of Response to Acetylcholinesterase Inhibitors in Alzheimer Disease Patients: Preliminary Data of a Genome-Wide Association Study

Massimo Franceschi[a], Giacomo Giacalone[b], Sara Lupoli[b], Paola Brambillla[b], Federica Esposito[b], Giuseppe Magnani[b], Elisabetta Coppi[b], Francesca Caso[b], Chiara Vismara[b], Daniela Galimberti[c], Elio Scarpini[c], Gianluigi Forloni[d], Diego Albani[d], Giancarlo Comi[b] and Filippo Martinelli Boneschi[b]
[a]*IRCCS Multimedica, Castellanza (Varese), Italy*
[b]*IRCCS S. Raffaele Scientific Institute, Milan, Italy*
[c]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*
[d]*Pharmacological Institute Mario Negri, Milan, Italy*

Background: The positive effect of Acetylcholinesterase Inhibitors (AChI) in Alzheimer's disease (AD) is restricted to a minority of AD patients.

Aims: We looked for genetic markers predictive of response to AChI treatment in AD patients.

Methods: As preliminary data of a genome-wide pharmacogenomic case-control association study (GWAS), we focused on 267 candidate genes belonging to ADME (Absorption, Distribution, Metabolization, Excretion) panel (www.pharmaadme.org). The study enrolled 183 AD patients treated with AChI, mean age at onset was 72 years, 68% of patients were female, follow-up ranged from 6 to 18 months. Annualized difference between Mini Mental State Examination (MMSE) performed at baseline and at the end of the follow-up (delta MMSE) was measured. Responders were defined for a worsening of no more than 1 point in delta MMSE, non-responders for a worsening of more than 3 points. Genotyping was performed using the Illumina® Human660 K BeadChip: 8037 SNPs belonging to ADME genes were tested for association after quality controls.

Results: Among the top 10 SNPs for allelic association *p*-value, one belonged to TAP1 gene and two to CYP7B1 gene (non significant after Bonferroni correction). A replication study, on an independent cohort, of these SNPs together with the top SNPs of the GWAS is ongoing.

FTD Clinical Characterization of PGRN Mutations in a Large Calabrian Kindred

Francesca Frangipane, Nicoletta Smirne, Rosanna Colao, Livia Bernardi, Gianfranco Puccio, Sabrina A.M. Curcio, Maria Mirabelli, Raffaele Maletta, Maria Anfossi, Maura Gallo, Silvana Geracitano, Maria G. Muraca, Alessandra Clodomiro, Annelisa Borelli, Raffaele Di Lorenzo, Francesco Comito, Vincenzo Valenti, Sandra Marzano, Rosa A. Leone and Amalia C. Bruni
Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy

Introduction: Mutations in the progranulin gene (PGRN) are responsible for familial forms of FTD.

Aims: To describe clinical phenotype of FTD associated to different PGRN mutations in an isolated calabrian population.

Methods: Sixteen FTD patients performed a complete neurological/neuropsychological evaluation. PGRN gene was sequenced in all subjects. Plasma levels of PGRN were measured.

Results: One known frameshift (1145insA in 12 related patients) and two novel missense (A266P and C126W, in 3 related patients and in 1 sporadic subject, respectively) PGRN mutations were identified. Reduced levels of PGRN protein in plasma were determined in the PGRN 1145insA and A266P mutated patients. All mutated patients presented at onset with behavioural FTD; the 1145insA carriers showed a dysexecutive profile: distractibility, deficit of planning, disinhibition, neurological examination evidenced extrapyramidal signs and primitive reflexes; the A266P carriers manifested apathy, reduction of verbal initiative (apathetic profile) and normal neurologic examination. The C126W carrier presented with paranoid delusions and irritability, normal neurologic examination. Mean of age at onset was statistically different among 1145insA carriers (64.2 + 12.5 yrs) and A266P carriers (75.7 + 2.9 yrs).

Conclusions: Our findings, related to different FTD phenotypes, seem to corroborate a genotype-phenotype relationship in PGRN mutations.

Neuropsychological Features of Creutzfeld-Jakob Disease

Daniela Frosini, Cristina Pagni, Chiara Pizzanelli, Mirco Cosottini, Irene Ghicopulos and Gloria Tognoni
Univeristy of Pisa, Pisa, Italy

Aims: To investigate cognitive profile in a group of 9 patients with sporadic Creutzfeld-Jakob disease (sCJD).

Methods: A retrospective study was conducted on data derived from neuropsychological evaluation of 9 patients with sCJD. All patients performed EEG, DWI MRI, tau and 14.3.3 protein level. Post mortem pathological findings were available in all but one patients and were consistent with the diagnosis.

Results: Cognitive symptoms were the reason for medical consulting in 5 patients, All patients who performed an extensive neuropsychological battery ($n = 6$) showed an impairment in at least one cognitive domain that, in 5 patients, concerned the executive functions. MMSE was impaired in all patients who performed it, while digit span was usually preserved. Furthermore, in all patients, DWI MRI was consistent with clinical diagnosis, 14.3.3 protein was present in and TAU protein was abnormally elevated.

Conclusions: Cognitive impairment may represent one of the earliest features of CJD that may precede, in some cases, the onset of psychiatric or neurological symptoms. Executive functions, specifically attention, seems to be particularly involved even though there is a variability in neuropsychological profiles probably due to different disease duration at the time of evaluation.

Depression in Subjects with Mild Cognitive Impairment does not Increase the Risk of Developing Alzheimer's Disease

S. Fusari Imperatori[a], B. Caracciolo[b], S. Pomati[a], L. Maggiore[a], I. Cova[a], D. Galimberti[c], E. Scarpini[c], F. Clerici[a], C. Mariani[a] and L. Fratiglioni[b]
[a]*University of Milan, Ospedale Sacco, Milan, Italy*
[b]*Karolinska Institutet, Stockholm, Sweden*
[c]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*

Aims: To examine the relationship between depression and the risk of progression of mild cognitive impairment (MCI) to Alzheimer's disease (AD) (NINCDS-ADRDA criteria) 169 MCI consecutive patients from the "Luigi Sacco" Hospital were followed-up for an average of 2.6 years.

Results: At baseline, depression was diagnosed according to DSM-IV criteria and depressive symptoms were assessed using the Geriatric Depression Scale (GDS). Eighty-two (48.5%) out of 169 MCI subjects progressed to AD. These subjects were older (76.1 ± 56.3 vs. 73.2 ± 7.8 years; $p = 0.01$) and had lower MMSE score (24.8 ± 2.8 vs. 26.0 ± 2.5; $p < 0.05$) as compared to non-converters. Minor depression occurred more frequently among non-converters (48.2% vs. 35.3%; $p < 0.05$). The multivariate analysis, adjusted for socio-demographic variables, MMSE score, MCI subtypes, and APOE-e4 allelic status showed that the risk of progression to AD in MCI patients was not associated to GDS scores (HR 0.96; 95% CI 0.92–1.00), major depression (HR 0.82; 95% CI 0.50–1.35) or minor depression (HR 0.79; 95% CI 0.49–1.27).

Conclusions: Depression co-occurring with MCI does not predict progression to AD. On the contrary, depressive symptoms occur more frequently in MCI that do not progress to AD. These data confirm that depression present at the time when MCI is detectable may be independent from AD-related neuropathology.

Binding of Lipid-Based Nanoparticles to Plasma Abeta: Relevance for new Therapeutic Strategies in Alzheimer's Disease

Gloria Galimberti, Elisa Conti, Fulvio Da Re, Marco Tironi, Massimo Masserini and Carlo Ferrarese
University of Milano-Bicocca, Monza, Italy

Background: Depletion of Abeta represents the most efficacious perspective to prevent beta-amyloid toxicity and Alzheimer's disease (AD) development. Nanoparticles (NPs) constitute an innovative vehicle potentially able to localize and interact with Abeta, *in vitro* and *ex vivo*. Studies performed in plasma from human subjects may represents an interesting opportunity to analyze the capability of NPs to bind the Abeta peptide present in periphery. However, it is noteworthy that Abeta and plasma proteins are in a state of dynamic equilibrium between bound and unbound forms depending on respective concentrations. So Abeta levels could be very high but only the free molecules can be measured by ELISA.

Aims and methods: For this reason a method to dissociate Abeta-plasma proteins complexes was set up to evaluate real Abeta content.

Results: Preliminary findings, performed in human plasma samples, confirmed an increase in detectable

plasma Abeta 1-42 after dissociation procedure with respects to non dissociated samples. Following incubation with lipid-based NPs at different time and concentrations, a slight decrease in Abeta levels was shown. Further studies on a larger group of controls and AD patients may support the capacity of liposomes to sequester Abeta from plasma suggesting new therapeutic opportunities.

Semantic Memory Impairment and Neurofunctional Alterations in Mild Cognitive Impairment

Chiara Ganazzoli[a], Simona Gardini[a], Fabrizio Fasano[a], Letizia Concari[a], Fabio Sambataro[a], Francesca Ferrari Pellegrini[b], Massimo Marchi[a], Annalena Venneri[c], Fernando Cuetos[d] and Paolo Caffarra[a]
[a]*University of Parma, Parma, Italy*
[b]*AUSL, Parma, Italy*
[c]*University of Hull, Hull, UK*
[d]*University of Oviedo, Oviedo, Spain*

Aims: The present preliminary study is aimed to investigate the semantic memory performance and the brain structural and functional patterns of MCI.

Methods: Ten MCI patients and ten healthy controls underwent semantic memory assessment and MRI investigation on a 3T GE Scanner. Semantic battery included naming and word-definition matching of objects, actions and famous people and semantic fluency for different categories. MRI protocol consisted in high resolution structural imaging and functional MRI during rest (eyes open). Connectivity Default Mode Network (DMN) was measured using independent component analysis.

Results: MCI scored significantly lower in total naming, naming of famous people and semantic fluency for fruits, politicians and singers, and showed less immediate recalls, compared to controls. The voxel-based morphometry analysis revealed higher atrophy in the right hippocampus and medial parahippocampal gyrus, and in the anterior part of the parahippocampal and fusiform gyrus bilaterally in MCI. DMN connectivity was significantly lower in posterior cingulate and precuneus in MCI compared to healthy controls.

Conclusions: Visual naming, especially for famous people, and semantic fluency for specific categories are damaged in MCI. Structural and functional alterations were detected in brain regions critical for memory processes, such as medio-temporal and precuneus regions, in MCI.

Multiple Features Targets Cancellation Test: Normative Data and Equivalent Scores

Roberta Ghiretti, Simone Pomati, Valentina Cucumo, Francesca Clerici and Claudio Mariani
University of Milan, Ospedale Sacco, Milan, Italy

Background: Multiple features targets cancellation test (MFTCT), a non-verbal cancellation task, has been shown to be sensitive to cognitive decline in patients with Alzheimer's disease (AD) and multi-infarct dementia (MID).

Aims and methods: To collect normative values in an Italian population sample. One hundred and twelve normal subjects were assessed with MFTCT. Time to complete the test (TIME) provided a measure of psychomotor speed and divided attention; hits and false alarms (FALSE) provided a measure of accuracy and selective attention.

Results: A direct relation was observed between age and TIME, and between education and hits and an inverse relation between education and FALSE. Adjusted scores were obtained by adding/subtracting the correction factors provided by the regression equations. Cutoffs were established as a result of non-parametric lower tolerance limits. Equivalent scores (ES) were obtained with the method described by Capitani and Laiacona. The mean values obtained by the subjects in our sample were similar to those of the control subjects of the original study.

Conclusions: By providing normative data for MFTCT our work broadens the number of tests that can be employed in the work-up of patients with dementia, particularly in the assessment of selective and divided attention.

Benton's Judgement of Line Orientation-Short form: Normative Data and Equivalent Scores

Roberta Ghiretti, Simone Pomati, Valentina Cucumo, Francesca Clerici and Claudio Mariani
University of Milan, Ospedale Sacco, Milan, Italy

Background: Benton's Judgement of Line Orientation (BJLO) is a widely used instrument to assess spatial perception and orientation. Shorter versions of the test (15-items) have been employed in the assessment of patients with dementia.

Aims and methods: To collect normative values in an Italian population sample (104 normal subjects) for the short version.

Results: A direct relation was observed between total score, age and education. Adjusted scores were obtained by adding/subtracting the correction factors provided by the regression equations. Cutoffs were established as a result of non-parametric lower tolerance limits. Equivalent scores (ES) were obtained with the method described by Capitani and Laiacona.

Conclusions: By providing normative data for BJLO our work broadens the number of tests that can be employed in the work-up of patients with dementia, particularly in the assessment of visuo-spatial functions.

Neurological, Cognitive and Imaging Features of Progressive Apraxia and Visuo-spatial dysfunction

Valeria Isella, Cristina Mapelli, Francesco Rucci, Francesca Ferri, Debora Traficante, Carlo Ferrarese and Ildebrando M. Appollonio
Clinica Neurologica, S. Gerardo, Università di Milano Bicocca, Monza, Italy

Aims and methods: In the present case series we describe the neurological, cognitive and neuroimaging features of 15 patients with mild cognitive impairment presenting with progressive visuospatial deficits and apraxia that were prominent with respect to memory impairment. Study participants underwent UPDRS part III, neuropsychological assessment, brain CT/MRI scan, SPECT/FDG-PET scan, and 123I-FP-CIT SPECT.

Results: Eight out of 15 patients (53%) showed clinical or imaging evidence of parkinsonism. With respect to cases with no extrapyramidal involvement, they presented with less severe visuo-spatial impairment, more severe limb apraxia and more frequent memory and language deficits. They were also older at disease onset, and showed more widesperad atrophy and major frontal plus minor occipital involvement at neuroimaging. No difference was detected in disease duration, MMSE score and executive function impairment.

Conclusions: Our findings suggest that progressive parietal dysfunction may actually be split into at least two distinct profiles: a visuospatial syndrome due to more posterior (parieto-occipital) degeneration, and a limb apraxia syndrome due to more anterior (parieto-frontal) degeneration, also showing parkinsonism and language and memory deficits. The first picture basically meets criteria for Posterior Cortical Atrophy, while the latter shows most, though not all, features of Corticobasal Syndrome.

Patient/doctor Relationship: a National Survey on Current Clinical Practice for the Diagnosis Disclosure

Fabio Izzicupo, Sabina Gainotti, Marco Massari, Angela Giusti, Francesca Galeotti, Nicola Vanacore and Roberto Raschetti
Istituto Superiore di Sanità, Rome, Italy

Background: In Italy there is little data available on clinicians' attitudes towards the disclosure of the diagnosis of Alzheimer's Disease (AD).

Aims and methods: The Istituto Superiore di Sanità has conducted a survey on 448 AD units, with a reply of 212 AD units (48.2%), 46 (21.7%) of which are located in Northern Italy, 25 (11/8%) in Central Italy and 141 (66.5%) in Southern Italy. Besides, a qualitative study was conducted with 5 focus group.

Results: Quantitative data indicate that clinicians often communicate the diagnosis to the patient's relatives (98.6%) and directly to the patient (70.5%). However, they use expressions like "memory disturbs" (79.7%) and "cognitive decline" (75%) more than "Alzheimer" (45.3%). The main reasons to avoid full disclosure are the fear that disclosure may worsen a patient's psychological condition (57.4%) and the opposition of the family (45.1%). However, clinicians believe that disclosure improves patient's adherence (60%) and helps understanding the causes of daily difficulties (52.6%). In the majority of AD units the problem has not been formally discussed (75.3%). Many clinicians would find specific training useful (95.7%).

Conclusions: Results of the qualitative research describe "how" do clinicians communicate with patients, which are the reasons for their choices and which strategies they find more successful.

Cerebrospinal Fluid Levels of Aβ 1-42 influence cholinergic cortical activity in Alzheimer's disease patients

Giacomo Koch[a,b], Zaira Esposito[a], Viola Giacobbe[b], Francesco Di Lorenzo[b], Giulia Bucchi[b], Sonia Bonnì[b], Carlo Caltagirone[a,b] and Alessandro Martorana[a,b]
[a]*Tor Vergata University, Rome, Italy*
[b]*Fondazione Santa Lucia IRCCS, Rome, Italy*

Background: In Alzheimer's disease (AD) the dysfunction of cholinergic neurons is considered a typical hallmark. It is known that fragments of amyloid beta protein (Aβ) and Tau protein are supposed to inter-

fere with synaptic transmission. In animal models of AD, Aβ interact with central acetylcholine transmission interfering with transmitter synthesis and release. In AD patients, central cholinergic function can be evaluated *in vivo* by using a neurophysiological tool called Short Afferent Latency Inhibition (SLAI).

Aims and methods: We aimed to investigate whether in AD patients ($n = 26$) the levels of cerebrospinal (CSF) biological markers of AD such as $A\beta_{1\text{-}42}$ and tau could influence the cortical cholinergic activity assessed through SLAI.

Results: We found that SLAI was decreased in AD patients in comparison to a group of healthy controls. In AD patients, there was a positive correlation between the individual amount of cholinergic activity assessed by SLAI and $A\beta_{1\text{-}42}$ CSF levels, but not with t-Tau CSF levels, suggesting that $A\beta_{1\text{-}42}$ CSF levels may impact mechanisms of cortical cholinergic activity.

Conclusions: This correlation confirms previous data obtained in experimental models, showing that cholinergic dysfunction may be the result of direct influence of $A\beta_{1\text{-}42}$ on neuronal function.

Posterior Cortical Atrophy Presentino as right Parietal Syndrome: a Neuropsychological Single Case Study

Federica Lucchelli, Alessia Monti and Roberto Cubelli
University of Trento, Rovereto, Italy

Case report: RI, a 63-year-old, left-handed male and a former lawyer, presented with a 3-year-long history of progressive visuo-spatial impairment and motor disturbances. As his wife reported, he had difficulties to correctly place and move his trunk and limbs (e.g., sitting on a chair or walking down stairs) and to use objects. Reportedly, language, memory and navigation abilities were spared. Brain MRI and 99mTc SPET pointed to pathological changes in the right posterior cortex. Behavioural observation confirmed a marked impairment in moving, with hints of left-sided motor neglect. RI's memory was surprisingly good, as he could remember most information from one session to the other and he could keep track of appointments; he always recognized the place, the examiners and the personnel. Neuropsychological assessment demonstrated a severe visuo-spatial impairment associated with clear-cut signs of left-sided neglect. Limb apraxia was also prominent in all standardized test, on imitation, pantomime and real object use. In contrast, object recognition and naming were fully preserved. All the data fit with the diagnosis of posterior cortical atrophy.

Conclusions: We interpret RI's neuropsychological pattern as the result of disproportionate damage to the right parietal cortex (with limb apraxia related to his left handedness) with sparing of temporal cortical areas.

Amnesia in Fronto-temporal Degeneration: Encoding or Retriva Deficits?

Federica Lucchelli[a], Susanna Venuta[a,b], Giorgio Rossi[b] and Alessia Monti[a]
[a]*University of Trento, Rovereto, Italy*
[b]*APSS, Trento, Italy*

Background: Early and severe amnesia in frontotemporal dementia (FTD) is more common than previously thought. It has been suggested that in the case of FTD the memory deficit could well be qualified as "frontal" amnesia, namely characterized by encoding and retrieval deficits in contrast with impaired consolidation typical of Alzheimer's disease.

Case report: NM, a 59-year-old lady, presented with a typical history of progressive behavioural and executive disturbances. An extensive neuropsychological assessment confirmed markedly impaired executive functions and social cognition. A distinctive neuroimaging pattern of frontal atrophy further supported the diagnosis of behavioural variant FTD. However, severe amnesia was reported as a prominent deficit since onset and standard memory tests were also found to be significantly impaired. To assess retrieval and encoding deficits, NM's amnesic profile was further investigated by several recognition tests and different versions of the Grober and Buschke test. Only recognition procedures led to significant improvement up to normal performance, while encoding manipulation and provision of cues were not effective.

Conclusions: Our results point to the overwhelming role of retrieval deficits, which appear to be fully compensated by the recognition procedure but are still partially at play when only encoding is checked for.

When "frontal" Dysfunction Takes Over: The Sense of Brain Imaging Asymmetry

Federica Lucchelli and Alessia Monti
University of Trento, Rovereto, Italy

Case report: MA, a 57-year-old man, was referred for evaluation of behavioural and cognitive disturbances. At the age of 47 he had presented dramatic

personality and behavioural changes, consisting of hypomania, compulsiveness, loss of insight and impaired social interaction. This led to relevant financial loss, bankruptcy and divorce. For some years he let himself go, living on the streets until, about one year before our assessment, his wife took care of him again. At that time dementia was diagnosed. At the time of our evaluation, he was deeply apathetic and emotionally unconcerned, but not overtly depressed. His behaviour was always adequate and when stimulated he was well cooperative. An extensive neuropsychological assessment demonstrated severe and pervasive impairment of executive functions. His memory performance showed a striking dissociation between spared verbal and impaired visuo-spatial tasks. Language was remarkably preserved, whereas visuo-spatial perceptual skills were mildly affected. MA's cognitive profile, primarily characterized by widespread impairment of frontal abilities, yet suggests disproportionate involvement of right hemisphere functions, in contrast with sparing of left hemisphere ones.

Conclusions: This fits well with brain MRI findings, that documented an unusual and marked asymmetry of atrophy, whereby the right hemisphere is much more severely affected than the left one.

Tha GAIA project: a pilot program for Alzheimer's disease. A follow-up study

Tiziana Maci, Graziella Quattrocchi, Mario Cirmi, Fabrizio Giammello, Francesco Le Pira, Santo Di Nuovo, Vincenzo Perciavalle and Mario Zappia
University of Catania, Catania, Italy

Aims: To evaluate patients and caregivers three months after the end of a pilot project, called GAIA ("Gruppo Alzheimer In Attività", i.e. "Alzheimer Group In Activity") assessing the effect of cognitive stimulation, motor activity and social aggregation on cognitive decline in AD.

Methods: We enrolled 14 AD patients, randomly divided in two groups without significant clinical and demographic differences: active treatment group and control group. Treatment group underwent protocols of both cognitive and motor stimulation as well as encouraged to socialization.

Results: At the end of treatment we found a significant improvement of mood and QoL in the treatment group, whereas we observed a significant worsening of both parameters in the control group. Caregivers of the treatment group exhibited a significant improvement of their mood and of their perception of patients' QoL. A three months follow-up showed that while treatment group maintains, although partially, the improvement obtained during the treatment, the controls continued their progressive worsening.

Conclusions: This investigation provides experimental evidence that an integrated approach based on cognitive stimulation, physical activity and socialization can improve QoL of AD patients and alleviate the caregivers' burden of care.

White Matter Integrity Assessment with Diffusion Tensor Imaging in Mild Cognitive Impairment

Laura Maggiore[a], Grazietta Gattellaro[b], Domenico Aquino[b], Anna R. Giovagnoli[b], Alessandra Erbetta[b], Francesca Clerici[a], Maria Grazia Bruzzone[b] and Claudio Mariani[a]
[a]*University of Milan, Sacco Hospital, Milan, Italy*
[b]*Fondazione IRCCS Istitute "Carlo Besta", Milan, Italy*

Aims and methods: In order to improve identification of people at risk of developing Alzheimer's disease we employed Diffusion Tensor Imaging (DTI) analysis to investigate the integrity of fiber tracts in Mild Cognitive Impairment (MCI) patients and controls. DTI is an advanced MR technique sensitive to white matter microstructure integrity in vivo by measuring directional changes in water diffusivity. Twenty-two patients with MCI and seventeen controls underwent conventional magnetic resonance imaging (MRI) 1.5-Tesla and DTI examination Fractional anisotropy (FA) and mean diffusivity (MD) were measured in region of interest (ROI).

Results: In MCI patients FA values were significantly decreased in inferior longitudinal fasciculus, anterior thalamus, anterior and posterior cingulum and fornix compared to the controls. Conversely, MD values were significantly increased in right inferior longitudinal fasciculus and anterior-posterior cingulum. No difference in FA and MD was found between MCI patients and controls in cortical spinal tract, corpus callosum and in prefrontal dorsolateral region.

Conclusions: These results are in agreement with those of previous studies DTI is a sensitive method for detecting subtle microstructural changes of several cortico-cortical and sub-cortical tracts that may be predictors of AD progression.

Progranulin plasma levels in patients with and without TDP-43 pathology

Michela Magistrello, Silvia Grifoni, Andrea Calvo, Cristina Moglia, Alessia Pellerino, Andrea Naldi, Salvatore Gallone, Adriano Chiò and Maria Teresa Giordana
University of Turin, ASO S. Giovanni Battista Molinette, Turin, Italy

Background: PGRN gene mutations resulting in haploinsufficiency are responsible of cases of familial frontotemporal dementia (FTLD); plasma progranulin levels are significantly reduced in subjects carrying the mutations. FTLD due to PGRN gene mutations is characterized by accumulation of TDP-43 protein within neurons, a pathologic phenotype common to other neurodegenerative conditions named TDP-43 proteinopathies, including amyotrophic lateral sclerosis. A possible mechanistic link between progranulin expression and TDP-43 pathology was hypothesized.

Aims and methods: With the aim to investigate whether plasma levels of progranulin reflect the expected TDP-43 pathology, we measured the levels of progranulin in 27 patients with ALS in comparison to 25 age-matched patients diagnosed as Alzheimer's dementia or frontotemporal dementia (FTD), by an ELISA method (Adipogen, Seul, Korea).

Results: None of patients carried PGRN gene mutations. We found that plasma progranulin levels were not significantly different in Alzheimer patients (mean 153.20 ng/ml, range 121.6–202.0) in comparisons with ALS patients (mean 161.61 ng/ml, range 107.0–268.0). Mean value in FTD patients was 148.52 (139.9–141.4).

Conclusions: Plasma progranulin levels do not reflect the expected TDP-43 pathology and do not clarify any possible mechanistic link of progranulin and TDP-43.

Clinical Phenotypic Variability in an Italian Family Bearing an Intronic Mutation in PGRN Gene

Gabriella Marcon[a], Giacomina Rossi[a], Giorgio Giaccone[a], Marina Grisoli[a], Anna R. Giovagnoli[a], Sergio Zanini[b], Onelio Geatti[c] and Fabrizio Tagliavini[a]
[a]*Fondazione IRCCS Istituto Neurologico Besta, Milano, Italy*
[b]*Istituto Scientifico E. Medea, Pasian di Prato (UD), Italy*
[c]*Azienda Ospedaliera-Universitaria, Udine, Italy*

Background: Frontotemporal dementia (FTD) is a complex presenile disorder characterized by behavioural changes and executive functions impairment, expression of neurodegeneration of frontal and temporal lobes. Recently, mutations in the gene encoding progranulin (PGRN) were reported and most of the 68 pathogenetic PGRN mutations described present a premature termination codon that induces the degradation of mutant RNA by nonsense mediated decay. In these mutations, prominent phenotypic variability within and among affected kindreds has been described.

Aims and methods: We have studied a novel Italian pedigree in which three affected members presented clinical evidence of dementia. Their characterization was documented with clinical records, imaging, sequential neurological examinations and cognitive assessments. Genetic analysis, performed after informed written consensus, revealed the presence of IVS6+5_8delGTGA PGRN mutation in all affected members. The mutation is a deletion that leads to haploinsufficiency.

Results: In the three patients the mutation is associated with different clinical phenotypes. In the proband the FTD is associated with executive functions and language impairment. Despite the clinical picture severity, the MRI showed only mild asymmetrical atrophy with enlargement of left silvian fissure and frontal sulci associated with a minimal enlargement of the left lateral ventricle. The second patient showed clinical Alzheimer's disease with deficits in all cortical functions and normal temporo-mesial structures by MRI scan. The third patient presented hallucinations with rapid progressive cognitive impairment, mimicking the onset of prion disorder.

Conclusions: The phenotypic variability and the singular MRI data, incompatible with the clinical picture, confirm the clinical complexity of PGRN mutations.

Progression to Dementia of a Population with aMCI: Clinical Variables Associated to Conversion

Marco Mauri[a], Elena Sinforiani[a], Simona Corbetta[b], Chiara Zucchella[a], Valentina Giarracca[b] and Giorgio Bono[b]
[a]*IRCCS Neurologico C Mondino, Pavia, Italy*
[b]*Insubria University, Varese, Italy*

Aims: To investigate clinical predictors and rate to conversion to dementia syndrome in a case-series of amnesic Mild Cognitive Impairment (aMCI).

Methods: Two hundred and eight aMCI subjects (mean age 73.61 SD 6.9 years, M/F 84/124) were fol-

lowed over a six-year period. The analysis considered cognito-motor-behavioral status, vascular risk factors and CT findings. Conversion to dementia was considered when current criteria were fitted (Alzheimer's Disease – AD: NINCDS-ADRDA; FrontoTemporal Dementia: Work Group 2001; Lewy Body Dementia: McKeith 2005; Vascular Dementia: NINDS-AIREN).

Results: After six years, 68.8% aMCI patiens had converted to ouvert dementia: mean time for conversion was 18.2 months (80.7% within three years, AD: 90.3%). Lower MMSE score (24 to 27) and an age over 75 years were significant predictors for dementia ($p < 0.01$); MCI patients with minor BPSDs showed a faster conversion rate ($p < 0.05$).

Conclusions: Lower cognitive performance and the association with minor BPSDs are relevant factors, among the aMCI patients, for the development of dementia and faster rate of conversion respectively.

Mild Cognitive Impairment: Spatial Abilities and Imaging Predictors for Incipient Dementia

Micaela Mitolo[a], Paolo Caffarra[b] and Francesca Pazzaglia[a]
[a] *University od Padova, Padova, Italy*
[b] *University of Parma, Parma, Italy*

Aims and methods: This is a prospective study in which clinical, cognitive and neuroimaging variables was collected at baseline in newly diagnosed patients with MCI and controls. These variables was used to identify those more strongly associated to the development of AD. All patients was assessed with the following neuropsychological battery: MMSE, Rey Auditory Verbal Learning Test, Digit Span, Rey-Osterrieth Complex Figure, Wisconsin Card Test, Tower of London test, RPM, Stroop Test, Clock Drawing Test and Corsi Visuo-spatial supraspan. Spatial and orientation abilities was assessed with new experimental instruments: Objects' Recognition Test, Map Learning Test, Route Learning Test. To investigate the relation between spatial impairment and metacognitive sphere we also administer four specific self-rating scales.

Results: A first phase was dedicated to the patients and controls recruitment and to the administration of a neuropsychological battery. Twenty-one MCI have been assessed until now (10 males and 11 females; mean age $74.67 + 6.67$). A second phase will be dedicated to a cognitive follow-up at 12 month after the initial evaluation, to validate the predictive diagnostic value of early functional brain impairment in cognitive processing detected with fMRI and to verify the specificity of the cognitive deficit for each MCI subtype.

Neuroscience and Law: Validation of new Neuropsychological Tests for Forensic use

Daniela Ovadia[a], Anna Sedda[b] and Gabriella Bottini[a]
[a] *Ospedale Niguarda, Milan, Italy*
[b] *University of Pavia, Pavia, Italy*

Background: Recent progress in neurosciences made the cooperation between jurists, neuroscientists and neuroethicists more an more complex. The new European Association for Neuroscience and Law (EANL) was launched to analyze the needs of jurists and the role of neuroscientists as forensic experts. In particular, neuroscience experts need new validated tools to answer with good efficacy and reliability the questions raised by the the judges and the courts.

Aims and methods: At the Cognitive and Neuropsychological Center of Niguarda Hospital we are designing and validating a new questionnaire for hypersexuality symptoms in patients with early stage frontotemporal dementia (FTD) and in epileptic patients who underwent surgery for pharmacoresistant epilepsy.

Results: Hypersexuality symptoms are frequent in FTD and apparently also after surgery for epilepsy but, in this case, their prevalence is unknown, although they can have legal and personal consequences. Our questionnaire is based on the new criteria for hypersexuality diagnosis proposed by the DSM-V and could be a useful tool in criminal, civil and family law judgements.

Conclusions: Our research will provide more information on the prevalence and incidence of hypersexuality and will help us in rewriting the informed consent forms for epileptic patients.

Prospective Memory in Mild Cognitive Impairment. Comparison between Self-evaluation Measures and Performance on an Experimental Task

Cristina Pagni, Cecilia Carlesi, Leda Volpi, Irene Falorni, Irene Ghicopulos, Cristina Frittelli and Gloria Tognoni
University of Pisa, Pisa, Italy

Aims: The present study aimed to investigate prospective memory (PM) in subjects with mild cognitive impairment (MCI).

Methods: Self administered questionnaire on memory functioning (The Memory Functioning Questionnaire and the Prospective Memory Questionnaire) together with an event-based prospective memory task were used to assess prospective memory dysfunction in amnestic MCI (a-MCI; $N = 12$), non amnestic MCI (na-MCI; $N = 6$) and multiple domain MCI (md-MCI; $N = 7$). A control group of 22 subjects, matched for age and education, complete the PM task. Separate scores were computed for correct execution of intended action (prospective component) and recall of intention (retrospective component).

Results: MCI group showed poorer performance with respect to controls in both prospective and retrospective component of the task ($p < 0.001$). A relative sparing of retrospective component was particularly evident in MCI participants presenting with na-MCI with respect to those with md-MCI. Correlation analyses revealed an association between Prospective Memory Questionnaire and retrospective component ($\text{rho} = -0.51$; $p < 0.01$).

Conclusions: These results suggest that PM impairment is evident in MCI subjects. PM measures could be used in routine evaluation also for that patients who report only subjective memory disturbances. Moreover, although the small sample size, MCI patients tend to correctly operate metamemory judgements.

Qualitative Differences in the Pattern of Memory Deficit of Patients with Alzheimer's Disease, Frontotemporal, Vascular and Lewy Body Dementia

Roberta Perri, Carlo Caltagirone and Giovanni A. Carlesimo
Tor Vergata University, Foundation Santa Lucia, Rome, Italy

Background: Impaired consolidation mechanisms due to mesio-temporal pathology in Alzheimer's disease (AD) make memory traces unavailable for retrieval. In frontotemporal dementia (FTD) frontal-lobe dysfunctions interfere with encoding/retrieval strategies. In vascular (VD) and Lewy-body dementia (LBD) both these mechanisms may operate.

Aims: To Assess qualitative memory differences in AD, FTD, VD and LBD patients by tests with different memoranda organization.

Methods: Subjects: 20 AD, 20 FTD, 20 VD and 20 LBD patients comparable for dementia severity, 34 matched controls (NCs). Tests: Delayed recall of 15-Word-list, Short prose passage.

Results: Dementia groups scored worse than NCs on both tests (consistently $p < 0.001$). In Word-list test AD performed slightly worse than FTD ($p = 0.04$) and similarly to VD and LBD. On Prose recall AD achieved the worst performance ($p < 0.01$). No differences were recorded among FTD, VD, LBD. The Group × Test interaction ($F = 8.22$, $p < 0.001$) confirmed the disproportionate deficit of AD as compared to other groups on Prose recall (consistently $p < 0.05$).

Conclusions: fv-FTD outperfomed AD patients specifically on Prose recall, suggesting that the well-organised memoranda enabled them to overcome their encoding deficit. VD and LBD groups performed as AD on Word-list and outperfomed them on Prose recall, suggesting the existence of consolidation and encoding problems in these pathologies.

Effects of Minimal Interference in aMCI and AD: a Longitudinal Study

Martina Pesallaccia[a], Michaela Dewar[b], Nelson Cowan[c], Leandro Provinciali[a] and Sergio Della Sala[b]
[a] *Università Politecnica delle Marche, Ancona, Italy*
[b] *University of Edinburgh, Edinburgh, UK*
[c] *University of Missouri-Columbia, USA*

Background: Delayed recall is at floor in AD and aMCI patients when learning is followed by further cognitive activity. It can be improved when learning is followed by a reduced interference. A strong association between delayed recall following 'minimal interference' (minRI) and disease severity has been showed, with aMCI performing better than AD and the degree of benefit from minRI probably declines with disease progression.

Methods: Twenty five aMCI, 24 AD and 25 controls were tested on Phase 1 and Phase 2 (after 1 year). All participants were presented with 15 words and asked to recall as many of them as possible, after presentation and after a 10 minute delay. In the interval participants either named drawings or they rested alone in the darkened testing room (minRI). Twenty aMCI was called back for a Phase 3 (2 years following Phase 1).

Results: Retention in the minRI condition dropped significantly over 1 year only in the AD. A significant correlation was obtained for change in minRI retention and disease severity over 2 years in the aMCI.

Conclusions: MinRI retention decreases as AD progresses, and appears to do so at a more accelerated rate in AD than in aMCI.

Neuropsychological Profile of CADASIL and Age-related Leukoencephalopathy Patients and Influence on Functional Performances: Observations from the MIcrovascular LEukoencephalopathy Study (MILES)

Francesca Pescini[a], Laura Ciolli[a], Emilia Salvadori[a], Alessandra Del Bene[a], Cristina Sarti[a], Annamaria Basile[b], Federica Squarzanti[b], Lucia Nardetto[b], Enza Zicari[c], Silvia Bianchi[c], Maria T. Dotti[c], Enrico Adriano[d], Maurizio Balestrino[d], Carlo Gandolfo[d], Leonardo Pantoni[a] and Domenico Inzitari[a]
[a] *University of Florence, Florence, Italy*
[b] *University of Padova, Padova, Italy*
[c] *University of Siena, Siena, Italy*
[d] *University of Genoa, Genoa, Italy*

Background: Microangiopathic leukoencephalopathy is frequently seen in the elderly with vascular risk factors (sporadic Age-Related Leukoencephalopathy-ARL). Similar white matter changes are found in CADASIL, a genetically-determined small vessel disease. Both conditions are characterized by progressive cognitive impairment and disability.

Aims: To assess the neuropsychological profile of 70 ARL and 55 CADASIL patients and the possible influence on functional performances.

Methods: Functional and neuropsychological performances were evaluated using a comprehensive battery. *Z* scores were calculated considering age and education. Compound measures were obtained using standard scores for the following domains: Memory, Speed and Executive Functions. Differences in the neuropsychological profile were explored using *t*-test. The predictive value of neuropsychological indexes on functional performances was valuated using correlation and logistic regression analyses.

Results: No significant difference was found between the neuropsychological indexes of the two groups (Memory, $t(121) = 1.3$, $p = 0.19$; Speed, $t(115) = -1.1$, $p = 0.29$; Executive Functions, $t(82) = 0.2$, $p = 0.85$). In CADASIL, Memory index was a significant predictor of functional performance ($B = 0.66$, $p < 0.01$), in ARL it was the Executive Functions index ($B = 2.24$, $p < 0.05$).

Conclusions: Our study shows that the neuropsychological profile is similar in CADASIL and ARL patients, but there is a different relation with functional tests: memory seems to have a greater impact on functional performance in CADASIL, executive functioning in ARL.

Implication of a Genetic Variant at PICALM in Italian Alzheimer's Disease Patients and Centenarians

Irene Piaceri[a], Silvia Bagnoli[a], Ersilia Lucenteforte[a], Michelangelo Mancuso[b], Andrea Tedde[a], Gabriele Siciliano[b], Silvia Piacentini[a], Laura Bracco[a], Sandro Sorbi[a] and Benedetta Nacmias[a]
[a] *University of Florence, Florence, Italy*
[b] *University of Pisa, Pisa, Italy*

Background: A common polymorphism (rs38511 79) in the PICALM (phosphatidylinositol-binding clathrin assembly protein) gene has been recently associated with reduced risk of developing late-onset Alzheimer's disease (LOAD).

Aims and methods: We analyzed the genotype and allele distributions of the PICALM polymorphism in 813 Italian subjects, including LOAD patients and centenarians.

Results: The segregation of the PICALM rs3851179 showed no statistically significant difference between LOAD cases and controls.

Conclusions: The implication of a genetic variant at PICALM is confirmed for the first time, in centenarians, thus suggesting a possible role in longevity.

Increased Levels of Tissue Factor Pathway Inhibitor in Cerebrospinal Fluid are Related to Neurodegeneration in Alzheimer's Disease Patients

Fabrizio Piazza[a], Daniela Galimberti[b], Barbara Borroni[c], Alessandro Padovani[c], Elio Scarpini[b] and Carlo Ferrarese[a]
[a] *San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy*
[b] *University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*
[c] *University of Brescia, Brescia, Italy*

Background: Although Alzheimer's Disease (AD) is mainly considered a neuronal disease, much evidence points to a vascular pathogenetic involvement in its etiology. We recently demonstrated that an impairment of endothelial function may occur in AD patients, associated with an increase of Tissue Factor Pathway Inhibitor (TFPI), the serine protease inhibitor induced by endothelial injury, and higher Homocysteine or lower Folate plasma levels.

Aims: To investigate central and plasmatic source of TFPI.

Methods: We evaluated the Cerebrospinal Fluid (CSF) levels in a cohort of subjects affected by AD, other neurodegenerative diseases and healthy controls, where the presence of major vascular disorders was ruled out with a thorough clinical, laboratory and neuroimaging assessment, and acute or chronic cerebrovascular disease patients. Moreover, to figure out if the increased TFPI levels are related to neurodegeneration, Tau and p-Tau proteins levels were also evaluated.

Results: Our study demonstrates for the first time an abnormally high CSF levels of TFPI in AD, also related to neurodegeneration, strengthening the hypothesis that an impairment of endothelial function may occurs despite the absence of manifest cerebrovascular lesions.

Conclusions: TFPI may represent a candidate marker of endothelial damage in AD and it might be used to monitor therapeutic interventions on vascular risk factors.

Phenotypic Heterogeneity of the GRN Asp22fs Mutation in a Large Italian Kindred

Anna M. Pietroboni[a], Giorgio G. Fumagalli[a], Laura Ghezzi[a], Chiara Fenoglio[a], Francesca Cortini[a], Maria Serpente[a], Claudia Cantoni[a], Emanuela Rotondo[a], Priscilla Corti[a], Miryam Carecchio[b], Mariateresa Bassi[c], Nereo Bresolin[a,c], Domenico Galbiati[c], Daniela Galimberti[a] and Elio Scarpini[a]
[a] *University of Milan, IRCCS Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy*
[b] *"Amedeo Avogadro" University, Novara, Italy*
[c] *IRCCS E. Medea, Associazione La Nostra Famiglia, Bosisio Parini (LC), Italy*

Background: The Asp22fs(g.63_64insC) mutation in progranulin gene (GRN) has been reported in one patient with Frontotemporal Dementia (FTD).

Aims: To describe the clinical heterogeneity associated with the GRN Asp22fs mutation in a large Italian family.

Methods: Clinical and instrumental workup of two symptomatic carriers in two generations has been carried out, together with genetic analysis of probands and of nine asymptomatic family members.

Results: The first proband was a 47-year old male clinically diagnosed with FTD with a positive family history. Evaluation of plasma GRN levels was consistent with the presence of a mutation in its encoding gene, that was demonstrated by sequencing [Asp22fs(g.63_64insC)]. Brain MRI showed multiple T2 and FLAIR hyperintense areas in the frontal lobe white matter and right hemisphere cortical atrophy. The second proband was his 79 years old uncle, presenting with a mild cognitive impairment. Brain MRI showed small T2 hyperintense lesions and widespread cortical atrophy. Cerebrospinal fluid Amyloid beta, tau and phosphotau protein levels were in both cases normal. Additional nine asymptomatic family members were studied.

Conclusions: This family's description expands the spectrum of clinical presentations of Frontotemporal Lobar degeneration caused by GRN mutations, suggesting that the diagnosis could be missed in some individuals with an atypical presentation.

PGRN and TARDBP Mutations in Frontotemporal Lobar Degeneration: Two Faces of TDP43 Proteinopathies

Andrea Pilotto[a], Barbara Borroni[a], Antonella Alberici[a], Silvana Archetti[b], Alice Papetti[a], Maura Cosseddu[a], Cristian Bonvicini[c], Roberto Del Bo[d], Marinella Turla[e], Emanuele Buratti[f], Giacomo P. Comi[d], Massimo Gennarelli[c], Monica Di Luca[d] and Alessandro Padovani[a]
[a] *University of Brescia, Brescia, Italy*
[b] *Spedali Civili Brescia, Brescia, Italy*
[c] *IRCCS Fatebenefratelli, Brescia, Italy*
[d] *University of Milan, Milan, Italy*
[e] *ValleCamonica Hospital, Esine (BS), Italy*
[f] *International Centre for Genetic Engineering and Biotechnology, Trieste, Italy*

Background: Monogenic forms of Frontotemporal Lobar Degeneration (FTLD) with TDP-43 positive inclusions have been associated with Progranulin (PGRN) or 43-kDa transactive response (TAR)-DNA-binding protein (TARDPB) mutations.

Aims: Distinguish the two different genetic conditions by defined clinical and neuropsychological features.

Methods: Three hundred FTLD patients genetic analysis revealed 13 PGRN and 6 TARDBP mutations carriers. These 19 patients underwent an extensive clinical and neuropsychological evaluation at disease presentation and during its progression.

Results: PGRN subjects revealed to have a Progressive Non-Fluent Aphasia or behavioral variant Frontotemporal Dementia (bvFTD), whilst TARDBP cases had bvFTD with or without motoneuron disease (FTD-MND). PGRN patients' disease mean onset was a decade before TARDBP ($p < 0.001$). The

two groups were comparable in all the investigated cognitive domains except for a worse phonological fluency in PGRN carriers ($P = 0.003$). Disease progression in both PGRN and TARDBP patients leaded to progressive executive dysfunction and to behavioral disturbances, however most of PGRN cases developed mutacism, progressive limb apraxia and parkinsonism while TARDBP patients did only seldom develop MND.

Conclusions: This preliminary report identifies different clinical phenotypes associated to PGRN and TARDBP mutations carriers, suggesting how FTLD TDP-43 may not be a single entity, but a complex disease involving various genes and pathways.

CSF Biomarkers Signature in FTLD

Sara Pompanin[a], Gianluigi Zanusso[a], Michele Fiorini[a], Nela Jelcic[a], Francesca Gnoato[a], Salvatore Monaco[b] and Annachiara Cagnin[a]
[a] *University of Padova, Padova, Italy*
[b] *University of Verona, Verona, Italy*

Background: Frontotemporal lobar degeneration (FTLD) present with behavioural (bvFTD) or linguistic deficits (progressive non fluent aphasia-PNFA; semantic dementia-SD), caused by heterogeneous neuropathology.

Aims: To evaluate CSF biomarkers in the differential diagnosis between FTLD and AD.

Methods: Twenty three FTLD (bvFTD = 15; PNFA–SD = 3; CBD-PSP = 5) and 11 AD patients underwent neuropsychological evaluation and lumbar puncture. CSF analysis of total Tau and 181-p Tau, Aβ40 and Aβ42 was performed by ELISA.

Results: CSF 181-p Tau and Aβ42/181-p Tau values are significantly different between bvFTLD (pTAU: mean 32.8 ± 9.9 pg/ml; Aβ42/pTau: 5.6 ± 3) and AD (pTAU: 93.9 ± 59 pg/ml, $p = 0.001$; Aβ42/pTau: 1.5 ± 1.2, $p = 0.001$). 181-p Tau cut-off level of 50 pg/ml could discriminate between bvFTLD and AD with a sensitivity of 70% and a specificity of 100% (accuracy 86%). Accuracy was increased to 90% by adding the recall memory test scores. In the linguistic variant (PNFA–SD) we found a high heterogeneity of CSF Aβ42/181-p Tau ratio, mirroring different pathological substrates including the frontal variant of AD.

Conclusions: Low CSF 181-p Tau level (below the threshold of 50 pg/ml) and high Aβ42/181-p Tau ratio are the biological signatures of FTLD and may be used in the differential diagnosis with atypical AD (frontal variant or corticobasal syndrome).

Late-onset OCD as Presenting Condition of Semantic Dementia

Sara Pompanin, Giulia Perini, Francesca Gnoato, Renzo Manara, Diego Checchin and Annachiara Cagnin
University of Padova, Padova, Italy

Background: Semantic dementia (SD) is a variant of frontotemporal lobar degeneration (FTLD) with progressive loss of words and objects knowledge and behavioural disorders such as obsessive-compulsive symptoms.

Aims: To describe a case of SD with late-onset obsessive-compulsive disorder (OCD) that lasted for ten years as isolated clinical condition before dementia onset.

Case description: A 64-year-old right-handed men who had OCD beginning at the age of 50 with disabling aggressive/religious obsessions and control compulsions (Y-BOCS = 21/40). At the age of 60 he was admitted to our Memory Clinic with mild cognitive impairment (MMSE = 26/30). Neuropsychological tests revealed the presence of language impairment and executive deficits. Routine blood and cerebrospinal fluid (CSF) studies were unremarkable. He underwent extensive workup with CSF biomarkers analysis (Aβ42/181p-TAU = 1.68), genetic test (negative for MAPT, GRN mutations), MRI (left temporal pole atrophy), 18FDG PET scan (left temporal and anterior cingulate hypometabolism) and DaT-Scan (left basal ganglia decreased uptake). Two years later he developed left extrapyramidal syndrome; OCD (Y-BOCS = 34/40) and anomic speech went worse.

Conclusions: Atypical onset OCD (idiopathic-OCD onset before 25 years meanly) can be primary presentation of neurodegenerative disorders like FTLD, mainly in SD variant.

Mid life Metabolic and Dietary Risk Factors of Dementia. A 15 Year Cohort Study in the Municipality of Bollate-Milan, Preliminary Results

Federica Prinelli[a], Francesca Clerici[b], Carla Pettenati[c], Fulvio Adorni[a], Antonio Russo[d], Claudio Mariani[e] and Massimo Musicco[a]

	Dementia		HR
	No	Yes	(95% CI)
	1210 (96.0)	51 (4.0)	
Age (yrs)			
40–49	219 (18.1)	2 (3.9)	1
50–59	548 (45.3)	17 (33.3)	2.31 (0.79–6.74)
60–69	348 (28.8)	26 (51.0)	6.09 (2.15–17.27)
70+	95 (7.9)	6 (11.8)	9.05 (2.83–28.87)
Gender			
Men	659 (54.5)	30 (58.8)	1
Women	551 (45.5)	21 (41.2)	0.87 (0.54–1.41)
BMI	27.0 ± 4.0	27.8 ± 4.3	1.06 (1.00–1.12)
Waist circumference (cm)	92.5 ± 12.3	95.1 ± 12.9	1.02 (1.00–1.04)
Glucose (mg/dL)	97.9 ± 25.8	98.7 ± 17.3	1.00 (0.99–1.01)
HDL-Chol (mg/dL)	57.8 ± 15.7	54.9 ± 13.2	0.99 (0.97–1.01)
Triglycerides (mg/dL)	134.0 ± 90.5	148.2 ± 80.8	1.00 (1.00–1.00)
Blood pressure			
Systolic (mm/Hg)	137.8 ± 18.5	142.8 ± 15.3	1.01 (1.00–1.02)
Diastolic (mm/Hg)	84.9 ± 8.9	84.7 ± 8.1	1.01 (0.98–1.03)
Metabolic syndrome			
No	799 (66.0)	29 (56.9)	1
Yes	411 (34.0)	22 (43.1)	1.52 (0.87–2.64)
Follow-up (yrs)	16.5 ± 1.9	16.3 ± 2.2	

[a]*ITB CNR Segrate Milano*
[b]*Dipartimento Neurologia AO Ospedale Luigi Sacco Milano*
[c]*Centro Alzheimer AO Ospedale G. Salvini Garbagnate Mi*
[d]*ASL Milano 1 Magenta Mi*
[e]*Cattedra di Neurologia Università di Milano*

Background: There is growing evidence that mid life dietary exposures and disturbances of glucose metabolism might increase the risk of dementia in late life. In particular the condition of metabolic syndrome (glucose intolerance plus two of the following: high triglycerides, low HDL cholesterol, hypertension and high abdominal fat) has been reported as a risk factor of dementia and in particular of Alzheimer disease.

Aims and methods: During 1994 we carried out an investigation on a healthy population of residents in Bollate a municipality of the province of Milan. The investigation was centered on dietary habits and on some routine laboratory evaluations. During 2010 we retrieved the persons of the cohort who potentially had a dementia from the two referral Alzheimer centers of the geographical area of Bollate (Sacco Hospital and Passirana Hospital) and from the health informative system of the local health authority. We considered as demented all the persons of the cohort who had a diagnosis of dementia in at least one of the two referral Alzheimer centers and/or had an hospitalization for dementia and/or were prescribed an antidementia drug (donepezil, rivastigmine, galantamine or memantine). The entire cohort was composed by 1261 subjects (689 men and 572 women) with a mean age of about 55 years. From 1994 to June 2010 we could assign a diagnosis of dementia to 51 subjects (30 men and 21 women). The risk of dementia was analyzed with survival analysis and the relative risk of dementia were estimated as hazard ratios with Cox's proportional hazard method.

Results: A part from age that was the most important predictor of the risk of dementia persons who developed dementia had higher body mass indexes, higher glucose and triglycerides blood levels, lower HDL cholesterol levels, higher systolic blood pressure and larger waist circumference. The presence of metabolic syndrome was associated with a 50% increase of the risk of dementia.

Conclusions: The preliminary results of this cohort study confirm the potential role of some metabolic disturbances in determining an increase of the risk of dementia.

Neuropsychological Staging of Alzheimer's Disease (AD)

Davide Quaranta, Camillo Marra, Maria G. Vita and Guido Gainotti
Università Cattolica del Sacro Cuore, Rome, Italy

Objectives: To define the steps of neuropsychological progression in AD.

Methods: Four hundred and five AD subjects underwent neuropsychological testing including: MMSE, RAVLT, Multiple Features Targets Cancellation, Raven's Matrices (PM'47), phonological and semantic fluency, copy of figures without/with landmarks, digit span, Stroop test. Subjects were stratified for severity into: Group A (MMSE > 23); Group B (19 < MMSE < 22); Group C (15 < MMSE < 18); Group D (MMSE < 15). The number of pathological performances (PP) was computed after age/education correction. Frequencies were compared by chi-square. Tests displaying a significant difference of PP incidence between contiguous groups were considered as markers of progression.

Results: Group A subjects were impaired mainly on RAVLT delayed recall. The following markers of progression were identified: – higher incidence of PP on PM'47 ($p < 0.001$) and semantic fluency ($p < 0.001$) in Group B; – higher incidence of PP on copy of figures with landmarks ($p < 0.001$) and RAVLT-immediate recall ($p = 0.001$) in Group C; – higher incidence of PP on phonological fluency ($p < 0.001$) and digit span backward ($p < 0.001$) in Group D.

Conclusions: Specific neuropsychological steps could define the progression of AD. After defects of episodic memory, deficits in semantic knowledge and abstract reasoning, then deficits in constructive abilities and finally deficits in working memory and verbal initiation are sequentially observed.

Association Between Alzheimer's Disease and the Hypocretin Receptor 2 Gene

Innocenzo Rainero[a], Elisa Rubino[a], Daniela Galimberti[b], Salvatore Gallone[a], Pierpaola Fenoglio[a], Chiara Fenoglio[b], Elio Scarpini[b] and Lorenzo Pinessi[a]
[a] *University of Turin, Turin, Italy*
[b] *University of Milan, IRCCS Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy*

Background: A recent study in animals suggested that hypocretins may play a role in Alzheimer's disease (AD) promoting the deposition of beta-amyloid. Hypocretins are hypothalamic neuropetides that regulate several physiological functions, like sleep-wake cycle, attention, and feeding.

Aims: To investigate the association of polymorphisms in the hypocretin gene system and AD.

Methods: A group of 261 Italian AD patients was selected for the study and compared with 261 controls. Cases and controls were genotyped for several SNPs of the HCRT, HCRTR1, and HCRTR2 genes.

Results: The genotype and allele distribution of the HCRTR2 G1246A polymorphism varied significantly between patients and controls. Homozygous carriers of the A-allele had an approximately twofold increase in AD risk (OR 1.75; 95% CI 1.25 to 2.46; $p = 0.0006$). No significant difference between the examined characteristics of the disease and different genotypes was found.

Conclusions: This is the first study that examined the association between hypocretin system genes and AD; so our data must be viewed cautiously. We found a significant association between the HCRTR2 gene and AD. Our data support the hypothesis that genetic variations within the HCRTR2 gene are risk factors for AD and may be involved in the disease pathogenesis.

Role of hnRNP-A1 and miR-590-3p in Neuronal Death: Genetics and Expression Analysis in Patients with Alzheimer's Disease and Frontotemporal Lobar Degeneration

Elisa Ridolfi[a], Chiara Villa[a], Chiara Fenoglio[a], Fran cesca Clerici[b], Alessandra Marcone[c], Luisa Benussi[d], Roberta Ghidoni[d], Salvatore Gallone[e], Francesca Cortini[a], Maria Serpente[a], Claudia Cantoni[a], Giorgio G. Fumagalli[a], Stefano Cappa[c], Giuliano Binetti[d], Massimo Franceschi[f], Innocenzo Rainero[e], Mariateresa Giordana[e], Claudio Mariani[b], Nereo Bresolin[a], Elio Scarpini[a] and Daniela Galimberti[a]
[a] *University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*
[b] *University of Milan, Ospedale Sacco, Milan, Italy*
[c] *Ospedale San Raffaele Turro, San Raffaele Scientific Institute, Milan, Italy*
[d] *IRCCS Centro S. Giovanni di Dio-FBF, Brescia, Italy*
[e] *University of Turin, Turin, Italy*
[f] *Clinica Neurologica, Casa di cura Santa Maria di Castellanza, Varese, Italy*

Aims and methods: An association study of Heterogeneous nuclear ribonucleoprotein (hnRNP)-A1 was carried out in a population of 274 patients with Frontotemporal Lobar Degeneration (FTLD) and 287 with Alzheimer's disease (AD) as compared with 344 age- and gender-matched controls. We evaluated expression levels of hnRNP-A1 and its regulatory microRNA (miR)-590-3p in blood cells from patients and controls.

Results: A statistically significant increased frequency of the hnRNP-A1 rs7967622 C/C genotype

was observed in FTLD, but not AD, patients versus controls (23.0 versus 15.4%; $p = 0.022$, OR: 1.64, CI: 1.09–2.46). Stratifying according to gender, a statistically significant increased frequency of the hnRNP-A1 rs7967622 C/C genotype was observed in male patients as compared with male controls (23.1 versus 11.3%; $p = 0.015$, OR: 2.36, CI: 1.22–4.58), but not in females. A significant increased hnRNP-A1 relative expression levels in PBMC was observed in patients with AD, not with FTLD, as compared with controls (2.724 ± 0.570 versus 1.076 ± 0.187, $p = 0.021$). Decreased relative expression levels of the hsa-miR-590-3p was observed in patients with AD versus controls (0.685 ± 0.080 versus 0.931 ± 0.111, $p = 0.079$), and correlated negatively with hnRNP-A1 mRNA levels ($r = -0.615$, $p = 0.0237$).

Conclusions: hnRNP-A1 and its miR-590-3p are disregulated in patients with AD, and hnRNP-A1 rs7967622 C/C genotype is likely a risk factor for FTLD in male populations.

Cognitive Neurosciences Contribution to Law in Emotional Processing

Anna Sedda[a], Daniela Ovadia[b], Roberto Sterzi[b] and Gabriella Bottini[a]
[a] *University of Pavia, Pavia, Italy*
[b] *Ospedale Niguarda, Milan, Italy*

Background: Many legal issues are concerned with the concept of mens rea. Recently, Law has turned to Neuroscience in order to obtain more exhaustive information. Several neurological diseases, in fact, may alter the behavioral and cognitive profile of subjects, impairing their decision making and emotional processes. Cognitive neurosciences may provide sensitive and effective instruments to distinguish between voluntary acts deviating from legality and atypical behaviors due to focal or diffuse brain damage.

Aims and methods: At the Cognitive Neuropsychology Center of Niguarda Cá Granda Hospital, we are studying emotional processing impairments whose consequences are strictly related to the law domain.

Results: On one hand, brain damaged subjects may manifest impaired facial emotion recognition, ending in compromised social interactions. On the other hand, it has been demonstrated that brain atrophy may alter the psychiatric profile, causing ex novo pathological manifestation or worsening of already present psychosis.

Conclusions: Protocols evaluating several components of emotional processing must be taken into consideration by Law when patients, affected for instance by dementia, manifest illegal social behaviors.

Titolo abstract: OLR1 and its Regulatory miR-369-3p: Genetics and Expression Analysis

Maria Serpente[a], Chiara Fenoglio[a], Francesca Clerici[b], Roberta Ghidoni[c], Luisa Benussi[c], Salvatore Gallone[d], Alessandra Marcone[e], Chiara Villa[a], Francesca Cortini[a], Claudia Cantoni[a], Elisa Ridolfi[a], Massimo Franceschi[f], Giuliano Binetti[c], Innocenzo Rainero[d], Stefano Cappa[e], Claudio Mariani[b], Nereo Bresolin[a], Elio Scarpini[a] and Daniela Galimberti[a]
[a] *University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*
[b] *University of Milan, Ospedale Sacco, Milan, Italy*
[c] *IRCCS Centro S. Giovanni di Dio-FBF, Brescia, Italy*
[d] *University of Turin, Turin, Italy*
[e] *Ospedale San Raffaele Turro, San Raffaele Scientific Institute, Milan, Italy*
[f] *Clinica Neurologica, Casa di cura Santa Maria di Castellanza, Varese, Italy*

Aims and methods: An association analysis of Oxidised LDL Receptor 1 (OLR1) was carried out in a population of 443 patients with Alzheimer's disease (AD) compared with 391 age-matched controls. In addition, we performed an expression analysis of OLR1 and its regulatory hsa-miR-369-3p in Peripheral Blood Mononuclear Cells (PBMC).

Results: An increased frequency of OLR1 rs10502 83C allele was observed in patients compared with controls (43% versus 46%, $p = 0.011$, OR: 1.48, 95% CI: 1.10–2.00). Stratifying according to gender, a statistically increased frequency of OLR1 rs1050283C allele was observed in female patients compared with female controls (37% versus 51%, $p < 0.001$, OR: 2.8982, 95% CI: 1.97–4.24), but not in males. Significantly decreased relative expression levels of OLR1 in PBMC was observed in patients carrying the rs1050283C allele as compared with non-carriers (0.23 ± 0.13 versus 0.92 ± 0.8, $p = 0.04$). A trend towards increased relative expression levels of the hsa-miRNA-369-3p were observed in patients carrying the rs1050283C allele (2.23 ± 1.35 versus 1.16 ± 0.31, $p > 0.05$). A tendency towards a negative correlation between OLR1 and hsa-miRNA-369-3p gene expression was found in patients carrying the rs1050283C allele ($r = -0.313$, $p = 0.05$).

Conclusions: The OLR1 rs1050283C allele is a risk factor for sporadic AD; OLR1 and its transcriptional regulatory factor hsa-miR-369-3p are de-regulated in patients carrying the rs1050283C allele.

Assessment of Peripheral Markers of Macroautophagy in Patients with Alzheimer's Disease

Giovanni Stefanoni[a], Gessica Sala[a], Chiara P. Zoia[a], Eleonora Verga[a], Diletta Cereda[a,b], Valeria Isella[a,b] and Carlo Ferrarese[a,b]
[a] *University of Milano-Bicocca, Monza, Italy*
[b] *San Gerardo Hospital, Monza, Italy*

Background: Emerging evidence supports the view that defective autophagy promotes neuronal cell death in most neurodegenerative diseases, including Alzheimer's disease (AD). Beclin-1 deficiency is known to lead to beta-amyloid accumulation in transgenic AD mice; furthermore, a reduction of beclin-1 has also been demonstrated in postmortem AD brains.

Aims and methods: We evaluated beclin-1 expression in peripheral blood mononuclear cells (PBMC) from 15 AD patients and 15 age-matched controls to identify a putative peripheral marker of macroautophagy dysfunction occurring in AD brains, useful as diagnostic tool and as parameter to monitor in *ex vivo* cells from patients the effect of possible therapeutic interventions aimed at activating autophagy. To verify whether PBMC represent a suitable model to test autophagy modulation, we exposed cultured PBMC to autophagy enhancer rapamycin, resulting in a significant 25% increase of beclin-1 immunoreactivity.

Results: Results obtained by Western blot analysis in a limited number of collected PBMC did not show significant difference in beclin-1 immunoreactivity between AD and controls, suggesting that peripheral expression of this protein does not mirror the alterations observed in the brain. We are concluding beclin-1 protein evaluation and setting up experiments of RTqPCR to quantify mRNA levels to verify the existence of possible alterations at this level.

Restless Legs Syndrome and Alzheimer's Disease

Giuseppina Talarico, Federica Letteri, Marco Prastaro, Giuseppe Tosto, Marco Canevelli, Elisa Piacentini, Marina Gasparini, Gianluigi Lenzi and Giuseppe Bruno
"Sapienza" University, Rome, Italy

Introduction: Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive neuronal loss in the central nervous system and, consequently, biochemical changes in neurotransmitter systems including the cholinergic and dopaminergic systems. Restless legs syndrome (RLS) is a neurological disorder characterized by an urge to move the legs and peculiar unpleasant sensations deep in the legs during period of rest and inactivity, such as at night, that typically relieve by movement. Its prevalence is about 8% of the population over 65. It is supposed that RLS may be due to dysfunction of dopamine system. Few studies were analyzed RLS in neurodegenerative diseases such as Alzheimer's Disease (AD).

Aims and methods: Three hundred and thirty-four subjects with diagnosis of AD were recruited at the "Memory Clinic" of the Department of Neurology and Psychiatry, University "Sapienza" in Rome. Thirteen subjects met the RLS criteria, revised by Allen et al. in 2003. To basal time, clinical assessments included general physical and neurological examination, laboratory tests, morphological (MRI/CT) and/or functional (SPECT/PET) neuroimaging, neuropsychological evaluation, Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) and Neuro-Psychiatric Inventory (NPI).

Results: RLS subjects were frequently male (76,9%) and younger than AD subject without RLS. Median time of RLS appearance was two years after the AD diagnosis (71.54 ± 7.24). MMSE, ADL and IADL at diagnosis and at time of RLS onset were not more different, while NPI total score showed a significant worsening (t: -2.61, p: 0.023), notably in subitem apathy (t: -3.95, p: 0.002). Moreover AD patients with RLS were more apathetic (t: 3.59, p: 0.001) than AD subjects without RLS and showed difference in short and long term visual memory (t: 2.51, p: 0.0013 and t: 2.61, p: 0.0010 respectively) and constructional ability (t: 2.38, p: 0.0021).

Conclusions: The RLS prevalence in our AD patients is about 4%. RLS appears to be associated with deficit in visual memory and neuropsychiatric symptoms such as apathy.

Mutation Analysis in the Presenilin Genes Linked to Italian Kindreds with Alzheimer's Disease

Andrea Tedde[a], Benedetta Nacmias[a], Silvia Bagnoli[a], Irene Piaceri[a], Silvia Piacentini[a] and Paolo Nichelli[b]

[a]*University of Florence, Florence, Italy*
[b]*University of Modena and Reggio Emlia, Reggio Emilia, Italy*

Background: Mutations in APP, PSEN1 and PSEN2 are the most common cause of autosomal dominant familial Alzheimer's disease (FAD).

Aims and methods: A genetic screening of DNA samples belonging to FAD families present in the DNA bank at the Department of Neurological and Psychiatric Sciences (University of Florence, Italy) was conducted by PCR and HRM analysis in the APP, PSEN1 and PSEN2 genes. Genetic variants were sequenced by ABI PRISM 310 sequencer. In silico prediction of the functional consequence of the missense variant was performed using SIFT (Sorting Intolerant From Tolerant), Polyphen and PMut bioinformatic softwares.

Results: We identified four Italian families with the following missense variants: a pedigree linked to Met139Thr mutation at the second transmembrane domain of PSEN1. A Leu166His mutation at the third transmembrane domain of PSEN1 was described in a family with a severe cognitive decline with a very early-onset (34 ys). Another pathogenetic mutation was identified in PSEN2 gene at exon 4 (N-terminal) resulting in a Arg71Trp substitution. Moreover, the Arg62His variant at the exon 4 (N-terminal) in the PSEN2 gene was found in a subject, but the nature of this variant was not clear because, according to the literature, it was present as common polymorphism in African populations.

Presenilins Mutations in a Small Cohort of Italian Patients with Alzheimer's Disease

Silvia Testi[a], Tiziana Cavallaro[a], Roberta Pantieri[b], Giuseppe Gambina[a] and Gianmaria Fabrizi[a]
[a]*Azienda Ospedaliera Universitaria Integrata, Verona, Italy*
[b]*Ospedale Bellaria, Bologna, Italy*

Objective: To define mutational frequencies of Presenilins genes in a small Italian series.

Background: Familial Alzheimer's Disease (FAD) is associated with mutations in Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) genes. PSEN1 and APP account for up to 70% and 15% of all cases whereas PSEN2 is the rarest cause.

Methods: We analyzed 45 unrelated index patients with AD ($n = 26$) or FAD ($n = 19$) and mean age of onset 64.38 (± 10.1). Mutational analysis was done by Denaturing High Performance Liquid Chromatography (DHPLC), automated direct sequencing and Real-Time PCR.

Results: In four unrelated FAD cases we identified one PSEN1 and three PSEN2 missense mutations; PSEN2 p.Arg71Trp (onset 59 years) and p.Met174Val (onset 75 years) were already reported in AD whereas PSEN2 p.Thr18Met (onset 72 years) and PSEN1 p.Ile437Asn (onset 70 years) were novel. Based upon phylogenetical and in silico analysis, PSEN1 p.Ile 437Asn and PSEN2 p.Arg71Trp and p.Thr18Met are likely pathogenic.

Conclusions: We identified two novel mutations of PSEN1 and PSEN2 as possible candidate to FAD. Mutational frequencies in our series diverged from the literature likely reflecting the relatively late age of onset in our series.

Somatoform Disorders in Parkinson's Disease Predicts the Appearance of Dementia and is Frequently Observed in Dementia with Lewy Bodies

Astrid Thomas, Laura Bonanni, Daniela Monaco, Stefania Bifolchetti, Leopoldo Ricciardi, Francesca Anzellotti, Iole Borrelli, Maria C. D'Amico, Fausta Ciccocioppo and Marco Onofrj
Università Chieti-Pescara, Fondazione Università, Cesi, Chieti, Italy

Aims and methods: Somatoform Disorders in Parkinson's Disease (SFMD) were assessed by direct observation of symptoms with definite diagnosis of PD, DLB, AD, MSA, PSP, FTD and by interviews with patients, caregivers, GPs, reviews of prior hospital admissions, in a cohort of 942 patients with neurodegenerative disorders and 1400 psychotic patients. In followed-up over 4 years matched groups of PD and DLB patients without and with SFMD were compared.

Results: The frequency of SFMD was higher in DLB (15 patients, 12%) and PD (29 patients, 7%) than in other neurodegenerative diseases (0–3%). SFMD consisted of conversion motor or sensory disorders, often accompanied by delusional thought content; in one patient catatonic symptoms were observed concomitantly with PD diagnosis. SFMD symptoms precede diagnosis by six months–10 years. Observation obtained in 28 PD and all DLB patients. SFMD symptoms recurred during follow-up, 9 PD and 8 DLB patients presented catatonic signs. Baseline demo-

graphic and clinical features did not differ between subjects with or without SFMD. Decline of cognitive function was greater in PD-SFMD patients than in those without SFMD ($p < 0.01$); it was comparable to that observed in DLB.

Conclusions: The frequency of SFMD (with catatonic signs) in PD and DLB suggests that SFMD should be studied and used as predictor factor in appearance of dementia.

Sentence Writing Component and Alzheimer's Disease Clinical Progression

Giuseppe Tosto, Giuseppina Talarico, Elisa Piacentini, Marco Canevelli, Federica Letteri, M.C. Viselli, F. Troili, Gianluigi Lenzi and Giuseppe Bruno
"Sapienza" University, Rome, Italy

Background: Written expressions of patients with Alzheimer's Disease (AD) have shown that agraphia is an early manifestation of the disease, mainly in the lexico-semantic area than in the syntactic aspects.

Aims and methods: The MMSE's "sentence-writing compound" of fifty mild-AD patients was evaluated at baseline and after 1 year of AChIs treatment.

Results: Our data demonstrate that initial cognitive performance does not correlate with sentence richness in term of subjects, verbs, names etc. instead of education identified as the most striking factor that accounts for those items. Baseline numerosity of grammatical/syntax errors, adverbs and conjunctions correlates with their numerosity after 1 year of follow up; the use of 1th person in the sentence is more likely to be present after 1 year if it is present at baseline. An early unmeaningful sentence seems to be the only risk for "non response" to drugs treatment, regardless of education; on the other side, only in highly educated patients grammatical errors at baseline seem to relate with poor response to AChIs.

Conclusions: Careful examination of written expressions in early AD appears as a meaningful way to follow up clinical evolution of the disease.

Titolo Abstract: Expanding the Phenotype of PGRN Mutations: Progressive Supranuclear Palsy?

Lucio Tremolizzo, Carlo Ferrarese and Ildebrando Appollonio
University of Milano-Bicocca, Monza, Italy

Background: Both frontotemporal lobar degeneration and corticobasal syndrome are clinical phenotypes which can be the expression of heterogeneous neuropathologies and progranulin (PGRN) mutations have been recently described as major contributors. By contrast, progressive supranuclear palsy is still regarded as one clinical syndrome with a unique neuropathological basis, i.e., tauopathy.

Case report: Here we describe the case of a patient affected by progressive supranuclear palsy (clinical and neuroradiological evidence) that started out with mild cognitive impairment in a familial history of early-onset dementia. The patient eventually resulted to be a carrier of a PGRN mutation.

Conclusions: To our knowledge this is the first report of such an association: an exhaustive discussion of the literature will be provided.

Apathy Evaluation Scale Efficacy in Evaluating Apathy Symptoms in Subjects Affected by Mild Cognitive Impairment

Barbara Vicini Chilovi, Salvatore Caratozzolo, Marina Zanetti, Giulia Mombelli, Luca Rozzini and Alessandro Padovani
University of Brescia, Brescia, Italy

Background: Apathy has been demonstrated an important symptom in the characterization of Mild Cognitive Impairment (MCI) evolution, being associated to an increased risk of progression towards dementia.

Aims: To describe the correlation between different psycho-behavioural symptoms evaluation instruments and the cognitive profile of MCI subjects with and without apathy.

Methods: Apathy and depression symptoms have been evaluated in 107 outpatients using two specific instruments: the Apathy Evaluation Scale (AES) and the Beck Depression Inventory (BDI). The Neuropsychiatry Inventory (NPI) has been administered to the caregivers.

Results: Sixty-three (57.3%) subjects have been classified as normal MCI (without apathy and depression), 15 (13.6%) as depressed MCI (with or without apathy), 29 (26.4%) as apathetic MCI. Any significant correlation has been found between the AES and apathy from the NPI, but a significant correlation has resulted between the BDI and apathy and between apathy and depression from the NPI. Apathetic MCI

showed a lower memory performance than the other groups.

Conclusions: Apathy is hardly distinguishable from depression, it is necessary to use a specific instrument as the AES to evaluate it in clinical practice. Apathetic MCI subjects identified through the AES seem to have an higher risk to develop Alzheimer's Disease.

Causal Frontotemporal Lobar Degeneration Mutations: a Novel Mutation in MAPT Associated with Non-fluent Progressive Aphasia Phenotype

Chiara Villa[a], Laura Ghezzi[a], Anna M. Pietroboni[a], Chiara Fenoglio[a], Francesca Cortini[a], Maria Serpente[a], Claudia Cantoni[a], Elisa Ridolfi[a], Alessandra Marcone[b], Luisa Benussi[c], Roberta Ghidoni[c], Francesca Jacini[a], Andrea Arighi[a], Giorgio G. Fumagalli[a], Alessandra Mandelli[a], Giuliano Binetti[c], Stefano Cappa[b], Nereo Bresolin[a], Elio Scarpini[a] and Daniela Galimberti[a]

[a]*University of Milan, Fondazione Cà Granda IRCCS Ospedale Policlinico, Milan, Italy*

[b]*Ospedale San Raffaele Turro, San Raffaele Scientific Institute, Milan, Italy*

[c]*IRCCS Centro S. Giovanni di Dio-FBF, Brescia, Italy*

Aims and methods: A mutation scanning of Microtubule Associated Protein Tau gene (MAPT) was carried out in 67 patients with Frontotemporal Lobar Degeneration (FTLD) with an early onset and without mutations in progranulin gene.

Results: A novel variant has been found in a patient diagnosed clinically with non-fluent Progressive Aphasia (PA), with a positive familial history for dementia. At 65 years she started developing progressive language disturbance, characterized by verbal production defict and articulation impairment. She came to our attention at 67 years. Her MMSE score was 22/30. A Brain CT scan showed ventricles' asymmetry (L > R) and signs of chronic vasculopathy. Cerebrospinal fluid analysis showed slightly decreased Abeta, slightly increased total tau and normal Ptau levels. She was diagnosed with PA according to current criteria. A novel exon 10 MAPT variant was identified (g.123798G > A), which leads to an amino acidic change (p.Gly304Ser) in the second microtubule binding domain. In silico analysis predicted that this variant is damaging on protein structure and function. Additional 168 FTLD patients and 503 controls screened did not carry the variant, suggesting that it is a mutation rather than a polymorphism.

Conclusions: The aminoacid change could compromise the ability of tau to properly regulate the dynamic behaviour of microtubules.

Cognitive Profile at Presentation and Rate of Progression of Alzheimer's Disease with Early (EOAD) and Late Onset (LOAD)

Maria Gabriella Vita, Camillo Marra, Davide Quaranta, Eugenia Scaricamazza, Giordano Lacidogna and Guido Gainotti

Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, Rome, Italy

Aims: To study if EOAD and LOAD are characterized by different pattern of neuropsychological presentation and evolution.

Methods: Four hundred and seventy seven AD were divided according to age at onset (EOAD < 66 and LOAD > 74). Patients underwent: MMSE, RAVLT immediate/delayed recall, Forward and Backward Digit Span (FS, BS), Phonological and Semantic Fluency (FVF, SVF), Stroop's Test (ST), Multiple Features Targets Cancellation (MFTC), Raven's Matrices (PM'47), Copy of figures without and with landmarks (CF, CFL). A two years follow-up evaluation was completed for 208 subjects.

Results: At baseline, EOAD patients showed significantly more pathological performances in RAVLTir, FVF, CF, BS, PM'47, ST. At follow-up the pattern of worsening did not differ in the two groups but EOAD progressed more severely on MMSE, RAVLT, CFL, FS, BS, MFTC, ST. Irrespectively of the group, global worsening was not influenced by early treatment with cholinesterase inhibitors, but subjects earlier treated showed a significantly slighter decline in PM'47 and SVF.

Conclusions: At presentation, EOAD showed more severe impairment in several cognitive domains. Both EOAD and LOAD evolved towards a diffuse cognitive decline, slower for LOAD in several domains, with comparable effects of therapy. These results suggest an unitary nosology for EOAD and LOAD; age at onset influences only disease severity.

Carotid Atherosclerosis as a Marker of Alzheimer's Disease Progression

Giovanna Viticchi[a], Mauro Silvestrini[a], Lorenzo Falsetti[b], Clotilde Balucani[c], Fabrizio Vernieri[d],

Raffaella Cerqua[a], Simona Luzzi[a], Marco Bartolini[a] and Leandro Provinciali[a]
[a]*Università Politecnica delle Marche, Ancona, Italy*
[b]*Ospedali Riuniti, Ancona, Italy*
[c]*University of Perugia, Perugia, Italy*
[d]*Università Campus Biomedico, Rome, Italy*

Background: There are not definite modifiable risk factors for Alzheimer's disease (AD), but in the last years several authors highlighted a vascular cerebral compromission in AD patients.

Objective: To assess whether cerebrovascular impairment, caused by internal carotid stenosis, influences a progression of cognitive decline in AD.

Methods: We enrolled 411 AD patients: each subject underwent a neuropsychological battery and a B-Mode ultrasound and Doppler velocity evaluation of neck vessels at the study beginning; in severe carotid stenosis, we evaluated the cerebrovascular reactivity to hypercapnia with transcranial Doppler ultrasonography using the breath-holding-index (BHI). After 12 months we repeated the same neuropsychological evaluation to each patient.

Results: Ninety eight patients had a severe carotid stenosis, 41 in the right side and 57 in the left side. Comparing MMSE score at beginning and at the end of the study, we found that patients with left stenosis showed a significant worse results respect to right stenosis or no stenosis subjects. In patients with carotid stenosis, an ipsilateral BHI values <0.69 predicts a worse MMSE score at 12 months.

Conclusions: Severe internal carotid artery stenosis and a deficit in cerebrovascular reactivity could play a significant role in cognitive impairment progression of AD.

Anosognosia and Behavioural Changes in Mild Cognitive Impairment

Leda Volpi, Cristina Pagni, Irene Falorni, Cecilia Carlesi, Irene Ghicopolus and Gloria Tognoni
University of Pisa, Pisa, Italy

Background: Anosognosia and Neuropsychiatric symptoms may variably associate in patients with Mild Cognitive Impairment (MCI), even thought little is known about their prevalence in this condition.

Aims and methods: Anosognosia Questionnaire for Dementia (AQ-D) was used to assess anosognosia in amnesic mild cognitive impairment (a-MCI; $N = 23$), non amnesic MCI (na-MCI; $N = 6$) and multiple domain MCI (md-MCI; $N = 12$). Caregivers completed the AQ-D and the ADCS-ADL-MCI to evaluate functional abilities. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI).

Results: Our findings indicate that only four individuals (3 a-MCI and 1 md-MCI) result anosognosic, while other four subjects over-estimated their defects, on the basis of AQ-D. Moreover, 32 patients exhibited behavioural abnormalities, irritability ($N = 13$), apathy and anxiety ($N = 11$) being the most frequent. Irritability and apathy were also the items causing the higher burden for care-givers. Apathy was more frequent in na-MCI patients, if comparing the three groups. No correlations were found between anosognosia and NPI scores.

Conclusions: These results suggest that the diagnosis of anosognosia is infrequent and that the awareness of cognitive functions is extremely variable in patients with MCI, ranging from low knowledge to exaggeration of symptoms. Furthermore, neuropsychiatric symptoms are common features of MCI.

Cerebrospinal Fluid Markers in Creutzfeldt-Jakob Disease

Gianluigi Zanusso, Michele Fiorini and Salvatore Monaco
University of Verona, Verona, Italy

Background: Sporadic Creutzfeklt-Jakob disease (sCJD) represents the most common human form of prion disorder accounting for about 90% of all cases. Intra vitam diagnostic criteria have been recently revised and include specific clinical signs, a typical EEG with periodic sharp and wave complexes and/or a high signal in basal ganglia at MRI and a positive 14-3-3 protein in the cerebrospinal fluid (CSF). At present, the distinct sCJD diseases phenotypes have been included in molecular groups, based on the genotype at codon 129 of the PRNP of the host and on the biochemical type of pathological prion protein detected in the brain.

Aims and methods: In the present study, we analyzed CSF samples from 60 subjects with definite sCJD diagnosis belonging to distinct molecular groups.

Results: All CSF samples resulted positive to 14-3-3 protein, except those cases with a dementing illness with a relatively long duration. In addition, the level of CSF Tau protein showed a consistent variation among groups depending on the clinical phenotype and the disease course. To further increase the sensibility and the specificity of CSF markers to differentiate

sCJD from other neurodegenerative disorders we also evaluated the levels of phosphotau181 as well as of A-beta 42.

Conclusions: The combination of these markers on the whole, definitely distinguish sCJD from other dementias.

Modulation of MAPK Pathway in Fibroblasts from Alzheimer's Disease Patients: A Possible Interaction between ERK and EAAT1 mRNA

Chiara P. Zoia, Eleonora Verga, Diletta Cereda, Valeria Isella, Lucio Tremolizzo and Carlo Ferrarese
University of Milano-Bicocca, S. Gerardo Hospital, Monza (Milan), Italy

Background: JNK, p38 and ERK1/2 activation has been demonstrated in the CNS of AD patients, since the early stages of disease, leading to neurodegeneration.

Methods: Fibroblasts from 15 patients, 7 MCI and 15 age-related controls were tested to investigate of MAPK-pathway alterations associated to the different stages of disease.

Results: p38- and JNK-phosphorylation were increased in AD fibroblasts without any correlation with disease-severity. In MCI subjects, a trend to phospho-p38/JNK increase was observed, too. Instead, ERK1/2 phosphorylation was reduced in fibroblasts from MCI and mild-to-moderate AD, compared to severe patients. An inverse correlation was observed between ERK1/2 phosphorylation and disease-severity. ERK-pathway is involved in non-amyloidogenic APP metabolism and anti-inflammatory processes and, by specific transcriptional factors, seems to modulate the expression of glutamate transporter (EAAT1) mRNA. By EZ-ChIP assay, we are testing CREB association with EAAT1-promoter to explain the mRNA EAAT1 increase, previously demonstrated correlating with disease-severity in AD fibroblasts.

Conclusions: Since recent evidence suggests that microRNAs may be a contributing factor in neurodegeneration, playing a dynamic role in neuroplasticity and stress responses, miRNAs involvement in EAAT1-mRNA up-regulation will be verified. Clarifying these pathways might help to develop new therapeutic strategies for AD.

Still Driving? An Observational Study in Dementia

Marta Zuffi, Stefania Castiglioni, Silvia De Battisti and Massimo Franceschi
Clinica Neurologica, Casa di cura Santa Maria di Castellanza, Varese, Italy

Background: Many people with dementia continue to drive despite cognitive deficits impair their ability to drive safely. In some countries this problem has been considered and specific guidelines have been proposed to determine the efficacy of driving risk reduction strategies. In Italy no systematic study has been conducted in order to clarify the characteristics of this problem.

Aims and methods: In the period 2008–2009 in our Clinic Memory we clinically assessed 490 patients for possible dementia, dividing them into 4 groups: Cortical Dementia (CD; 357 patients); Subcortical Dementia (SD; 44 patients); Mild Cognitive Impairment (MCI; 34 patients); people without cognitive impairment or with other medical conditions (55 patients).

Results: More than a third of 51% patients who got driving license continue to drive car, despite the perceived risk frequently referred by caregivers on Clinical Dementia Rating (CDR). The comparison of patients currently driving car with those who don't drive anymore shows statistically significant differences in the CD group. Patients who continue to drive are younger, cognitively less compromised (MMSE, MODA, CDR), have less severe psychiatric symptoms (NPI) and obtain better scores on neuropsychological tests of logic memory (short story), attention (attentive matrices) and abstract reasoning (Raven matrices).

Convergent Validity of the Italian Version of MOUSEPAD: Preliminary Analyses on Neuropsychiatric Symptoms in 240 Italian Alzheimer's Disease Patients Enrolled in the EVOLUTION Switch Study

Gianfranco Spalletta[a], Carlo Caltagirone[a,e], Alessandro Padovani[b], Sandro Sorbi[c], Mahmood Attar[d] and Delia Colombo[d] on behalf of the EVOLUTION Study Group
[a] *IRCCS Santa Lucia Foundation, Rome, Italy*
[b] *University of Brescia, Brescia, Italy*
[c] *University of Florence, Florence, Italy*
[d] *Novartis Farma Italia, Origgio (Varese), Italy*
[e] *University of Rome "Tor Vergata", Rome, Italy*

Background: Neuropsychiatric symptom improvement is an outcome of Alzheimer's disease (AD) treatment. Switching from one CheI to another CheI may potentially affect neuropsychiatric symptom severity.

Thus, it is important to validate new instruments, such as the MOUSEPAD, and we are doing it in the EVOLUTION, a 9-month switch (from one CheI to another CheI) study that aims to enroll 800 Italian AD patients from 40 sites throughout Italy.

Objective: Describing the convergent validity of MOUSEPAD Italian version in patients with Alzheimer's disease (AD) enrolled in a switch cholinesterase inhibitor (CheI) study.

Methods: MOUSEPAD was translated in Italian, corrected for semantic congruence, and back-translated in English for language congruence. Neuropsychiatric Inventory (NPI), MOUSEPAD, ADL, and MMSE were administered at 240 patients at the baseline and after 3, 6 and 9 month follow-up. Preliminary analyses here reported regard convergent validity which was assessed by comparing MOUSEPAD with NPI scores at the baseline using Kruskal-Wallis test.

Results: At baseline, MOUSEPAD hallucinations, delusions, aggression, sleep, and eating domain scores increased as NPI severity increased (Kruskal-Wallis' $p < 0.0001$; DF = 3; Chi-square > 43.1 for all analyses).

Conclusions: MOUSEPAD has a convergent relationship with the NPI. Sensitivity to change and inter-rater reliability during 9-month follow-up will be validated in further analyses.

Support: Study supported by an unrestricted grant by Novartis, Italy.

Journal of Alzheimer's Disease 23 (2011) S83–S87
IOS Press

Author Index

ISSN 1387-2877/11/$27.50