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MRI Studies in Frontotemporal Dementia

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Doctoral dissertation

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ABSTRACT

Frontotemporal dementia (FTD) accounts for a variable degree of degenerative diseases, ranging between 7 and 15% in different countries, and its symptoms can overlap with those of AD and other dementias. Magnetic resonance (MR) imaging has proved useful in supporting the clinical evaluation during the diagnostic process. Different techniques have been used to quantify brain atrophy on MR images, from manual tracing of regions of interest, to the most recent voxel-based morphometry (VBM), that allows analysis of the whole brain in one comparison, without previous defining of regions of interest.
The goals of this study were to use both traditional and novel methods for quantification of gray matter atrophy in FTD in order to deepen the current knowledge of the disease, to improve the differential diagnosis with AD or other dementias, and to try to understand the pathogenesis of this condition.
Existing MR images from 10 FTD subjects, 27 AD and 27 controls were compared with traditional methods for quantification of brain atrophy using manual or semiautomatic tracing of the regions of interest (ROI), or with voxel by voxel comparison of MR images normalized on a template, using the SPM99 program.
Using manual and semiautomatic tracing a differential pattern of atrophy in FTD and AD has been defined through a set of relevant ROIs: frontal brain and horns, temporal brain and horns, and hippocampus. This pattern could separate the two patient groups with 90% sensitivity and 93% specificity.
Manual tracing of the amygdala allowed to investigate the nature of the different behavioral disturbances in AD and FTD. FTD patients were found to exhibit less amygdaloid atrophy than AD patients, therefore the greater prevalence of amygdaloid-related symptoms usually reported in FTD patients has been interpreted as being a consequence of the disconnection of fronto-limbic circuitry in these patients.
The pattern of atrophy in single patients has been investigated in order to isolate possible subtypes of FTD. Two patterns of atrophy were isolated, a symmetric, and an asymmetric pattern, depending on the distribution of atrophy (similar or unbalanced between the right and left lobes). The “symmetric” patients had lower age at onset and more severe atrophy than the “asymmetric” ones. Moreover, findings from this study point to a possible role of the APOE genotype in modulating the distribution of atrophy in FTD, since 100% of the ε4 alleles were found in the subgroup of patients with symmetric atrophy. The investigation of the role of APOE in FTD was deepened using the SPM99 program to compare the patients carrying the ε4 allele with the non carriers. FTD patients carrying the ε4 allele exhibited more right frontotemporal atrophy than the non carriers. The same analysis was also carried out in the AD patients: the ε4 carriers exhibited more medial-temporal atrophy than the non carriers. These results were interpreted as indicating that the ε4 carriers have higher brain vulnerability and this probably interacts with the specific effects of the disease, increasing atrophy in the typically affected regions.
Finally, a general analysis of the entire pattern of atrophy was carried out with SPM99 comparing FTD patients with controls. This analysis detected the involvement of the whole rostral limbic system, a circuit known to be involved in tuning and monitoring the behavioral output. This is consistent with the behavioral picture of FTD and with recent findings describing cognition and social competence in these patients.

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Brescia, January 2006

Marina Boccardi

ABBREVIATIONS

AC	anterior commissure
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
APOE	apolipoprotein E
ATC	anterior temporal cortex
BBSI	brain boundary shift integral
CDR	clinical dementia rating
CSF	cerebrospinal fluid
CT	computerized tomography
DLB	dementia with Lewy bodies
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
GM	grey matter
ICA	intracranial area
MMSE	mini mental state exam
MR	magnetic resonance
MRI	magnetic resonance imaging
OFC	orbitofrontal cortex
PA	progressive aphasia
PC	posterior commissure
PD	Parkinson's disease
PFC	prefrontal cortex
PSP	progressive supranuclear palsy
RLS	rostral limbic system
ROI	region of interest
SD	semantic dementia
SPET	single photon emission tomography
SSRI	selective serotonin reuptake inhibitor (SSRI).
VBM	voxel based morphometry
VMFC	ventromedial frontal cortex

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications that are referred to in the text by Roman numerals **I-V.**

I. Boccardi M, Laakso MP, Bresciani L, Galluzzi S, Geroldi C, Beltramello A, Soininen H, Frisoni GB. The MRI pattern of frontal and temporal brain atrophy in frontotemporal dementia. Neurobiol Aging 2003; 24:95-103.

II. Boccardi M, Pennanen C, Laakso MP, Testa C, Geroldi C, Soininen H, Frisoni GB. Amygdaloid atrophy in frontotemporal dementia and Alzheimer's disease. Neurosci Lett 2002; 335: 139-43.

III. Boccardi M, Laakso MP, Bresciani L, Geroldi C, Beltramello A, Frisoni GB. Clinical characteristics of frontotemporal patients with symmetric brain atrophy. Eur Arch. Psychiatry Clin Neurosci 2002; 252: 235-9.

IV. Boccardi M, Sabattoli F, Testa C, Beltramello A, Soininen H, Frisoni GB. APOE and modulation of Alzheimer's disease and frontotemporal dementia. Neurosci. Lett 2004; 356:167-70.

V. Boccardi M, Sabattoli F, Laakso M, Testa C, Rossi R, Beltramello A, Soininen H, Frisoni GB. Frontotemporal dementia as a neural system disease. Neurobiol. Aging 2005; 26:37-44.

CONTENTS

1. INTRODUCTION

The large increase in the incidence of the degenerative dementias observed in the last decades has sharpened the clinical discrimination of their different forms, but the evaluation of individual cases still is subject to error. The overlap between different kinds of dementia is variable and constitutes a source of uncertainty that clinicians would wish to rule out, especially should specific therapies become available with selective effects on these conditions. At present, discrimination of the different degenerative conditions and clarification of their clinical characterization and pathogenesis is also necessary to permit focus allocation of financial resources to interventions thus maximizing the benefits of this intervention. A number of treatments are available for Alzheimer's disease (AD), ranging from molecules modifying the pathogenetic mechanisms of disease to behavioral and rehabilitative interventions. The same treatments are not equally efficacious in frontotemporal dementia (FTD), nor are there as many alternatives available for treatment of these patients. On the other hand, their behavioral problems may require allocation of resources for special care.

Insight into the pathogenesis of Alzheimer's disease is more advanced than in FTD, as can be judged by the greater availability of different kinds of therapies. A deeper insight into the pathogenesis of FTD might not only improve the allocation of resources for providing the available treatments, but might also help the development of new specific therapies for this debilitating disease.

FTD is diagnosed primarily as a behavioral syndrome accompanied by a cognitive involvement mainly characterized by impairment of frontal components. Memory and other cognitive functions can also be impaired, but the behavioral disturbances are more prominent and constitute the main feature distinguishing FTD from other more frequent causes of dementia, such as AD. In the diagnostic process, especially the differential diagnosis of FTD, neuroimaging provides a particularly useful tool. In fact, the clinical evaluation of some functions may not be possible due to the typical lack of motivation of FTD patients. Moreover, the typical tendency of FTD to impoverishment of language, or even to mutism, leads to a decline in performance that cannot be interpreted unequivocally as a true impairment of the tested functions. The combination of clinical and neuroimaging evaluations maximizes the accuracy of the diagnostic process. Imaging tools may also provide information which partially overlaps between

these different diseases, but with careful selection, these tools can add value to the diagnostic process.

Even in the clinical setting alone many ambiguities have existed for long years. AD has been traditionally considered as a disease of the limbic structures, since the medial temporal regions are involved. Nonetheless, the important disturbance of adaptive behavior in FTD patients, as well as their severe lack of motivation and emotional involvement in social interactions leads one to wonder whether this is not much more a "limbic" disease than AD. Work by Damasio (Damasio, 1995) combined "frontal" functions and limbic components into a global interpretation of human brain functioning, and recently most sectors of basic neuroscience are supporting this kind of approach, and adopting it to explain experimental data and human behavior. These concepts might find larger use also in clinical settings, and provide a concrete improvement in both the differential diagnosis and pathogenetic explanations of diseases.

This work covers only a limited part of this overall goal, i.e. the use of MRI techniques in the diagnosis and in the explanation of some clinical correlates. Nonetheless, it does try to gather new concepts to explain neuroimaging and clinical findings, possibly providing additional lines of research that might assist in the investigation of pathogenetic mechanisms of FTD.

2. REVIEW OF THE LITERATURE

2.1 Historical account

The identification of FTD has its historical roots in the studies of Arnold Pick, head of the Department of Psychiatry, University of Prague, at the end of the nineteenth century. The clinical characterization of Pick's patients relied on the cognitive decline associated with marked behavioral and language disturbances. Gross anatomic *post mortem* observation showed global brain atrophy, but degeneration was more severe in the left lobe. At the time, the notion that brain degeneration might be unbalanced in its distribution, rather than homogenously diffuse in the brain, was new, and this constituted the main finding of Pick. Other similar cases were described by Richter (Richter, 1918), Lüers and Spatz (Lüers and Spatz, 1957) and Tissot (Tissot, 1975).

The histological characterization of Pick's disease was carried out in 1911 by Alois Alzheimer, who described the "Pick's bodies", "Pick's cells", and the cortical spongiosis. Plaques and neurofibrillary tangles were not observed in the brain tissue of these patients, which confirmed the peculiar characterization of this nosological entity (Alzheimer, 1911).

The denomination "Pick's disease" was introduced by Gans in 1922, referring to this set of observations, and acknowledging Pick's initial description. Gans emphasized that a marked frontal atrophy was generally compromised in all lobar atrophy diseases accompanied by aspontaneity and disorders of attention, behavior and language. (Gans, 1922)

In 1927, the first separation between frontal and temporal involvement was theorized by Schneider. He observed that the pathologic involvement of the temporal lobe was associated with language disturbances, while apathy characterized those patients with frontal atrophy (Schneider, 1927). The term "Pick's disease" was used for both of these patterns of atrophy. Nonetheless, it was observed in these years that the Pick's bodies or cells might not be present at the histopathological examination (Schneider, 1927;1929).

In 1975 Tissot described a series of 32 patients with clinical and pathological assessment, where patients were divided into three groups based on pathological findings: the first group showing both Pick bodies and Pick cells, the second group had only Pick cells, and the third group exhibited no Pick pathology.

The clinical picture was characterized by mood, language, attention and behavioral disorders which were evident from the initial stages of disease. Motor function could be slower, and increasingly impaired in subsequent stages of disease. A greater involvement of language was also described in these later stages, while the cognitive impairment consisted mainly in planning and orientation deficits. Behavioral problems extended to eating behavior, and alteration in blood pressure values were registered (Tissot, 1975).

More recently, researchers from Manchester, UK (Neary et al., 1998) and Lund, Sweden (Gustafson, Risberg, Brun, Englud, 1987) described this type of lobar atrophy as an entity separate from AD. They also observed that the typical Pick bodies could be present, but were absent from the majority of the cases with frontal lobe degeneration. About 10% of patients with organic dementia presented with unspecific gray matter degeneration without any histological Alzheimer or Pick pathology. Neuropathology was evident at the microscopical investigation more than at gross inspection, and consisted of neuronal loss, gliosis and spongiosis mainly involving laminae 1-3.

White matter changes were less severe, and roughly corresponded to the distribution of the cortical degeneration, being probably its consequence. The clinical picture was characterized by a positive family history for dementia (50%, versus 30% reported for other kinds of dementia), insidious onset with an early change of personality, lack of insight, disinhibition, emotional lability, and other behavioral symptoms. The behavioral picture was accompanied by a frequent involvement of speech, with symptoms ranging from stereotyped phrases and echolalia to mutism. Altered dietary and oral behavior were detected as secondary symptoms. Sparing of memory and spatial ability discriminated this kind of dementia from AD. Regional cerebral blood flow recordings available for a group of these autopsied patients confirmed severely decreased values in the prefrontal regions, which were even more pronounced in the Pick patients.

2.2 Consensus criteria

In 1994 the first consensus statement was produced based on the clinical evaluation of a very large sample of patients, and on the pathological observation of 60 of them. The

document was meant to agree on a common definition of frontotemporal dementia, intended to characterize the non-Alzheimer lobar atrophy described by the Lund and Manchester groups.

In these first criteria, the clinical picture of frontotemporal dementia was depicted as a set of core and supportive diagnostic features. Most core features had long been described, such as emotional unconcern, behavioral and speech disorders. A more complete description of behavioral disturbances, delineating a wide impairment of the diverse frontal functions, was provided. Supportive features like presenile age at onset of disease and a positive family history of similar condition were also reported. Overall, clinical features described correspond to the FTD type of frontotemporal dementia, as reported by the successively defined criteria (Neary et al, 1998). The Authors stated in this report that progressive aphasia shows a spectrum of histological changes overlapping with that of FTD, but with more posterior distribution in the temporal cortex, and that features of that condition were not discussed in that consensus statement. With respect to the pathological characteristics, the cases were separated into three categories: one with Pick-type pathology, one lacking distinctive histopathology, one with evidence of motor neuron disease (Lund and Manchester groups, 1994). As to the type lacking distinctive histopathology the Authors report that, in cases with particularly pronounced behavioral aberrations, and, in particular, greater frequency of stereotypic behaviors, atrophy of the amygdala, striatum, and hippocampus is more evident than neocortical atrophy, and suggest that this may represent a clinical subtype. On the other hand, Pick's disease was described, from a pathological point of view, as characterized by cortical atrophy with similar distribution, but more intense and circumscribed. The same was reported for cortical atrophy in FTD with motor-neuron disease, that had, in addition, involvement of motor neurons.

In 1998, these criteria were revised in order to account for two clinical profiles that share a number of features with frontotemporal dementia, but present more marked language disturbances, and less important behavioral deficits, at least during initial stages of disease: progressive non fluent aphasia (PA) and semantic dementia (SD). Together with the clinical subtype characterized by behavioral disturbances, and termed frontotemporal dementia (FTD), this set of conditions was globally named frontotemporal lobar degeneration (FTLD), in order to account for the distribution of

the neuropathological changes, that affect the frontal and temporal lobes. In this consensus criteria, the Authors stated that the relative severity and distribution of such fronto-temporal atrophy give rise to the three different syndromes, posterior temporal atrophy being associated with the two subtypes mainly involving language, but the kind of histological changes underlying them are basically two. One consists in microvacuolar changes without specific histological features, the other in severe astrocytic gliosis with or without ballooned cells and inclusion bodies (Pick type). Nonetheless, pathological data were not further discussed, nor were they associated to distinct clinical subtypes in these criteria. .

Clinically, all of these conditions were described as presenting with insidious onset and gradual progression. PA was defined as being characterized by nonfluent spontaneous speech associated with anomia or agrammatism or phonemic paraphasias. Supportive features list other language impairment, such as impaired repetition or alexia, and early preservation of social skills, that eventually decline resembling the typical pattern of FTD.

SD is described as being characterized by loss of word meaning, manifesting in impaired naming and comprehension, and fluent but empty spontaneous speech. Semantic paraphasias or agnosia for objects or familiar faces could accompany these symptoms, while preserved repetition distinguished SD from PA. In contrast to PA, behavior can be impaired early, but this feature is not strictly required for diagnosis.

Finally, FTD was defined as being primarily characterized by the early decline in personal and social conduct, emotional blunting and loss of insight. A typical pattern of impaired frontal functions was supportive in the diagnosis, as well as speech deficits and physical signs, ranging from primitive reflexes to labile blood pressure (Neary et al., 1998).

Most recently, the clinical and pathological criteria were reassessed at the Frontotemporal Dementia and Pick's Disease Criteria Conference in Bethesda, 2000 (McKhann et al., 2001), where the definition of the disease bended to the side of pathological aspects rather than of the clinical ones. The main conclusion of this work was that it is not possible, at present, to fit the different phenotypes of FTLD with different pathological characterization, and therefore the different phenotypes should be collectively referred to as FTD. The authors recognized that the different phenotypes

previously described as PA and SD do differ from the behavioral variant of the disease, but that there is not sufficient evidence to separate these conditions nosologically. From a clinical point of view, the Work Group of McKhann and collaborators rather distinguished among two clinical phenotypes, one mainly involving behavior, the other affecting language (McKhann et al., 2001). The Authors underline that in the research community the terms *primary progressive aphasia* and *semantic dementia* are commonly adopted, "although the changes in language may be the initial presentation of the disease" but, "as the disease progresses, behavioral changes may occur". Therefore, they state that "patients with FTD present with 2 patterns: gradual and progressive changes in behavior, or gradual and progressive language dysfunction", these being core clinical features whether they have early presentation, and a level of severity that interferes with the normal social or occupational functioning. Main differential features distinguishing from AD are summarized by the Work Group mainly in differences in the age at onset (rarely after 75 for FTD), in selectively preserved orientation and ability to track recent events, lack of concern for own condition, and greater risk for motor abnormalities.

Of particular interest, the Work Group delineated neuropathological recommendations for evaluation of the condition. First of all, it is stated that neither severity, nor distribution of atrophy has been observed to be constantly associated to any of the considered clinical conditions. Microscopic examination using histochemical and immunohistochemical methods, besides using typical tools able to exclude AD or LBD pathology, should carry out biochemical analysis of the insoluble tau, conjoined with testing for ubiquitin, required because some characteristic lesions are negative to tau, but positive to ubiquitin. Finally, the basic distinction allowed by pathological examination distinguishes between tau-positive inclusions and presence of insoluble tau, tau- or ubiquitin-negative inclusion without detectable insoluble tau, and tau-negative but ubiquitin-positive inclusions, without detectable insoluble tau. Within this framework, tau-positive conditions seem to gather the clinical diagnoses of corticobasal degeneration, progressive supranuclear palsy, Pick's disease, frontotemporal dementia with parkinsonism linked to chromosome 17. Tau-negative conditions are characterized by undetectable insoluble tau, be they ubiquitin-positive or negative. Among these, frontotemporal dementia with motor neuron disease is associated to ubiquitin-positive

but tau-negative inclusions, while ubiquitin-negative inclusions seem to correspond to frontotemporal dementia lacking distinctive histopathology (McKhann et al, 2001).

2.3 Epidemiology of FTD

As a dementia with presenile onset and rather short duration, the prevalence on FTD is low in senile patients and higher in younger ones. In particular, a proportion of 15% of dementia cases has been found in two studies (Ratnavalli et al., 2002), while a proportion of 3% was identified in a population-based sample of 85 year olds (Gislason et al., 2003). Although some authors state that men and women can be equally affected by FTD (Snowden et al., 2002, Binetti et al, 2002), numerous studies report a higher percentage of men in their FTD samples (Ratnavalli et al., 2002). The mean duration is 8 years, but the variability is extremely wide (2 to 20) (Snowden et al., 2002).

2.4 Histopathology of FTD

In the history of the characterization of FTD there has been a tendency to refer to it as Pick's disease, due to the initial descriptions. Indeed, Pick bodies can be detected at pathological examination, but the pathological findings in subjects with the clinical symptoms of FTD can vary considerably. Focusing on results obtained with immunohistochemical staining with antibodies to tau, ubiquitin and αB crystallin, a number of different diseases can be separated, all causing the typical symptoms of FTD. For this reason, the most recent approach has consisted of including a variety of pathological characteristics as possible findings in FTD.

The diagnosis of FTD lacking distinctive histopathology is generally confirmed when no intraneuronal inclusions are found with antisera to tau and ubiquitin, and when there is microvacuolation of cortical layer II in the frontal and anterior temporal cortices, which can be severe and transcortical, with variable degrees of subcortical gliosis. Mild or moderate atrophy can be accompanied by a variable number of αB crystallin-immunoreactive swollen cortical neurons (Jackson and Lowe, 1996). Enlarged criteria, including different types of histological findings associated with FTD symptoms, can

also include cytoplasmatic inclusions in small nonpyramidal neurons in the upper cortical level of the frontal and temporal cortex, and in the amygdala, basal ganglia and brain stem. Neurofibrillary tangles can also be observed, as can ubiquitin-positive inclusions, the latter generally when FTD is associated with motor neuron disease (McKahnn et al., 2001).

Recently, a neuropathological characterization (Mott et al., 2005) tried to validate the guidelines elaborated by the Bethesda Work Group, by investigating 21 FTD patients with traditional histochemical stains and tau and ubiquitin tests. The Authors have divided the FTD cases into six neuropathologic categories by traditional examination (Pick disease, corticobasal degeneration, dementia lacking distinctive histopathology, progressive supranuclear palsy, frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions, and neurofibrillary tangle dementia). All cases were then independently evaluated by the insoluble tau isoform pattern indicated by the last criteria (McKhann et al., 2001), including 3R, 4R, 3R/4R, and no insoluble tau: the patterns strongly correlated with the independently derived histopathologic diagnoses, with cases characterized by predominant 3R corresponding to Pick's disease, cases with predominant 4R tau corresponding to either corticobasal degeneration or progressive supranuclear palsy, and cases with 3R/4R being either a combination of Pick's and AD, or frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions. Insoluble tau was reduced in dementia lacking distinctive histopathology and in frontotemporal lobar degeneration with motor neuron disease. Observations about ApoE in these cases showed that the ε4 allele is overrepresented in Pick's Disease and in dementia lacking distinctive histopathology. This whole study provided a first validation of the general framework proposed by the Bethesda group (McKhann et al., 2001).

2.5 FTD and genetics

FTD was first linked to chromosome 17 in 1994, when the locus of the "disinhibition-dementia-parkinsonism-amyotrophy complex" was identified on chromosome 17q21-22 (Wilhelmsen et al., 1994). Subsequently, mutations of the tau protein, encoded on chromosome 17, have been repeatedly demonstrated in patients belonging to the wide

family of frontotemporal dementia. These mutations involve both exons and introns around the microtubule binding region of tau. Nevertheless, only a small percentage of patients with FTD carries tau mutations, nonetheless most of them have abnormal accumulation of tau protein. At the same time, patients with very similar mutations are affected by very different frontotemporal syndromes (Rosen et al., 2000).

Contrary to what happens in AD, the APOE-ε4 allele does not represent a risk factor for frontotemporal dementia, although it is over-represented in a number of samples. Based on the recent validation of the last criteria for diagnosis of FTD, the ε4 allele is overrepresented in Pick's Disease and in dementia lacking distinctive histopathology (Mott et al., 2005).

The motor-neuron disease, when linked to frontotemporal dementia, has also been described to correspond to a genetic locus on human chromosome 9q21-q22.

2.6 Clinical differential diagnosis from AD

Although AD and FTD have definitely different clinical phenotypes, FTD can be, and often actually is misdiagnosed as AD. The opposite may also happen, particularly when "frontal" symptoms occur. The frontal lobes had the most recent development both phylogenetically and ontogenetically, and require high metabolic effort, as well as integrity of connected structures, to carry out their functions. Therefore, frontal symptoms can be frequently observed in dementia patients other than FTD. Moreover, a frontal variant AD has been described (Johnson et al., 1999), that pathologic examination detected to be characterized by a higher concentration of neurofibrillary tangles in the frontal lobes compared to typical AD brains (senile plaques pathology in the frontal and entorhinal regions did not differ between the two groups). Therefore, when the currently adopted clinical criteria for diagnosing AD (McKhann et al, 1984) were tested as to their accuracy in differentiating AD from FTD, specificity to FTD was found to be very poor (0.23), notwithstanding a high sensitivity in detecting AD (0.93) (Varma et al., 1999). This requires to consider FTD criteria together with AD ones in evaluating a new dementia patient. The criteria elaborated in 1984 (Neary et al., 1998)

correctly classified 93% of patients with FTD and 97% of AD in a validation study (Rosen et al., 2002).

Other characteristics are of help in the clinical evaluation of people with dementia. Patients with FTD are usually younger than patients with AD (Neary et al., 1996), and they are unaware of the early change in their personalities and inappropriate behavior. In contrast, AD patients are aware of the changes and maybe able to hide them, but become understandably depressed and upset due to this awareness of their condition. The stereotypy of language and behavior, ranging from apathy to disinhibition, is quite different from the typical AD patients, who are still able to interact appropriately in social contexts.

From a neuropsychological point of view, it has been observed that the first symptoms differentially characterized not only FTD and AD, but also FTD with mainly right, left or bilateral atrophy (Lindau et al., 2000). In detail, memory loss first presented in AD , while disinhibition characterized right-sided FTD, and language dysfunction left-sided FTD. Executive function was most frequent in bilateral FTD.

Anyway, although a number of tests are typically differentially impaired in the two conditions, the reliability of test performances has been repeatedly debated, even when these were rather typical for the two dementias (Grossi et al., 2002).

For this reason, biological markers are being sought in order to help in the differential diagnosis. Biological markers can be detected in vivo via cerebrospinal fluid (CSF) analysis extracted by lumbar puncture or, alternatively, via visualization of cerebral structures or function with neuroimaging techniques. CSF analysis showed that, contrary to AD, presenting with reduced Aβ and increased total tau levels compared to controls, FTD patients exhibit increased Aβ, and variably described levels of tau, which is generally higher than observed in controls, but lower than in AD patients (Rosso et al., 2005).

2.7 Clinical manifestations of FTD

FTD has been constantly described with the same peculiar set of clinical characteristics mainly involving altered personality, behavior and language. Nonetheless, the diagnosis

of this condition is still challenging, due to the considerable overlap of its symptoms with those of AD (Varma et al., 1999).

Heterogeneity in the combination of symptoms in different geographic areas can be observed. For example, in the Finnish variant of FTD (Nasu-Hakola disease or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy) systemic bone cysts are known to be associated to the ordinary set of symptoms of frontotemporal dementia (Hakola et al., 1974). The combination of neuropsychiatric symptoms and bone cysts is unique to this disease, that is also described in Japan and Italy. The molecular defect has been identified in loss-of-function mutations in the TYROBP gene in Finnish and Japanese patients (Paloneva et al., 2000), and in the TREM2 gene in other families of different ethnic origins (Soragna et al., 2003).

2.7.1 Physical symptoms

Primitive reflexes, incontinence and altered blood pressure values are also observed. Although some observations describe lower blood pressure as a common symptom in degenerative dementias (Passant et al., 1996), this is commonly reported as a defining symptom in FTD (Neary et al., 1998).

Together with altered dietary behavior and the Klüver-Bucy-like symptoms, they seem to indicate the involvement of rather deep or ancient structures, in contrast with the ordinary description of cortical lobar atrophy.

Akinesia and other extrapyramidal symptoms are likely to occur in FTD and help distinguish it from other degenerative disorders (Rosen et al., 2002).

Although amyotrophic lateral sclerosis (ALS) can be independently associated to FTD, a high prevalence of this condition (up to 38%) (Lipton et al., 2004) is registered. Recent studies have attempted to identify the basis for this concurrence (Prudlo et al., 2004, Lipton et al., 2004), which seems more striking after the recent publication of “frontal” symptoms in patients with ALS (Lomen-Hoerth, 2004).

2.7.2 Language

Language involvement is observed even in the early stages of disease, and can end in mutism at later stages. Even in patients that seem to have preservation of language, a specific problem related to verb processing has been described (Hodges and Miller, 2001)

Linguistic functions can be considered to be as badly disrupted as other kinds of behaviors. For example, it can be stereotyped and repetitive resembling the frontal symptoms of perseveration and of stereotyped behavior. Furthermore, as with the presence of other core features such as emotional blunting, it can be aspontaneous and scarce being due to a lack of motivation (Neary et al., 1998).

Linguistic functions are severely involved in the other two types of frontotemporal lobar degeneration (semantic dementia and progressive nonfluent aphasia) where language impairment is the main characteristic of the disease.

2.7.3 Behavioral symptoms

Cognitive functions are clearly impaired in FTD, but neuropsychological tests often produce contradictory results even when the evaluated functions are those typically impaired in this kind of dementia. For example, an attempt to discriminate AD from FTD might involve tests of memory function and executive functions, which are thought to be differentially impaired in the two conditions, but the neuropsychological patterns described in literature are not so clear-cut, nor consistent across different studies. This neuropsychological inconsistence confirmed the belief that FTD is primarily a neurobehavioral syndrome (Perry and Miller, 2001), where abnormalities become evident especially in dealing with one's own environment, rather than in isolated and easy measurable cognitive functions.

If we wish to classify and define the abnormal behavior of FTD patients, their problems fall into a wide variety of alterations, from physiological self-regulation to interpersonal relationships. Altered functions also exhibit a wide range of manifestations. For example, altered food intake range from unbalanced dietary preferences such as

excessive intake of carbohydrates, to consumption of non edible objects. Similarly, improper social behavior might range from excessive jocularity to apathetic behavior.
As some of these symptoms might overlap with other kinds of dementia such as AD, some researchers have tried to define which of them best discriminate between the two conditions. In 2000 Bozeat et al showed that stereotypic and altered eating behavior, together with loss of social awareness, could reliably differentiate FTD from AD, and that this pattern of symptoms was quite similar to that of semantic dementia. This study suggested that a common network might underlie both syndromes and, above all, that FTD might consist of a neuropsychiatric syndrome due to disruption of a specific network, putatively the anterior limbic system, connecting emotional structures like the amygdala to the ventral frontal cortex, with the function of guiding adaptive behavior. Subsequent studies investigating the nature of behavioral abnormality in these patients consistently added to the evidence of disruption of this kind of self-regulating network (see Study V).
In this evolution of neurobehavioral studies of these patients, therefore, there has been a shift of attention from single behavioral problems (change in personality, emotional unconcern, disinhibition, etc.) to more basic and general behavioral problems (i.e. disruption of self-regulating and adaptive behavior) that better describe the disruption of specific brain networks, and more economically gather apparently heterogenic symptoms into wider and more informative diagnostic categories.
In the following sections, the typical symptoms of FTD will be reviewed in a "traditional" way, and will be finally gathered into the more recent interpretation of the syndrome.

2.7.4 Change of personality

The clinical picture of FTD is characterized by early changes in personality. This kind of symptom is particularly strange as well as vaguely defined. It refers to altered personal and social conduct, and behavioral changes mainly consisting of disinhibition, jocularity, irritability, euphoria, emotional unconcern or apathy. Personality alterations include changes in taste, for example in music listening (Geroldi et al., 2000), as well as

the birth of new artistic abilities (Miller et al., 2000). Profound alterations of the self such as change in political, social and religious values have been thought to be associated to the asymmetric involvement of the non-dominant hemisphere (Miller et al., 2001).

2.7.5 Emotional unconcern

FTD patients are apparently unaware of their social context showing inappropriate behavior and emotional unconcern. Apathy is a frequently observed feature in these patients, but it should not be considered as a depression trait (Levy et al., 1998). While depression can be a normal emotional reaction to a negative condition, apathy rather refers to some sort of disconnection from motivational sources, causing lack of initiation and loss of motivation or drive. The behavior of these patients resembles that of a passive organism automatically and stereotypically reacting to stimulation rather than actively searching for relief or seeking a solution to its own problems.
Paradoxically, in the same condition, disinhibition is found, which seems to be a diametrically opposite symptom, but this in fact points to the disruption of a system regulating emotional behavior.
This form of emotional unconcern was recently characterized in the Theory of Mind functions (Lough et al., 2001; Gregory et al., 2002), which means that these patients are unable to empathically participate to another one's situation and to behave appropriately. Insight into one's own situation and the related appropriate behavior are equally lacking.

2.7.6 Other cognitive functions

Features such as obsessive-compulsive symptoms can be related to frontal dysfunction. Other behavioral features (stereotypy, perseverative behavior, etc.) denote in fact a marked frontal involvement, but some frontal functions may be relatively intact during neuropsychological testing (Rahman et al., 1999; Lough et al., 2001) despite the marked

alterations in behavior, this being the case in some non demented frontal patients (Damasio, 1995). Rahman and colleagues (1999) argued that the heterogeneity of the frontal cortex and of its connections and functions accounts for the particular patterns of frontal impairment of FTD, and this is why many typically frontal tests, such as the Wisconsin Card Sorting Test, the Tower of London or working memory tests can be unimpaired in mild FTD patients, who show instead altered behavior in decision making tasks. In decision making tasks (Rogers et al., 1999) and other tests sensitive to orbitofrontal function, such as the gambling task (Bechara et al., 1997), FTD patients are able to make accurate probability judgments, but cannot adjust their bets appropriately, appearing as greater risk-takers than controls, as well as other "frontal" patients (Bechara et al., 1994; Bechara et al., 1998). This behavior has been interpreted as an inability to anticipate future outcomes, but the "anticipation" should be considered as an "emotional" anticipation, *driving* the patient to modify his/her behavior accordingly, rather than a pure "cognitive" prevision of possible outcomes (Damasio, 1995). This kind of impairment indicates that neurological involvement should be expected located in the ventromedial rather than dorsolateral frontal cortex.

Memory and orientation are relatively preserved compared to AD, but still abnormal, and those changes increase the difficulties in the differential diagnosis. Some tests very typically failed by AD patients, such as those of episodic memory, especially for the location of objects in space (Swainson et al., 2001), are performed well by FTD patients, and are therefore rather useful in making a clinical diagnosis (Lee et al., 2003). FTD patients show impairment in the reversal learning stages, which has been interpreted by some authors as being due to an involvement of the ventral striatum, data supported by experimental work on primates (Divac et al, 1967), as well as from cytoarchitectonic connections (Williams et al., 1993).

The most recent studies in the field of social cognition showed that the Theory of Mind is impaired in FTD patients (Hodges and Miller, 2001) and that it dissociates from frontal executive function (Lough et al, 2001). One aspect linked to the Theory of Mind is the ability to recognize emotion from facial expression. The first study assessing this function in FTD appeared in 1999, and compared these patients to AD subjects and healthy controls (Lavenu et al., 1999). While all subjects could correctly distinguish neutral faces from those expressing emotions, FTD patients had a poorer ability than

AD patients in naming anger, sadness and disgust. Both FTD and AD patients had worse performance than controls in naming fear and contempt, but the more circumscribed impairment of AD points to involvement of different systems in these patients.

2.7.7 Recent interpretations of clinical data about FTD

The evidence that FTD patients might show unexpectedly little impairment in frontal test as well as the confusing overlap in cognitive performance with AD demanded a move away from strategies for the interpretation of the disease based on single function impairment to a more general system impairment. This happened thanks to a variety of heterogenic evidence, ranging from the recently explored behavioral alterations of neurological frontal patients, to the developing of the new field of social cognition. Indeed, critical observations in the field of cognition recently shifted the focus of attention of researchers from the "cognitive" to the "emotional" level. Actually, as effectively pointed out by Damasio (Damasio, 1998) in the course of numerous contributions, "emotion" has long been neglected in the cognitive neurosciences, and misleadingly considered as being opposite to the typically "cognitive" aspects of brain functioning. Instead, emotion is a kind of cognitive information that allows the organism to adapt to its environments according to different survival needs. What characterizes emotion, giving it the features that make it appear so different from cognition, is that the drives derived from it can scarcely be controlled and pushily guide behavior despite one's own "will". What was not considered until recent times was that this "pushy" feature of emotion is what guarantees survival to the organism, as emotion guides behavior relating to survival issues that should not be disregarded.

The second step in the evolution of knowledge in this field consisted in the concept that this newly recognized function, i.e. the guiding behavior in the direction of "emotionally" marked physiological goals, is mediated by the frontal lobes, whose connections to the limbic regions of the brain are particularly rich. The frontal lobes are the optimal region to carry out this sort of functions, for many reasons, e.g. a) they have a complete representation of the entire organism and b) they are involved in the control

of behavior, and can therefore provide optimal satisfaction to the organism's needs by behaving in a way finalized to modify the environment and answer to that need (Goldberg 2002). In these terms, it is clear that "emotion", rather than being an irrational function of the brain, is a very rational aspect, aimed at guaranteeing optimal survival of the individual in its environment (Damasio, 1995).

When one considers human beings, the social context is a particularly important part of the environment to which the individual has to adapt, and that the individual can utilize to reach personal aims. For this reason, particularly in primates another newly recognized function has evolved, consisting of the concept of "social competence". This includes understanding and prevision of the state of mind in other individuals of the species, recognizing of cues directly indicating their internal conditions (like facial expression of emotions) and empathy. Empathy is the force that guarantees social cohesion, and a biological basis for empathy has been recently recognized in the so-called mirror-neurons (Rizzolatti et al., 1999).

All of these recent approaches are being intensely investigated by neurobiologists, that are progressively more able to connect and relate them to human brain structure (Adolphs 2001). It is increasingly clear that a great number of pathologic conditions are characterized by impairment in different components of this complex "adaptive" system and that these impairments might be central to the disease, as seems to be the case in autism, or might be a secondary component, caused by other major damage (such as the impaired recognition of some emotions in Huntington disease). The set of symptoms described in the previous sections point to a new explanation of FTD, considering this syndrome to represent the disruption of such adaptive system. This interpretation fits the evidence of the inconsistent results obtained in traditional "cognitive" tests, the failure in tests of social competence and the well known disruption of personal and social conduct. The search for a biological marker, previously sought primarily in order to discriminate the condition from other kinds of dementias, may now be guided by this more unitary interpretation of the disease, clearly pointing to the involvement of definite systems (Adolphs, 2001).

2.7.8 Studies of bizarre symptoms in FTD

The set of symptoms described in the last paragraphs point to the involvement of a set of structures implicated in functions that best distinguish the human being: emotional understanding and taking part in social roles, maintaining proper conduct, finalizing behaviour to convenient goals. People lacking functions of this kind typically encounter difficulties when they are involved in activities or interpersonal relationships, which is particularly troublesome for any attempt at rehabilitative treatment. The strange condition and conduct of these patients, who are usually unaware of their illness and presenting a wide range of symptoms from simple apathy to inappropriate positive – even euphoric- moods, inevitably gave rise to a number of particularly original studies addressing these peculiar traits. As bizarre was the content of the visual hallucinations of a young euphoric patient diagnosed as FTD (Reischle et al., 2003), equally bizarre are other described traits such as an alteration in the *humanness*, inducing FTD patients with predominant right atrophy to judge as "human" the morphed or masked faces not recognized as "human" by other FTD patients with left involvement or controls (Mendez et al., 2004). Similarly, other authors measured *agreeableness* of FTD patients according to the NEO-Five Factor Inventory score obtained by care-givers' evaluation of the patient, and found it to be negatively correlated to left and positively correlated to right orbitofrontal volume (Rankin et al., 2004). The peculiarity of such behaviors and findings more than once induced researchers to wonder whether FTD is a dementing disorder uniquely determining loss of function, or whether some positive aspects and functions could actually be gained. In one of these studies, a lawyer who previously considered pop music to be "mere noise" actively sought out tapes of a popular Italian pop group, which he then played over and over at full volume for most of the duration of his disease, while a grandmother shared with her 11-year-old granddaughter a strange enthusiasm for pop music (Geroldi et al, 2000). Similarly, several studies from a group long describing FTD reported *acquisition of artistic drive* from the visual to the musical field, and describe this condition as often being associated to anterior temporal atrophy (Miller et al., 1998; 2000; 2004). Left hemisphere damage is also thought to be responsible for the release of supposedly "right" artistic drive. Similar data are actually common to other pathological conditions such as autism (Munoz-Yunta et al., 2003) or

epilepsy with frontal focus (Finkelstein et al., 1991). Indeed such studies provide an unexpected opportunity to explore creativity and artistic talent as complex and yet mysterious human abilities.

2.8 Brain morphology in FTD

2.8.1 Atrophic structures in FTD

Brain morphology, as investigated at structural neuroimaging studies, is constantly characterized in FTD patients by atrophy of the anterior section of the temporal lobes and of the frontal lobes, which is paralleled by decreased perfusion detected at functional imaging (McKhann et al., 2001). This pattern of anomalies is typical and distinctive of FTD, since involvement of the parietal lobe usually corresponds to AD pathology. In some patients atrophy of deep structures, like the corpus striatum and the amygdala, is observed (the Lund and Manchester group, 1994).

As to frontal morphology, atrophy has been observed in diverse sectors of this lobe: dorsolateral, orbitofrontal, ventromedial and anterior cingulate (Rosen et al., 2002). The anterior temporal atrophy mainly characterized SD in a direct comparison of the two syndromes (Rosen et al., 2002), but can be found in FTD as well.

The observation of amygdaloid and striatal atrophy comes from pathological studies (Filley et al, 1994).

2.8.2 Different involvement of the two hemispheres

One of the most typical features of FTD is asymmetry, which is evident at both the clinical and biological levels. The involvement of language, that can be affected early and disproportionately (Neary et al., 1998), indicates greater involvement of the left hemisphere. In other cases, behavioral disturbances predominate, which may indicate greater right hemisphere involvement (Mychack et al., 2001). At the biological level, strikingly asymmetric hypometabolism and atrophy, as detected with *in vivo* imaging methods, have been repeatedly described, as well as an asymmetric distribution of

lesions on pathological studies (Miller and Gearhart, 1999; Filley et al., 1994). However, asymmetry may also be absent. Miller and Gearhart analyzed 15 FTD patients with single photon emission tomography (SPET) and magnetic resonance imaging (MRI), and observed symmetric hypoperfusion in 3, and symmetric atrophy in 7 of the subjects (Miller and Gearhart, 1999). Filley and colleagues reported symmetric involvement in 2 of 4 FTD patients at pathological evaluation (Filley et al., 1994).

2.9 Therapies for FTD

Insight into the neurochemical involvement on FTD is still in its infancy, and there are few studies on this aspect. Observations that cholinergic activity are decreased in the nucleus basalis of Meynert of both AD and FTD have led to attempts to use acetylcholinesterase inhibitors in FTD, but this kind of treatment does not have any scientific evidence of efficacy in this disease (Perry and Miller 2001).

Clinical observations lead to the proposal that the serotonergic system could be involved. Weight gain, altered food preferences and obsessive compulsive symptoms may be due to frontal and subcortical serotonin loss (Miller et al., 1995). Indeed, serotonergic receptor abnormalities have been observed at autopsy in FTD patients (Sparks et al., 1991). Neuropsychological and neuropharmacological studies seem to confirm the possibility of a specific serotonergic involvement: increases in deliberation times similar to those observed in FTD in decision making tasks were in fact observed in normal subjects with low levels of 5-HT induced by consumption of a low tryptophan drink (Rogers et al, 1999). These subjects also showed altered performance in performing a simple reversal rule, thus resembling FTD performance in these kinds of tasks (Park et al., 1994).

Selective serotonin reuptake inhibitors (SSRI) are currently being used for treatment of FTD symptoms (Swartz et al., 1997), in particular, against impulsive behavior (Coccaro, 1989), aberrant dietary (Yager, 1988) and obsessive-compulsive behavior (Hollander, 1996). Initial results indicated some benefits, but more systematic studies failed to confirm this proposal (Deakin et al, 2004). Thus, data on efficacy of this treatment must be considered as controversial (Deakin et al., 2004).

2.10 Imaging diagnostic tools in FTD

Structural and functional tools are used in clinical diagnosis with the aims of excluding nondegenerative causes of cognitive impairment and of helping in the diagnosis, in particular the differential diagnosis between different kinds of dementias (DeCarli, 2001). The finding of a reduced volume is a strong index of grey matter degeneration at structural examination, but initial stages may not present such alterations. Functional findings, usually indicating frontal hypoperfusion (Diehl et al., 2004), may be ambiguous, since they can overlap with other conditions (Soderstrom et al., 2002) but can help diagnosis in very initial stages of disease, when structural imaging is still normal, as a confirmation of a clinical diagnosis already based on the behavior and symptoms. For these reasons, some clinicians rely more on functional findings, while others seek the more concrete data of structural imaging.

2.10.1 The development of the most frequently used structural imaging tools

Imaging studies have evolved very rapidly in recent years, particularly as a consequence of the growing precision and complexity of the software used in processing the source images. Before the late ‘70s there was no mention about volumetric measures on brain imaging scans of any kind. However, in 1975, the first report appeared highlighting the utility of CT (computerized tomography) scans in separating dementia cases from possibly reversible causes of cognitive impairment (Fox et al., 1975). In 1985 tracing of regions of interest and computation of their volume was used in order to define normal morphology in CT scans (Thompson et al., 1985). In the same years, the first evidence of clinical utility of MR imaging for cerebral disease was described (Huk et al., 1984). Pioneer studies using automated procedures to extract volumes from imaging scans emerged in the ‘80s (Bloch et al., 1986), and at the end of that decade a volumetric MR study of the temporal lobe in normal subjects was published (Jack et al., 1988). In 1989, the first volumetric rendering for MR images was developed, that could segment brain tissue, and display it on three-dimensional views of brain structures as well as modern software do (Rusinek et al., 1989). With aid of a phantom, the accuracy of

measurements was repeatedly tested, and in 1990 the first group of AD patients was assessed (Ashtary et al, 1990). Immediately after that, a stereotaxic method for MR images was devised to simulate surgical procedures beforehand, allowing positioning with a precision of 1 millimeter (Derosier et al., 1991), and in 1994 the Talairach space was used to try find an unambiguous membership of each 3D point to a brain structure (Collins et al., 1994). During those years, researchers handled the problem of warping the individual brains in order to fit an ideal model, so that comparisons between different individuals could be carried out by limiting individual variance (Mazziotta et al., 1991). When the first voxel-based techniques were developed (Wright et al., 1995), software was already available capable of generating parametric images representing the distribution of different elements in histological section (Albe et al., 1985) and this could be used in comparing MRI scans. At present, the statistic parametric mapping (SPM) is widely used to compare volumes in groups of individuals. A recent advance in this approach has permitted non parametric comparison based on Bayesian a priory probability (SPM2).

Different characteristics of MR imaging can be used for rather heterogenic aims, from visualization of function –contrary to the typical use of this technique- (Belliveau et al., 1991) to identification of the connection fibers (Wolff and Balaban, 1989), depending on which physical property of the brain matter one wishes to evaluate. While this last technique has never been used in FTD studies, an activation study using functional MRI recently demonstrated reduced frontal activation in these patients (Rombouts et al., 2003).

2.10.2 Structural MRI studies in FTD

Regional atrophy detected with magnetic resonance imaging (MRI) can be considered as a biological *marker* of degenerative diseases. In AD, accurate volumetric measurements have indicated that atrophy in the medial temporal lobe can be detected early in the disease course and this has been proposed as being a diagnostic indicator (Jack et al., 1992). On the contrary, atrophy in the frontal and temporal lobes in FTD is a more controversial diagnostic marker for many reasons. First, different studies have

provided contrasting results. Some have found frontal and asymmetrical atrophy in FTD patients (Miller et al., 1999; Duara et al., 1999) while others could not find any evidence for frontal and temporal atrophy in small series of typical and very early FTD patients (Hokoishi et al., 1999; Gregory et al., 1999). Second, most studies either did not compare atrophy in FTD patients to that of controls or other types of dementia (Miller et al., 1999; Gregory et al., 1999), or else gave only visual subjective ratings of the extent of atrophy (Miller et al., 1999; Gregory et al., 1999; Larsson et al., 2000). Unexpected results derived from the comparison of very typical ROIs that might separate different conditions such as AD and FTD: the volumes of hippocampus and entorhinal cortex in AD and FTD were measured, but these volumes had good discriminative power only for AD *versus* controls (Frisoni et al., 1999). The failure of this strategy, that was aimed at measuring structures considered to be severely involved in AD and not crucially damaged in FTD, suggested that a *pattern of atrophy* in different regions, rather than the amount of atrophy in a single region, could be more informative in the differential diagnostic process. The first authors who used the "pattern" approach to characterize different diseases successfully separated dementia with Lewy body (DLB), AD, and vascular dementia (Barber et al., 2000), and postmortem volumes of progressive supranuclear palsy (PSP), Parkinson's disease (PD) and DLB (Cordato et al., 2000). In the first study, MRI scans were quantitatively compared indicating a different distribution of atrophy through the ventricles, frontal and temporal lobes, hippocampus and amygdala. The relative preservation of frontal lobes was constant in the three diagnostic conditions, which were separated mainly by the medial temporal volumes, that showed severe atrophy in AD, a tendency towards atrophy in vascular disease and very mild involvement in dementia with Lewy Bodies. In the second study, postmortem measures were taken from whole gray and white matter, lobar cortices, medial temporal structures, basal ganglia and thalamus, and indicated very severe involvement of globus pallidus and amygdala in PSP, and, to a lesser degree, of frontal and parietal cortices. Together with the finding of relative preservation of hippocampus, the whole pattern helped distinguish PSP from DLB, where this structure was involved, while the globus pallidus was not affected. The whole pattern was, again, distinct in PD, where only the medial temporal structures, and particularly the amygdala, revealed significant atrophy (Table 1).

Table 1. Brain volumes in different kinds of dementia.

Volumes at MRI	DLB	AD	VaD		Volumes at autopsy	PSP	PD	DLB
Whole brain	n.s	↓	↓		Whole gray matter	↓	n.s.	n.s.
Ventricles	↑	↑	↑		Internal globus pallidus	↓↓	n.s.	n.s.
Frontal cortex	n.s	n.s	n.s		Frontal cortex	↓↓	n.s.	↓↓
Temporal cortex	↓	↓	↓		Parietal cortex	↓	n.s.	n.s.
Hippocampus	↓	↓↓	↓		Hippocampus	↓	n.s.	↓↓
Amygdala	n.s	↓↓	↓		Amygdala	↓↓	↓↓	↓

Modified from Barber et al., 2000 and from Cordato et al., 2000

These works suggested that the pattern of atrophy might be more informative and discriminative between the different diseases and be superior to the single region approach, since atrophy of single regions may overlap in the different diagnostic groups.

Some authors have studied the pattern of atrophy in FTD patients but have not investigated its discriminative power from other types of dementia (Fukui and Kertesz, 2000; Kitagaki et al., 1998) and others claimed that they could not obtain a good discriminative power (Frisoni et al., 1999). MRI-based measures of lobar volumes of FTD, primary progressive aphasia and AD patients were compared, and the right and left frontal volumes provided a correct classification of 93% of FTD and primary progressive aphasia patients, but specificity versus AD patients was not reported (Fukui and Kertesz, 2000).

Table 2: MR Imaging morphometric studies on FTD.

Author	Year of publication	Structure of interest	Method of analysis		Atrophic structures	Other studied characteristics
Williams et al.	2005	whole GM	VBM		anterior temporal lobes subcallosal gyrus,dorso-mesial PFC,paracingulate region	Semantic knowledge Aberrant behavior
Rankin et al.	2004	OFC amygdala	ROI tracing		(correlation study)	Agreeableness
McMillan et al.	2004	Whole GM	VBM		Left temporal lobe	Confrontation naming
Liu et al.	2004	PFC, VMFC, anterior temporal lobe, amygdala	ROI tracing		PFC, VMFC	Aberrant behavior
Gee et al	2003	Whole GM	VBM		Left temporal lobe Left frontal lobe	Naming
Simons et al.	2002	hippocampus	ROI tracing		hippocampus	Recollection based memory
Rosen et al.	2002b	PFC, OFC, ATC, amygdala	ROI tracing		ATC, amygdala, OFC	Emotion comprehension
Rosen et al.	2002a	Whole GM	VBM		Anterior Cingulate, OFC, anterior insula	-
Chan et al.	2001	Whole GM	BBSI		PFC	Rate of atrophy
Fukui et al.	2000	Lobes and basal ganglia	Semiautomated ROI segmentation		Frontal lobe	Neuropsychological functions
Laakso et al.	2000	Hippocampus, entorhinal cortex	Manual ROI tacing		Anterior hippocampus, entorhinal cortex	Topographic distribution of atrophy within the atrophic structure
Frisoni et al.	1999	Hippocampus and entorhinal cortex	Manual ROI tracing		Hippocampus, entorhinal cortex	-
Kitagaki et al.	1998	Whole cortical surface	Automated ROI segmentation		PFC, AT, and whole cortex	Asymmetry of atrophy
Kaufer et al.	1997	Corpus callosum and pericallosum regions	Semiautomated ROI tracing		Anterior corpus callosum	MMSE

Overall, imaging studies on FTD have the main gap of focusing attention on single regions of interest that turn out to be of little help in discriminative diagnosis and pathogenesis comprehension, with few exceptions. These exceptions, on the other hand, did not investigate the discriminative power of such findings in the differential diagnosis with other kinds of dementias, mainly AD. As well, the comprehension of the pathogenesis of FTD and the origin of its symptoms is far from exhaustive. Finalized researches seeking the origins of individual symptoms, or of the whole syndrome, are lacking in the literature.

As well, other minor aspects were disregarded or corresponded to contrasting results. For example, the distribution of atrophy among the right and left hemispheres was variably described in different studies, that analyzed different samples or used different techniques (i.e. volumes or perfusion). Another aspect is the representation of the ε4 allele of APOE: among the contrasting results about the allelic frequency, studies investigating its role in the clinical or morphological expression of the disease are lacking.

3. AIMS OF THE STUDY

This study was undertaken when no voxel-based morphometry (VBM) studies on FTD were available. The few morphometric works had been carried out with manual or, at best, semiautomated techniques. Regions of interest were those in common with AD, chosen in order to try discriminate FTD from this condition. Unfortunately, a similar, although less severe, distribution of atrophy in these regions is present also in FTD, preventing one from making an accurate discrimination of the different dementias based on these biological markers. Studies that considered regions outside the medial temporal, (i.e. the corpus callosum, or the hemispheric surface) only provided confirmation of the "anterior" atrophy already known to characterize FTD (Table 2).

Given the relatively paucity of quantitative data on structural imaging in FTD, the poor discriminative power of these data in the separation of FTD and AD, and the poverty of comprehension of the pathogenesis of the disease, this study was designed with the aim of deepening the knowledge of quantitative brain morphology with the first purpose of improving differential diagnosis with AD and other forms of degenerative dementias (study I). As noted above, the failure of studies examining single, although highly characterizing, regions of interest motivated us to change the strategy, and to adopt a "pattern" approach similar to those described in Study I, first used by Barber and Cordato. This kind of approach is aimed at finding more informative and discriminative biological markers, and, eventually, at tracking networks that could account for the complex and contradictory clinical picture of FTD.

Indeed, in addition to this diagnostic aim, a deeper insight into the neurological mechanisms underlying symptoms and neuropathology was sought. The counterintuitive data about behavioral symptoms motivated us to investigate the pathogenesis of the disease starting from the examination of key structures, for example the amygdala. In fact, Klüver-Bucy-like symptoms are mainly found in FTD, but amygdaloid atrophy was demonstrated, and considered rather typical of AD. The availability of techniques for manual tracing allowed us to investigate with good precision this aspect, and the results hinted at the disruption of a more complex circuit (Study II). Again, as in the case of the "pattern" approach, data derived from single structures attempt to associate function to activity in single structures, and equally

dysfunction to involvement of the "correspondent" structures. This way of interpreting functions and dysfunction is limited, and probably not true for complex cognitive functions. This problem has been partially overcome by the availability of new methods such as voxel based morphometry (VBM), allowing the investigators to compare at the same time all gray matter structures of groups of patients and controls, without pre-selection of regions of interest that might preclude unexpected findings. The search for the involvement of a specific neural system, allowed by this technique, was motivated by the above imaging studies, and by the most recent data on neuropsychological and clinical performance of FTD patients (see section 2), that show apparently contradictory data such as only minor impairment in some frontal tests but severe behavioral inadequacy in their environment (study V).

In addition to the studies aimed at defining which structures were involved in FTD, the characterization of the distribution of atrophy between the hemispheres and the impact of the APOE ε4 allele in FTD were investigated. With respect to distribution of atrophy, much has been written about mainly left or mainly right distribution in patients where language or behavior were, respectively, preferentially involved (Study III). Our data, mainly addressing a degree of asymmetry in the distribution of atrophy, also pointed to an influence of the APOE genotype. The ε4 allele of APOE is more frequent in FTD patients than in the normal population (Stevens et al., 1997), but it is not recognized as a risk factor for this condition. This observation, together with the knowledge that this kind of genotype seemed to impact on the distribution of atrophy, motivated us to investigate how the APOE ε4 allele modulates the morphologic phenotype of FTD (study IV).

4. MATERIALS AND METHODS

4.1 Subjects

The original dataset including the patients examined in this work was compounded of a total of 91 subjects (Frisoni et al, 1996): 14 patients with diagnosis of FTD, 46 with AD (33 with mild, 13 with moderate severity), and 31 normal controls. The number of patients (mainly AD, but also 4 controls and 1 FTD) was further reduced, for technical reasons (impossibility to transfer images from the optic disk to the CD). Moreover, 3 FTD patients were not confirmed at follow-up evaluation (two were diagnosed as PPA, one displayed no deterioration over 3 years). As well, one control subject developed multi-system atrophy and was therefore excluded from subsequent analyses. In the course of study III, one FTD patient was observed to have an abnormal proportion of cerebral lobes and ventricles: this patient, included in the first studies, was excluded from the last ones, being considered as a morphological outlier, and study III initially considered 10 patients, but due to volumetric values of this study finally included only the other 9. The final numbers of our experimental groups were: 9 FTD (10 in studies I and II), 27 AD, 27 controls (26 in studies IV and V, because of the case who developed multiple-system atrophy). Availability of genotype information further reduced numbers in study IV.

The demented were outpatients at the Alzheimer's Unit, Brescia, Italy. Routine dementia assessment and work-up were carried out in all patients. History was taken from a knowledgeable informant (usually the patient's spouse), and was particularly focused on those symptoms that might help in the diagnostic differentiation of the dementia forms (implicit and explicit memory, language and executive functions, behavioral disturbances, disability in daily activities, hallucinations and other psychiatric symptoms, and falls). Laboratory studies included complete blood count, chemistry profile, chest x-ray, thyroid function, B_{12} and folic acid, electrocardiography, electroencephalography, and computed tomography scan. The neurological examination (including elicitation of primitive reflexes such as grasping, sucking, palmomental, and snout) was performed by a neurologist, and the physical examination by a geriatrician. A comprehensive neuropsychological battery taking about 90 minutes on average was

part of the routine assessment and included verbal and non-verbal memory, language and comprehension, limb praxis, visuo-spatial functions, frontal functions (Frisoni et al., 1996). Individual tests that could not be carried out in those patients with more severe cognitive or linguistic impairment were not administered. However, all patients were able to complete at least 50% of the tests in the battery.

In the original series (Frisoni et al., 1996), the diagnosis of FTD was made on clinical grounds based on pathologically verified clinical descriptions (Gustafson et al., 1987) and guidelines (the Lund and Manchester criteria) available at that time (Lund and Manchester groups, 1994; Miller et al, 1997). Behavioral aberrations were considered in relation to the diagnostic profile, but were not systematically recorded. After clinical evaluation, patients underwent single photon emission tomography (SPET) with HM-PAO. All patients who satisfied the criteria for FTD before SPET imaging also showed anterior frontal or anterior temporal hypoperfusion (Frisoni et al., 1995). Thus, in the present study anterior hypoperfusion on SPET was confirmatory of a diagnosis independently made on clinical grounds. Moreover, the diagnosis of FTD was supported by the follow-up evaluations, carried out from a minimum of eight months to a maximum of three years. After excluding two patients with progressive aphasia in the absence of other cognitive and behavioral disturbances, one who displayed no deterioration in three years and the subjects from whom compatible data for volumetric analysis were not available, 10 FTD subjects remained. These were retrospectively assessed and judged to fulfill the recently published criteria for the diagnosis of frontotemporal lobar degeneration (Neary et al., 1998) of FTD type, representing a rather homogenous clinical phenotype. In the course of the present study, one more subject was excluded as a morphological outlier after the individual analysis of each pattern of brain volumes, which revealed an abnormal lobar proportion in this subject. Of the remaining patients, information about APOE was available from eight.

AD patients fulfilled NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). None of them had clinical features suggestive of dementia with Lewy Bodies (DLB), such as hallucinations, parkinsonism, sensitivity to neuroleptic medication, fluctuations, and falls.

The vascular component for all the subjects was excluded on the basis of clinical assessment, computed tomography and MRI.

Although a formal behavioral assessment was not carried out in all patients at the time of MRI imaging, the Neuropsychiatric Inventory was administered to some patients at a later time (Rozzini et al., 1997), showing that FTD and AD patients had distinct behavioral profiles that were consistent with recent descriptions (Miller et al., 1997). The Italian version of the Mini-Mental State Examination (MMSE) was used to assess cognition (Magni et al., 1996). Of the original 46 AD patients, 27 had MRI images suitable for volumetric analyses of the present study, and 25 had information about APOE.

For all patients, disease duration was computed from the estimated onset to the date of MRI imaging. The estimated onset was assessed from informants and defined as the time of the first appearance of memory, behavioral, language, or other symptoms that could be due to the degenerative brain disease. Overall dementia severity was assessed with the Clinical Dementia Rating scale (CDR) (Huges et al., 1982), which combines information on memory disturbances and daily function. Information on basic (bathing, dressing, grooming, walking, feeding, continence) and instrumental (using the telephone, shopping, cooking, doing housework, doing laundry, using public transportation, taking medications, and handling finances) activities of daily living was taken from a proxy informant.

Controls were patients' relatives (mostly spouses) who themselves had no detectable cognitive deficit. They had a negative history of neurological disease, though some reported mild subjective memory problems which did not result in impairment of daily activities. All had MMSE administered, and were judged not to be demented by a neurologist and a psychologist involved in the evaluation of the patients. Of the original 31 controls, 27 had MRI images suitable for volumetric analyses. During the course of this study, one developed multi-system atrophy and was excluded from subsequent analyses, that were thus carried out with 26 controls.

Apolipoprotein E phenotyping was performed on patients and controls with isoelectric focusing on delipidated plasma samples (Kohlmeier et al., 1992).

Written informed consent was obtained from both cases and controls or their primary caregivers, after discussion of risks and benefits of participation. No compensation was provided. The study was approved by the local ethics committee.

Although the patients groups were the same throughout the whole research project, some differences in patient selection occurred in each individual study, due to methodological needs.

In Study III, the analysis of the individual patterns of atrophy revealed a very anomalous morphology of one FTD patient, who had abnormal lobar and ventricular proportions compared to controls. This subject was considered as a "morphological outlier", and therefore excluded from all subsequent analyses.

In Study IV, patient selection was obviously conditioned by the absence of missing values for the APOE genotype. Moreover, AD patients were selected based on age at onset, since there are data (Farrer et al., 1997) indicating that APOE genotype does not have any important impact when the disease occurs at a very early or very late age.

4.2 Brain measurements

MRI was performed in the Radiology Department, University of Verona with a 1.5 Tesla unit (Siemens, Magnetom) and a standard head coil. A gradient-echo 3D-technique was employed for image acquisition with: TR 10 msec; TE 4 msec; TI 300 msec; flip angle 10°; field of view 250 mm; acquisition 2; matrix 160×256. Total acquisition time was 7:40 minutes.

Brain measurements were carried out with traditional ROI-based methods, in a manual or semi-automated way, and with voxel by voxel comparisons (voxel based morphometry, VBM), a recent technique that requires sophisticated preprocessing by expert operators, but allows completely automatic comparisons between groups.

4.2.1 ROI-based morphometry

In order to carry out traditional volumetric analyses, images were transferred to a standard work consolle for manual tracing or to a Sun workstation (Sun Microsystem Inc., Mountain View, CA) for the semiautomated procedure, reassembled in order to reconstruct a 3D brain, aligned on the 3 dimensions in order to correct for tilting, and resliced into coronal slices 2 mm thick perpendicular to the AC-PC plane.

Alignment on the coronal plane was made on a slice where the sylvian aqueduct could be appreciated in its maximum length: a straight line was drawn from the lower wedge of the falx cerebri, to the lower visible point of the sylvian aqueduct. Alignment on the axial plane was done on a slice at the level of the lateral ventricles, where the anterior and posterior wedges of the falx cerebri were definite and symmetric: a straight line was drawn from the anterior to the posterior wedge of the falx cerebri. Alignment on the sagittal plane was conducted on the mid-sagittal slice, where the genu of the corpus callosum could be appreciated: a straight line was drawn from the point of convergence of the fornices to the lower margin of the superior culliculum.

Traditional volumetric techniques then require an expert operator to select the regions of interest (ROIs) and trace their exact boundary (manual tracing) or a wide boundary containing the ROI (semiautomatic thresholding). The tracings are made on each slice where the target structure is visible, and their area is summed up and multiplied by slice thickness in order to compute the volume of the whole structure.

As a measure of head size, we used the intracranial area (ICA), measured on a coronal section at the level of the anterior commissure and expressed in cm^2. ICA was used to normalize brain volumes.

Volumes of interest in this work were the frontal brain, frontal horns, temporal brain, temporal horns, and hippocampus and amygdalae. The right and left sides of these structures were measured and considered separately.

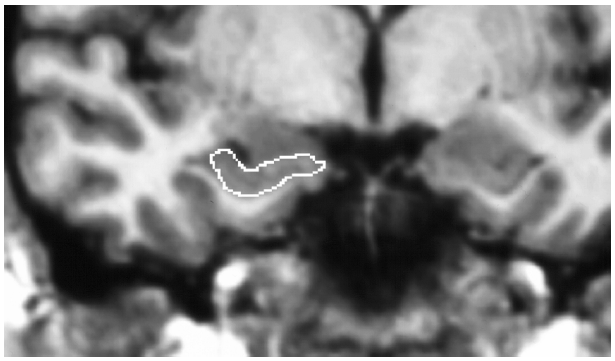
4.2.1.1 Manual tracing

Hippocampus. The hippocampus and amygdala were manually traced by expert operators following the visible boundaries on each slice where the structure appeared.

In particular, the ROIs for the hippocampus were traced following a standardized and validated protocol. (Laakso et al., 1996) The volume of the hippocampus (considered as dentate gyrus, hippocampus proper, and the subicular complex) was measured starting from its appearance below the amygdala. The uncal portion of the rostral hippocampus that is located ventral to the caudal amygdala was included into the hippocampus. The tracing ended posteriorly in the section where the crura of the fornices depart from the

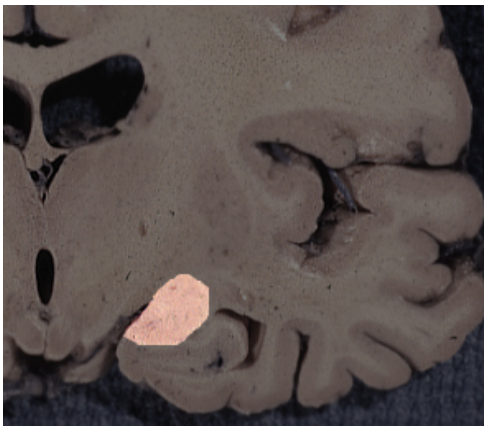
lateral wall of the lateral ventricles. Intraclass correlation coefficients for hippocampal measurements were 0.95 for intra-rater and 0.90 for inter-rater variability.

Figure 1.
Manual tracing
of the hippocampus



Amygdala. Volumes of the amygdalae were traced from where the amygdala forms the typical bulk in the medial temporal lobe. The tracing continued to the posterior by avoiding the hippocampus and the rhinal cortices until the disappearance of the amygdala above the hippocampus. The intraclass correlation coefficient for intra-rater reliability was 0.93.

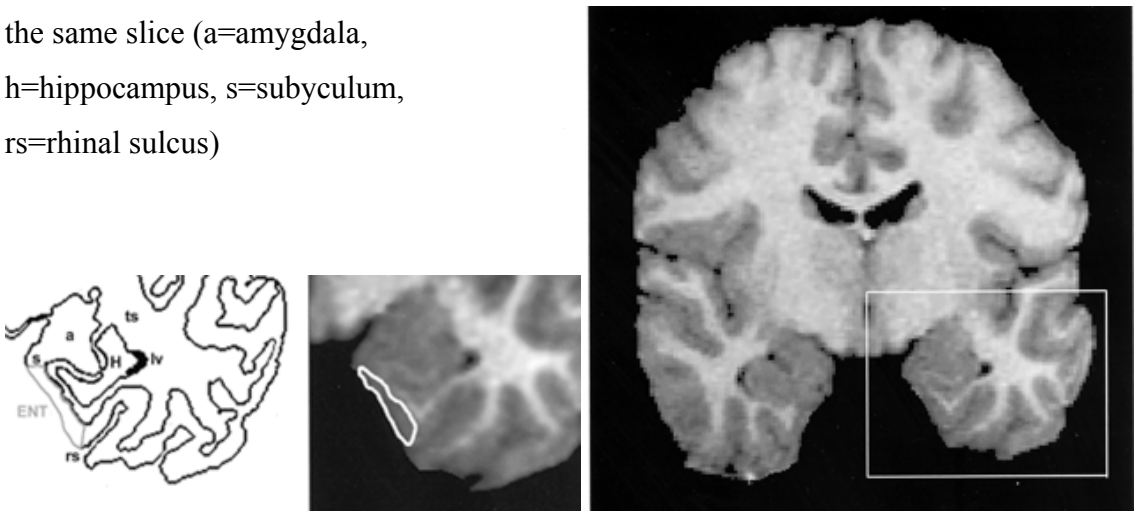
Figure 2. Location of the amygdala
above the hippocampus.



Entorhinal cortex. The entorhinal volumes were traced according to the criteria by Insausti et al. (Insausti et al., 1998). The first slice measured was the one after the appearance of the limen insula when the temporal lobe can be first appreciated to be attached to the rest of the brain when proceeding from anterior, and the last slice was the one where the uncus and gyrus intralimbicus could no longer be appreciated. The

intraclass correlation coefficient for intrarater reliability for entorhinal volumes was 0.90.

Figure 3. Manual tracing of the entorhinal cortex (ENT), and its location relative to other brain structures visible in the same slice (a=amygdala, h=hippocampus, s=subyculum, rs=rhinal sulcus)



4.2.1.2 Semiautomatic thresholding

MRI images were analyzed with the software QUANTA (DeCarli etal., 1992). This combines manual tracing of a crudely defined region of interest (ROI) – completely comprising the structure to be measured – with an automatic thresholding procedure separating cerebrospinal fluid (CSF) from brain pixels.

The segmentation of brain from non-brain tissue was carried out through several phases: histogram representation of pixels distribution (based on color gradients), gaussian modeling of the pixel distribution separately for CSF and brain pixels, and identification of the optimal cutoff to separate CSF from brain pixels on the basis of maximum likelihood functions (DeCarli et al., 1992). When the distribution of pixels was such that two separate gaussian functions could not be identified, the threshold was set manually in the graph representing the pixel distribution. This occurred only in the anteriormost ROIs of the frontal and temporal brain, comprising a relatively low number of pixels.

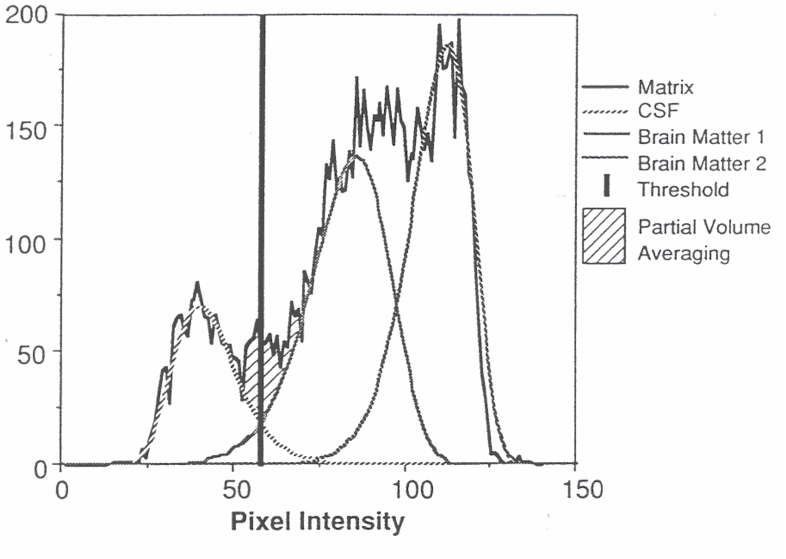
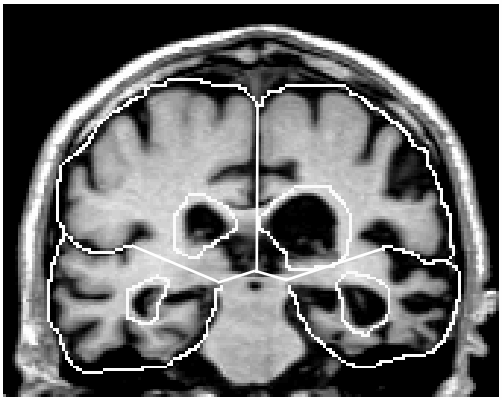


Figure 4:
Gaussian modeling of the pixel distribution separately for CSF and brain pixels, and identification of the optimal cutoff to separate CSF from brain pixels on the basis of maximum likelihood functions.

Tracing of the regions of interest. Tracing of ROIs was made on aligned coronal slices proceeding from anterior to posterior. The first ROIs, both for the frontal and temporal lobes, were traced on the slices where the brain matter could initially be appreciated, and the last ROIs on the slice where the sylvian acqueduct appeared.

Figure 5: Tracing of the frontal and temporal lobes and horns for the semiautomated thresholding procedure.



4.2.2 Voxel by voxel brain measurements

In the VBM method, the brains of groups of subjects are modified in a preprocessing phase, in order to fit a reference template, such that a stereotactic point refers to the same structure in each normalized brain. Then automatic statistical analyses are carried out, that compare the concentration of gray matter in each voxel.

4.2.2.1 Preprocessing

After removing the voxels below the cerebellum with MRIcro (www.psychology.nottingham.ac.uk/staff/cr1/mricro.html), MRI scans were analysed with SPM99 (www.fil.ion.ucl.ac.uk/spm) running under Matlab 6.0 (Mathworks, Sherborn, MA, USA) on a Sun Sparc Ultra 30 workstation (Sun Microsystem Inc., Mountain View, CA). The following pre-processing was carried out: creation of a gray matter template, normalization of the gray matter to the template, and smoothing. A complete description of the pre-processing procedures can be found elsewhere (Ashburner et al., 2000). Gray matter template. This is made through creation of a customized template of the whole brain, normalization of the original images to the template, extraction of the gray matter, and averaging. The customized template of the whole brain was obtained through normalization of the images of controls to the T1-stereotactic template of SPM99 (Evans et al., 1994) using a 12-parameter affine

transformation followed by averaging of the normalized images. Then, the anterior commissure was identified and defined as the origin of the spatial coordinates (Ashburner et al., 1997).

The normalization of the original images to the template was obtained through a 12-parameter affine transformation. The gray matter of controls was then extracted through segmentation of images into gray matter, white matter, and CSF with a modified mixture model cluster algorithm and averaged thus obtaining a stereotactic customized gray matter template.

Normalization. The gray matter of cases was extracted with the same procedure as described above for controls and together with the gray matter of controls, was normalized onto the gray matter template with affine and non-linear transformations, medium regularization, re-slicing $2 \times 2 \times 2$ mm, and no masking (Baron et al., 2001). The resulting images were visually inspected one by one in order to exclude gross segmentation errors.

Smoothing. The normalized gray matter images were smoothed with an isotropic Gaussian filter of 8 mm.

4.3 Statistical analyses

Statistical analyses were carried out with SPSS (SPSS Inc, Chicaco, IL) for all of the sociodemographic data and those from the manual tracings. For voxel based computations, statistical comparisons were carried out by the SPM99 program.

4.3.1 ROI based volumetry

Due to the low number of subjects of the FTD group, the significance of comparisons among groups was assessed by Mann-Whitney U-test. Significance between proportions was assessed by the Chi-square test. Pearson's correlation coefficients were computed to address the effect of age on brain volumes and asymmetries. The critical level for

statistical significance was set at 0.05 for all tests.

The effect of brain size was controlled by normalizing the volumes of the brain structures of interest by ICA with the formula: (volume/ICA×100). The combined effect of age and brain size was controlled for with a multivariate approach by transforming crude volumes into W-scores according to the formula:

$$W = \frac{\text{(observed value)} - \text{(predicted age- and ICA-specific value in controls)}}{\text{standard deviation of residuals in controls}}$$

where age- and ICA-specific values and residuals (the distance of each value from the regression line) in controls are computed by linear regression analysis (Jack et al., 1997) carried out on the 27 controls' volumes of interest. W-scores are thus the distance in standard deviation units of an observed value from the expected age- and ICA-specific value.

Brain asymmetry in the structures of interest was defined as the ratio of the right to the left crude value. For the effect of gender on brain asymmetry (Coffey et al., 1998), variables of asymmetry were expressed in age- and gender-specific W-scores (for the definition of asymmetry, correcting for ICA is superfluous). The loss of brain tissue was computed for both normalized volumes and W-scores and defined as the percent change with respect to mean control values (set at 100).

In order to test the ability of atrophy variables to separate FTD from AD patients, multivariate discriminant analysis was used. This technique minimizes the overlap between the two groups by computing a multivariate function that allows a score (discriminant score) to be computed for each subject. The discriminant scores are such that they separate the two groups with the smallest possible overlapping, resulting in maximal overall sensitivity and specificity.

Measures of atrophy expressed as W-scores contributing to the separation of the groups were assessed in discriminant models in two ways. The first approach (exploratory) consisted in building models with a priori selection of variables, chosen on the basis of clinical plausibility. The second approach (algorithmic) consisted of testing the independent contribution of each variable in the separation of FTD from AD through a

stepwise selection algorithm. This enters into the model the variables that contribute (based on the smallest Wilks' λ of the discriminant function, and on F-to-enter for Wilks' λ greater than 3.0), and excludes those variables that do not contribute to separating the groups (based on F-to-remove values for Wilks' λ lower than 2.0). Likelihood ratios (LR) (Simel et al., 1993) computed as sensitivity/(1-specificity) and 95% confidence intervals (CI) (Simel et al, 1991) are provided for each discriminant model. CI were computed with the logarithmic method (Gardner et al., 1989).
For the more specific analysis of symmetry of atrophy in FTD, symmetry of the frontotemporal atrophy was operationalized as the difference between right and left W-scores lower than 1 both in the frontal regions (mean between brain and horns) and in the temporal regions (brain and horns).

$$\frac{\Delta FB + \Delta FH}{2} < 1 \text{ AND } \frac{\Delta TB + \Delta TH}{2} < 1$$

where Δ indicates the difference between right and left.

If the patient had a difference higher than 1 (mean between brain and horn) in the frontal or in the temporal lobe, the patient was classified as being asymmetric.

4.3.2 VBM

In the comparisons carried out with the SPM99 program, the "Compare populations – AnCova" procedure was used to compare the gray matter concentration between cases and controls, and statistical significance was set at $p<0.05$ corrected for multiple comparisons. Age was used as a covariate.

In the VBM comparisons, patients carrying the ε4 allele *versus* the non carriers, the "Single Subjects – Conditions and Covariates" procedure was used to compare the gray matter concentration between carriers and non carriers. The regions specifically

atrophic in patients carrying and not carrying the ε4 allele were detected by contrasting all patients to controls and inclusively masking atrophy of the carriers relative to that of the non carriers and *vice versa.* Statistical significance was set at $p<0.05$ corrected for multiple comparisons. Age and sex were used as nuisance variables for all subjects. In FTD, the MMSE score was also entered as a nuisance variable in order to correct for the different cognitive level that was found between carriers of the ε4 allele and the non-carriers.

5. RESULTS

5.1 Clinical and sociodemographic features of patients and controls.

FTD were relatively younger and more often men than AD patients and controls (Table 3). Overall, dementia severity was similar between FTD and AD patients. Although FTD patients scored 4 points lower than AD patients on the MMSE, global severity of dementia and functional impairment were not different. Language disturbances were more frequent and severe in FTD (50 vs. 4%), and the difference in the MMSE was interpreted as being a consequence of this difference (Frisoni et al., 1999). The frequency of the ε4 allele in FTD was intermediate between that of AD patients and controls. Brain size was smaller in AD patients.

The same pattern of differences was found in all of the five studies, although the number of subjects differed slightly due to methodological reasons (see methods).

Cognitive performance as measured at neuropsychological tests was not a final objective of these studies, rather it had been considered during the diagnostic process. Anyway, FTD patients showed, besides the fall in performance at classical frontal tests (WCST, verbal fluency, etc.), a pattern of selectively preserved memory compared to AD, and had better performance at logical and verbal memory. Performance at Rey's figure trials showed lower performance at the copying task, but better performance in the recall task (Frisoni et al, 1996). Topographic disorientation was entirely absent in the FTD group, while the linguistic function displayed impairment in FTD, and was almost intact in AD. Recording of aberrant behavior or altered dietary habits had double

frequency compared to AD (Frisoni et al, 1999).

Table 3. Clinical and demographic features of patients and controls as in study I.

	FTD		AD		Controls	
	n=10		n=27		n=27	
Age, years	63 (5) *		73 (9) †		70 (8) †	
Sex, men	7 (70%) *		5 (19%) †		10 (37%) †	
Education, years	7 (4)		7 (4)		8 (3)	
Disease duration, months	30 (14)		42 (26)		-	
Mini-Mental State Examination	16 (9) *		20 (4) *		29 (1) †	
Clinical dementia rating						
0	0	*	0	*	27 (100%)	†
0.5	4 (40%)		8 (30%)		0	
1	2 (20%)		11 (40%)		0	
2-3	4 (40%)		8 (30%)		0	
Instrumental Activities of Daily Living, n. of functions lost	3.0 (2.4)		3.7 (2.4)		-	
ApoE ε4, n/total alleles §	3/18 (17%)		18/50 (36%) *		5/50 (10%) †	
Intracranial area, cm²	174 (11) †		162 (11) *		169 (13) †	

Values denote mean (standard deviation) or number (percentage).
* † ¶ groups with different marks are significantly different on Mann-Whitney or χ^2 tests. No marks denotes no difference between groups.
§ ApoE phenotyping was performed in 9 subjects with FTD, 25 with AD, and 25 controls.

5.2 The pattern of atrophy as a biological marker (Study I)

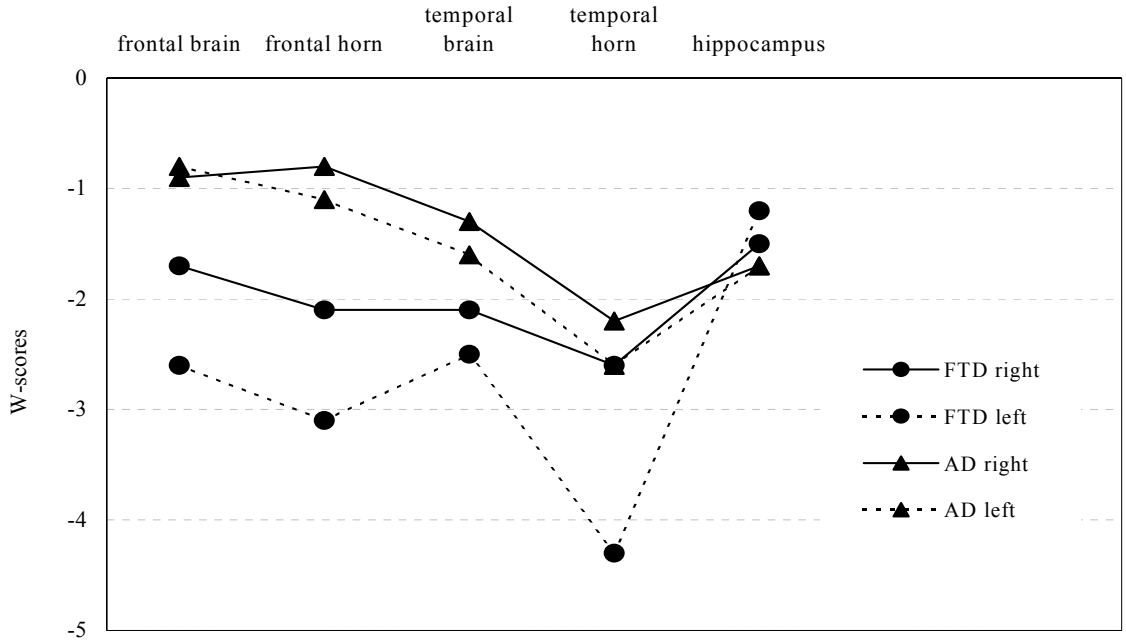
The research question in this study consisted in defining the pattern of volumes of a set of key structures rather than of a single structure, that could have a satisfying discriminative power in the separation of FTD and AD.

When the effect of age (younger in FTD) was taken into account with the computation of W-scores, atrophy in the left frontal regions was found to be greater in FTD than in AD patients. The difference was more marked in the left frontal horn (p=0.008 on

Mann-Whitney test) than brain matter (p=0.01). A non-significant tendency for more atrophic temporal brain matter and larger temporal horns was found in FTD compared to AD, but only approached statistical significance in the right temporal brain (W-scores of –2.1 and –1.3, p=0.07) (Table 4).

The low power of the volumes of single brain structures in the discrimination between AD and FTD lead us to consider a more complex pattern including a group of relevant structures rather than one single structure.

Figure 6. Pattern of atrophy in AD and FTD



Within each diagnostic group, atrophy was distributed differently across regions (Figure 6). In FTD patients, the regions showing the overall greatest atrophy were the temporal regions (average W-scores across right and left brain and horns: -2.9, SD 2.4), mildly less atrophic were the frontal regions (-2.4, SD 2.1), while the hippocampi showed the least atrophy (average W-scores across right and left hippocampi: -1.3, SD 1.5). The atrophy profile of AD patients was different in that the most atrophic regions were the temporal (-1.9, SD 1.8) and the hippocampi (-1.8, SD 0.9), while relatively less atrophic

were the frontal regions (-0.9, SD 1.5). In both the frontal and temporal regions, the most accurate markers of atrophy were the ventricle horns.

5.2.1 Correlation of atrophic regions with cognitive function

The regions more strongly associated with disease severity (as indicated by the MMSE) in FTD were the left temporal and frontal brain ($r=0.71$, $p=0.02$, and $r=0.60$, $p=0.06$) whereas in AD it was the right temporal horn ($r=0.38$, $p=0.05$).

Table 4. Regional brain measures of frontotemporal dementia (FTD) and Alzheimer's disease (AD) patients and controls.

		Crude values			Normalized for cranial size					Normalized for cranial size and age			
								% diff. from controls				% diff. from controls	
		FTD	AD	controls	FTD	AD	controls	FTD	AD	FTD	AD	FTD	AD
Frontal lobe													
Brain	R	180 (31)	173 (22)	196 (19)	1032 (157) *	1066 (131) *	1160 (108)	11	8	-1.7 (2.0) *	-0.9 (1.2) *	12	7
	L	170 (25)	171 (21)	193 (19)	977 (140) *	1058 (128) *	1143 (112)	14	7	-2.6 (1.9) †	-0.8 (1.2) *	17	6
Horn	R	14.7 (6.4)	13.1 (6.2)	9.1 (5.6)	85 (38) *	80 (39) *	53 (31)	61	52	-2.1 (2.1) *	-0.8 (1.6) *	121	46
	L	17.6 (6.8)	13.3 (6.3)	8.9 (4.4)	102 (41) *	82 (39) *	52 (24)	96	57	-3.1 (2.3) †	-1.1 (1.8) *	182	53
Temporal lobe													
Brain	R	37.3(11.6)	37.5 (6.6)	53.1 (10.4)	213 (62) *	232 (43) *	313 (57)	32	26	-2.1 (1.2) *	-1.3 (0.7) *	35	24
	L	35.6 (10.1)	35.5 (6.5)	46.3 (6.5)	204 (56) *	220 (45) *	273 (29)	25	20	-2.5 (1.9) *	-1.6 (1.4) *	26	19
Horn	R	1.4 (0.9)	1.6 (0.9)	0.7 (0.4)	8 (6) *	10 (5) *	4 (2)	105	141	-2.6 (3.0) *	-2.2 (2.4) *	161	109
	L	1.6 (0.9)	1.3 (0.9)	0.5 (0.4)	9 (5) *	8 (5) *	3 (2)	211	180	-4.3 (3.3) *	-2.6 (2.8) *	316	135
Hippocampus													
	R	1.6 (0.5)	1.3 (0.4)	1.9 (0.4)	9 (3) *	8 (2)*	12 (2)	23	33	-1.5 (1.4) *	-1.7 (0.9) *	25	33
	L	1.5 (0.5)	1.2 (0.3)	1.8 (0.3)	9 (3)	7 (2) †	11 (2)	17	30	-1.2 (1.7) †	-1.9 (0.9) *	18	32

Values denote mean (SD) values of crude volumes (in cm^3), of volumes normalized for cranial size (computed with the formula: volume/ICA*100) (ICA=intracranial area), and of atrophy, corrected for cranial size and age (W-scores). W-scores are age- and head size-specific normalized distances (in standard deviation units) of patients' measures of atrophy from the specific expected value, computed from the distribution of normal controls.
Horns volumes are polarized, so that greater atrophy is denoted by greater negative values in all cases.
* significantly different from controls and † from controls as well as from the other patient group according to Mann-Whitney test.
No mark denotes no difference between groups.
Percent change denotes the difference with controls in normalized values and in age- and head size-specific W-scores. Greater positive values denote greater atrophy in all cases.

5.2.2 Interhemispheric distribution of atrophy in AD and FTD

Figure 6 also shows that atrophy was more asymmetrical in FTD than AD patients throughout all frontal and temporal regions, though this was most evident in the temporal horns. Asymmetry values, indicated by the right/left ratios, of the temporal horns were 0.88 (SD 0.39) in FTD, 1.29 (0.47) in AD, and 1.60 (1.25) in controls, indicating that the left temporal horn was relatively more enlarged in FTD patients than in controls ($p=0.008$), while the difference was not significant between AD patients and controls ($p=0.39$). This asymmetry pattern was even clearer when right/left ratios were expressed in W-scores, allowing us to control for the normal effect of age and gender on asymmetry. W-scores were -1.27 (SD 0.61) in FTD, and 0.05 (0.55) in AD patients. The difference was significant between FTD and controls ($p=0.0002$), non-significant between AD and controls ($p=0.47$), and significant between FTD and AD patients ($p<0.00005$). The W-scores of asymmetry were computed for the other brain regions, indicating overall greater asymmetry with prevalent left atrophy of FTD (absolute values of W-scores ranging between 0.64 and 1.14) vs. AD patients (0.12 to 0.27).

5.2.3 The pattern of atrophy as a discriminating tool in the differential diagnosis from AD

The discriminant exploratory models (Table 5) were built based on the W-scores of single regions (each including brain and horns) and on W-scores of asymmetry in two or more regions. The final exploratory model included the two previous models (the fifth and sixth in Table 5) that best discriminated patients groups, and achieved a sensitivity of 90% and specificity of 93% in the discrimination of FTD from AD. The algorithmic approach selected two variables that separated the two groups with lower sensitivity (80%) but higher specificity (96%).

Table 5. Separation of FTD from AD patients by regional atrophy measures.

Model		Correct classification		
		AD (n=27)	FTD (n=10)	LR (95% CI)
Exploratory	1) RFB, RFH	20 (74%)	5 (50%)	1.9 (0.8 to 4.7)
	2) LFB, LFH	22 (82%)	7 (70%)	3.8 (1.5 to 9.2)
	3) RTB, RTH	18 (67%)	5 (50%)	1.5 (0.7 to 3.4)
	4) LTB, LTH	18 (67%)	6 (60%)	1.8 (0.9 to 3.7)
	5) AsyFB, AsyTB	23 (85%)	8 (80%)	5.4 (2.1 to 14.0)
	6) AsyFH, AsyTH	24 (89%)	8 (80%)	7.2 (2.4 to 21.8)
	7) AsyFH, AsyTH, AsyFB, AsyTB	25 (93%)	9 (90%)	12.1 (3.2 to 46.8)
Algorithmic	AsyTH, RTB	26 (96%)	8 (80%)	21.6 (3.1 to 151.2)

RFB = right frontal brain, LFB = left frontal brain, RFH = right frontal horn, LFH = left frontal horn, RTB = right temporal brain, LTB = left temporal brain, RTH = right temporal horn, LTH = left temporal horn, AsyFB = asymmetry of frontal brain, AsyFH = asymmetry of frontal horns, AsyTB = asymmetry of temporal brain, AsyTH = asymmetry of temporal horns,.
LR: likelihood ratio. CI: confidence interval.
Classification figures were computed with a discriminant function algorithm on the basis of age and head-size specific scores (W-scores, see Table 4).

5.3 Amygdaloid atrophy in FTD and AD (Study II)

Objective of this study consisted in investigating amygdaloid volumes with comparison to both AD and control groups, given the counterintuitive observation that Klüver-Bucy symptoms, known to derive from amygdaloid damage, are more frequently registered in FTD patients rather than in AD, where amygdaloid atrophy has been repeatedly ascertained.

The analysis of the amygdalae in AD and FTD showed that their normalized volumes were different from control values in both demented groups: FTD vs. controls ($p<0.005$), AD vs. controls ($p<0.0005$), but not between the two patient groups ($p>0.15$). However, there was a trend for increasing atrophy from controls, through FTD, to AD (p for trend <0.00005) (Table 6).

The comparisons of the FTD amygdaloid volumes were also carried out without a subject with motor neuron disease, where amygdaloid metabolism was already demonstrated to be lower than in controls (Garraux et al., 1999). Normalized volumes of this subject were 0.726 and 0.632 for right and left amygdala, and the results of comparisons among groups did not change.

5.3.1 A disconnection hypothesis for behavioral symptoms in FTD

As FTD patients are characterized by behavioral disturbances, some of which are typically due to amygdaloid damage, actually more severe in AD, the hypothesis arose that behavioral disturbances require not only amygdaloid damage, but also a disruption of their connection to the frontal lobes, which are functionally associated to the limbic areas, particularly to the amygdala. This disconnection hypothesis was provisionally tested by computing the ratio between the frontal lobes and amygdaloid volumes, and correcting it by age. The W-scores of this ratio ($W=0.6 \pm 1.4$ *versus* 2.1 ± 2.0; $p=0.04$) indicated larger frontal relative to amygdaloid volume in AD patients, which is compatible with the hypothesis of a greater preservation of the fronto-limbic circuitry helping control of this kind of behavior in these patients.

Table 6. Crude and corrected amygdaloid and frontal volumes

	Amygdalae					
	Crude values, cm^3		Normalized values		Loss, %	
	right	left	right	left	right	left
Controls	1.16 (0.18)	1.11 (0.17)	0.91 (0.13)	0.87 (0.11)	0.0	0.0
FTD	0.96 (0.26)	0.88 (0.19)	* 0.74 (0.21)	* 0.69 (0.16)	18.6	21.6
AD	0.77 (0.17)	0.78 (0.20)	* 0.64 (0.15)	* 0.64 (0.18)	30.2	26.3
	Frontal lobes					
	Crude values, cm^3		Normalized values (W-scores)		Loss, %	
	right	left	right	left	right	left
Controls	196 (19)	193 (19)	Ref (0.0)	Ref (0.0)	0	0
FTD	180 (31)	170 (25)	*-1.7 (2.0)	†-2.6 (1.9)	12	17
AD	172 (23)	170 (21)	*-0.9 (1.2)	*-0.8 (1.2)	7	6

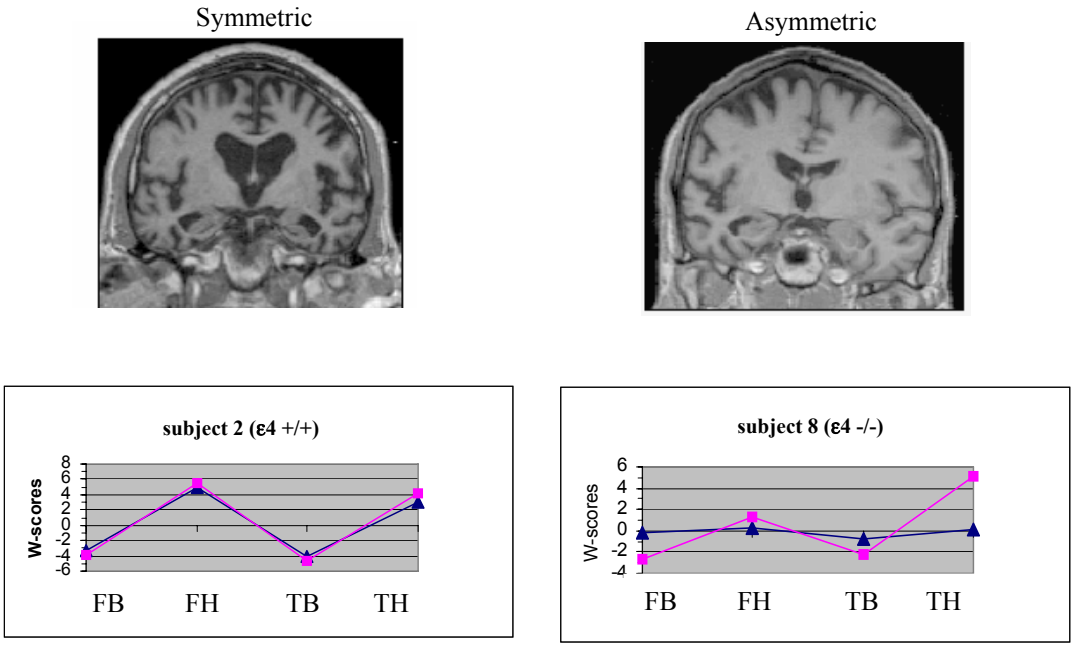
*Difference from the unmarked group on Mann-Whitney U test and † between groups.
Normalized values are volumes corrected for cranial size. Percent loss is computed with respect to the mean normalized volumes of the control subjects. W-scores are obtained by dividing the difference between the observed volume and the expected volumes for a subject of the same age and cranial size by the standard deviation of residuals in controls. Expected values and residuals are computed in controls with a linear regression analysis where age and cranial size are independent variables. By definition, the W-scores of controls are equal to 0 and negative values indicate shrinkage.

5.4 Symmetric versus asymmetric phenotype of FTD (Study III)

Aim of this study was to try identify whether a different distribution of atrophy (symmetrical *versus* asymmetrical), that is variably reported in different studies was associated to clinical or other differences in disease presentation.

Quantification of the symmetry of atrophy distribution distinguished 3 patients with symmetric atrophy and 6 with clearly asymmetric atrophy (Figure 7).

Figure 7. Examples of symmetric and asymmetric patients with frontotemporal dementia.



Upper part: MR scan. Lower part: quantification of atrophy with W-scores (see methods).
FB = frontal brain, FH = frontal horn, TB = temporal brain, TH = temporal horn.
▲= right ■ = left. Negative W-scores indicate shrinkage, positive values indicate enlargement. Note different scales of atrophy.

"Symmetric" patients had greater atrophy in the frontal and temporal regions (Table 7). Moreover, medial temporal atrophy was absent, or rather minor in the asymmetric, and markedly greater in the symmetric patients. The difference between the two groups was close to statistical significance for the hippocampi, and significant for the entorhinal cortex. Global values of frontotemporal, medial temporal and overall atrophy indicate significantly greater atrophy in symmetric patients.

Table 7. Atrophy of frontal, temporal and medial temporal regions in the symmetric and asymmetric groups.

Region		Symmetric n = 3	Asymmetric n = 6	p
Frontal region				
Brain	R	-3.78 (0.47)	-0.91 (1.70)	0.04
	L	-4.09 (0.32)	-2.20 (2.01)	n.s.
Horn*	R	-4.49 (1.33)	-1.41 (1.09)	0.04
	L	-5.03 (0.91)	-2.94 (1.52)	0.07
Temporal region				
Brain	R	-3.82 (0.17)	-1.38 (0.55)	0.02
	L	-4.07 (0.46)	-1.75 (2.11)	n.s.
Horn*	R	-5.43 (2.49)	-1.86 (2.29)	n.s.
	L	-5.22 (2.14)	-4.71 (3.53)	n.s.
Overall fronto-temporal atrophy		**-6.61 (1.05)**	**-2.72 (1.69)**	**0.02**
Medial temporal region				
Hippocampus	R	-2.87 (1.32)	-0.97 (1.18)	0.07
	L	-2.59 (1.83)	-0.82 (1.23)	0.07
Entorhinal cortex	R	-3.18 (0.26)	-0.76 (1.16)	0.02
	L	-2.38 (0.81)	-0.92 (1.03)	0.04
Overall medial temporal atrophy		**-3.46 (1.13)**	**-1.22 (1.16)**	**0.04**
Overall atrophy		**-3.66 (1.11)**	**-1.31 (1.19)**	**0.04**

Values denote mean (SD) values of atrophy expressed as W-scores. Overall values of atrophy are the W-score of the sum of crude right and left frontal and temporal brain and horns (overall frontotemporal), right and left hippocampus and entorhinal cortex (overall medial temporal, and of all brain regions considered in the study (overall atrophy). * Polarized so that negative values indicate atrophy. p = significance in Mann-Whitney test.

5.4.1 Clinical correlates of the symmetric phenotype and putative link with APOE

The patients with a symmetric phenotype, in spite of similar disease duration and clinical severity, had a younger age at onset of disease (53 ± 2.0 vs. 62 ± 2.5, exact p = 0.02), and a higher prevalence of the ε4 allele of the apolipoprotein E (50% vs. 0%, p = 0.02).

5.5 APOE as a modulator of the clinical phenotype of degenerative diseases (Study IV)

In this study, the role of APOE in the disease expression was investigated, after the observation (study III) that FTD patients with symmetrical atrophy have higher representation of the ε4 allele.

5.5.1. Sociodemographic features

In this study, AD patients were selected based on age at onset of dementia, in order to exclude very early and very late age at onset, where the effect of APOE is questionable (Farrer et al., 1997). Nonetheless, age and age at onset closely reflected those of unselected patients, since both lower and higher values were excluded, and thus differed significantly from the younger group of FTD, resembling the same pattern of sociodemographic features as in the other studies.

Comparisons of patients carrying and not carrying the ε4 allele within each patient group indicated that the ε4+ AD subjects were 100% women, differing significantly (p=0.02) from the ε4- subjects.

5.5.2 Volumetry of ε4 carriers and non carriers

Voxel by voxel analyses showed significantly greater atrophy of the amygdalae and head of hippocampi in the AD patients carrying the allele compared to the non carriers (Table 8, Figure 8a). FTD patients carrying the ε4 allele were characterized by greater right lobar atrophy, evident in the frontotemporal regions at uncorrected p (Figure 8b), and with a single cluster in the right ventral striatum at p corrected for multiple comparisons (Table 8).

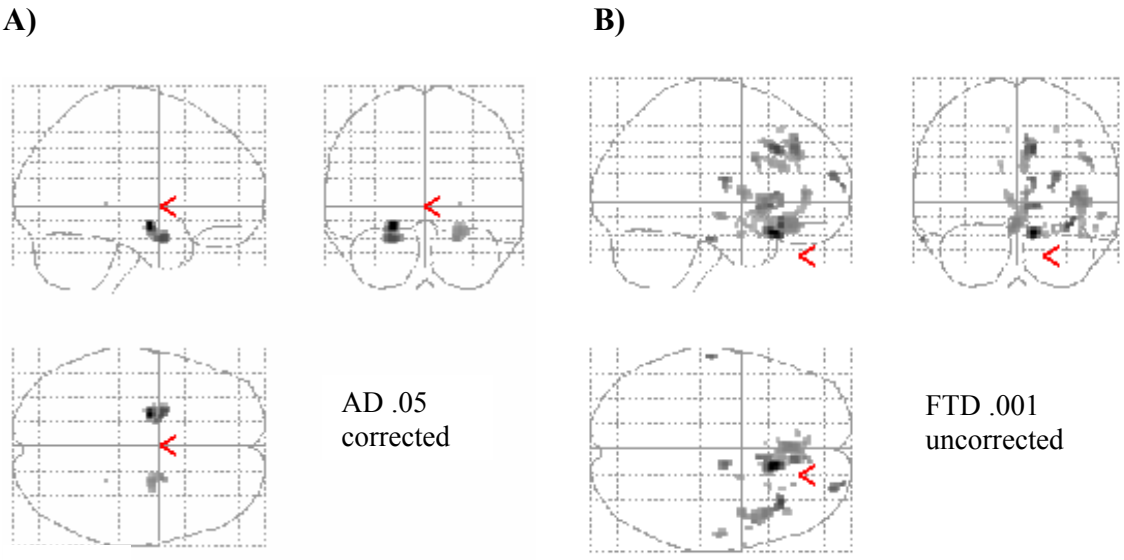
The opposite comparisons (non carriers *versus* carriers) did not reveal any significant changes in voxels densities in any of the patient groups, indicating lower severity of atrophy of the ε4- subjects.

Table 8. Atrophic regions in AD and FTD patients carrying the ε4 allele vs the non carriers, at p<0.05 corrected

Cluster size	Region	Stereotactic coordinates			Z
		x	y	z	
	AD ε4+ vs ε4-				
121	L amygdala	-22	-6	-14	6.24
	L amygdala	-24	2	-22	5.66
60	R amygdala	22	2	-22	5.19
1	R hippocampal tail	24	-36	2	4.89
	FTD ε4+ vs ε4-				
10	R ventral striatum	10	22	-20	5.42

Reading example: the first line denotes the presence of a 3D cluster made of 121 contiguous voxels of significantly decreased (p<0.05 corrected for multiple comparisons) gray matter density. The most significant voxel of the cluster has stereotactic coordinates of –22, -6, -14, and is located in the left amygdala. Within the same cluster there is a second peak of significance more than 8 mm distant from the former and located at -24, 2, -22.

Figure 8. A) Atrophy in AD patients carrying the ε4 allele vs the non carriers at p<0.05 corrected. B) Atrophy in FTD patients carrying the ε4 allele vs the non carriers (for illustrative purposes, the FTD figure shows atrophy at p<0.001 uncorrected)



5.6 Frontotemporal dementia as a neural-system disease (Study V)

FTD is characterized by frontal atrophy, but neuropsychological tests for frontal function often fail to detect anomalies during the early stages of disease. As has been demonstrated for neurological frontal patients, disruption of a circuit including the frontal structures might be primarily involved as the origin of the disease, rather than damage to the frontal lobes *per se*. This analysis of global brain atrophy in FTD, allowed by the VBM techniques that became available during the course of these studies, was aimed to test the hypothesis that a circuit involved in the control of behavior could be disrupted. The anterior limbic system, which is known for controlling adaptive behavior, was the main candidate, and some of its structures were already demonstrated to be atrophic in previous studies.

As shown in table 9, five regions of the rostral limbic system were indeed atrophic in FTD at p<0.05 corrected for multiple comparisons. Particularly large areas of atrophy were found in the anterior cingulate and ventromedial frontal cortex, but the right ventral striatum, posterior amygdalae, and anterior insulae were also involved.

The periaqueductal gray, the only region constituting the rostral limbic system that was not atrophic at $p<0.05$ corrected, displayed atrophy at $p<0.001$ uncorrected (Figure 9).

Isolated spots of atrophy were noted in the left frontal gyri including Broca's area and in the left inferior temporal gyrus (Table 9).

Table 9. Atrophic regions in frontotemporal dementia.

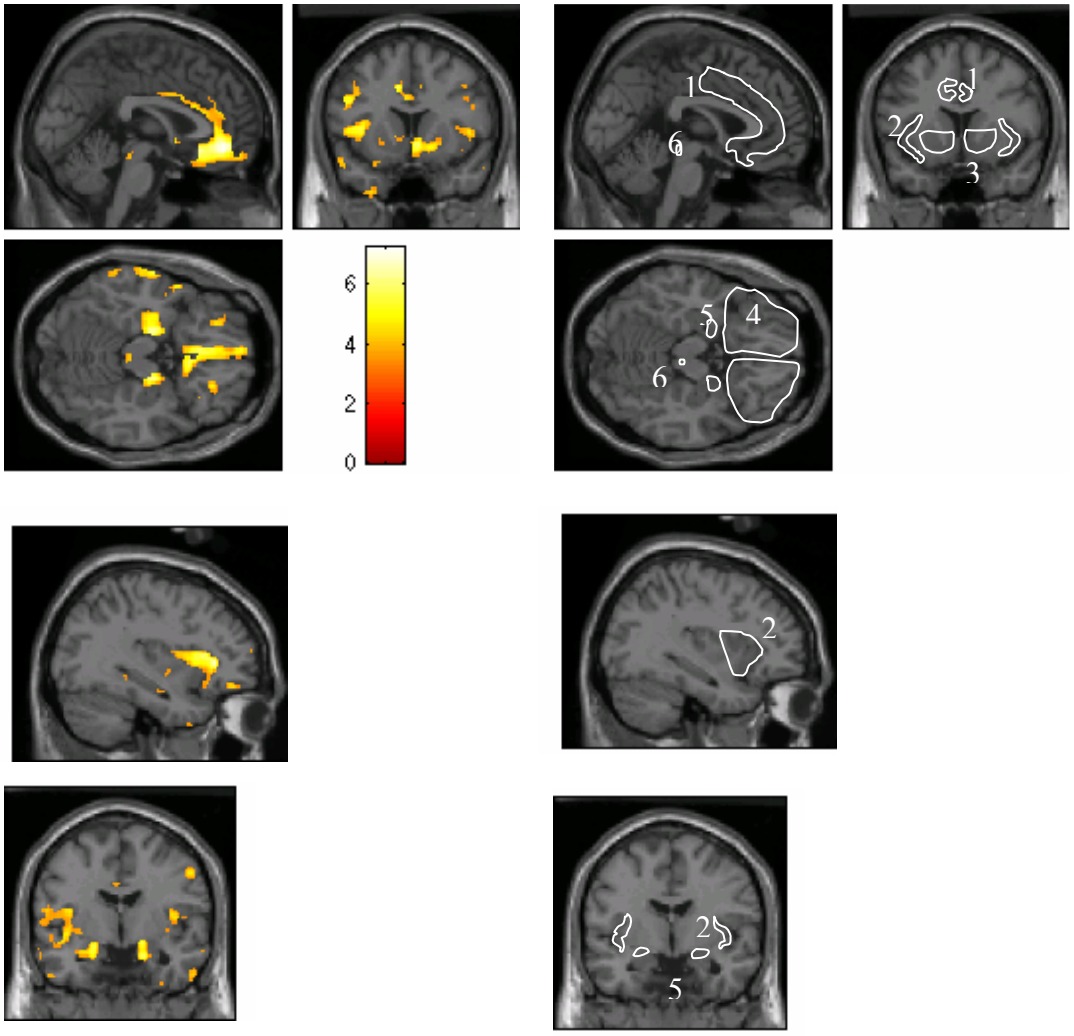
Cluster size		Region	BA	Stereotactic coordinates			Z
147	*	L ventromedial PFC	10	-2	44	-10	5.52
	*	R/L anterior cingulate	32	0	26	-10	5.07
32	*	L anterior insula	-	-38	30	2	5.44
	*	L anterior insula	-	-32	22	10	5.43
19	*	R ventromedial PFC	25	4	6	-6	5.36
8		L Broca's area	44	-52	8	18	5.27
20	*	R posterior amygdala	-	18	-10	-14	5.16
14		L inferior temporal gyrus	20	-62	-28	-24	5.14
8	*	R ventromedial PFC	11	8	18	-18	5.08
2		L dorsolateral PFC	9	-4	50	24	5.06
23	*	L posterior amygdala	-	-18	-10	-14	5.02
6	*	R anterior insula	-	38	22	8	4.95
3	*	R caudate head	-	14	20	-2	4.92
1	*	L anterior cingulate	32	-4	32	18	4.84
5	*	L anterior cingulate	32	-8	14	38	4.83
2		R uncus	28	18	-6	-22	4.80
4	*	R anterior cingulate	32	10	22	36	4.78
2	*	R anterior cingulate	32	8	34	26	4.77
1		L dorsolateral PFC	9	-4	46	24	4.77

R = right, L = left, PFC = prefrontal cortex, BA = Brodmann area. Cluster size is in number of voxels.
Reading example: the first line denotes the presence of a 3D cluster made of 147 contiguous voxels of significantly decreased ($p<0.05$ corrected for multiple comparisons) gray matter density. The most significant voxel of the cluster has stereotactic coordinates of –2, 44, -10, and is located in the left ventromedial frontal cortex (Brodmann area 10). Within the same cluster there is a second peak of significance more than 8 mm distant from the former and located at 0, 26, -10.
* Region belonging to the rostral limbic system.

Figure 9. Atrophic regions in frontotemporal dementia and anatomic structures belonging to the rostral limbic system.

a) Structures atrophic in frontotemporal dementia compared to controls. For illustrative purposes, atrophy at $p<0.001$ uncorrected is shown.

b) The rostral limbic system includes 1) the anterior cingulate cortex 2), the anterior insula, 3) the ventral striatum, 4) the ventromedial prefrontal cortex (including the gyrus rectus), 5) the amygdalae, and 6) the periaqueductal gray.



6. DISCUSSION

6.1 Compound volumetric measures as discriminative tools in the differential diagnosis

The single region markers are unsatisfactory if one whishes to differentiate patients with FTD from AD patients (Frisoni et al., 1999). Moreover, this approach has the disadvantage of being strongly dependent on the stage of the disease, given the progressive nature of atrophy in all regions, at least in AD (Fox et al., 1999; Fox et al., 2000; Jack et al., 2000. This study, analyzing a wider set of structures, indicated that FTD is characterized by a particular pattern of atrophy where the hippocampus exhibits mild atrophy, while the frontal and the temporal regions suffer strikingly more severe atrophy. The pattern is different from that of AD patients, who show moderate hippocampal atrophy, temporal atrophy of similar degree, and milder frontal atrophy. Moreover, FTD patients exhibit greater asymmetry, with the left regions being more atrophic than the right. It should be stressed that this approach might identify a constant pattern of atrophy, that does not vary through different stages of disease severity.
When used as a discriminative tool, the atrophy profile approach proved to be satisfactory, with specificity values of 93% and sensitivity of 90%, where single, albeit typical, structure-based approach did not discriminate at all among groups in the same patients (Frisoni et al., 1999).

6.1.1 Symmetry as additional information in the pattern approach

FTD is known to be an asymmetrical disease. For example, the early impairment of language indicates that the left hemisphere is more involved than the right (Grossman et al, 1996), while behavioral symptoms seem to be associated with a greater involvement of the right hemisphere (Mychack et al., 2001). In accordance with this hypothesis, asymmetrical hypoperfusion has repeatedly been demonstrated with SPET studies of FTD (Frisoni et al., 1995; Miller and Gearhart, 1999). However, structural imaging studies have paid little attention to atrophy asymmetry. A laterality index has been

computed (Kitagaki et al., 1998) on the basis of hemispheric volumes, and from the data reported in the paper the sensitivity and specificity can be computed to be around 40 and 95%. The authors did not compute a regional laterality index for the frontal and temporal regions. Since moderate to severe cortical atrophy in the anterior superior temporal region alone was able to correctly classify 13/18 FTD and 16/18 AD patients (sensitivity and specificity of 72 and 89%), it can be hypothesized that a regional laterality index in these areas might have yielded even higher figures. It is significant that in our sample the asymmetry of the frontal and temporal horns alone was able to discriminate FTD from AD patients with 80% sensitivity and 89% specificity. Nonetheless, a laterality index is not sufficient itself as a marker for the differentiation of FTD and AD, first, because the small sample size of our patient group does not allow us to make wider generalization, secondly, because evidence exists that some FTD patients might have symmetric atrophy (Miller and Gearhart, 1999).

6.2 The failure of the single structure approach in understanding the nature of the disease

As no single structure marker has proved sufficient in discriminating FTD from AD, the analogous attempt to explain the FTD syndrome based on the most typically affected structure (i.e. the frontal lobe) has been equally ineffective. The first hint of this problem came from Study II, where evidence of similar extents of amygdaloid atrophy were observed, but very different "amygdaloid-related" symptoms were exhibited in AD and FTD.

Previous studies on amygdaloid function or volume have not detected any amygdaloid involvement in FTD (Garraux et al., 1999; Rosen et al., 2002). This claim, which in fact does not seem compatible with the typical FTD symptoms (Neary et al., 1998), is not confirmed by our work, since we detected a tissue loss of about 20% in the amygdalae of the FTD group. Moreover, the amygdaloid atrophy tended to be greater in AD patients, up to 30%.

After the experiments of Klüver and Bucy on monkeys, symptoms like hyperorality, hypersexuality, absence of fear have also been related to amygdaloid involvement in man (Marlow et al., 1975; Lily et al., 1983; Gerstenbrand et al., 1983). The fact that

amygdaloid atrophy appeared to be less extensive in FTD than in AD in our study is not consistent with the clinical observation that symptoms considered to be largely due to amygdaloid damage are more frequent in FTD than in AD (Förstl et al., 1993; McKhann et al., 1984; Neary et al., 1998). One possible explanation might be that these symptoms are not due to amygdaloid damage *per se*, but to disruption of a neural system including this structure. This might include the frontal lobes, which are particularly damaged in FTD (Fukuy and Kertesz, 2000) and which have close connections with the amygdalae (Szesko et al., 1999). This view is supported by the greater frontal/amygdaloid ratio in AD as compared to FTD patients, indicating a disproportionate frontal preservation in AD compared to FTD. This explanation for Klüver-Bucy-like symptoms is based on results obtained through mathematical modeling of the frontal/amygdaloid ratios in order to account for the effect of younger age in FTD patients, and will need to be replicated in age-matched groups.

However, the hypothesis is consistent with findings of other authors, who, contrary to expectations, found Klüver-Bucy-like symptoms in patients without amygdaloid involvement, and attributed them to disruption of fronto-limbic connections (Carrol et al., 2001; Takahashi and Kawamura, 2001).

6.3 Different phenotypes of FTD

Frontotemporal lobar degeneration syndromes are characterized by different symptoms accompanied by differential involvement of brain regions (see section 2.2 about clinical criteria). When a frontal or a temporal variant of FTD (fvFTD or tvFTD respectively) are mentioned in the current literature, they actually refer to FTD or semantic dementia, which are already recognized as discrete clinical entities in the most widely used clinical criteria (Neary et al., 1998). When individual phenotypes of FTD are considered, based on the specific pattern of atrophy of each patient, a greater right or left involvement has been described (Mychack et al., 2001).

In our FTD patient group, we did not find any evidence of subjects with right versus left hemispheric involvement. When subjects had significant right atrophy, they also exhibited left atrophy to the same degree, almost as if left hemispheric atrophy was a

constant feature of the disease. More exactly, a minority of our patients (30%) presented with symmetric frontotemporal and medial temporal atrophy, of a more severe degree compared to those patients with an asymmetric involvement.

Some relevant observations can be made. First of all, the patients with symmetric atrophy had an earlier onset of disease. Second, they presented with more severe global and medial temporal atrophy despite equal global clinical severity duration. Third, in the patients with asymmetric disease, only the left frontal and temporal regions were affected, while right frontotemporal and bilateral medial temporal regions were only mildly atrophic. Finally, the patients with symmetric presentation also had greater frequency of the ApoE ε4 alleles, while no patients with asymmetric atrophy carried this allele.

The asymmetric involvement of the brain in FTD is viewed as the cause of the wide variety of symptoms of this type of dementia (mainly linguistic or behavioral, considered to represent left and/or right involvement, respectively) (Mychack et al., 2001). Symmetric involvement would imply that both linguistic and behavioral symptoms are both present and severe, but lack of detailed data of our patients from earlier does not allow us to test this hypothesis.

A more symmetric distribution of atrophy might be due to a very advanced stage of disease, and represent a floor effect. Our symmetric patients had a mean disease duration 5 months longer than the asymmetric subjects. As the initial pattern of atrophy in the degenerative dementias has been shown to remain unchanged as the disease progresses for at least 2-3 years (Smith et al., 1992), it does not seem likely that the minor difference of disease duration is responsible for the different distribution of atrophy in our groups.

6.4 Influence of the APOE genotype on the phenotype of FTD

In Study III, “symmetric” FTD patients had a higher percentage of the APOE ε4 allele, that was not detected at all in the genotype of “asymmetric” subjects. Nonetheless, it is not possible to consider that this allele is the only responsible for symmetric distribution of atrophy: even though asymmetric patients did not possess any ε4 alleles, its

prevalence in the symmetric patients was 50%, and one of the three symmetric patients was ε4-/-.

An influence of the ε4 allele on the symmetric phenotype cannot be ruled out, but a subsequent VBM study was undertaken in order to better evaluate its real contribution to brain morphology in the individuals affected by FTD.

Unfortunately, patients in this study are very few in number, and the following observations will definitely need to be replicated in larger samples.

6.4.1 Effects of the ε4 allele on brain morphology of demented patients: evidence from the literature

The genetic asset (the presence of ApoE ε4 allele) is consistent with a theory of greater brain vulnerability in ε4 carriers. The greater frequency of the ε4 allele might be at least in part responsible for greater and symmetric atrophy, as well as a younger age at onset. Smaller brain volumes in normal and AD subjects carrying the ε4 allele have repeatedly been addressed (Berg et al., 1998), as well as reduced asymmetry (Lehtovirta et al., 2000). In addition, the ε4 allele might contribute to the younger age at onset(Berg et al., 1998), although this effect in FTD is more controversial (Minthon et al., 1997; Pickering-Brown et al., 2000). Indeed, the identification of different polymorphisms of the ApoE itself suggests that the interaction of this gene with the clinical phenotypes might be particularly complex (Zill et al., 2001).

6.4.2 APOE and modulation of the effects of the AD and FTD

In the VBM study, carried out to examine the role of APOE, carriers of the ε4 allele were separated from the non carriers in both the AD and FTD groups. The results indicated that the carriers had greater atrophy in the regions typically affected in each condition: frontotemporal areas in FTD, medial-temporal regions in AD, almost as if the effect of the ε4 allele consisted of amplifying the effects of the disease. The ε4 allele is

widely known to be a risk factor for AD. Our results favor the hypothesis of a similar role in FTD, but data in the literature are contrasting.

6.4.2.1 Neurophysiologic hypotheses for the detrimental effect of ε4

The particularly high prevalence of ε4 alleles in the small sample of patients with symmetric atrophy is compatible with subsequent VBM findings of greater right lobar atrophy of the patients carrying the allele compared to the non carriers, characterized by left atrophy (Study III) as frequently observed in FTD.

Different pathways can be hypothesized to explain the observed modulation of the ε4 allele of APOE on brain atrophy. The first effecț seems to be a rather general increase in brain vulnerability, as is apparent in both AD and FTD groups. The greater brain vulnerability of the subjects carrying the ε4 allele might be explained by lower efficacy to carry out repair mechanisms (Weisgraber and Mahley, 1996). This effect is consistent with the hypothesis that ε4 is the ancestral human APOE allele (Mahley and Ral, 1999), from which the others have evolved in the direction of prolonging healthy ageing (Finch and Sapolsky, 1999).

More complex effects are also plausible in the role of ε4 of modulating brain atrophy. A different brain morphology is demonstrated even in the healthy carriers, and points to a direct role for APOE in the development of these regions. This role is plausible in the light of recent data indicating that receptors for the LDL bind both Reelin, a signaling protein that regulates neuronal migration during brain development and ApoE (Weeber et al., 2002). The perfusion of mouse hippocampal slices with Reelin significantly enhanced long term potentiation (LTP) in CA1, indicating that this protein controls synaptic plasticity in the adult brain. Different isoforms of ApoE compete differently with Reelin. The ε4 derived APOE protein has greater affinity, and this binding contrasts with Reelin's effects of facilitating LTP and brain plasticity.

Reduced neural sprouting has indeed been demonstrated to be associated with the ε4 allele of APOE not only in cultured neurons but also in AD patients (Finch and Sapolsky, 1999).

The ε4 allele might thus have an effect in modulating brain plasticity in the adult brain, but, given the described interaction with Reelin receptors and the demonstrated reduced neural sprouting, it is plausible that it can induce gross or subtle differences in brain morphology even during the early stages of development. An interaction of these effects with other detrimental consequences of specific diseases or genetic conditions might explain why the greater atrophy exhibits differential localization in the different diseases: medio-temporal in AD, frontotemporal in FTD.

6.5 Frontotemporal dementia as a neural system disease

Finally, the VBM study examining the whole pattern of atrophy in FTD detected the involvement of the whole rostral limbic system, consisting in the anterior cingulate, orbitofrontal and anterior insular cortex, ventral striatum, amygdale and periaqueductal grey (Study V).

Atrophy of the anterior cingulate and orbitofrontal cortices has been found in previous neuroimaging studies (Rosen et al., 2002) and atrophy of the amygdalae and striatum in pathological studies (Filley et al., 1994). To our knowledge, the insular cortex and the periaqueductal gray have never been reported to be atrophic. Beyond the novel notion of atrophy in these structures, it is relevant to consider what the present data add to current hypotheses on FTD: involvement of these structures points to damage of an entire system, which can in effect account for the apparently heterogeneous symptoms of FTD.

The rostral limbic system is a limbic circuit involved in the control of the organism's behavioral outputs, and is based on the specific connections of the affective and cognitive divisions of the anterior cingulate cortex, that includes Brodmann areas 25, 33 and rostral 24, responsible for affective functions, and caudal areas 24 and 32, carrying out cognitive functions mainly of response selection (Devinsky et al., 1995; Botvinick et al., 2001). This structure integrates the heterogeneous information from (and to) the amygdala, the periaqueductal gray, the ventromedial and anterior insular cortices, and the ventral striatum (Devinsky et al., 1995; Vogt et al., 1992). The rostral limbic system is involved in processing the environmental information to the organism's benefit, in

order to monitor or program the behavioral output compatible with survival (Damasio, 1998).

This complex function can be performed thanks to the output of a central structure, the amygdala, which processes the value of internal and external stimuli, represents these values in the form of emotion to the brain and to subjective experience, and permanently associates this emotion to external stimuli (associative learning) (Calder et al., 2001; Clark, 1995; Gallagher and Holland, 1994; Rolls 2000a). The ventral striatum and the ventromedial prefrontal cortices contribute to this function by allowing reversal conditioning (i.e. association of the external stimulus with a different – even opposite – reward value that follows environmental changes), which does not occur in the amygdala (Rolls, 2000a; Rolls 2000b; Schoenbaum et al., 2000; Setlow et al., 2003), before programming and performing the consequent behavioral outputs (Cardinal et al., 2002; Cardinal et al., 2001). The first and primitive processing of such motor output comes from the periaqueductal gray, also closely connected to the amygdala, that activates different innate strategies for coping with the environment based on primitive attack-escape reactions (Misslin, 2003). The amygdala has also a role in eating behavior (Gallagher and Holland, 1994) which, together with the behavioral symptoms belonging to the clusters of "social awareness", was the symptom best distinguishing FTD from Alzheimer's disease in a systematic neuropsychiatric study (Bozeat et al., 2000). Hyperorality is one of the classical Klüver-Bucy-like symptoms which have long been associated with amygdaloid damage, and are characteristic for FTD as defined by the consensus criteria of the Lund and Manchester groups (Lund and Manchester Groups, 1994). Moreover, the amygdala, in close connection with the ventromedial prefrontal and anterior cingulate cortices, influences other higher order functions such as decision making (Damasio, 1996; Rolls 200a; Rolls 200b) and theory of mind tasks (Stone et al., 2003) which have recently been demonstrated to be severely impaired in FTD (Gregory et al., 2002).

If we wish to dissect the concept of "appropriate behavior", and try to define it comprehensively, starting from internal stimulus or potential external input, via all the mechanisms of evaluation, filtering, selection, execution, etc. to the resulting output - correct behavior in a given situation - this might be too ambitious a task from the point of view of this study. Instead, it is proposed to proceed through the atrophic structures

of the rostral limbic system to some extent, and to contemplate their individual contributions to the global function of the system and to the behavioral disturbances observed in FTD.

The largest areas of atrophy in this study were observed in the anterior cingulate and in the ventromedial prefrontal cortex bilaterally.

The main function of the anterior cingulate cortex consists of the detection of conflict within the ongoing information processing. Conflict detection is fundamental in order to activate the appropriate executive functions that allow an aware processing of the stimuli, strategy shift, and other superior functions that enhance information processing when routine processing is not sufficient (Devinski et al, 1995; Botvinick et al., 2001). This function can be carried out by virtue of the property of the anterior cingulate of integrating the heterogeneous information there converging from the different structures of the circuit (Devinski et al, 1995; Botvinick et al., 2001; Vogt, 1992; Adolphs, 2001). Subsequent to conflict detection, the anterior cingulate cortex has also a critical role in the process of response selection (Devinski et al, 1995; Botvinick et al., 2001). Pathology in the anterior cingulate could in part explain also other non-behavioral but diagnostic features of FTD, such as mutism and low or labile blood pressure (Persinger, 2001), via dysregulation of the endocrine and autonomic nervous systems (Devinski et al, 1995) as well as its connection with other RLS structures also involved in these functions, as described below.

With respect to the ventromedial prefrontal cortex, this is the main region coupling affective information and the mechanisms of action selection. It is of particular importance in evaluating and weighing the outcome (reward vs. punishment) related with a given choice. Individuals with ventromedial damage may perform normally in some frontal tests, such as the Wisconsin Card Sorting Test, but are impaired in their choices, tending to choose what produces an immediate and large reward, but in the long run leads to even larger punishment or larger net losses in a given paradigm (Schoenbaum et al., 2000; Damasio, 1998; Rosen et al., 2002). This is in line with the impulsivity and deficits in selection observed in patients with FTD.

Within the ventromedial prefrontal cortex, the gyrus rectus, that has been associated with some conditions with a behavioral component such as Tourette syndrome

(McAbee et al., 1999) and autism (Siegel et al., 1992), can explain similar features often observed in FTD.

The particularly close connection of the ventromedial prefrontal cortex with the amygdala (Szeszko, 1999) is compatible with "autistic" symptoms as well as with the impairment in the "theory of mind" (ToM) which has been demonstrated to be severe in both autism and FTD (Gregory et al., 2002). The theory of mind refers to the ability to put oneself in other people's position, and to be able to infer other people's mental states, thoughts and feelings. A failing in this ability means that one will encounter difficulties in social interactions with other individuals.

The performance in the theory of mind tasks in patients with FTD has been shown to correlate with ventromedial atrophy in MRI when the amount of atrophy was qualitatively rated (Gregory et al., 2002) but the authors themselves state that other key structures for the ToM tasks, like the amygdala (Stone et al., 2003), were not considered.

The amygdala in fact was found to be atrophic in our sample. This is the most seminal structure in understanding, experiencing, and storage of emotional significance of events. In that role it processes the emotional content of events and mediates the subsequent behavioral, autonomic and endocrine responses.

The contributions of anterior insula to cognition and behavior include awareness of oneself (Damasio, 1998), damage of which may be observed as a loss of insight. The anterior insula, according to the somatic markers hypothesis, is a key structure for keeping emotion in check by the organism and it belongs to the system which is activated according to the somatic markers hypothesis (Damasio, 1995; Damasio, 1998). Beyond the typical aberrant behaviors, autonomic dysregulation due to insular damage may be responsible for other features such as the low or labile blood pressure (Miller et al, 1997) observed in FTD patients. Moreover, the insula subserves emotion recognition, particularly that of disgust (Adolphs, 2001; Calder et al., 2001), eating behaviors, which are commonly altered in FTD, as well as impairments in linguistic functions, in part explaining the mutism observed in FTD (Shuren et al., 1993; Habib et al, 1995).

Turning to the ventral striatum, it has been demonstrated to be involved in disgust perception (Calder et al., 2001), conditioning, inhibition of impulsive behavior

(Cardinal et al., 2002; Cardinal et al., 2001) conditioning behavioral expression (Cardinal et al., 2001; Adolphs, 2002), and context-dependent action selection (Lawrence et al., 2000) but its function can perhaps be better described as the final, concrete component of the motor output control as tuned by the whole rostral limbic system.

Finally, the periaqueductal gray integrates signals from the body in order to activate different innate strategies for coping with the environment (Lawrence et al., 2000). It also seems to have a role in language output, as revealed by clinical studies (Esposito et al., 1999).

There were other regions experiencing atrophy e.g. minor changes outside the rostral limbic system. These included a small cluster in the Broca's area, which may be related with the language disorder in FTD. On the left side, there were small areas of atrophy on the superior, middle and inferior frontal gyri. These are part of the dorsolateral prefrontal cortex, whose pathology may contribute to the clinical picture of executive dysfunction observed in FTD. Another isolated area of atrophy was found in the left inferior temporal gyrus.

6.6 Comparison with previous research

Newness of this study, compared to previous research, consists, first of all, in detection of atrophy in structures previously undetected *in vivo*, like the insula and the periaqueductal grey matter. This result was allowed by the use of VBM, which allows to compare all cerebral districts in one comparison, at the voxel level. Moreover, this kind of comparison allowed to gather the atrophic structures into one functional system that is hypothesized to be selectively impaired in FTD. This is not possible with the classical ROI approach, that provides information about morphometry of a chosen structure, but does not allow to know anything about all of the others, be they functionally connected or not.

Only one VBM study was previously conducted on FTD patients by Rosen and colleagues (Rosen et al., 2002). In 8 patients, at $p<0.05$ corrected, they found atrophy in the ventromedial frontal cortex, anterior insular and cingulate cortices, and in two clusters corresponding to the dorsolateral and premotor frontal cortices. These regions

are among those found to be atrophic also in our study. The presence of fewer atrophic regions in Rosen et al.'s study might be due to at least two reasons: first, their patients seem to be more mildly affected than our own (MMSE 23 vs 14), and second, the 12 mm filter that they used might have reduced the sensitivity for the detection of atrophy in small structures. Unfortunately, the authors did not report the size of the clusters of atrophy, and further comparisons between the two studies can not be performed. In our study, the cluster size of the dorsolateral prefrontal and premotor cortex was extremely small at $p<0.05$ corrected (see Table 9), while the anterior insula, anterior cingulate and ventromedial frontal gyri corresponded to larger clusters.

6.7 Main finding of the work

Data from this work suggest a unifying model that can account for the whole syndrome of FTD. Indeed, the rostral limbic system, which controls adaptive behavior, is entirely impaired in the FTD patients examined, and this impairment can account for the complex behavioral syndrome observed in this patients. On the other side, the finding might be considered as secondary to the clinical diagnosis of FTD, which relies on such behavioral disturbances. Future research, studying patients selected based on neuropathological characterization according to the most recent criteria (McKhann et al., 2001) will allow to understand whether this system is impaired due to the biological changes that define the disease, or whether the clinical features consisting in behavioral aberrations are just overlapping among very different conditions, that variably affect the rostral limbic system. In this case, impairment of this system would be found due to a "circular" reasoning, selecting patients with behavioral aberrations as carriers of the studied disease..

Since FTD is categorized as a FTLD together with SD and PA, one might wonder whether the rostral limbic system might be involved also in SD and PA. The different phenotypes of the three conditions do not support this hypothesis in that comprehension and production of verbal language, primarily impaired in SD and PA respectively, do not seem to rely on the integrity of the rostral limbic system. However, since symptoms typical of FTD such as frontal behavioral disturbances can develop also in the more advanced stages of SD and PA (Neary et al., 1998) and atrophic regions are partly

overlapping (Rosen et al., 2002), this hypothesis cannot be definitely ruled out. Maybe, "enlargement" of the rostral limbic system, possibly including other circuits very closely connected at a functional level, might account for these similar syndromes. One possible hypothesis might hint to the mirror neurons system. These sets of neurons, first described by the group of Rizzolatti in 1989 (di Pellegrino et al., 1992; Gallese et al, 1996), are hypothesized to be involved in emotion comprehension (Gallese et al., 2004), but also, for example, in *language* production and comprehension (Arbib, 2005), that are respectively impaired in PPA and in SD. It is possible that such system might be differentially involved in the different subtypes of FTLD, and, combined with the relative involvement of the RLS, give rise to the different clinical syndromes. This hypothesis is highly speculative, although it might suggest future directions for research.

6.7 Limitations of the work

General limitations of the study involve the very limited number of subjects, and the single dataset investigated. Replication of these findings in different, and possibly larger, patient samples should be carried out to credit our results. In addition, the heterogeneity of sociodemographic features of our subjects forced to statistically intervene to make the data comparable. FTD patients were younger than AD ones and than controls, and more often men. Of course, statistical expedients, such as computation of W-scores, have been adopted in order to reduce the effect of intervening variables such as age and sex, nonetheless these procedures are palliative solutions for this kind of problem.

In greater detail, this study was carried out in a limited number of subjects. W-scores for asymmetry were computed with a regression model based on a relatively small group of controls (10 males and 17 females) and 2 covariates (age and gender). A statistical rule of thumb dictates that at least 10 subjects per covariate are the minimum to obtain reasonably stable estimates. We might therefore be relatively satisfied by the control group, but it must be recognized that since we had only 10 FTD patients, this might have led to unstable estimates of sensitivity and specificity values, capitalizing on

chance fluctuations. Further studies with larger groups are warranted in the future to provide the necessary cross validation.

Second, we considered our 10 FTD patients as a single group, while it is now clear that FTD can have a heterogeneous distribution of pathology and clinical manifestations. This view is consistent with our findings of higher standard deviation in all structures in FTD patients (average SD=2.1, range between 1.4 and 3.3) compared to AD (average SD=1.5, range between 0.7 and 2.8) and might account for those situations where greater atrophy seems to be present in FTD but it is not significantly different from AD due to the high standard deviation values in FTD (see for example the left temporal horns, Table 4).

Third, we did not record accurately all of the behavioral symptoms of our demented patients and their severity. Such information would have been particularly relevant for studies II and V, where a link was sought between brain morphology and the behavioral aberrations characterizing FTD. Therefore, some of our hypotheses, like that of disruption of a fronto-limbic connection drawn from the volumetry of the amygdalae, are speculative. For example, we have not systematically recorded behavioral and Klüver-Bucy-like symptoms in our patients, and cannot test it systematically. However, the clinical criteria that we used to isolate patients with FTD are devised in a way that they indirectly lend support to such hypotheses. The typical Klüver-Bucy symptoms comprise bulimia, hyperorality, hypersexuality, an irresistible impulse to touch objects, and a loss of normal fear and anger (Klüver and Bucy, 1997; Lilly et al., 1983). Most of these are included in the clinical criteria for FTD (Neary et al., 1998), and it is accepted that these patients show these symptoms early (Neary et al., 1998; Carroll et al., 2001) while in AD patients they occur later in the disease course (Förstl et al., 1993). Therefore, it is very likely that our FTD patients had more Klüver-Bucy, as well as other behavioral symptoms than the AD patients, although accurate recording is lacking in our study. Moreover the other clinical tests, investigating disease severity (CDR, MMSE) might not be the elective choice for this kind of dementia, in that they are primarily designed to stage disease severity in AD, which is clinically very different. Indeed, appropriate testing for evaluating disease severity in FTD can hardly be defined, and research in this direction is warranted in future work.

Finally, none of our patients underwent autopsy, and replication of these findings in pathology-proven FTD patients is necessary. Nonetheless, when diagnoses are carried out by expert clinicians, a specificity of 99% has been observed, at pathological diagnosis (Knopman et al., 2005).

6.8 Future studies

Future studies should, first of all, include larger patients group.

More accurate registration of behavioral symptoms could allow us to formulate more certain conclusions about the pathogenesis of behavioral aberrations, permitting precise correlations with discrete structures or identifying the involvement of wider circuits as already hinted at in these studies.

The evolution of MR techniques for image preprocessing and comparisons will also make it possible to carry out analogous studies on more solid theoretical grounds. For example, VMB analyses can now be carried out with new software, so called SPM2, that differs from SPM99 in that it allows more accurate image preprocessing and is based on Bayesian probability. This last characteristic aids in the statistical analyses without the assumptions required by parametric statistics. Tests with a low number of subjects, or even single-case analysis, can be appropriately carried out. Adoption of such a tool might highlight patterns of atrophy in “each” patient with FTD, and this would aid in assessing the degree of the generalizability of results obtained from groups of patients.

Confirmation of previous results with these kinds of tools, and possibly in single subjects, would also boost accurate diagnosis, allowing early detection of a very specific pattern of atrophy. This application would be of great clinical importance.

Finally, replication in autopsy confirmed cases would increase the reliability of the neuroimaging results.

7. CONCLUSIONS

This study investigated two main fields of interest in FTD studies with MRI: that of the morphological characterization of the brain of these patients, mainly aimed at helping in the diagnosis and differential diagnosis from other kinds of dementias, and that of the tentative explanation of the clinical symptoms of the disease.

In summary:

1) The structures typically atrophic in FTD were also atrophic in AD although to a lesser degree, and vice-versa, preventing accurate differential diagnosis based on the volume of single structures.

2) The differential diagnosis from AD was greatly improved by a compounded biological marker, including *a set* of brain structures typically involved in both diseases.

3) Laterality information was particularly informative, in that FTD is a particularly "asymmetric" disorder

4) However, asymmetry is not found in 100% of FTD patients. A minority of them exhibit a clearly symmetric atrophy, that is accompanied by a greater severity of neurodegeneration, younger age at onset and presence of the ε4 allele of APOE.

5) The APOE ε4 allele is not recognized as a risk factor for FTD, but seems to modulate neurodegeneration by increasing brain susceptibility to the effects of the disease

6) Single structure atrophy, which is insufficient for the differential diagnosis, is also unsatisfactory in the explanation of clinical symptoms: similar amygdaloid atrophy was found in AD and FTD, but these have disproportionately more amygdaloid-related symptoms

7) Wider brain circuits should be considered for the explanation of the clinical symptoms. In particular, the amygdaloid-related symptoms might be better explained by disruption of fronto-limbic connections.

8) FTD might be a consequence of disruption not only of fronto-limbic connections, but also of a wider circuit at control of behavior, the rostral limbic system, that includes also other limbic structures. The involvement of this whole system, as observed in the VBM analyses, might account for the clinical manifestations of this disease.

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APPENDIX: ORIGINAL PUBLICATIONS I-V

I

The MRI pattern of frontal and temporal brain atrophy in frontotemporal dementia

Boccardi M., Laakso M.P., Bresciani L., Galluzzi S., Geroldi, C.
Beltramello A., Soininen H., Frisoni G.B.

Neurobiology of Aging 2003;24:95-103

II

Amygdaloid atrophy in frontotemporal dementia and Alzheimer's Disease

Boccardi M., Pennanen C., Laakso M.P., Testa C., Geroldi C., Soininen H., Frisoni G.B.

Neuroscience Letters 2002;335:139-43

III

Clinical characteristics of frontotemporal patients with symmetric brain atrophy

Boccardi M., Laakso M.P., Bresciani L., Geroldi C., Beltramello A., Frisoni G.B.

European Archives of Psychiatry and Clinical Neuroscience
2002;252:235-9

IV

APOE and modulation of Alzheimer's and frontotemporal dementia

Boccardi M., Sabattoli F., Testa C., Beltramello A., Soininen H.,

Frisoni G.B.

Neuroscience Letters 2004;356:167-170

V

Frontotemporal dementia as a neural system disease

Boccardi M., Sabattoli F., Laakso M.P., Testa C., Rossi R., Beltramello A., Soininen H., Frisoni G.B.

Neurobiology of Aging 2005;26:37-44

PUBLICATIONS
SERIES OF REPORTS, DEPARTMENT OF NEUROLOGY

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