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**CLINICAL DIFFERENTIATION BETWEEN FRONTOTEMPORAL
DEMENTIA AND ALZHEIMER'S DISEASE**

Psychometric, behavioral, neuroimaging and
neurophysiological information

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It is my hope that *the natural occurrence and course* of diseases in animals will be studied in order to enhance the knowledge and treatment of diseases in humans, and vice versa.

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ABSTRACT

Frontotemporal dementia (FTD) initially affects the anterior regions of the brain, and gradually spreads to other cerebral areas. Behavioral alterations are described as the hallmark of FTD, whereas cognition is mostly found to be relatively spared. Alzheimer's disease (AD) starts in the posterior brain areas, and successively involves even other regions. Typical for AD are cognitive deficits, but behavioral and emotional changes have also been reported. With progression, the clinical distinctions between the diseases may be blurred, and it is uncertain to what extent and by which means they are possible to clinically differentiate. FTD is in focus of the thesis. The general aim of the thesis was to investigate FTD and AD from a differential diagnostic point of view, with the use of preclinical, neuropsychological (psychometric tests), behavioral, volumetric, and radiologic information.

In study I it was found that it is possible to differentiate FTD from AD with the help of small subsets of behavioral observations (5 items), and neuropsychological tests (5 tests). The hit rate of the set of behavioral items was very high, 97%. These abnormal behaviors were more pronounced in FTD than in AD. The hit rate for the psychometric predictors was slightly lower, 90%. In this set of psychometric predictors was included a test of verbal fluency. This function was particularly low in the FTD group as compared to the AD group.

The topic for study II were the earliest signs of FTD and AD. The results indicated that clear behavioral and cognitive differences existed between the FTD and AD patients prior to their first clinical visit. The earliest signs of FTD were changes in behavior, whereas the first symptoms of AD were cognitive, particularly memory deficits. Disinhibition was the most prominent early behavioral alteration in FTD, and it was associated with right-sided frontotemporal atrophy. Language dysfunctions was commonest in the left-sided group and loss of executive functions most frequent in the FTD group with bilateral frontotemporal degeneration.

In study III was investigated the relationship between behavior, cognition, and loss of regional frontotemporal brain volumes in FTD patients. The study suggested that the frontal lobes have a limited importance for cognition, and that there is a relation between behavior and cognition. The correlations between behavior, cognitive functions and regional volume loss did not show any consistent patterns, outlining that thinking is such a complex process that it demands cooperation from different parts of the brain in both hemispheres. This multiregional dependency of thinking is probably reflected in neuropsychological tests.

In study IV it was found that FTD patients were marked by a pathological EEG, namely by an absence of an increase in slow quantitative EEG (qEEG) activities, and a decrease in fast activities. AD patients were characterized by an increase in slow qEEG frequencies and a smaller decrease in fast activities. Neuropsychological measures were better predictors of FTD versus AD than qEEG measures, but the most efficient predictor was a model combining neuropsychological tests and qEEG. The classification accuracy for this combination of modes of investigation amounted to 93.3%.

Study V showed a typical pattern of anterior cortical hypoperfusion in FTD, and of posterior cortical blood flow reduction in AD patients. Calculations of likelihood ratio (LR) disclosed that regional cerebral blood flow (rCBF) measures added more to the pretest probability than the psychometric measures. The best rCBF predictor of FTD versus AD was the perfusion in the left anterior cingulate cortex, where the LR was 11.9, which is very high.

When comparing the efficiency of the five modes of investigation for the differentiation between FTD and AD, the behavioral observations and rCBF measurements appears to be equally useful. Neuropsychological tests may be useful, provided that the patient groups are enough dissimilar. The EEG method must be used in combination with neuropsychological tests to contribute to classification accuracy.

LIST OF ORIGINAL PUBLICATIONS

Below are listed the studies on which this thesis is based. In the text they are referred to by their roman numerals.

- I** Lindau M, Almkvist O, Johansson S-E, Wahlund L-O: Cognitive and behavioral differentiation of frontal lobe degeneration of the non-Alzheimer type and Alzheimer's disease. *Dementia* 1998;9:205-213.
- II** Lindau M, Almkvist O, Kushi J, Boone K, Johansson S.E, Wahlund L.O, Cummings J.L, Miller B.L: First symptoms – Frontotemporal dementia versus Alzheimer's disease. *Dementia* 2000;11:286-293.
- III** Lindau M, Andersen C, Johansson S-E, Julin P, Blomberg M, Wahlund L-O, Almkvist O: Functional specialization or interaction in the frontal lobes: volumetric measurements in relation to cognition and behavior in frontotemporal dementia. A pilot study. *Alzheimer's Reports* 2001;4:45-53.
- IV** Lindau M, Jelic V, Johansson S-E, Andersen C, Wahlund L-O, Almkvist O: Quantitative EEG abnormalities and cognitive dysfunctions in frontotemporal dementia and Alzheimer's disease. *Dementia* 2002, in press.
- V** Lindau M, Huang C, Johansson S-E, Julin P, Wahlund L-O, Almkvist O: Single photon emission computed tomography (SPECT) measurements and cognition in frontotemporal dementia, Alzheimer's disease and healthy controls (submitted).

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
BPD	Bipolar disorder
BPSD	Behavioral and psychological symptoms of dementia
CBD	Corticobasal degeneration
CC	Consensus criteria for frontotemporal lobar degeneration, 1998
CERAD	Consortium to Establish a Registry for Alzheimer's Disease (Morris, 1989)
CT	Computed Tomography
DSM III	Diagnostic and Statistical Manual ed.3. (American Psychiatric Association, 1987)
DSM IV	Diagnostic and Statistical Manual ed.4. (American Psychiatric Association, 1994)
EEG	Electroencephalogram
fvFTD	Frontal variant of frontotemporal dementia
FLD	Frontal lobe dementia
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FTDP 17	Frontotemporal dementia and parkinsonism linked to chromosome 17
GFP	Global Field Power
HD	Huntington's disease
IVD	Ischemic vascular dementia
LBD	Lewy body dementia
LM	Lund & Manchester Groups clinical and neuropathological criteria for frontotemporal dementia, 1994
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination (Folstein, 1975)
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association work group (McKhann, 1984)
OCD	Obsessive-compulsive disorder
PA	Progressive nonfluent aphasia
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PET	Positron Emission Tomography
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
qEEG	Quantitative Electroencephalogram
rCBF	Regional cerebral blood flow
SZP	Schizophrenia
SD	Semantic dementia
SPECT	Single Photon Emission Computed Tomography
VaD	Vascular dementia

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1. INTRODUCTION

1.1 The centuries old debate about the interpretation of the clinical signs of FTD and general aim of the thesis

1.1.1 The Immortals of Luggnagg

Historically, dementia has been known ever since the romans. During the seventeenth and eighteenth centuries the concept of dementia were given medical as well as legal meanings (Berrios 1987). Common for the medical definitions was that they were rather diffuse and could refer to any of the types of the dementias that later have been recognized, in the nineteenth century and after that. Centuries back in time, observations of dementia were also made outside the scientific world, e.g. in the pure literature. In a debate in the Lancet in the beginning of 1990 (Lewis 1993, Crichton 1993) it was referred that one early, elegant description was written by Jonathan Swift (1667-1745) in Gulliver's Travels (1726) of what has more than 250 years later been recognized as a kind of progressing dementia (Crichton 1993). Today, the question is debated in the Lancet whether the kind of dementia that Swift portrayed in Gulliver's Travels was Alzheimer's disease or Pick's disease. The latter disorder is interesting in this study because of its clinical similarities with Frontotemporal dementia¹ (FTD), which is the focus for the present thesis.

In portraying the Struldbrugs or Immortals of Luggnagg Swift wrote: "When they came to four- score years, which is reckoned the extremity of living in this country...They were not only opinionative, peevish, covetous, morose, vain, talkative, but incapable of friendship, and dead to all natural affection ...Envy and impotent desires are their prevailing passions...They have no remembrance of anything but what they learned and observed in their youth and middle age, and even that is very imperfect...At ninety they lose their teeth and hair, they have at that age no distinction of taste, but eat and drink whatever they can get, without relish and appetite...In talking they forget the common appellation of things, and the names of persons, even those who are their nearest friends and relations. For the same reason, they

¹ According to the refined consensus criteria for Frontotemporal lobar degeneration (FTLD, Neary 1998) FTD, which in the first study of this thesis was labeled FLD, is only one variant of the larger frontal syndrome, FTLD, also including progressive nonfluent aphasia and semantic dementia. In current research FLD/FTD is also named the frontal variant of FTD (fv FTD), signifying the subdivision of FTLD that is associated with predominantly progressive personality change and executive difficulties (Bozeat 2000).

never can amuse themselves with reading, because their memory will not serve to carry them from the beginning of a sentence to the end” (Swift J 1913, p. 221-222).

In the debate in the *Lancet* it is referred, that based on earlier sources it has now been postulated that Swift himself had been afflicted with the same disease as he depicted in his book. In 1735, ten years before the death of Swift, his friends observed a deterioration of his memory: Three years later Swift himself wrote ”I have entirely lost my memory”. “In 1740 he noted, ‘I hardly understand one word I write’. In 1742 he was declared incompetent and his affairs placed in the hands of caretakers because ’[He] hath for these nine months past, been gradually failing in his memory and understanding and [is] of such unsound mind and memory that he is incapable of transacting any business, or managing, conducting, or taking care either of his estate or person” (Lewis 1993, p. 504). Towards the end of his life Swift exhibited “bouts of walking, a progressive aphasia and the inability to recognize anyone” (Lewis 1993, p. 504). The meanings about what kind of dementia Swift portrayed in *Gulliver’s Travels* and suffered from himself are said to go apart. In 1952 it was suggested that Swift suffered from ”cerebral arteriosclerosis” and ”involutional melancholia” (Lewis 1993, p. 504).

In the current debate it is proposed that the disease that Swift let the *Struldbrugs* illustrate was Alzheimer’s disease, and that it was Alzheimer’s disease that also caused the death of the writer (Lewis 1993). However, this interpretation is contradicted by the view that the early and pronounced personality changes of the *Immortals of Luggnagg* together with the “absence of cortical deficits typical of Alzheimer’s disease, such as apraxias and visuospatial disorientation”, more points towards Pick’s disease or syndrome. It has also been emphasized that the alert clinician should remember that ”dementia is not always caused by Alzheimer’s disease” (Chrichton, 1993, p. 874).

The passage from *Gulliver’s Travels* and the current debate about its interpretation and the cause of the death of the writer illustrate the ambiguity of the signs of dementia and particularly that of Alzheimer’s disease and Pick’s disease, or frontotemporal dementia. This particular question is also what this thesis is all about, namely how and by which means is it possible to distinguish frontotemporal dementia from Alzheimer’s disease using clinical methods.

1.2 Overview of frontotemporal dementia: clinical features

1.2.1 Pick's disease

Much of what today is known about FTD and even semantic dementia or other types of language disorders originates in the discoveries made by Arnold Pick more than a century ago. The type of dementia that Pick discovered, Pick's disease, is in actual research sometimes treated as an equivalent to FTD². The following summary of Pick's disease is made to highlight how Pick's disease is related to FTD, the latter disease being in focus of the present thesis. In 1892 Arnold Pick described a 71-year-old man who developed transcortical sensory aphasia within the context of dementia. During the preceding two years this man had become increasingly feeble-minded, getting furious and threatening his wife with a knife. He had also become increasingly childish. By admission to the hospital the patient had suffered from progressive memory deficits since three years. At autopsy, the patient presented disproportionate atrophy of the left temporal lobe, apart from the superior temporal gyrus (Pick 1892). With this case report, Pick wished to demonstrate that a "diffuse" atrophic process can produce focal neurological signs – in this case transcortical sensory aphasia – by locally intensified atrophy. Pick's findings were later described by Alzheimer and Altman as argyrophilic inclusions (later named Pick bodies) and swollen achromatic cells (later Pick cells, Altman 1923), in the absence of senile plaques and tangles (Alzheimer 1911). An important feature of Pick's disease, demonstrated by Altman and others, is the *characteristic corticolaminar and regional distribution of atrophy*. Authors interested primarily in putative cytoskeletal markers for dementing diseases sometimes overlook this observation. Furthermore, the original definition of Pick's disease did not hinge on the presence of ballooned neurons and/or argyrophilic intraneuronal inclusions (Onari 1926; *contra* McKhann 2001). Pick also reported further cases with language disturbance, amnesic aphasia, which at autopsy were shown to be associated with left temporal lobe atrophy (Binetti 1998). In fact,

² Pick considered his 1892 case and others to be "focalized" variants of senile dementia. Thus, he did not claim to have discovered a special type of dementia. The term "Pick's atrophy" or Pick's disease was introduced in the 1920's.

Pick (1904) referred to such cases as “left temporal lobe atrophy” (linksseitige Schläfenlappenatrophie).

In addition to the identification of language and behavioral disturbances, the scientific contribution of Pick was that he pointed out the existence of focal and circumscribed atrophy, which contradicted the contemporary opinion, namely that senile atrophy without exception is diffuse (Rossor 2001). At present, the absence of fundamental genetic and molecular biological data, makes the question whether Pick’s disease and FTD are two separate diseases or not still unanswered (Litvan 1997, Mann 1998). Some authors use the term Pick’s disease synonymously with FTD, while others use it exclusively to label specific intraneuronal inclusions (Hodges 2001 a). It has been recommended that the clinical label Pick’s disease should be restricted to histologically confirmed cases with Pick bodies and Pick cells (Pasquier 1997). In the present study it has not been possible to decide whether some of the patients actually suffered from Pick’s disease, since so few of the participants have come to autopsy.

1.2.2 Frontotemporal dementia: diagnostic criteria

In 1994, the Lund & Manchester Groups (LM) presented clinical and neuropathological criteria for frontotemporal dementia (The Lund and Manchester Groups 1994). Before the advent of the LM criteria there were no uniform guidelines for the assessment of FTD. The LM criteria represented a great leap forward for the investigation and understanding of FTD. The essence of the LM core criteria of FTD is that FTD is a behavioral disorder characterized by an insidious onset and slow progression. The behavioral abnormalities range from early loss of social awareness, early signs of disinhibition and hyperorality to mental rigidity and early loss of insight into the pathological change of the own mental state. Core criteria are also affective symptoms, e.g. depression, hypochondriasis, emotional unconcern and amimia, speech disorder, and physical signs such as early primitive reflexes and late akinesia. The final core clinical criteria are a normal EEG, brain imaging (structural or functional) with predominantly frontal or anterior temporal abnormalities or both, and profound failure on frontal lobe sensible tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder. As supportive diagnostic features are mentioned onset before 65 years, a positive family history, and signs of motor neuron disease (LM 1994). In an evaluation of these criteria it was found that a small subset of the behavioral criteria differentiated FTD from AD

to 100% (Miller 1997). A year later (1998) appeared refined consensus criteria for frontotemporal lobar degeneration (CC, Neary 1998). Reflecting the current scientific paradigm that frontotemporal degenerative changes represents an heterogeneous group of diseases (Rosen 2002 a) depending on the site and type of, but not clinically distinguishable, histological changes (Snowden 2002), the consensus criteria also included criteria for progressive nonfluent aphasia (PA) and semantic dementia (SD), first described by Mesulam as Primary Progressive Aphasia (PPA, Mesulam 1982). The core diagnostic features of FTD were reduced to five early signs (Neary 1998), as compared to the original LM criteria, namely insidious onset and gradual progression, early decline in social and interpersonal conduct, early impairment in regulation of personal conduct, early emotional blunting and early loss of insight. Most of the remaining core criteria were considered as supportive diagnostic features.

The LM and consensus criteria does not attempt to localize the frontal lobe dysfunctions. A logical way to conceive the frontal lobe dysfunctions is a division of the frontal lobes into three separate regions, the orbitobasal (ventromedial), the medial (medial frontal-anterior cingulate cortex) and the dorsolateral region. Changes in the orbital region have been associated with disinhibition, antisocial behavior, stereotypies (Hogdes 2001 b), and at advances stages in Pick's disease, Kluver-Bucy like behavior (Cummings 1981) such as hypersexuality and hyperorality (Hogdes 2001 b). Damage to the medial region has been connected with apathy, and to the dorsolateral area with executive difficulties (Hogdes 2001 b). This division of the frontal lobes originally goes back to a work by Alexander and colleagues (Alexander 1986).

1.2.3 Epidemiology of frontotemporal dementia and Alzheimer's disease

Relative to Alzheimer's disease, Frontotemporal dementia is a fairly small disorder. FTD encompasses around 20% of all dementias (Snowden 2002), whereas Alzheimer's disease accounts for between 50 and 75% of the dementias, depending on the criteria used to assess the diagnosis (Tolnay 2001). The onset of FTD is usually between 45 and 65 years (Snowden. 2002). With the enhanced knowledge about the prevalence of AD, the more recently established diagnosis of Mild Cognitive Impairment, (MCI), and the identification of a presymptomatic phase of AD (Honig 2001), the limits of onset of AD appears somewhat diffuse. AD is usually found to occur in late life , but occasionally the onset occurs before 60 years (presenile dementia, Greicius 2002). The incidence of FTD is equal between men and

women, and the mean duration of the disease is 8 years, with a range from two to 20 years (Snowden 2002). AD is more represented among women than men (Gao 1998). The duration of AD has been estimated to range between five and nine years (Greicius 2002).

1.2.4 Radiology, neuropathology and familial types of frontotemporal dementia and related disorders

FTD patients are distinguished by frontal, temporal or anterior temporal atrophy on magnetic resonance imaging (MRI), and computed tomography (CT, Snowden 1996). Occasionally, MRI may be normal in the very beginning of the disease (Miller 1991). Single photon emission computed tomography (SPECT) and positron emission tomography (PET) reveal abnormalities in the anterior cerebral hemispheres. In most studies the electroencephalogram (EEG) is normal in FTD patients (Miller 1991, Pasquier 1997, Neary 2000 a). Atrophy in FTD may be unilateral or bilateral (Miller 1997), but even if the atrophy is bilateral there may be some asymmetry with a dominance for either left-sided or right-sided frontal degeneration (Neary 2000 b). Predominantly left-sided frontal hypoperfusion has been associated with nonfluent aphasia, self-depreciation, depression and social withdrawal, whereas right-sided frontal hypoperfusion has been associated with behavioral changes and poorly modulated affects (Mychack 2001). This latter localization of dysfunctions emphasize the importance of the hemispheric site of the degeneration, whereas the previously described division in the orbital, medial and dorsolateral area stresses the cerebral regional localization of the behavioral alterations (Hogdes 2001 b).

The neuropathology of FTD and related dementias is described in Table 1. In Pick's disease, the pathology is most concentrated to the limbic system and striatum, but is also present in the frontal and temporal cortex (Snowden 2002). Pick's disease belongs to the tauopathies (Tolnay 2001). In FTD the atrophy is most prominent in the frontal and temporal regions, but the limbic system and striatum may also be mildly involved (Snowden 2002). During the last years the knowledge about the underlying mechanisms of FTD has largely expanded. It has been found that the clinical pictures of FTD and the Kluver-Bucy syndrome may be associated with presenilin-1 mutations (Tang-Wai 2002). In case of FTD, a linkage to chromosome 3 has also been found (Brown 1995). Besides the typical microvacuolation in FTD (Snowden 2002), ubiquitinated neuritic degeneration has been identified in the frontotemporal cortex in five FTD cases without motor neuron disease, using immunohistochemistry (Tolnay 1995). In Familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP 17), the pathology is most observed in the superficial

cortical layers of the frontal and temporal lobes, the basal ganglia and substantia nigra (Tolnay 2001). Corticobasal degeneration (CBD) was earlier conceived as a motor syndrome, but it has become more and more obvious that the disease may present as dementia (Grimes 1999, Tolnay 2001). In CBD swollen achromatic neurons are concentrated to the parietal cortex, and basophilic inclusion bodies to the substantia nigra and

Table 1. Neuropathology of dementias

Disease	Histological markers	Protein aggregates/ Genetics
Pick's disease	Loss of large cortical nerve cells, gliosis, minimal or no spongiform change or microvacuolation, often swollen neurons or inclusions	tau
Frontotemporal dementia	Loss of large cortical nerve cells, spongiform degeneration or microvacuolation	ubiquitin presenilin-1 linkage to chromosome 3
Familial frontotemporal dementia and parkinsonism linked to chromosome 17	Neuron loss, gliosis, spongiosis	tau
Corticobasal degeneration	Swollen achromatic neurons, basophilic inclusion bodies	tau
Alzheimers disease	Neuritic plaques, neurofibrillary tangles	presenilin-1 presenilin-2 β -amyloid precursor protein

basal nuclei (Neary 1997). In AD the atrophy is particularly prominent in the medial and posterior cortices (Neary 1994, Cummings 2002). Concerning the genetics in AD, mutations in three different genes have been identified: β -amyloid precursor protein, presenilin-1 and presenilin-2, which are located on chromosomes 21, 14 and 1 respectively (Honig 2001). Familial types of FTD occur in approximately 50% of the cases (Snowden 2002). In AD barely 1% of the disorder is inherited with strict autosomal dominant pattern (Honig 2001).

1.2.4.1 Subtypes of frontotemporal dementia

1.2.4.1.1 Semantic dementia

Semantic dementia is a disorder characterized by loss of meaning and understanding of verbal stimuli as well as nonverbal stimuli (Neary 2000 a), e.g. not being able to read the clock. There is a breakdown of the semantic memory (Warrington 1975). Semantic memory is defined as the permanent conceptual knowledge about things in the world and their interrelationships (Tulving 1972). When semantic memory is damaged, concept formation becomes disintegrated, with consequences for e.g. naming, word comprehension and object recognition (Neary 2000 b, Hodges 2001 b). Patients with semantic dementia are still able to read a word aloud and even to spell regular words, although the words have lost their conceptual meaning, so called semantic anomia (Edwards-Lee 1997). The spoken language is typically fluent and unconstrained, the syntax is preserved, and phonological errors are absent, but the speech is devoid of substance and contains paraphasias (e.g. dog for camel, Neary 2000 b). In the spontaneous speech patients merely use the words that are accessible, but not always adequate (Snowden 1999). Visuospatial ability and episodic memory are fairly well preserved in the early stages, which distinguishes this disorder from AD. Due to the initial preservation of visuospatial thinking and episodic memory, the phonological and grammatical structure of language and the fluency of speech, the early signs of semantic dementia are subtle. Behavioral alterations are usually mild at presentation, but when they occur they have a compulsive and stereotype character. With progression of the disease, even the speech becomes increasingly stereotyped. At the end stage patients may become mute (Neary 2000 b, Hodges 2001 b).

Neuroimaging typically reveal temporal lobe hypoperfusion on HMPAO-SPECT, and temporal lobe atrophy on MRI (Neary 2000 b, Hodges 2001 b). EEG continues to be normal throughout the disease course (Neary 2000 b). The atrophy is mostly asymmetrical, with a larger involvement of the left temporal lobe than the right (Hodges 2001 b). The right occipitotemporal region has been found to be important for face recognition (Meadows 1974). In accordance with this localization of functions, cases with predominantly right-sided temporal lobe atrophy have been reported to have difficulties with the recognition of faces, which indicates that a new type of visuospatial dementia may be possible to identify. With time this inability develops to prosopagnosia (Evans 1995, Hodges 2001 b). Patients with right-sided temporal lobe atrophy have also been found to be more likely to develop bizarre behavior, than those with left-sided temporal lobe degeneration (Edwards-Lee 1997).

Demographic characteristics are similar to the demographic features in FTD and progressive aphasia. There may also be familial variants of semantic dementia (Neary 2000 a).

1.2.4.1.2 Progressive nonfluent aphasia

Progressive nonfluent aphasia (PA) initially affects the production of language. Early clinical manifestations of PA are speech dysfluency, forced, hesitant word production, and stuttering. Phonologic errors, word distortions and word finding difficulties are apparent in the spontaneous speech. Reading is strained, writing telegraphic and words are misspelled, reflecting the spoken output (Neary 2000 a). The linguistic problems gradually evolve to word deafness and muteness (Hodges 2001 b). Word comprehension remains unaffected in the initial stages of the disease, but deteriorates with progression, although the amount of the comprehension difficulties is hard to assess, because of the communication problems. Social skills and insight into the disorder remain intact in the early stages, but behavioral alterations similar to those in FTD may occur later in the disease course (Neary 2000 a). Visuospatial skills and episodic memory as well as other non-linguistic cognitive abilities are fairly unaffected for long, rendering it possible for patients to continue with their work several years after the onset of the disease (Neary 2000 b). However, with progression, PA evolves into a general cognitive dysfunction and dementia (Andersen 1997).

The dominant anatomic feature in PA is asymmetrical atrophy, comparatively mild and diffuse on the right side, but gross on the left side, and especially involving the frontotemporal, frontoparietal and lateral parieto-occipital areas. The left-sided limbic system, basal ganglia and thalamus are also atrophied. EEG is frequently found to be normal. PA has been identified in a family with FTD, and PA has also appeared in combination with MND. Both these associations reveal the link to FTD (Neary 2000 a).

1.3 Differential diagnosis

1.3.1 Frontotemporal dementia and Alzheimer's disease

Previously, senile decay was considered as equivalent with vascular processes, reflected in the term hardening of the arteries (McKahn 2001) or arteriosclerosis. When dementia was no longer perceived as arteriosclerosis, there was instead a stress on Alzheimer's disease (AD), with misdiagnoses of many different kinds of dementia as AD as a consequence. FTD is one of the primary degenerative diseases that sometimes has been mistaken for AD (Klatka 1996).

FTD may also be confounded with psychiatric disturbances, due to its comparatively early onset and pronounced behavioral alterations. A case has been reported where one 37-year-old woman developing e.g. hyperphagia, hypersexuality and disinhibition after delivery, initially was misdiagnosed and treated as post partum depression, although she later revealed disproportionate frontal lobe atrophy on MRI (Dell 2002).

As highlighted in the LM (1994) and the CC (1998) criteria, FTD is characterized by behavioral and emotional disturbances. Conversely, AD is more of a cognitive disorder, although the clinical differences between FTD and AD are not always clear-cut. The prevailing view is that AD usually starts with episodic memory deficits, reflecting medial temporal lobe atrophy, while social and emotional behavior initially are intact (Miller 1991, Rosen 2002 a). Gradually AD progresses as to involve even other cognitive domains, such as visuospatial skills, indicating changes in the parietal association cortex (Rascovsky 2002). Executive problems (see section 1.4) are not among the standard criteria of AD, but have occasionally been observed. Although changes in social and emotional behavior are not said to usually occur until late in the disease course of AD (Miller 1991, Rosen 2002 a), apathy and emotional indifference have been mentioned as early signs of AD. Even lack of insight and poor judgement have been found in AD. Language problems are frequent in AD, starting as anomia and progressing to fluent aphasia (Mega 1999, Cummings 2002, McKhann 2001). In FTD, memory is usually considered to be fairly well preserved, and when memory problems appears in FTD, they are explained as the effects of failing executive organizational and retrieval strategies, rather than as the results of primary amnesia. Spatial thinking is frequently found to be intact in FTD. In the cognitive domain the most prominent sign of FTD are executive dysfunctions (Neary 2000 b). Conduct in FTD is marked by a wide range of odd behaviors (Miller 1991, Snowden 1996). As in AD language problems occurs in FTD. Two types are mentioned, either economy of utterances, particularly in apathetic patients (Neary 2000 b), and pressure of speech, foremost in disinhibited patients (Neary 2000 a).

From this comparison between the clinical signs of AD and FTD it can be concluded that there is a considerable overlap in memory dysfunctions, executive disabilities, emotional disturbances and language problems, which of course may blur the clinical pictures and complicate the differentiation between the diseases. It has also been noted that neuropsychological differences between FTD and AD may be subtle, and that the diseases instead mirror each other (Pachana 1996). Some authors even claim that most FTD patients fulfill the criteria of AD (Pasquier 1999, Varma 1999), and that standard tests are poor in

separating FTD and AD (Gregory 1997). Clinical diagnosis of FTD and AD has all the same been considered possible, but then based on personality and behavioral changes, neuroimaging patterns and electroencephalogram (EEG) (Pasquier 1999).

1.3.2 Behavioral and psychological symptoms of dementia

Although personality changes are cardinal symptoms of FTD, neuropsychiatric disturbances occur in many types of dementia (Robert 2002). However, not all dementia patients develop this kind of symptoms (Shinosaki 2000). According to the International Psychogeriatric Association (IPA) consensus statement (1996) behavioral disturbances in dementia should be labeled behavioral and psychological symptoms of dementia (BPSD) and denote: "signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia" (Finkel 1996). Behavioral problems in FTD are usually not labeled BPSD, although many of the neuropsychiatric symptoms in FTD also are included in BPSD.

In the literature, BPSD is reported to have been known since long. However, research about BPSD has been delayed, partly because they are hard to investigate: the BPSD problems are highly individual, depending on personality traits and environmental factors, and therefore difficult to categorize, and dementia patients have difficulties in describing their symptoms (Shinosaki 2000). One of the first authors to report BPSD was Alzheimer. The woman that was his original patient had symptoms of dementia, as well as paranoid delusions and delusions of infidelity. She also was aggressive (Finkel 2000). Now, it is recognized that BPSD in AD, such as depression, social withdrawal and paranoia may precede the diagnosis by up to two years (Jost 1996). With progression of the disease, BPSD aggravate in AD, and symptoms like agitation, apathy and aberrant motor behavior becomes increasingly conspicuous (Cummings 1998; Robert 2002). BPSD are also salient in Lewy body dementia (LBD). Typical for LBD is fluctuating cognitive impairment, visual hallucinations, and parkinsonism (McKeith 1996). Other types of dementias where BPSD are frequent are Parkinson's disease with dementia (PDD) and vascular dementia (VaD). Characteristic neuropsychiatric signs of PDD are depression, hallucinations, delusions and apathy (Aarsland 2001, Robert 2002). In VaD salient neuropsychiatric signs are anxiety and depression, besides the neuropsychological deficits (Robert 2002).

Efforts have been made to explain the occurrence of BPSD in dementias. In AD it has been suggested that changes in the limbic system, which is important for the processing of feelings,

may underlie the presence of BPSD. Degeneration of the orbitofrontal cortex in AD has been associated with agitation and aberrant motor behavior, and atrophy of the anterior cingulate cortex with apathy (Tekin 2001). Depressive symptoms in AD have also been linked to damage to the locus coeruleus (Lyketsos 2000) in the brain stem. In VaD neuropsychiatric symptoms have been reported to originate in ischemic lesions in subcortical areas that interfere with circuits connecting the prefrontal cortex to the basal ganglia, or with nonspecific thalamocortical projections (Kurz 2001). It has further been referred that cholinergic deficiencies have some importance for the appearance of BPSD in AD as well as LBD, PDD and VaD. In AD, BPSD have been associated with cholinergic deficits in the limbic and paralimbic system. In LBD, neuropsychiatric symptoms have been linked to disruptions of cholinergic and dopaminergic projections due to the presence of Lewy bodies in the brainstem, subcortical nuclei, the limbic and neocortex. Knowledge about the mechanisms underlying PDD is still incomplete, but behavioral manifestations such as hallucinations are thought to result from degeneration of cholinergic nuclei in the brainstem, in its turn leading to loss of innervation to the occipital cortex and thalamus (Robert 2002). The relationship between BPSD and cognitive dysfunctions in dementia has not been extensively investigated, but there are some indications of a relation between the two symptom domains. A significant correlation has e.g. been reported between the increase of apathy and worsening of cognitive decline in AD (Cummings 1999).

From this review can be concluded that that BPSD are not unique for FTD, but instead exists in AD as well as in most of the commonest dementias. Also, BPSD probably have effects on cognition. This means that most dementias are characterized by BPSD as well as cognitive decline. This further complicates the possibilities of differential diagnosis. On the other hand, a common trait for BPSD in AD, LBD, PDD and VaD is that this kind of non-cognitive symptoms appears to originate from destruction of frontal regions and associated subcortical structures, as a result from neuronal loss or cholinergic dysfunctions. These localizations further strengthens the nearly axiomatic assumption that the frontal lobes are the main seat for the regulation of behavior. FTD specifically strikes the frontotemporal region, but apparently other atrophied regions may cause BPSD, through the rupture of their connections to the areas in the frontal lobes that are important for the regulation of behavior. The clinical prerequisites to differentiate FTD from AD and the other dementias where BPSD may occur, seems to be knowledge of the specific behavioral and cognitive profiles of the different dementias, as well as about the typical patterns on neuroimaging and on neurophysiological examination. There

may be some overlap between the clinical presentations of the diseases, but focus for diagnosis must be on the differences.

1.3.3 FTD and psychiatric diseases

1.3.3.1 Obsessive compulsive disorder

Although there are many similarities between FTD and several psychiatric diseases, eg. obsessive-compulsive disorder (OCD), bipolar disorder (BPD) and schizophrenia (SZP), there hardly exist any systematic comparisons in the literature between cognition, behavior and neuropathology in FTD and these psychiatric disorders. Therefore, the following presentation will be restricted to a description of traits of FTD reported in FTD studies, that resemble on characteristic traits of OCD, BPD and SZP, reported in studies of solely these psychiatric disorders.

Repetitive and compulsive behavior may occur in FTD. Compulsiveness in FTD have a variety of expressions, such as motor mannerism, behavioral routines, verbal stereotypes or touching and counting behavior (Snowden 2002). OCD is a mental disturbance that in some respects may resemble FTD. Obsessive compulsive disorder occurs in children as well as in adults (Steinberger 2002), and is characterized by obsessions, i.e. intrusive ideas, thoughts or images that often cause anxiety or distress, and compulsions, i.e. involuntary repetitive acts that the person feels compelled to perform, frequently according to rigid rules, in order to be relieved from the obsessions (Jenike 2001). In a case study it was reported that a 45 year old woman felt compelled to put 5 ice cubes in a glass instead of 4, in order to prevent someone to die. The woman knew that this act was completely irrational, but although she was aware of this irrationality, she could not stop doing it. Other compulsions are not related to anxiety, but rather to a need to obtain satisfaction or a feeling of completeness by performing the act. OCD patients mostly have insight in their disorder and know that their acts are illogical, but this knowledge does not prevent them from performing the compulsive behaviors (Jenike 2001). According to the DSM IV criteria, OCD may sometimes also be associated with poor insight.

OCD usually imply different kinds of cognitive impairment, although compulsions such as ritualized handwashing or checking have not been possible to explain from specific failures on neuropsychological tests (Nielen 2002). There are evidences for a neurologic substrate for OCD. PET (Baxter 1987, Rauch 1994) and functional MRI (fMRI) studies (Breiter 1996) have shown increased brain activity in the frontal lobes, cingulum and basal ganglia in OCD

patients as compared to healthy control subjects. Striatal lesions have been reported in some OCD patients (Weiss 2000), as well as in FTD patients with repetitive behavior.

Compulsiveness in FTD has also been related to orbitofrontal and anterior temporal changes (Snowden 2002). In OCD it has further been found that patients have more grey matter and less white matter than normal controls, which might be interpreted as a developmental abnormality (Jenike 1996, Jenike 2001).

1.3.3.2 Bipolar Disorder

The orbitofrontal variant of FTD is characterized by disinhibited and outgoing behavior, whereas atrophy in the medial frontal-anterior cingulate region is connected with apathy (Hodges 2001 b). These extremes of FTD resemble BPD. In a case-study of typical BPD patients, a 47-year-old woman was described, that exhibited a series of classical hypomanic symptoms during the manic phases of her disease. These symptoms included e.g. euphoria, flight of ideas, hyperactivity, distractibility, impaired judgement with hypersexuality and excessive phone calling. During the depressive phases she experienced e.g. depression, insomnia, reduced appetite, decreased energy, psychomotor retardation, forgetfulness, pathological guilt and suicidal thoughts. The episodes amounted to three a year, with a return to a normal baseline in between (Lauterbach 1995). Most studies indicate few and less severe cognitive deficits in younger and/or euthymic patients than in chronic elderly, psychotic or multiple-episode patients, indicating a possible toxic disease process. BPD has been related to several types of neuroanatomical abnormalities. The disease has been associated with white matter hyperintensities, but such changes are not unique for BPD, since signal hyperintensities have also been found in cardiovascular diseases. BPD has further been reported to involve the frontal cortex and the basal ganglia structures. As in schizophrenia there are indications in BPD of ventricular and sulcal widening (Bearden 2001). In BPD reduced cerebellar output to cortical, thalamic, basal ganglia, limbic or other circuits, as well as nigral pars reticulata dysfunction has been found to play an important role for particularly rapid-cycling types of BPD and dystonia (Lauterbach 1995).

1.3.3.3 Schizophrenia

Psychotic features sometimes appear in FTD. The psychotic strains, the existence of an apathetic variant of FTD, the loss of insight that is so characteristic for the disease, and the comparatively early onset, may erroneously make FTD appear as schizophrenia (Gustafson 1993). According to DSM IV the onset of SZP often occurs in the late teenage, and mid 30-s. Onset before adolescence is unusual, although cases with onset at the age of 5 or 6 years have been reported. Schizophrenia is usually divided in two main types of symptoms: *positive* and

negative. *Positive* symptoms are hallucinations, delusions, thought disorder, ego-disturbance and catatonia (Carpenter 1988). *Negative* symptoms are flat affect, reduced emotional repertoire, poverty of speech, curbing of interests and lack of will-power (Carpenter 1988, Galderesi 2002). Poor insight may also be one prominent symptom of SZP (Lysaker 1998). Although loss of insight is central for FTD, the concept of insight is seldom defined in FTD studies. A good definition of poor insight is used in a study of neurocognitive function and insight in schizophrenia, namely: “unawareness of symptoms, unawareness of the need for treatment and unawareness of the consequences of the disorder” (p. 298, Lysaker 1998). As in OCD and BPD cognitive dysfunctions has been reported in schizophrenia. In one study, general cognitive ability (WAIS-R IQ) was found to be significantly lower in patients with nondeficit (positive) schizophrenia (IQ mean 81.9, SD 15.1) relative healthy control subjects (IQ mean 94.5, SD 13.9) as well as in deficit (negative) schizophrenia (IQ mean 76.2, SD 12.9) relative controls. IQ in deficit SZP was also significantly lower than in nondeficit SZP. Executive dysfunctions were present in both disease groups, but more pronounced in nondeficit SZP than in deficit SZP, in comparison with healthy subjects. Neuropsychological findings concerning focused/sustained attention suggested impairment in frontoparietal circuits (Galderesi 2002). Neuroanatomical changes such as ventricular and sulcal enlargement in SZP have already been mentioned (Bearden 2001). Other changes in SZP are volume reduction of heteromodal cortical areas and mesiotemporal structures (Bearden 2001).

The psychological rationale for many of the psychiatric abnormalities in the the world of ideas and in behavior are well penetrated, whereas in the research about FTD and AD, psychiatric concepts are mostly used without assessing the meaning of these concepts in dementia. That is, acts that appear as e.g. compulsive in FTD may not fulfill the psychiatric criteria of compulsiveness, because the reasons behind the behavior may be quite different in FTD than in the psychiatric disorder. However, some efforts have been made to investigate the content of delusions in dementia. It has e.g. been claimed that the content of delusions in dementia is comparatively simple, and might be associated with the cognitive decline in the disease (Shinosaki 2000). Among the neuropsychiatric symptoms that have been reported in AD are persecutory delusions, delusional jealousy, suspicion of being poisoned, “phantom boarder” symptom (experiencing imaginary guests living in the own house), believing that the images on television were real, and seeing another person than themselves when looking into the mirror (Förstl 1994). Clinically, none of these mental distortions appear to be simpler in AD, than the psychotic symptoms in patients with functional psychoses, but it might be

speculated that the more affected the cognition, the simpler the mental distortions, and that this may apply for dementias as well as for psychiatric diseases.

As is evident from the comparisons between FTD, OCD, BPD and SZP frontotemporal and/or associated subcortical structures are involved in all of these diseases. Neuropsychological impairment occurs in all the three psychiatric diseases, as well as selectively executive deficits (SZP). There is however a considerable lack of knowledge about how the neuropsychological profile in FTD is related to the profiles in psychiatric diseases.

1.3.3.4 Depression

According to DSM IV there are two types of depression, major depression characterized by e.g. either depressed mood or loss of interest or pleasure, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death, suicidal ideation, or suicide attempt, and dysthymic disorder denoting e.g. poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions or feelings of hopelessness (DSM IV). Concerning the relationship between depression and cognition there are conflicting evidences. In one study it was found that depression was associated with mild as well as severe dementia (Sultzer 1992), whereas in another no such relationship was found (Cooper 1990).

In elderly people anxiety often coexist with depression. Cognitive impairment due to depression in elderly is often conceived as pseudo-dementia or depression with dementia, and it has been claimed that it is important to distinguish this condition from predementia (Gottfries 1998). The prevalence of depression in dementia patients has been compared with the occurrence of dementia in elderly persons without dementia. The total amount of depressive symptoms were not more frequent in dementia patients than in healthy subjects, but there was a tendency towards more motivational symptoms (e.g. fatigue, subjective slowing in thinking and in movements, lack of energy and loss of interest) and less mood symptoms (e.g. worries, depressed mood, feelings that life is not worth living and wishes to die) in subjects with dementia than in subjects without dementia (Janzing 2002).

The occurrence of depression in different dementia types has also been investigated. In a study of patients with AD, FTD and VaD the relation between depression, assessed as

presence of depressed mood and anxiety, and regional brain pathology, it was found that 35% of the patients had symptoms of depression, and that a depressive symptomatology was significantly more frequent in patients with subcortical lesions than in patients with degeneration in any of the other examined brain areas. The relation between subcortical atrophy and depression was explained as a rupture of the anatomical circuits that connects subcortical nuclei with the limbic system and the prefrontal cortex. The absence of correlation between FTD and depression was not interpreted down to the last letter. As a whole, the results were instead interpreted as if depression was associated with disturbances in the fronto-subcortical neural networks (Lind 2002). These findings are congruent with another study where the prevalence of minor and major depression in ischemic vascular dementia (IVD), AD, mixed dementia, AD/IVD, was examined. The study indicated a higher prevalence of depression in IVD than in AD. Neither minor nor major depression had any effect on cognitive impairment, when the cognitive ability was assessed by MMSE (Hargrave 2000).

Depression may be confounded with apathy, due to an apparent similar clinical presentation. The relationship between depression and apathy has been studied in AD and FTD patients, and subjects with Parkinson's disease (PD), progressive supranuclear palsy (PSP) and Huntington's disease (HD). In the whole sample, no correlation was found between depression and apathy, suggesting that these disturbances are two different entities. In the subsamples it appeared as if depression and apathy were disease-specific. AD, FTD and PSP patients revealed more apathy, whereas PD and HD more of depression. Apathy was significantly correlated with lower cognitive levels, assessed by MMSE, but there was no consistent relationship between depression and increased cognitive impairment (Levy 1998).

One reason that was given to the confounding in the literature of depression with apathy was that there may be an overlap between the items included in depression and apathy scales. Another reason was that similar circuits could be involved in depression and apathy. Variations in neurotransmitter involvement should account for the differences underlying the two symptoms. One conclusion of the study was that apathy and depression should be considered as distinct neuropsychiatric syndromes (Levy 1998).

Thus, it appears as if there is no automatic relationship between depression and cognitive impairment, neither in non demented persons – although this is stipulated in the DSM IV criteria for major and minor depression - nor in dementia patients. Depression, as well as

apathy, seems to be disease-specific, with apathy being more frequent in FTD, AD and PSP, whereas depression is more typical for PD and HD. Apathy appears to be associated with cognitive decline, suggesting an association between frontal-subcortical circuits and cognitive functions.

1.3.3.5 How are psychiatric diseases related to the risk of developing dementia?

The risk for patients with affective disorders (schizophrenia included) of developing dementia has been evaluated in large samples and compared to the risk of getting dementia in the general population. It was found that patients with unipolar as well as bipolar affective disorder had a higher risk of developing dementia than patients with schizophrenia and neurosis (neurosis depressiva included in the latter diagnosis). It was also found that all the psychiatric patient groups had a higher risk of developing dementia than sex- and age-matched samples of the general population. The lower risk for schizophrenic patients to develop dementia as compared to unipolar and bipolar patients was explained as a possible result of an avoidance to assign dementia as an auxiliary diagnosis, since cognitive impairment may be part of schizophrenia. Despite this, the risk of dementia in schizophrenia was more elevated than in the general population (Kessing 1999).

From this review of the literature about the psychiatric disturbances, depression and the risk of dementia can be concluded that neuropsychological deficits appear in OCD, BPD and SZP. Depression is not always associated with cognitive impairment, but it may be, and there are some indications of a relationship between apathy and cognitive decline. Depression and apathy seems to be disease-specific, with apathy being more frequent in FTD, AD and PSP, than depression. The psychiatric disorders as well as depression and apathy all involves the frontal lobes and associated subcortical structures. The psychiatric diseases and neurosis depressiva carries an increased risk of developing dementia.

The psychiatric symptoms, cognitive deficits and frontal-subcortical involvement make these diagnoses appear very similar to FTD. However, several studies about cognitive functioning in psychiatric diseases and depression have used MMSE (Folstein 1975) to assess the cognitive levels. MMSE is not an instrument for a thorough investigation of cognition. Maybe, cognition has been somewhat neglected in studies of psychiatric diseases and depression, since these disorders have been conceived as primarily affective. More careful analysis of cognition in the affective disorders and depression would be helpful to distinguish

these disturbances from FTD and AD, in case that some of these psychiatric diseases are conceived as possible differential diagnoses.

1.4. Theories of frontal lobe functioning and neuropsychological core concepts

1.4.1 Theories

In a recently described synopsis of frontal lobe functions and dysfunctions by Fuster (1999), the prefrontal cortex is described as the most highly interconnected part of the neocortex. The main features of this synopsis will be described. According to the synopsis the prefrontal cortex receives input from the brainstem, the hypothalamus, the limbic system (amygdala and hippocampus) the thalamus, and from other neocortical areas, particularly from the postrolandic association cortex. Input from the brainstem, hypothalamus and limbic system brings information about the internal milieu, and the hippocampus mediates information that is necessary for the establishment of motor memory. The prefrontal cortex responds with efferent impulses to all the afferent impulses from these structures.

The prefrontal cortex, and particularly the dorsolateral area, house the executive functions. The spoken language is another important frontal lobe function. Regarding the executive ability, the prefrontal cortex and particularly the dorsolateral region, have representational as well as operant functions. The latter function consists of the creation and representation of schemas or plans for behavior. These plans are formed under the influence of inputs from the amygdala, the hippocampus and the postrolandic cortex, as well as from the brainstem, which is supposed to be in charge of the maintenance of drive and motivation of the organism. Any kind of action presupposes the temporal organization of sequences. The creation of a temporal “gestalt” requires integration of every single component involved in the behavioral sequence in progress. According to Fuster (1999), three mental operations are important prerequisites for the formation of the gestalt: 1. preparatory set 2. working memory 3. inhibitory control.

1. Set is described as motor attention oriented towards the action in preparation, the representation of the plan and, simultaneously, towards long term motor memories that are temporarily activated for the execution of the plan. A certain type of “set cells” have been discovered in monkeys in the dorsolateral area. In the synopsis it is assumed that these “set cells” are activated during the preparation for action and prepares the motor mechanisms for it.

The association with the motor apparatus suggests links to the premotor cortex, basal ganglia and pyramidal system.

2. Certain “memory cells” (neocortical neurons) have been identified in monkeys. These memory cells were intermingled with the “set-cells” in the dorsolateral area. The memory cells look back in time to the immediately preceding sensory information, on which the impending action is going to be built. These memory cells constitute a widespread network of neocortical neurons, that are kept active by the prefrontal cortex as long as it is necessary for the prospective action. The prefrontal cortex is still considered as important for working memory, but it is emphasized that it receives its importance from being a part of the cortico-cortical interactions between the prefrontal cortex and the postrolandic areas, that are necessary for the formation of working memory. It is claimed that the localization of the working memory to the prefrontal cortex is a misconception.

3. The most prominent function of the orbitofrontal cortex is the protection of the goal-directed behavior from interference. Interference may have many sources. Interferences may come from the context of the behavioral gestalt, and divert the behavior from its goal. Other interferences may be inborn, like instincts. Well-established behavioral routines may also inappropriately interfere with ongoing activities. There have not been found any electrophysiological correlates to the inhibitory function of the orbitofrontal cortex, but it is suggested that it should be selectively mediated by the GABA-ergic system, and the inhibitory cortico-hypothalamic pathways that descends from the orbitofrontal cortex.

Another explanation to the regulative orbitofrontal function is made with reference to reward-punishment reinforcement contingencies. Recently, it has been proposed that the orbitofrontal region, anterior cingulate cortex and the insula are critical for the establishment of reward-punishment reinforcement contingencies. Damage to these regions may result in an inability to relate incoming and internal stimuli to good or bad outcomes, and to decide upon the appropriate course of action. Because of the incapacity to evaluate the outcomes of different actions, this may result in disinhibited behavior, or in an inability to abandon previous courses of action, with mental rigidity as a consequence (Rosen 2002 b). Problems with stopping may thus show up as disinhibition (Lezak, 1995). Dysfunctions in the reward-punishment system may also contribute to obsessive-compulsive behavior (Rosen 2002 b).

According to the synopsis (Fuster 1999), lesions in the dorsolateral area may cause a wide variety of symptoms. Among the most common symptoms of the dorsolateral syndrome are lack of drive, motivation and attention as well as working memory deficits. These deficits results in an inability to create new behavior, i.e. to formulate plans or new schemas of action, or speech, and a confinement to old habits. The defect in the motor set - lack of drive, inability to make decisions and deficient preparation for impending actions - ends up in inabilities to execute the action. Together, these behavioral alterations are labeled the dysexecutive syndrome. Lesions in the medial/cingulate area are associated with an even more pronounced apathy, than the lack of drive that is connected with dorsolateral lesions. The kind of apathy that is associated with the medial/cingulate syndrome is reflected in inattention and disinterest, and generally, in a lack of spontaneity in all the aspects of action and speech. Movement is also reduced. The orbitofrontal syndrome is marked by a malfunction in the inhibitory control of the orbital cortex. This also results in an attention disorder, but of another kind than in the other syndromes. The attention disorder of the orbitofrontal syndrome does not consist of difficulties to focus and concentrate, but rather of problems with the exclusionary aspect of attention. The patient becomes unable to suppress or inhibit interference from distracting stimuli, and turns hyperactive. Other symptoms of this syndrome are euphoria, inappropriate childish humour and obedience to instincts, without moral restraints (Fuster 1999).

In the synopsis (Fuster 1999), schizophrenia is also considered as a disorder that among other regions of the brain involve the prefrontal cortex. It is emphasized that the pathogenesis of schizophrenia is of a specific kind, and that injuries to the prefrontal cortex does not result in schizophrenia. This disorder is associated with disturbances in neurotransmitter systems, and particularly in the dopaminergic systems, which are largely represented in the prefrontal cortex. Disturbances in those systems affect the connectivity of the prefrontal cortex with the limbic system, the basal ganglia and the remaining neocortical regions, with impairment of those emotions and cognitive functions that are associated with this connectivity as a consequence (Fuster 1999).

1.4.2 Concepts

The concepts that are used in the thesis are concepts that usually are investigated in studies of FTD and AD. They might be conceived as efforts to operationalize the above described models of frontal lobe functioning, although the underlying anatomical mechanisms of the

concepts in many cases are unclear. Some of the concepts, which are defined according to state of the art, are overlapping. This is thought to reflect that the products of mind are the result of cerebral cooperation.

Conceptually, motivation may be divided in *emotions* and *feelings*. According to one definition, the *emotion* is the bodily part of the *feeling*. Through the evolution, the internal milieu (viscera and the muskuloskeletal system) as well as targets in the brain, as the monoaminergic nuclei in the brainstem tegmentum, have been prepared to react to emotional stimuli, e.g. hunger, thirst, pain, joy or sadness, with certain patterns of responses. The *feeling* is the mental representation, or interpretation, of these physical, emotional reactions (Damasio 2001). In the present thesis, there has been made no difference between the bodily reactions and mental representations. These two sides of the coin have been named *emotion*, since this term is most frequently used in this sense in the current literature.

The *self* is the inner experience of being a whole distinguished from other persons. The *self* is the subjective experience of the own person, and include domains such as semantic knowledge about personal attributes, autobiographical memories, and motivations to maintain self-schemas (will). Changes in learned self-concepts have been associated with nondominant frontal lobe degeneration (Miller 2001). The *self* is not the same as the Freudian *ego*. The *ego* is part of the structural hypothesis. According to this hypothesis, the *ego* has got observational, executive and cognitive tasks in its mediation between inner and outer demands, and strive for adaptation (Fenichel 1966). Defined in that way, many of the tasks of the *ego* are in current research taken over by the *executive* and *cognitive* functions. *Executive* abilities refers to the organizing aspect of the realization of cognitive tasks, which enables the individual to engage in independent and goal-directed behavior (Lezak 1995).

In the conceptual schemas in this thesis, the *executive* ability denotes a series of functions, which are necessary for the implementation of all kinds of tasks. In order to realize a *plan*, the actor must be able to *initiate*, *maintain*, *switch*, and *stop* behavioral sequences (Lezak 1995). *Initiation* of actions are closely related to *volition*, and severe problems of starting may result in apathy. *Purposive action* presupposes that the actor is *aware* of the goal. *Self-awareness* may be the same as being mentally conscious, which means being at the same time the actor and being able to observe and influence the own activities. This state may be compared to dreaming, when the dreamer is the illusory actor in the dream, but without possibilities to influence the course of events in the dream. Self-awareness (monitoring ongoing activities) is

necessary for *self-correction*, i.e. the ability to initiate changes that are perceived as necessary to obtain the goal (Lezak 1995). Deficiencies in self-awareness may result in loss of insight, which is typical for FTD. The *maintaining*, *switching*, and *organizing of behavior* as well as *self-direction* have been localized to the dorsolateral area (Mega 1994).

Personality is a term that often appears in the literature about frontal lobes, FTD and even AD. Strictly, it should denote a consistent pattern of *behavior*, although there are some doubts in the literature if the *behavior* of a person always is consistent in similar situations (Hergenhahn 1984). In the literature about FTD, *personality* is used in a wide variety of senses. Sometimes it equals emotions and feelings, sometimes executive abilities and *behavior*, now and then the self, and it also happens that personality is used as a common appellation for all these concepts. In the analytical schemas used in this thesis, the label *behavior* has usually been restricted to executive functions and emotions. Occasionally *behavior* has only denoted executive abilities, as opposed to emotions.

Cognition refers to the “information-handling aspect” of mental activities (Lezak, 1995 p. 20). Cognitive functioning may be divided into five subdivisions: *perception* which is closely related to attention, and signifies abilities to select, register and interpret information, *memory* which denotes the encoding, storage and retrieval of information, for shorter or longer periods of time (Lezak, 1995 p. 25), and *learning*, i.e. the transference of knowledge acquired in one situation to another. *Thinking* designate “the mental organization and reorganization of information” (Lezak 1995, p. 22). *Language* might be conceived as an expressive function, i.e. “the means through which information is communicated or acted upon” (Lezak, 1995 p. 22). Usually, cognitive functions are supposed to be localized to the posterior areas of the brain (see study III). However, the frontal lobes are known to be crucial for attention, short-term memory (Stuss 1994) and for verbal fluency (Lezak 1995).

Dementia affects the mind as well as the body. The word *dementia* originates in the Latin root *demens*, meaning “being out of one’s mind” (Berrios 1987, p. 830). In current clinical language dementia may refer to on the one hand a deteriorated mental estate or process irrespective of etiology, on the other to cognitive decline with neurodegenerative causes. Ever since at least the seventeenth century dementia has been associated with cognitive decline in old age (Berrios 1987).

Table 2. Demographic characteristics of FTD and AD patients and healthy control subjects. Mean values.

	FTD					AD					Healthy control subjects				
	n	Sex M/F	Test age	Educ	MMSE years	n	Sex M/F	Test age	Educ	MMSE years	n	Sex M/F	Test age	Educ	MMSE years
I	14	5/9	64.3	10.2	16.3	3.4	15	8/7	63.7	9.7	15.0	4.3	-	-	-
II	52	25/27	64.0*	-	18.6	-	101	38/63	71.0*	-	18.2	-	-	-	-
III	13	5/8	58.4	10.2	18.6	2.6	-	-	-	-	-	-	10	4/6	62.2
IV	19	6/13	58.9	11.5	22.4	3.0	16	5/11	59.4	9.3	20.1	3.1	19	9/10	61.7
V	18	6/12	60.1	11.2	21.2	2.5	14	7/7	59.6	10.4	19.8	2.8	20	7/13	61.3
														12.4	29.4

* In study II test age signifies the age at first clinical investigation, not the age at first symptoms

1.5 Aim of the thesis

As should be evident from the introduction, there are both clinical similarities and differences between FTD and AD. The general aim of the thesis was to investigate FTD in relation to AD from a differential diagnostic point of view, with the use of preclinical, neuropsychological, behavioral, volumetric, radiologic and neurophysiologic information.

2. METHODS

2.1 Subjects

Study I. FTD and AD patients

Two groups of patients were included in the study: 14 FTD patients and 15 AD patients (Table 2). The subjects were recruited from patients consecutively referred to the Department of Geriatric Medicine, Huddinge University Hospital. For clinical diagnosis all patients underwent a comprehensive examination including neuroimaging (computerized tomography, CT, magnetic resonance imaging, MRI, in some of the cases single-photon emission computed tomography, SPECT), in most of the cases, electroencephalography (EEG), interviews with relatives, and neuropsychological examination. This neuropsychological information was not used for the purposes of the study. The FTD patients fulfilled the DSM III criteria for primary degenerative dementia and the LM clinical criteria for frontotemporal dementia. The AD patients were defined according to the DSM III criteria for AD and the recommendations of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) work group (McKhann 1984). The disease groups were matched on group level with respect to age, years of education, and general cognitive ability, assessed with Mini Mental State Examination (MMSE, Folstein 1975). For the purpose of the study, all patients were subjected to neuropsychological testing with 12 psychometric tests and observation of 40 behavioral items.

Study II. FTD and AD patients

Even in this study two groups of patients participated: 52 FTD patients and 101 AD patients (Table 2). The subjects were recruited among patients consecutively referred to the UCLA

Alzheimer's disease Center, Los Angeles, USA, where they had undergone an extensive clinical examination for diagnostic purposes. This examination comprised neuropsychological assessment, neurobehavioral examination and neuroimaging (MRI, SPECT). The neuropsychological information was used only for diagnostic purposes, not for the evaluation of first symptoms, which was the topic of the study. FTD patients conformed to the Lund and Manchester Groups (1994) criteria for FTD, and AD patients to the recommendation of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD, Morris 1989).

Study III. FTD patients and healthy controls

The FTD sample comprised 13 subjects, and the control group 10 healthy persons, matched at group level in age, years of education, and sex (Table 2). The ways of recruitment and clinical investigation for diagnosis of the patients were the same as in study I. Diagnostic criteria for the FTD patients were the CC criteria. The control subjects were recruited through advertisements in the press and through a seminar for members of the Swedish Pensioner Society in Huddinge. All control subjects were declared fit after a medical and neuropsychological examination as extensive as the one of the FTD patients.

Study IV. FTD and AD patients and healthy controls

The FTD sample consisted of 19 subjects and the AD group of 16 patients (Table 2). The ways of recruitment and clinical diagnostic investigation of the patients were the same as in study I. As in study III FTD patients fulfilled the CC criteria. AD patients conformed to the DSM IV criteria for AD. The control group of healthy subjects encompassed 19 individuals, recruited as in study III and through a Driving and aging project. Patients as well as control subjects were matched at group level with respect to age, sex, and in case of the patients, also to years of education and MMSE-score. The controls were declared fit after the same type of clinical investigation as the patients.

Study V. FTD and AD patients and healthy controls

The FTD sample encompassed 18 subjects and the AD group 14 patients (Table 2). Ways of recruitment and clinical investigation of the patient groups were the same as in study I. Diagnostic criteria were the same as in study IV. The control group consisted of 20 healthy individuals, recruited and selected as in study IV. Patients were matched on group level as

regards age, years of education, duration of the disease and MMSE level, whereas the controls with respect to age and education.

2.2 Neuropsychological methods

Study I. Cognition and behavior

The following cognitive functions were investigated: conceptual ability, shifting, executive strategy, estimation ability, visuospatial thinking, temporal sequencing, complex attention/concentration and secondary (episodic) memory. The behavioral items comprised 20 types of executive deviations, and 20 types of emotional disturbances. The cognitive items were: reduced alertness and fluctuations in alertness, psychomotor slowness, tremor, fragmentation, distortion of size, rotations, closing in, arrowdrawing, perseverations, verbal stereotypes, lack of planning, impoverished speech, confabulations, lack of insight and self-criticism, reduced understanding of test instructions, rule breaking errors, a specific variant of breaking rules, “run away behavior”, and utilization behavior. For reasons of simplicity the emotional items can be classified in two groups: one class of behavior that covered different kinds of lack of control and hyperactivity, and one class that covered different types of indifferent and neurotic behavior.

Study II. First symptoms

Prior to the neuropsychological testing and brain imaging, patients and caregivers were interviewed by the examining physician about the first symptoms that they could associate with what was later identified as the disease. The answers were recorded in casebooks. It was this information about the earliest symptoms in the everyday life that was the target of the study, not the neuropsychological results.

Study III. Cognition and behavior

The neuropsychological functions assessed in the study were the same as in study I, with the addition of a task measuring working memory. However, the specific tests evaluating these functions were somewhat different as compared to those in study I. The items for the behavioral observations were also roughly the same as those in study I. The items in study III

were graded according to a scale from 0 points to 3 points, where 0 points signified absence of the symptom and 3 points the most severe variant of the symptom.

Study IV. Cognition

The following cognitive functions were evaluated in the study: abstract thinking, attention and concentration, visuospatial thinking, short term memory, episodic and semantic memory. Behavioral observations were not part of this study.

Study V. Cognition

The test battery in this study was the same as in study IV, except for the addition of the FAS test, assessing word fluency. As in study IV, no observations of behavior were included in the study.

2.3. Neuroimaging and neurophysiology

Study III. Quantification of MRI scans

According to the method (Andersen 2000) the volume of the frontal lobe was divided into four main parts, left- and right-sided anterior volumes reaching from the most frontal gyri to the anterior border of the corpus callosum, and left- and right-sided volumes from the latter structure to the anterior commissure. Differences in head size were corrected by dividing the regional frontal volume of each subject with the intracranial volume of each individual.

Study IV. EEG method

The global field power (GFP) which corresponds to the generalized EEG amplitude in μV was calculated for six frequency bands: δ (1.0 – 3.5 Hz), θ . (4.0 – 7.5 Hz), α (8.0 - 11.0 Hz), β_1 (12.0 – 15.5 Hz), β_2 (16.0 – 19.5 Hz), β_3 (20.0 – 23.5 Hz). Spectral ratio was analysed as a ratio of the sum of fast frequency bands $\alpha + \beta_1 + \beta_2 + \beta_3$ and slow frequency bands $\delta + \theta$. Values of GFP and spectral ratio were logarithmically transformed in order to normalize data distribution for further statistical analyses.

Study V. SPECT registration and quantification

Image registration and quantification were carried through with the BRASS program (Radau 2000). The relative regional cerebral blood flow (rCBF) in the selected regions was calculated as cerebellar ratios (mean value of region/mean value of bilateral cerebellar cortex). The quantification evaluations were performed in 23 regions, which include bilateral cerebellum cortex, sensorimotor cortex, occipital lobe, superior parietal lobe, parieto-temporal association cortex, dorsal frontal and orbital frontal lobes, temporal lobe, anterior and posterior cingulate cortex, subcortical region as well as pons and midbrain. The definitions of the regions are shown in article V, Fig. 1.

2.4 Data analysis: statistical methods

Study I. The group size was statistically determined by a power analysis. The power in a t-test should be at least 75% with $p=0.05$. The smallest difference of interest between the means was decided to be one standard deviation. On the basis of these assumptions the number of patients in each group was calculated to be 14 subjects. A two-factor ANOVA with diagnostic groups (FTD and AD) and level of cognitive decline ($MMSE \leq 14$ and ≥ 15 , determined by mean split) was performed on each psychometric test and behavioral item. In order to decide which parameters, psychometric tests or behavioral observations, that best predicted the clinical diagnosis, a discriminant analysis was performed.

Study II. The reported first symptoms were classified according to the current conceptualization of behavioral and cognitive symptoms on brain lesions. SPECT scans from the FTD group were visually inspected and classified into mainly bilateral (15), left- (19) or right-sided (18) hypoperfusion. The proportions of the symptoms were analysed with Fisher's exact test, two tailed. A factor analysis was performed in order to reduce the amount of variables and to discern typical patterns.

Study III. The interrater reliability of the behavioral observations was tested with the Kappa statistics, the relationship between the regional brain volumes with one way analysis of variance (ANOVA), and the relation between test results, behavioral items and volumetric measurements analysed with Spearman Rank Correlation test.

Study IV. Quantitative electroencephalogram (qEEG) variables were analysed with ANOVA, and the neuropsychological test results by the Mann-Whitney U test. The neuropsychological test results, demographic and qEEG-variables were further subjected to a logistic regression, in order to decide which of the parameters that best predicted the diagnoses.

Study V. Group differences between rCBF measures were analysed with ANOVA. Test results for FTD and AD patients and controls were analysed with Mann-Whitney U test. The relative importance of neuropsychological tests, demographic data, and rCBF-measures were further subjected to a logistic regression. To control for possible correlations between the predictors of the logistic models, the predictors were tested with Spearman Rank Correlation test. Finally, likelihood ratio (LR) was calculated to find out how much the post-tests (SPECT and neuropsychological models) added to the pretest probability.

2.5 Ethical approvals

Study I-V were approved by the Ethical committee, Huddinge University Hospital: No. 12/96 (study I), 352/02 (study II), 159/01 (study III), 450/01 (study IV), 103/02 (study V).

3. RESULTS

Study I. Cognitive and behavioral profiles of FTD and AD

OBJECTIVE. The aim of the study was to investigate whether it is possible to separate FTD from AD with the help of neuropsychological methods, and, if so, which features would best predict the clinical diagnosis?

RESULTS. The performance levels on the psychometric tests were generally lower among patients with advanced dementia (low MMSE-scores) than among subjects with less advanced dementia (high MMSE-scores), but FTD and AD patients only differed significantly on a few neuropsychological test. Word fluency (FAS) was significantly lower in the FTD group than in the AD group, whereas the secondary memory assessed by word list, free recall, was considerably lower in AD than in FTD. There was no significant interaction between the diagnostic groups, level of general cognitive decline (MMSE-level) and psychometric tests, signifying that the relation between performance levels remained unchanged across the levels

of cognitive decline. FTD patients revealed more deviant behavior than AD patients, but the majority of items did not differ significantly between the groups. AD patients were significantly slower than FTD patients and disclosed significantly less motivation than the FTD patients, whereas FTD patients had significantly more rule-breaking behavior, verbal stereotypes, confabulations, lack of insight and self-criticism as well as utilization behavior. They were also significantly more euphoric, impulsive and had greater difficulties with adjustment. The level of cognitive decline did generally not influence the behavior. The discriminant analysis indicated that the best predictors of FTD and AD was the following combination of tests: FAS, Digit Symbol (assessing the attentional function), Estimations, Word list free recall and recognition, number of correct answers (hits). Except for the FAS test and word list free recall, none of these measures differed significantly on the ANOVA, but the linear discriminant functions suggested a higher performance on Digit Symbol in the FTD group than in the AD group, Estimations a more reduced judgement among the FTD than among the AD patients, and a higher memory function with cued recall in the FTD group than in the AD group. The classification accuracy for this combination of tests was 90%. The behavioral variables were even more efficient. A combination of lack of insight, rule-breaking, run away behavior, difficulties in adjustment and euphoria yielded a 97% correct classification of the patients. In all these respects behavioral abnormalities were more frequent in the FTD group than in the AD group.

Study II. Identification and localization of first symptoms in FTD and AD

OBJECTIVE. In this work, the purpose was to identify the early, preclinical signs of FTD and AD, and to define whether the earliest symptoms of FTD were associated with bilateral, left- or right-sided degeneration.

RESULTS. Fourteen early symptoms were identified. At the preclinical stage, FTD patients disclosed significantly more disinhibition, social awkwardness, passivity/apathy and executive dysfunctions than AD patients. Disinhibition was most frequent in FTD patients with right-sided hypoperfusion, and social awkwardness significantly more represented in all three subgroups of FTD as compared to AD. Passivity/apathy was significantly more frequent in the unilateral FTD groups than in AD. Memory problems were minimal in the FTD group, but strongly represented in the AD group at the very beginning of the disease. Dysexecutive signs were most pronounced in the bilateral subgroup of FTD. Language problems were present in FTD as well as AD, but significantly more frequent in the left-sided FTD group.

Study III. Cognitive and behavioral dysfunctions and irregular patterns of atrophy in FTD

OBJECTIVE. This study aimed at investigating how regional volumetric measurements of frontal lobe atrophy were related to cognitive function and behavioral indices in patients at different stages of FTD. The aim was also to penetrate the relationship between cognition and behavior. Finally, the aim was to determine whether the findings suggest a localizationist or interactionist view of frontal lobe functioning.

LOCALIZATIONISM VERSUS INTERACTIONISM. The dominant view of the anatomical and functional organization of the brain is that the left hemisphere is specialized on verbal tasks, whereas the right side on visuospatial thinking. Mostly, this division alludes to the temporo-parieto-occipital areas, where cognition is mainly localized, but there are some indications in the literature that this specialization also is thought to cover the frontal lobes. This way of conceiving the organization of the brain may be labeled a localizationistic view. Another way of understanding the organization of the brain is that several parts on both sides of the brain are involved in the mediation of one and the same cognitive ability or behavior. This view may be named the interactionistic standpoint.

RESULTS. All the regional brain volumes of the FTD patients were significantly smaller than the volumes of the controls, certifying atrophy in the FTD group. The Kappa statistics indicated that the interrater reliability on the behavioral variables was good. Correlational analysis between test results and brain volumes showed significant correlations between elementary arithmetic skills and Poppelreuter's overlapping figures (visual perception) and left-sided anterior frontal loss of brain volume. Copying of a triangle (visuospatial ability) was related to left-sided posterior volume loss, whereas Digit Span backwards (working memory) was correlated with atrophy in the left as well as right posterior regions. The majority of the significant correlations between behavior and loss of brain volume was of executive character. Reversions and rotations were associated with anterior right-sided atrophy, whereas fragmentation correlated bilaterally with volume reduction in the anterior frontal regions. Lack of strategy was connected with anterior left-sided as well as posterior right-sided degeneration. Confabulation was correlated with bilateral posterior atrophy, and concrete thinking with posterior left-sided loss of brain volume.

The only emotional items that were correlated with regional atrophy was anxiousness and aggressiveness, both exclusively related to shrinkage of the anterior right-sided frontal area. Finally, there were some correlations between behavior and cognitive tests, namely between elementary arithmetic skills and lack of strategy, and between Digit Span Backwards, reversions and rotations, concrete thinking and confabulation.

Study IV. Cognitive profiles of FTD and AD and the relative usefulness of neuropsychological methods and electroencephalogram

OBJECTIVE. Here, the purpose was to study the relationship between quantitative qEEG measures in FTD, AD and healthy control subjects, and to investigate the relative usefulness of qEEG, neuropsychological tests or a combination of both in the classification of the patient groups.

RESULTS. According to the Mann-Whitney U test, the cognitive performance levels in the FTD group were considerably higher in several respects than in the AD group: The attentional function was significantly higher, visuospatial thinking selectively higher, as well as the episodic memory. ANOVA indicated two different types of qEEG pathology in FTD and AD. Whereas the FTD patients were characterized by an absence of increase in slow qEEG activities (δ and θ), and a decrease in fast activities (α , β_1 – β_3) relative the controls, AD patients were marked by an increase in slow activities, primarily relative to controls in the δ band, and a lesser decrease in fast activities. The logistic regression showed that the best qEEG predictor of FTD versus AD was a model combining θ , α , and β_3 measures. Here, the classification accuracy amounted to 71%. The most efficient neuropsychological predictors of FTD were high levels of visuospatial thinking (Block Design), and episodic memory (Word list, free recall), where the classification accuracy was 80%. Among the logistic models that combined qEEG and neuropsychological measures the best predictors of FTD were a combination between the δ and θ frequency bands, and comparatively high levels of visuospatial thinking (Block Design) and episodic memory (Word list, free recall). Classification accuracy for this model was 93.3%.

Study V: Cognitive profiles of FTD and AD and the relative usefulness of neuropsychological methods and single photon emission computed tomography

OBJECTIVE. The aim of this work was to investigate to what extent neuropsychological tests and regional cerebral blood flow (rCBF) assessed by SPECT, respectively or combined, contribute to the accuracy of differential diagnosis of FTD and AD.

RESULTS. Neuropsychologically, FTD and AD patients scored significantly lower on practically all examined cognitive functions than the controls. Comparisons between FTD and AD patients revealed only one significant difference, namely on the attentional task (Digit Symbol), where the AD patients performed lower. Significant reductions in cerebral blood flow were found in FTD patients relative controls in the right orbital frontal cortex, the right parieto-temporal cortex, the dorsal frontal cortices bilaterally, and in the anterior cingulate cortex bilaterally. In AD patients versus controls, there was only a significant reduction in rCBF, in the parieto-temporal cortices, bilaterally. Group comparisons between FTD and AD patients indicated a significantly lower rCBF in the FTD group bilaterally in the orbital frontal cortices, dorsal frontal and cingulate cortices. In the left parieto-temporal cortex and the left occipital cortex blood flow was lower in the AD group. Comparisons between cerebral blood flow at more progressed dementia levels (below median 20.5 MMSE points) and less progressed dementia levels (above 20.5 points) indicated that there were no significant differences between the stages in the disease groups respectively. The logistic regression resulted in three plausible regression models, one univariate model using the time to complete the Trail Making Test, part A, overall classification accuracy 72%, one univariate rCBF model using the blood flow in the left anterior cingulate cortex, classification accuracy 87.5%, and one including the blood flow in the right orbital frontal cortex, classification accuracy 87.5%. LR for TMT A time was 2.8, indicating a small effect of this test. LR for blood flow in the right orbital frontal cortex was 6.4, i.e. this regional measure had a moderate effect on the pretest probability. LR for the perfusion in the left anterior cingulate cortex was 11.9, indicating that this measure had a decisive effect on the pretest probability.

3.1 Summary of findings

Study I. The most efficient neuropsychological instruments for the differentiation between FTD and AD

The main findings of the study were that word fluency was dramatically lower in the FTD group than in the AD group, and that the FAS test was the best single instrument to

differentiate between FTD and AD. The secondary memory was selectively lower in AD than in FTD. These findings are congruent with what have earlier been reported in the literature. It is however important to note that performance levels on the secondary memory tests revealed amnesia in both disease groups, which concerning FTD, contradicts earlier reports. There were further no differences in constructional abilities between the disease groups, which also contrasts previous findings, since spatial thinking usually is said to be fairly preserved in FTD. The behavioral profiles of FTD and AD revealed a double dissociation: whereas FTD patients were characterized by impulsivity and increased activity, AD patients were marked by amotivation and psychomotor slowness. The best psychometric predictors of FTD and AD was a combination of the FAS test, Digit Symbol, Estimations and Word list, free recall and recognition, hits, yielding a 90% correct classification of the groups. Behavioral observations were even more efficient as predicting instrument. With a combination between observations of lack of insight, rule breaking errors, difficulties in adjustment and euphoria the hit rate was 97%. A general conclusion of the study was that it is possible to separate FTD from AD with neuropsychological methods.

Study II. Behavioral abnormalities as early symptoms of FTD and cognitive dysfunctions as early symptoms of AD

Clear-cut behavioral and cognitive differences were present in FTD and AD patients at the preclinical stage. The earliest symptoms of FTD were mostly behavioral, whereas the initial signs of AD were cognitive. Disinhibition was most represented in the asymmetric right-sided FTD group, language dysfunction in the left-sided group and dysexecutive symptoms in the bilateral group. The anatomical site was determining for the type of first symptom of FTD.

Study III. Suggestions of an interactionistic organization of thinking

The study suggested that the frontal lobes have a limited importance for cognition, and that there seems to exist a relationship between cognition and behavior in FTD, probably implying that the deficits in executive ability reduces the access and use of cognitive abilities. The correlations between cognitive functions and regional volume loss did not show any consistent patterns, outlining that thinking is such a complex process that it demands cooperation from different parts of the brain. On the whole, the correlational analyses pointed to an interactionist organization of the brain, rather than to a localizationistic way of functioning.

Study IV. Neuropsychological tests and electroencephalogram as the most efficient mode of clinical differentiation between FTD and AD

Cognitive ability was selectively much better in the FTD group than in the AD group. EEG has usually been considered as normal in FTD. In contrast to what has earlier been reported, FTD patients were marked by a pathological EEG, namely by an absence of an increase in slow qEEG activities, and a decrease in fast activities. AD patients were characterized by an increase in slow qEEG frequencies and a smaller decrease in fast activities.

Neuropsychological measures were better predictors of FTD versus AD than qEEG measures, but the most efficient predictor was a model combining neuropsychological tests and qEEG.

Study V. Single photon emission computed tomography as more efficient than neuropsychological tests in the differentiation between FTD and AD

The study showed a typical pattern of anterior cortical hypoperfusion in FTD, and of posterior cortical blood flow reduction in AD patients. Calculations of LR disclosed that rCBF measures added more to the pretest probability than the neuropsychological measures. The best rCBF predictor of FTD versus AD was the perfusion in the left anterior cingulate cortex, where the LR was 11.9, which is very high.

4. DISCUSSION

To be able to evaluate the outcomes of the studies in the present thesis, it is necessary to make several methodological considerations. First, the question whether there has been an independent assessment (blind) or not must be taken into consideration. Second, the reliability and validity of diagnostic criteria are important for the selection of patients. Third, the mode of recruitment influence the composition of the samples. Forth, there is the problem with circularity. Fifth, how have other types of dementia been excluded, and sixth, psychiatric disorders? Seventh, do the samples reflect clinical or prototypical patients? Eighth, what is known about the representativity of the control groups? Ninth, how well does the tests differentiate the target diseases from one another and from other diseases? Tenth, how valid are observations made by relatives? The *external* as well as *internal validity* is influenced by several of these aspects. (For a detailed discussion of point one to nine and *external/internal validity*, see Qizilbash 2002). The *external validity* may be defined as the “extent to which the patient group and the control group are representative of their respective populations; the extent to which the tests used are representative of the underlying cognitive function and brain

structure involved” (Almkvist 1993, p. 35) or the possibilities to generalize the results to the whole populations. The *internal validity* is the same as the “extent to which the true causative factors have been identified” (Almkvist 1993, p. 35).

4.1 Mode of assessment

Except for partly in study II, none of the clinical diagnoses has been made blinded, in the sense that clinicians have had to identify FTD and AD patients among a wide variety of other conditions that may be confounded with FTD and AD. This of course implies a certain risk for bias. In study I were included patients that were clinically diagnosed as FTD according to the LM criteria, and patients that fulfilled the DSM III and NINCDS-ADRDA (McKhann 1984) criteria for AD. In study, IV and V clinical AD diagnoses according to DSM IV served as inclusion criteria for the AD patients. In study III, IV and V the clinical FTD diagnoses were rediagnosed by a physician to assure accordance with the CC criteria. This way of diagnostic assessment has certified that the clinical pictures of the patients and the diagnostic criteria were congruous, but the mode of assessment does not guarantee that FTD and AD patients may be distinguished from other, similar diseases with the help of those criteria. In study II, the ratings of the presence of first symptoms in the dictated histories as well as the classification of the SPECT scans of the FTD patients were made blinded to the diagnoses, which is a clear advantage with this study.

4.2 Reliability and validity of diagnostic criteria

The LM criteria have been criticized for suffering from deficits in reliability and validity. It has been remarked that no investigation of the interrater reliability has been published, and further that no formal criteria has been established for the occurrence of degeneration of motor neurons associated with FTD, pathological changes in Pick’s disease and FTD. Other adverse remarks are that the LM criteria does not stipulate how many core features that are required for diagnosis. Towards this background the LM criteria have not been recommended for clinical use (Qizilbash 2002). In other studies it has been claimed that most FTD patients correspond to the criteria of AD (Gregory 1997, Pasquier 1999, Varma 1999). In contrast to these opinions, in the present thesis it has been possible to initially differentiate the diseases by using the LM criteria, later CC criteria, and the DSM III (1987) and DSM IV (1994) criteria, the guidelines from the Consortium to Establish a Registry for Alzheimer’s Disease (Morris1989) and the NINCDS-ADRDA (McKhann 1984). This is shown by the fact that in

all the studies where FTD and AD patients have been compared in more detailed analyses, the patient groups have revealed rather distinct clinical pictures, respectively, although the neuropsychological differences between FTD and AD patients sometimes have been subtle (study V).

4.3 Mode of recruitment

All FTD and AD patients have been selected among patients consecutively referred to the Department of Geriatric Medicine, Huddinge University Hospital (study I, III, IV, V) and to the UCLA Alzheimer's Disease Center, Los Angeles (study II). However, in none of the studies all of the consecutively referred patients during a certain period of time have been included. This is because of a series of reasons. The matching criteria have restricted the samples. The aim has generally been to match the patients on group level with respect to age, education and MMSE level. Since the onset of FTD is earlier than in AD (cp. age at first visit study II), the claim that the patient groups should be similar in age might have biased the samples in a certain way. The included FTD patients might be slightly older than is general in the FTD population, whereas the AD patients probably are somewhat younger than is general in the AD population. The including of relatively older FTD patients and comparatively younger AD patients have somewhat limited the external validity.

Other requirements for inclusion have been ability to perform neuropsychological test and an informed willingness to participate in the studies. In several cases the possibilities for patients to be accompanied to the clinic by relatives have also been deciding for the composition of the samples. These requirements have thus restricted the samples to encompass patients on a certain level of cognitive functioning (testability), with a positive attitude towards that kind of extra work that is associated with a comprehensive examination, and when applicable, with a good social network permitting the engagement of accompanying persons. These three aspects seems however inevitable in all studies of dementia patients. Important consequences of these requirements are however that non consenting patients that sometimes lack a sufficiently good social network have been excluded, which also in a measure have limited the external validity. The causes of unwillingness to participate are not clear, but one reason may of course be a lack of an accompanying person. In study I, the FTD sample was dominated by disinhibited FTD patients, who could be supposed to be particularly positive towards participating, whereas the AD sample was characterized by amotivated patients. With respect to the AD patients, this means that amotivated patients have not consistently refrained

from participating. In study II the FTD sample was also dominated by disinhibited patients. The amount of passive/apathetic patients was smaller. The proportions in study I and II might reflect the real proportions between these two types of disturbances in FTD, although it is not certified that the proportions are not due to sampling characteristics. In study IV and V behavior was not analysed.

4.4 The problem of circularity

With the exception for 14 FTD patients in study II, the diagnoses have generally not been validated through autopsy. This means that the diagnoses in the discriminant analysis (study I) and the logistic regression analyses (study IV, V) have been compared to the original, clinical diagnoses, which may imply some circularity. Even other studies have had to cope with the problem of circularity (Bozeat 2000). Calculating the likelihood ratios is one way of partly solving this problem, but the optimal solution would of course have been to compare with the pathology.

Despite a certain degree of circularity, conducting this kind of studies based on clinical diagnoses must be considered as very valuable. Clinical studies reflect the patients as they are, when coming for examination, and when no autopsy data for them is yet available. It is thus on the basis of these clinical presentations that the diagnoses have to be made. Clinical diagnostic criteria are often partly built on pathological examination (LM, CC), which represents a certain validation.

From the studies in this thesis it is possible to conclude that the initial clinical diagnoses have been adequate, since relatively clear-cut differences between the diseases have appeared in the more detailed analyses. The contribution of the different studies to the initial diagnoses is that they quantitatively have measured the relative importance for differential diagnosis of different clinical neuropsychological evaluations and visually inspected interpretations of CT or MRI scans, and SPECT as well as EEG data, which is not possible to do by qualitative evaluation. By analysing the data in the ways that have been done, it has also been possible to pin-point, from a large amount of information, the tests, cerebral regions and EEG frequency bands that are the most important for differential diagnoses.

4.5 Exclusion of other dementias

FTD is part of the larger the larger complex, frontotemporal lobar degeneration, which also includes SD and PA. This means that there are two diseases that are in certain respects very much alike FTD. SD and PA are characterized by typical language disturbances, and early (SD) or late in the disease course (PA) by behavioral changes (Neary 2000 a). The language disturbances in SD and PA are rather specific, which makes these two variants of FTLD quite distinguishable from FTD and AD, which also are characterized by language problems. The exclusion of SD and PA patients is one of the reasons to why the FTD samples in most of the studies became so restricted. The other reason is of course that FTD is a comparatively small disease, only covering approximately 20% of the dementias (Snowden 2002). In the study performed in USA, the FTD sample was large, due to that the reception area is larger in USA than in Sweden.

Since so few FTD diagnoses are confirmed by autopsy, it is not possible to decide whether the FTD samples encompasses patients suffering from e.g. Pick's disease, or familial types of FTD. The possible inclusion of Pick patients does not make any difference for the clinical picture, since the clinical manifestations of Pick's disease are similar to those in FTD. Systematic comparisons between sporadic and inherited FTD are rare, which makes it impossible to decide whether the clinical pictures differ or not. This means that the actual samples may contain familial types of FTD. Concerning MND, none of the FTD patients have shown bulbar features or limb amyotrophy at the time of examination, although it is uncertain whether they have developed such symptoms later on (Hodges 2001 a). CBD has been found to be easily distinguished from FTD, SD and PA, due to its typical degeneration of processes related to skilled movement (Neary 1997). Progressive supranuclear palsy (PSP) patients usually presents with an extreme slowing, and sensorimotor deficits such as oculomotor problems and falling tendencies, although mental changes may precede these symptoms (Lezak 1995). None of the FTD patients in the samples have shown any sensorimotor symptoms. Since the duration of the disease in the different studies was around two, three years, it is not probable that PSP patients could have been included, since they ought to have developed e.g. sensorimotor problems by the time of examination, if the disease started with cognitive problems. PSP has been reported to be easier confounded with Parkinson's disease and AD than with FTD (Lezak 1995). AD might further be mixed up with Lewy body dementia (LBD). In LBD parkinsonian signs, mental and motor slowness, fluctuating vigilance and attention, and distinct visual hallucinations are prominent (The dementia study

group 2000). All the included AD patients have carefully been scrutinized for LBD symptoms, and the risk of inclusion of LBD patients is therefore minimal.

BPSD is present in most dementias, and thus not unique for FTD or AD. It has been claimed that neuropsychiatric symptoms are not disease specific, but that the identification of combinations of neuropsychiatric symptoms and specific profiles, might help in the differentiation between dementia types (Assal 2002). The careful evaluations of differentially diagnostic relevant dementias makes it less probable that the FTD and AD samples should include patients with other types of dementias with BPSD. These careful differential diagnostic considerations have contributed to keep the internal validity of the diseases groups as high as possible.

4.6 Exclusion of psychiatric disorders

As is evident from the review of the literature about psychiatric disorders, they are not easily distinguished from FTD with the help of neuropsychological tests, although they are well defined disease entities (DSM IV). In the few cases where psychiatric disorders have been suspected, it has been investigated whereas the symptoms, such as concrete thinking or flight of ideas, have been susceptible to changes in the emotional impact of the surrounding situation. Symptoms of organic brain lesion tend to occur consistently, whereas psychiatric symptoms may vary according to the situation (Lezak 1995). The same technique has been applied to depression, which occasionally may result in cognitive deficits. Besides this kind of observations, depression scales have also been used to exclude depressive patients from the FTD as well as AD samples.

4.7 Clinical versus prototypical patients

All the included FTD and AD patients have been very carefully scrutinized to fulfill the diagnostic criteria for each of the diseases. However, despite this, in clinical patients it is not possible to totally exclude some cerebral involvement that is not in perfect agreement with the criteria. This is obvious in study V, where the more detailed analysis revealed a perfusion deficit in the right parieto-temporal region in the FTD group, besides the more typical anterior hypoperfusion. This potential involvement of atrophy outside the regions that should be typically degenerated in FTD and even AD, may of course have influenced primarily the neuropsychological pictures, due to the multiregional dependency of neuropsychological

tests, and reduced the differences between the diseases. If all the comparisons had been made on prototypical patients at equivalent stages of the diseases, it is possible that more clear-cut differences would have appeared. It is therefore extremely important that diagnostic criteria states whether the guidelines refers to prototypical patients or to clinical patients, where the pattern of atrophy may be less distinct.

4.8 The representativity of the control groups

The control groups (study III, IV, V) have not been systematically compared to other healthy, elderly individuals, with respect to cognition, neuroimaging or neurophysiology, which means that it is not possible to thoroughly evaluate to which extent the control groups are representative for the healthy, elderly population. The control groups only encompasses persons that have been positive towards the investigations, which of course is inevitable in all studies. All the investigations performed in study III, IV, and V however showed considerable differences between the patients and the healthy individuals. The volumetric measurements indicated significantly larger brain volumes in healthy controls than among FTD patients (study III). EEG activity was also significantly different in FTD and AD patients versus controls (study IV). Finally, cognitive ability was clearly higher in the control group than in the FTD and AD groups (study V), and comparisons between rCBF showed a significantly higher blood flow in the controls group than in the patient groups, in areas that are typically affected in FTD and AD (study V). None of the individuals in the control groups were related to the patients by ties of kinship. Since no comparison has been made with other groups of healthy elderly persons, neither the internal, nor the external validity is certified.

4.9 Evaluating the differentiating capacity of tests

The tests (neuropsychological, neuroimaging and neurophysiological) have been applied solely on patients diagnosed with FTD and AD and on healthy control subjects. Concerning the patients, the optimal way would have been to apply the tests on FTD and AD patients as well as on patients with similar diseases. It is only when applying the tests on a wide spectrum of diseases that the true differentiating capacity of a test may be evaluated. This has not been possible in the present thesis. This means that the results of the thesis only pin-points the differences that emerges in the comparisons between FTD and AD, but does not say anything about how these features are related to the features in other, similar diseases.

It has been claimed that traditional neuropsychological tests are poor in separating FTD from AD (Gregory 1997). This thesis has shown that the classification accuracy of neuropsychological tests versus behavioral observations was very high, and just slightly lower than the accuracy of behavioral observations (study I). This means that in study I the neuropsychological tests fairly well caught the functions of the frontal lobes, as well as cognitive abilities, whereas the behavioral observations were an even better instrument to describe frontal functions. Psychometric tests were better than EEG alone, but a combination between these two modes of investigation was much better than any of the measures alone (study IV). As compared to SPECT, neuropsychological test were relatively weak (study V). This result must be seen in relation to the study I, where the neuropsychological tests were very efficient. In study I, there were also some more significant differences between the psychometric tests than in the study V, where they were extremely few between FTD and AD patients.

There is an emerging debate about the adequacy of MMSE in the study of FTD patients. It has been claimed that MMSE does not enough reflect frontal lobe functions, but rather cognitive, posterior functions. This should be a reason to why patients with FTD manages rather well on the MMSE. According to this reasoning, the FTD patients in the present thesis should be relatively more progressed in their diseases than the AD patients, since the FTD and AD patients have been matched on group level with respect to the MMSE scores. However, in the thesis there is a tendency that the FTD patients perform better on neuropsychological tests than AD patients, irrespective of the equal MMSE levels. This shows that the MMSE might be a somewhat superficial instrument, that does not adequately reflect the differences between FTD and AD.

4.10 How reliable are observations made by relatives?

Reports about first symptoms (study II) and onset of the diseases have mostly relied on observations made by relatives. Several problems are associated with this kind of procedure to get hold of the information about the earliest signs. There are probably differences in education between the relatives, and people are naturally observant to a greater or less extent. There is also a risk that some relatives due to emotional reasons may have denied symptoms, and others may have overestimated the abilities of the patient when being healthy, so that the difference between the healthy and demented condition appears as larger than it actually was. There may be variations in memory capacity between the observers. Finally, since the patients

already were diagnosed when the relatives were questioned about the earliest signs (study II), the knowledge about the meaning of the diagnose might have biased them in their reports about first symptoms. These deficits of course have a negative effect on the validity of the reports, although they appears as inevitable, unless relatives also are investigated to - if possible - fulfill the requirements of uniformity.

4.11 Summary of methodological considerations

Concerning the internal and external validity there are both pros and cons. The diagnostic procedure included actions that have contributed to a higher internal validity. The criteria used for initial diagnoses adequately separated the diseases. In addition, other dementias as well as psychiatric diagnoses were carefully excluded. These measures have favored the homogeneity of the diagnostic groups, i.e. the internal validity, and made it possible to interpret the results in terms of disease entities.

The initial samples of FTD and AD included hospital-based clinical samples of patients with unclear relation to populations of FTD and AD individuals. Furthermore, there were other measures that have reduced the external validity, which may be exemplified by the matching procedure that have been used in order to make samples of FTD and AD groups comparable in terms of age, education and global cognitive functioning (MMSE). The FTD patients might be older than what is usual in the FTD populations, and the AD patients slightly younger. Other measures that may have reduced the external validity is exemplified by the fact that there were reasons for non-participation that were unclear. It is also a common observation that FTD patients have difficulties to comply with psychological testing, which may have excluded some FTD patients. Other reason for exclusion were related to the requirement of relatives making observations of early symptoms (study II). Although, the thorough clinical diagnostic procedure have made the disease groups relatively clean, it is with reservation for restrictions in primarily external validity that the results of this thesis should be interpreted.

4.12 The contributions of the studies

The studies have in many respects confirmed earlier knowledge, i.e. that FTD is characterized by behavioral disturbances, from the onset of the disease and throughout the disease course (study I, II, III), whereas AD is marked by cognitive deficits, from the earliest stage and henceforth (I, II, IV, V) – although most of the cognitive differences between FTD and AD

patients did not reach significance, particularly in study V. In certain respects the findings of the present thesis contradicts earlier results, and those concerns the presence of severe cognitive decline in FTD and the EEG pattern of FTD. Possibly, the thesis also stresses the interdependence between behavior and cognition in FTD more than is usual in FTD studies. An attempt will be made to integrate the findings of the present thesis with the ideas of the synopsis of frontal lobe functions and dysfunctions by Fuster (1999), the anatomofunctional model of frontal-subcortical circuits (Mega 1994), and the HERA model (Tulving 1994). Generally, the present thesis confirms the patterns of these frameworks.

In study I, FTD patients revealed emotional disturbances i.e. impulsivity and regression, as well as executive problems, which according to Mega (1994) and Fuster (1999) indicates orbitofrontal as well as dorsolateral involvement in the group. AD patients had more pronounced memory problems, reflecting temporal lobe atrophy (Rosen 2002 a). Concerning disinhibition, the behavioral picture of FTD patients was similar in study II, where it was found that this kind of aberrant behavior was mostly related to right-sided frontotemporal degeneration. However, social awkwardness was associated with right- as well as left-sided and bilateral hypoperfusion. Social awkwardness could be considered as a subdivision of disinhibition, but even if social awkwardness had been analysed as disinhibition, there would still had been an overweight for right-sided frontotemporal involvement in this kind of disturbance. Interestingly, in study III aggression and anxiety were also associated with anterior right sided atrophy, as shown by the pattern of volume loss. These patterns of results suggests that disinhibition, aggression and anxiety may be related to degeneration in foremost the right-sided orbital or anterior (study III) frontal region. Passivity/apathy was less frequent in study II than disinhibited behavior, and present in left and right-sided, as well as bilateral patients. The present thesis does not give any clues to the possible regional localization of passivity/apathy observed in the samples (study II). According to Fuster (1999) apathy might reflect the dorsolateral as well as medial/cingulate syndrome, although the kind of apathy differ between the syndromes. If the framework of Mega (1994) is applied, apathy would primarily reflect disturbances in the anterior cingulate circuit.

In study II, executive dysfunctions in FTD patients were related to foremost bilateral reduction of blood flow. In study III, the patterns of quantified volume loss associated with executive dysfunctions in FTD outlined a network of interaction between the anterior and posterior frontotemporal brain halves, in the production of dysexecutive behavior. Concerning the association between executive dysfunctions and bilateral degeneration, the patterns in

these two studies coincides. As compared to the localization of emotions in study III, there might be a slight overweight for dorsolateral or posterior (study III) involvement in executive functions, which is in support of the synopsis (Fuster 1999).

Despite the rare cognitive differences between FTD and AD in study V, different cognitive profiles in FTD and AD are discernible in the thesis. Relative AD patients, FTD patients are characterized by a larger reduction of word fluency (study I), a slightly but not significantly more deteriorated judgement (study I), a higher attentional function assessed by Digit Symbol (study I, IV, V), less mental slowing (study IV), a higher visuospatial ability (study IV), and a higher secondary or episodic memory function (study I, IV), the latter referring to memories that involves the own person and that are acquired in a particular temporal-spatial situation (Tulving 1983).

According to study III there is some evidence for a cooperation between behavior and cognition. This conclusion is in accordance with Fuster's (1999) idea that the prefrontal cortex receives and reciprocates input from e.g. the postrolandic association cortex. It appears as if the research about frontal lobe functions stresses the connections between the frontal lobes and posterior areas more, than much of the research about FTD. The LM and later CC criteria stipulates profound failure on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder. This requirement is treated as a supportive criteria in the CC. In the present thesis, FTD patients have higher performance levels on cognitive tests than AD patients. However, from study V is evident that FTD patients have severe cognitive deficits relative healthy control subject. The findings of the present thesis thus suggests that besides behavioral problems, there are prominent cognitive deficits in FTD, but not so pronounced as in AD. The cognitive problems in FTD are probably due to lack of orbitofrontal regulative abilities and dorsolateral executive deficits.

Concerning cognition in FTD it was found in study II that verbal disturbances were clearly related to left-sided frontotemporal hypoperfusion. This contradicts the general conclusion of study III; that the patterns of cognitive dysfunctions and the distribution of atrophy rather suggests an interaction between several hemispheric cerebral regions in the processing of cognitive functions, than a localization of functions to specific hemispheric areas. These findings are also in accordance with the hemispheric encoding/retrieval asymmetry (HERA) model of prefrontal activation (Tulving 1994). In support of this model it has been discovered that "Left prefrontal cortical regions are differentially more involved in retrieval of

information from semantic memory and in simultaneously encoding novel aspects of the retrieved information into episodic memory. Right prefrontal cortical regions, on the other hand, are differentially more involved in episodic memory retrieval” (Tulving 1994, p. 2016). This conclusion considers only the memory systems, but it has also been recommended that the HERA model of prefrontal asymmetric involvement should be applied to the other higher prefrontal functions, such as conscious awareness, attention, supervisory and executive functions (Tulving 1994). The reasons for the contradictory findings concerning verbal ability in study II and III are still unclear, and more research with uniform psychological and neuroimaging techniques of investigation are required to solve the problem.

The absence of clear-cut neuropsychological differences between the FTD and AD samples in study V contrasts the fact that the rCBF measures in this work revealed distinct differences in blood flow reduction in the disease groups, with anterior cortical hypoperfusion in the FTD group, and posterior hypoperfusion in the AD group. Despite this, the patient groups have obviously been cognitively more similar than those in study I and study IV. Apparently, the variations in rCBF were not large enough to permeate the neuropsychological test, which means that there is a risk that neuropsychological test are not enough susceptible to differences in cognitive ability between FTD and AD. No quantitative evaluation of the likelihood ratios of the methods across the studies have been made, but when roughly comparing the efficiency in classification of the five modes of investigation (Table 3) in the different studies, behavioral observations (study I) and SPECT measurements (study V) appears to be approximately equally useful. Cognitive disturbances, i.e. memory problems, accounts for approximately the same proportion of early signs in AD as behavioral problems (disinhibition) does in FTD (study II). Neuropsychological tests may be a useful instrument to differentiate between FTD and AD, provided that the patient groups are enough dissimilar (study I, IV). The EEG method must be used in combination with neuropsychological tests to contribute to classification accuracy (study IV). In the investigation of FTD patients (study III) neuropsychological tests (foremost Poppelreuter) and behavior (foremost lack of strategy) appears as equally useful in the localization of atrophy.

Table 3. Summary of results in study I-V

Study	Item	Likelihood ratio	Classification accuracy %	Proportions in AD/FTD %	Rho* (FTD)
I	Nps tests/behavior	—	90/97	—	—
II	Cognition/behavior	—	—	76/78	—
III	Nps tests/behavior	—	—	—	0.77/0.68
IV	Nps tests/EEG	—	80/71	—	—
	Nps test+EEG	—	93%	—	—
V	Nps tests/SPECT	2.8/11.9	—	—	—

Nps = neuropsychological

* strongest Spearman rank correlations

Visually analysed EEG is usually found to be normal in FTD. A normal EEG is also among the LM core criteria of FTD, and the CC supportive criteria of FTD. However, this view is contradicted by the findings in study IV, where the FTD patients as well as AD patients were characterized by an abnormal qEEG. Relative to controls, the FTD patients were marked by an absence of an increase in slow qEEG activities and a decrease in fast activities, whereas AD patients were marked by an increase in slow activities and a smaller decrease in fast activities.

5. CONCLUSIONS

The earliest signs of FTD appears to be behavioral. Primarily disinhibited behavior, and to a lesser extent passivity and executive dysfunctions, characterize the early stage of FTD, whereas the initial symptoms of AD are cognitive, primarily in form of memory deficits (study II). In the thesis disinhibition (study II), aggression and anxiety (study III) have been primarily related to degeneration in the right-sided orbital or anterior frontal region, which is in accordance with earlier anatomofunctional models. Passivity at the initial stage of FTD was associated with left as well as right-sided and bilateral frontotemporal degeneration (study II). According to earlier knowledge, apathy might reflect dorsolateral as well as cingulate changes. Concerning the executive functions, the thesis have shown that executive disabilities are associated with bilateral, anterior frontal and, possibly more pronounced, dorsolateral abnormalities (study II, III). These findings also coincide with earlier suggestions. In the thesis there are clinical indications that FTD and AD stay mainly dissimilar throughout the disease courses (study I, study V). Contrary to many other studies, the thesis states that cognition is deteriorated in FTD as well as AD (study I, IV, V), although cognition is

generally better preserved among FTD patients than among AD patients. In the thesis is also emphasized the importance of behavioral abnormalities for cognitive decline in FTD (study III). The usefulness of neuropsychological tests in differentiating between FTD and AD has not been completely established in the thesis (study I, V), which might be due to the multiregional dependency of thinking reflected in neuropsychological tests (study III), and possible sampling characteristics. Observations of behavior seems so far to be a more reliable method than traditional neuropsychological tests in differentiating FTD from AD. When the usefulness of neuropsychological tests and EEG are compared, the possibilities to distinguish between FTD and AD are clearly ameliorated by a combination of neuropsychological measures and EEG. According to the findings of the thesis, EEG is not normal in FTD, but rather characterized by an abnormal pattern that is quite different from the EEG abnormalities associated with AD (study IV). Relative neuropsychological tests, functional imaging has proved to be a better differentiating instrument (study V).

The present thesis has barely approached the gigantic question about the organization of brain functions. One all-embracing suggestion for future studies may be borrowed from P.S. Goldman-Rakic (p. 152, 1988): “The question of how the brain organizes its subsystems to produce integrated behavior is perhaps the most challenging that can be posed; hopefully, new approaches to this issue can be informed by anatomical findings and insights”.

Another theme that the present thesis has evoked, is the need for comparisons between the neuropsychology of psychiatric patients and FTD patients, in order to detect possible differences in their performances. Evaluations of the relative importance of all the investigated methods as well as PET for the differential diagnosis of FTD and AD are also needed for the refinement of diagnoses.

6. EPILOGUE

Towards the background of what is found in the present thesis, how would the Struldbrugs or Immortals of Luggnagg and Jonathan Smith be diagnosed? In the debate about this question in the *Lancet* it is proposed that Swift in *Gulliver's Travels* depicted different stages of Pick's disease (Crichton 1993). It is true that what appears as the onset of the disease of the Struldbrugs was characterized by the whole repertoire of behavioral abnormalities, which of course are indicative of FTD and Pick's disease. However, the prominent memory deficits are more typical of AD. One should not forget, that Swift wrote with the liberty of a writer,

without any restrictions to perfectly delineate a disease. The most probable is that Swift let the Struldbrugs illustrate a mixture of mental degenerative diseases, and that he also wished to delineate the gradual decline of mental abilities associated with those diseases. Today, we would probably say that the different kinds of behavioral and emotional abnormalities that the Struldbrugs revealed were BPSD, which could be associated with any kind of dementia. When entering the topic of memory decline, Swift is obviously approaching AD, since the memory deficits of the Struldbrugs are so severe. As shown by this thesis, memory problems are present also in FTD, but they do not appear to be as large as those of the Struldbrugs. The conclusion is that BPSD of the Struldbrugs could illustrate any kind of dementia. It is probable that Swift saw memory deficits as typical for ageing, and that he inserted memory problems, that is symptoms of AD, in the conglomeration of symptoms. It does not seem as if Swift depicted one and the same disease from the onset and further on; it rather seems as if he described many kinds of dementia, among which AD could be one.

What kind of disease did Jonathan Swift suffer from? Swift died at the age of 78 years. Ten years earlier his friends observed a decline of his memory. This suggests a senile dementia of some kind. The comparatively high age at onset, and the early memory problems does not immediately indicate FTD or Pick's disease. One thing that is quite remarkable in the survivals of Swift, is that he was so clearly conscious of his memory problems. This does not either suggest FTD or Pick, but rather AD. Bouts of walking are typical for far progressed FTD patients, but does occur even in old AD patients (Cooper 1990). To conclude, according to this thesis Swift suffered from AD.

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