Differences in Activation of the Visual System in Mild Cognitive Impaired Subjects compared to Healthy Subjects measured using functional magnetic resonance imaging (fMRI)

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Preface

This work was conducted in the Alzheimer Memorial Center and Geriatric Psychiatry Branch, Department of Psychiatry of the Ludwig-Maximilians-University.

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Abstract

Introduction:

Mild Cognitive Impairment (MCI) is a cognitive stage between normal aging and Dementia. It is a heterogeneous group of patients, where most of them develop Alzheimer's disease (AD), others stabilize, and a few revert to normal. AD's first clinical symptoms are related to memory, but it has been shown that AD involves also a processing disorder in the visual sensory pathways. Accurate visual function facilitates memory, attention and executive functions, so that perceptual dysfunction contributes to the severity of cognitive impairment.

Objective:

The objective of the work is to measure changes in activation in the visual system between MCI patients and old Healthy Control (HC) subjects, using two different visual processing tasks with functional Magnet Resonance Imaging (fMRI). This is the first study which makes such a comparison between MCI and HC using fMRI.

Methods:

Brain activation was measured using fMRI. The MCI group was composed of 16 subjects and the HC group was composed of 19 subjects. All subjects performed two tasks: location matching (position of objects) and face matching (characteristics of the objects), which selectively activate one of the visual system pathways in healthy people. Answers were given by pressing a single button.

Results:

Performance of the task was not significantly different in both groups. The HC group selectively activated ventral pathway for face matching and the dorsal pathways for location

matching. In contrast the MCI subjects did not selectively activate the ventral and dorsal pathways of the visual system. Additionally they showed higher activation in the left frontal lobe compared to HC when performing the location matching Task

Conclusions:

The results suggest that even when behavioural performance between groups is the same, the neural system which supports performance may differ. MCI subjects compensate their deficits using additional brain areas to help them to maintain performance. In this case MCI subjects used the left frontal lobe in addition to perform the location matching task.

This work presents the usability of brain imaging techniques especially fMRI to better understand the underlying pathology of MCI and its subtypes as prodromal conditions of AD.

Deutsche Übersetzung der Zusammenfassung:

Hintergrund:

Die Leichte Kognitive Störung (LKS) ist ein pathologischer Status zwischen „normalem Altern“ und Demenz. In Wirklichkeit ist es eine gemischte Gruppe von Patienten. Die meisten dieser Patienten entwickeln eine Demenz vom Alzheimer Typ , einige Patienten stabilisieren sich und wenige bekommen verlieren ihre kognitive Störung wieder. Die ersten Symptome, die bei AD Patienten auftreten, betreffen vorwiegend das Gedächtnis, aber frühere Untersuchungen haben gezeigt, dass es ebenso zu Verarbeitungsdefiziten im visuellen System kommt. Die visuellen Funktionen sind auch Grundlage für Gedächtnis, Aufmerksamkeit und Handlungsfähigkeit, so dass Wahrnehmungsstörungen zur Schwere der kognitiven Störung beitragen.

Ziele:

Ziel der Arbeit ist der Vergleich der Aktivierungsmuster im visuellen System zwischen LKS Patienten und gesunden Probanden gleichen Alters mittels funktioneller Magnetresonanztomographie (fMRT). Das dafür entwickelte Paradigma besteht aus zwei visuellen Verarbeitungstestanordnungen Diese Arbeit ist die erste Untersuchung dieser Art bei MCI Patienten und gesunden Probanden.

Methoden:

Die Messung der Gehirnaktivität erfolgte mittels fMRT. Die Gruppe der Patienten mit bestand aus 16 Probanden und die Gruppe der Gesunden bestand aus 19 Probanden. Alle Probanden führten zwei Tests aus: „location matching“ (Erkennen der Position von Objekten) und „face matching“ (Erkenn der Charakteristika von Objekten). Die gewählten visuellen Verarbeitungstests aktivieren selektiv den dorsalen oder ventralen visuellen Pfad bei gesunden Probanden. Die Antworten wurden durch Drücken eines Knopfes gegeben.

Ergebnisse:

Die Leistung bei beiden Tests zeigte für beide Gruppen keinen statistisch signifikanten Unterschied. Die gesunden Probanden zeigten eine selektive Aktivierung des ventralen Pfades für „face matching“ und des dorsalen Pfades für „location matching“. Im Gegensatz dazu zeigten die LKS Probanden keine selektive Aktivierung des ventralen oder dorsalen Pfades des visuellen Systems. Beim „location matching“ Test zeigten sie erhöhte Aktivität im linken frontalen Lappen im Vergleich zu den gesunden Probanden.

Schlussfolgerung:

Die Ergebnisse deuten darauf hin, dass trotz nicht signifikant unterschiedlicher Leistungen für beide Gruppen, die neuronalen Systeme, die diese Leistungen unterstützen, verschieden sein können. Die Patienten mit LKS kompensieren ihre Defizite durch die Rekrutierung von zusätzlichen Gehirnarealen, um dadurch ihre Leistung beibehalten zu können. In der vorliegenden Untersuchung benutzten Patienten mit LKS zusätzlich den linken frontalen Lappen, um den „location matching“ Test zu bewältigen.

Diese Studie zeigt die Anwendbarkeit von neuroradiologischen Methoden und im besonderen von fMRI in der Untersuchung von Demenzen, um die pathologische Grundlage der LKS und ihrer Subtypen als Vorstufen der AD besser zu verstehen.

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1. ALZHEIMER'S DISEASE

Dementia is characterized by a clinical syndrome of deficits in several aspects of basic or complex cognition. The word itself suggests both loss of mind and brain: from Latin, de- "down from" or "out of", and mens- "mind" or "brain" (Arciniegas B. and Bersford T.P., 2001).

Meta-analyses of studies done in developed countries have established Dementia prevalence from around 1% to 5% at the age of 65 years, which doubles every 4 years to reach about 30% at 80 years (Ritchie and Lovestone, 2002).

Alzheimer's disease (AD) is the most common cause of Dementia, with 70% prevalence. It is a progressive, neurodegenerative disorder characterized by decline of cognitive functions.

1.1. Epidemiology: Incidence, Prevalence and Economic Impact

The mean age of the population is increasing quickly in the western world because of increasing life expectancy and decreasing birth rates. The actual prediction for the number of 80 year old people in 2050 is about 8 Million in Germany (it was about 3 Million in 2000). The highest risk factor for Dementia is age, so that as the mean population age rises, the prevalence of new Dementia cases will rise proportionately. It will be necessary, in the near future, to consider the public health impact. Care for AD patients is expensive; the mean cost of care for an early stage AD patient is now 43,000 Euro per year, advance stage care costs 92,000 Euro per year.

The Rotterdam-Study looked at a population of 7,528 individuals between the ages of 55 and 106. From this population 474 received the diagnosis of Dementia. The rates at age 55-59 were about 0.4% and at age 95 and up the rates were 43.2%. Of these 474 cases, 339 were diagnosed as AD, a rate of 72% (Ott et al., 1995). The total prevalence in Germany

now is between 765,000 – 1.1 Million, but in 20 years it is estimated to increase to about 2 Million. It can be considered that AD will be the most frequent old age illness in the western world. The number of new AD cases in Germany per year is about 115,000 and about two third of the patients are over 80 years old (Hampel et al, 2003).

1.2. Pathology

1.2.1. Neuropathology

AD is characterized by the accumulation of insoluble fibrous material, which is not randomly distributed, but has a characteristic pattern. The fibrous material is found in the form of extracellular amyloid deposits and intraneuronal neurofibrillary changes:

a) The extracellular amyloid plaques, or senile plaques, have limited significance for differentiation of neuropathological stages. The cerebral cortex, in particular the isocortex, is the predilection site for the deposition of amyloid. In early stages there is a big inter-individual variation of these deposits; but at the end-stage of amiloyd accumulation, there is a fairly constant distribution pattern of the pathological material.

b) The neurofibrillary changes occur in form of neuritic plaques, neurofibrillary tangles (NFT) and neuropil threads (NT). Neuritic plaques vary from one individual to another, in opposition with NFT and NT that have a distribution pattern which permits the differentiation of six stages (Braak and Braak, 1991):

- stages I-II (transentorhinal stages): they are characterized by an either mild or severe alteration of the transentorhinal region.
- stages III-IV (limbic stages): they are marked by an affection of the transentorhinal region and entorhinal cortex. Mild involvement of the first Ammon's horn sector.
- stages V-VI (isocortical stages): they are marked by the destruction of all

isocortical association areas.

The main component of the amyloid deposits is the 4.2 kD peptid ß-Amyloid (Aß). Each is made of an amyloid nucleus, around which there is a fibrillary amyloid ring.

NFT are a pair of neurofilaments, which are developed in the cell soma and extended to dendrites. They are composed of associated microtubular protein 2, ubiquitin, Aß and Tau-protein. In the NFT of AD patients, we find the hyperphosphorilated form of the Tau-protein (Hampel et al, 2003). When cell dies due to these deposits, they revert to "ghost tangles".

NT are agrophilic processes of nerve cells throughout the neuropil.

1.2.2. Changes in neural function

We find changes in the neuronal glucose and energy transmission in AD. There is a neuronal energy failure and abnormalities in the cellular Ca2+ homeostasis and glucose-related amino-acid metabolism. It is supposed to occur first at the axodendritic terminals of the acetylcholinergic-glutamatergic circuit, causing damage at the synaptic sites (Hoyer, 1993).

1.2.3. Loss of synaptic connexions

Patients with AD have a decreased number of synapses. There is evidence of neural plasticity in the AD neuropil; we find that synaptic contact size is increased in patients to compensate the loss of synapses. In end stages there is no longer the possibility for compensation and both (synapse number and synaptic contact) are in decline (DeKosky and Scheff, 1990).

1.2.4. Neuronal loss

Neuronal loss and neurofibrillary tangles increase in parallel with the duration and

severity of illness. In contrast there is no correlation between the number of senile plaques, amount of neural loss, and the number of neurofibrillary tangles and duration of disease (Gomez-Isla et al., 1997).

Cortical cholinergic denervation is due to cytoskeletal pathology. But in a few areas, such as the cingulated cortex, the cholinergic fiber loss seems to be unrelated with the density of tangles (Geula et al., 1998).

1.2.5. Neurodegeneration process in different brain regions

Only a few neuronal types are altered in AD. Cytoskeletal alterations occur first in form of neurofibrillary tangles and neuropil threads in the allocortex. These lesions have a predictable sequence of appearance in other territories of the cerebral cortex and subcortical nuclei. Some components of the brain are devastated while other parts remain intact until the end phase of the disease. At the beginning of the degenerative process the illness remains subclinical for years. By the time clinical symptoms appear, neocortical association areas are usually already affected. The destruction seems to have an inverse sequence relative to cortical myelination; the last myelinated areas are affected first (Braak et al., 1999).

AD pathology results from the disruption of cortical circuitry; it produces the halt of communication between some cortical areas, with anatomic isolation and fragmentation of many cortical zones. But not all circuits are equally vulnerable to AD pathology; two cortical systems that are involved in the neural processing of memory are selectively affected. The first consists of the connexions between the hippocampus and its neighbouring cortical structures within the temporal lobe. The second is the cortical cholinergic system that originates in neurons within the basal forebrain and innervates the entire cortical mantel. The selective vulnerability of these circuits is the probable reason for the early marked loss of memory observed in these patients (Geula, 1998).

AD is a disease of the cerebral cortex and the subcortical nuclei which innervate it; the primary target of the disease is the cerebral cortex and the interconnected subcortical nuclei are secondarily affected (German et al., 1987).

1.2.6. Neurochemical changes

One of the most important modulatory neurotransmitter systems in the brain is the cholinergic system. It controls activities that depend on selective attention (an essential component of conscious awareness) (Perry et al., 1999). In AD the most significant change is the loss of cortical cholinergic markers. There is a loss of choline acetyltransferase (ChAT) activity. The severity of Dementia and the numbers of neurofibrillary tangles are correlated with the reduction in the ChAT activity (DeKosky et al., 1992; Wilcock et al., 1982). The most affected cortical areas of the brain are the temporal association areas, but the anterior cingulate cortex, primary visual, primary somatosensory, and primary motor cortex are relatively preserved at the beginning (Geula and Mesulam, 1996).

1.3. Cognitive changes

The symptoms begin gradually. The pattern of symptom appearance is correlated with the anatomic neuronal degeneration, and the pathological processes of AD. For example the building of NFT, affect the cortical association areas (frontal, temporal, parietal, and limbic lobes) as well as the linkages among them. The earliest changes occur in the enthorhinal cortex and hippocampus, with pathology progression in the other areas (Braak and Braak, 1991).

Due to the early neurodegenerative effects on the hippocampus, we can find short-term memory impairment as the first sign of the disease, such as memory process and recall from new information (Petersen et al., 1994).

The symptoms begin creeping and slowly progress, often they appear together with depressive symptoms together. The cognitive impairment increases with the course of the illness. Episodic and semantic memory as well as temporal and spatial orientation, are affected in the progression of the disease (Bondi et al., 2005). Later there is a deficit in long-term memory as well, but experiences from the childhood remain the longest in memory (Sagar et al., 1988), and patients lose their ability to manage their activities of daily living, so that the complete care of the patients needs to be provided by others.

1.4. Risk Factors

The most important risk factor for AD is age. In addition other risk factors have been identified: female gender, apolipoprotein ε4 allele, low serum levels of folate and vitamin B12, elevated plasma and total homocysteine levels, smoking, family history of AD or Dementia, fewer years of formal education, lower income, and lower occupational status (Launer et al., 1999).

Education and occupational status: there is a diversity of opinion about the role of education and occupational status as a risk factor for AD. Some studies show that lower education and lack of occupation are risk factors (Mortel et al., 1995; 1994; 2003; Ott et al., 1995). But other studies do not confirm this theory (Beard et al., 1992; Fratiglioni, 1996). The results of the EURODEM Group were that the association between low education and risk for AD could only be shown in women (Letenneur et al., 2000; Fratiglioni, 1996). However some studies found that low education level can increase the risk of non-AD Dementia (Cobb et al., 1995; Bickel and Cooper, 1994).

Genetic: We can differentiate two genetic groups for the apparition of AD: the first represents 90% of the cases and occur sporadically. The second group is hereditary and represents the remaining 10% of the cases. It is called the familial form of AD (Haass and

Baumeister, 1998). The relative risk of AD for people with family history (at least one first degree relative with Dementia) is 3.5 times higher. For those with two or more affected relatives the risk is 7.5 times higher.

Head traumatic injury: In the study performed by Mortimer et al., a re-analysis of the data from 11 case-control studies was performed to investigate the association between head trauma and AD (Mortimer et al., 1991). The findings of the analysis support an association between reported head trauma and AD. But the EURODERM-study, contrary to previous reports, found that head trauma was not a risk factor for AD (Launer et al., 1999). In this study the association between the risk of AD and some factors like gender, head trauma etc was investigated. The authors performed a pool analysis of four European population-based prospective studies of individuals of 65 years and older, with 528 incipient Dementia patients.

Gender: The studies of prevalence like the EURODEM-study showed that for women incidence rates of AD are higher than for men (Launer et al., 1999).

1.5. Clinical Diagnosis

AD is characterized by a long preclinical period during which cognitive deficits are detectable. At the beginning, symptom apparition progresses slowly. The pattern of symptom apparition is correlated with the anatomic neuronal degeneration: the earliest changes occur in the enthorhinal cortex and hippocampus with development of neurofibrillary tangles; the accumulation of ß-amyloid occurs in neocortex (Braak and Braak, 1991), so that we almost always find short term memory impairment as the first sign of the disease (Petersen et al., 1994). Later on the temporal and parietal lobes suffer pathological changes as well, so that language and visuoconstructive deficits appear.

Patients suffering from mild AD also show impairment in long-term memory.

Memory of personal and public events from the distant past is less affected than recent memory in the early stages of disease. But the magnitude of the retrograde loss is related to severity of Dementia (Sagar et al., 1988). Patients are severely affected in the activities of daily living when orientation problems appear.

A detailed description of clinically relevant topics of the illness and its evolution can be assessed through the severity levels or stages of the illness. These "stratified severity levels" or stages are considered as clinical estimations of the evolution of the disease. Within the context of AD there are a variety of clinical severity rating scales. One of the more widely used is the Mini-Mental State Exam (MMSE), but the scores of this test do not give a full comprehensive picture of the patient's clinical status. It is necessary to have a global scale, including ratings for deficits in all areas considered to be essential for the clinical diagnosis of AD. The Global Deterioration Scale (GDS) (Reisberg et al., 1982) is a global measure for the assessment of cognitive decline secondary to normal aging and also AD. It is based on the patient's status encompassing the areas of cognitive, functional (for example activities of daily living) and behavioural pathology.

Another battery of test very useful in the diagnosis of AD is called CERAD (Consortium to Establish a Registry for Alzheimer's disease). It was developed to provide a brief, comprehensive, and reliable battery of clinical and neuropsychological tests for the assessment of patients with the clinical diagnosis of AD (Morris et al., 1989b; Morris et al., 1988).

2. MILD COGNITIVE IMPAIRMENT AND COGNITIVE DECLINE

Mild Cognitive Impairment (MCI) has received a considerable amount of interest in recent years. In fact in the development of the characterization of the clinical diagnosis related to AD and Dementia, the definition of MCI has been changing. Formerly, Mild Cognitive Impairment was thought to be part of the normal process of aging. MCI is now understood to be a diagnosable pathology (as distinct from normal aging). With new diagnostic criteria the number of old people understood to be suffering from some kind of pathological cognitive impairment has increased. In addition, MCI has been considered as a possible prodromal phase of AD and other types of Dementia, a transitional state between normal aging and AD.

Normal "healthy" aging means aging without disease. Aging is a major risk factor for developing Dementia, but does not necessarily lead to age-related diseases. Many old people do not have symptoms of disease and live normal lives. Early pathological disease-related changes constitute the beginning of Dementia rather than the normal concomitants of aging, even in the absence of any clinical symptoms (Thal et al., 2004) .

The prevalence of MCI is about 16-34% (Devanand et al., 1997). Some studies show that 2-3 years after diagnosis, 70% of MCI patients have developed Dementia (Dartigues et al., 1997).

In people who are destined to develop AD, there is a progressive decline in cognitive function. The criteria for clinically probable AD are defined by the symptoms of people who already have a substantial degree of cognitive decline. The condition of MCI makes it possible to identify these individuals at an earlier point in the cognitive decline. The recognition of MCI as a pathological condition and not a manifestation of normal aging has received attention as a clinically useful entity (Petersen, 2004).

2.1. Outcome

Using the Mayo criteria (see 2.2.), the progression from MCI to Dementia is considered to be about 12% per year, while the progression from normal cognition to Dementia is about 1-2% per year (Petersen, 2000). But there is some diversity in rates of progression between authors due to differences in the definition of the patient groups, and different implementation of criteria and length of follow up in the studies.

To unify this criteria it is very important to use appropriate and sensitive neuropsychological and functional measures to diagnose MCI and to use reliable methods to determine progression or improvement of cognitive impairment (Luis et al., 2003).

2.2. Clinical Characterization

There is no agreement on the diagnostic criteria of MCI. In general these individuals have some cognitive impairment (they can be differentiated from healthy people) but not enough to fulfil the criteria of Dementia (Petersen et al., 1999).

The Mayo Alzheimer's Disease Research Center has had some original diagnostic criteria focused on the memory impairment: memory complaint (preferably corroborated by an informant), objective memory impairment for age, relatively preserved general cognition for age, intact activities of daily living and lack of Dementia (Petersen et al., 1999). But these criteria have been modified in recent years, as it is known that other cognitive domains are also impaired in some types of MCI.

Clinical subtypes of MCI have been proposed. All individuals who show symptoms of MCI may not have the same development. Some of them develop AD, while others progress to other types of Dementia. There are also some individuals who will never progress to any type of Dementia. Due to the heterogeneousness of this disease it is proposed that there are several subtypes of MCI (Petersen et al., 2001). Clinical trials have been used with some

inclusion and exclusion criteria to make the definitions of the subtypes of MCI. A consensus conference in 2001 proposed three subsets of MCI (see Table 1):

-*MCI Amnestic (a-MCI)*: it is the most common form of MCI, and it is thought to be a forerunner of AD. This characterization agrees with the original Mayo criteria for MCI.

-*MCI Multiple domain (md-MCI)*: involves impairment in different cognitive domains such as language, visuospatial skills with or without memory impairment (amnesia), so that we have:

-*md-MCI + a*: possibly a forerunner of AD and Vascular Dementia (VD)

-*md-MCI – a*: possibly a forerunner of Vascular Dementia and Dementia with Lewy Bodies (DLB)

-*MCI single nonmemory domain*: presents impairment in one single domain other than memory. This subtype could be the forerunner of Frontotemporal Dementia (FTD) and Dementia with Lewy bodies (DLB).

In addition to these subtypes, there can also be multiple aetiologies or causes for each subtype. The combination of clinical subtypes and putative aetiologies can be useful in predicting the ultimate type of Dementia.

2.3. Amnestic MCI

The criteria necessary to meet the diagnosis of a-MCI are:

-Memory complaint usually corroborated by an informant: this is a 'soft' criterion and it is meant to capture the notion of a change in performance, because it represents a change in function for the person.

-Objective memory impairment for age: it can be identified with neuropsychological testing, but there is still no agreement about the scores which determine the pathology. It is necessary to make a precise history from the patient to note if his level of performance is

really impaired in comparison with his intellectual level.

-Essentially preserved general cognitive function: it refers to the other nonmemory domains.

-Largely intact functional activities: this information should be obtained from the patient and informant. There are often some deficits in daily function because of the memory problems, but this is not considered to constitute a major disability.

-Not demented: this must be judged by the clinician with the results of the other four criteria. In general MCI subjects appear more normal than not. The difficult distinction is between normal aging and MCI rather than between MCI and AD.

2.4. Biological Basis of Cognitive Deficits due to MCI

Impairment in multiple cognitive domains several years before the clinical diagnosis is characteristic for AD. Many brain structures and functions are affected even before symptoms appear, such as the Medial Temporal Lobe (MTL). MLT atrophy is linked to loss of episodic memory (Backman et al., 2004). Episodic memory is not a unique status among cognitive measures in differentiating those who will develop AD versus those who will not. To better understand the pathological aspects of the preclinical state of AD, it is possible to relate the cognitive systems breakdown to the brain structures affected:

-volume reduction of anterior cingulate and temporal sulcus, posterior cingulate and neocortical temporoparietal regions and frontal regions

-decreased blood flow in posterior cingulate and precuneus

-reduced glucose metabolism in temporoparietal regions

-deposits of amyloid plaques in the temporal and frontal cortex

-increase of white matter hyperintensities

2.5. Biomarkers

In the MCI stage there are no clinical methods to determine which patients will progress to AD, except for a very long clinical follow up. And there is a great clinical need for diagnostic instruments to identify incipient AD (Blennow, 2004).

There is currently no agreement on the best biomarker for early diagnosis of AD. There are two choices as most potentially useful biomarkers (de Leon et al., 2004): magnetic resonance imaging (MRI) and Cerebro-spinal fluid (CSF) studies. But these biomarkers also present problems:

-MRI volume changes are not specific for AD and require intensive skilled labour

-The measurement of total T-tau level and amyloid ß42 are not really specific for AD and do not change with disease progression

-Aß42 levels are not easily interpreted because production and clearance are not well characterized

-CSF acquisition is invasive

2.6. Onset of precipitous decline

Cognitive decline may not be expected until some biological events (e.g. the accumulation of amyloid and neurofibrillary tangles, inflammation, oxidative stress, loss of synapses, death of neurons) have reached a certain threshold. Until this moment the brain is able to compensate for the pathological changes of AD.

There are individual differences with regard to onset and rate of change in preclinical AD, some have a very fast decline before diagnosis, and others show gradual decline over a longer period.

2.7. Recommendations for the general criteria for MCI:

-Not normal, not demented (does not meet DSM IV and ICD 10 criteria for a Dementia syndrome)

-Cognitive Decline

-Self and/or informant report of impairment on objective cognitive tasks

and/or

-Evidence of decline over time on objective cognitive tasks

-Preserved basic activities of daily living / minimal impairment in complex instrumental functions.

Future research should focus on identifying the prevalence of the three clinical presentations of MCI and also to establish the aetiology behind the impairment, both with clinical data and population based studies (Winblad et al., 2004).

Table 1. Clinical subtypes of mild cognitive impairment

Clinical Clasification	Degenerative (Aetiology)	Vascular	Psychiatric	Trauma
MCI amnestic	AD		Depr	
MCI Multiple Domain + Amnesia	AD	VaD	Depr	
MCI Multiple Domain - Amnesia	DLB	VaD		
MCI single Nonmemory Domain	FTD DLB			

Classification of clinical subtypes of mild cognitive impairment with presumed aetiology
[Petersen et al. 1999]

AD- Alzheimer's disease
Depr- Depression
VaD- Vascular Dementia
DLB- Dementia with Lewy Bodies
FTD- Frontotemporal Dementia

3. THE ROLE OF NEUROIMAGING IN MCI AND AD

In the recent past, neuroimaging has come to play an important role in the diagnosis of Dementias. Dementia is a growing social problem and the development and advancing of neuroimaging provides the necessary means for rigorous and early diagnosis. This is particularly true in light of new therapeutical research, which points to new therapies that will be more effective in preventing or slowing disease progression (Bastos Leite et al., 2004).

In the pathological process of Dementia, patients suffer anatomical brain changes. Even in healthy individuals, after the fifth decade of life, we find some changes in brain anatomy, such as reductions in brain weight (Dekaban, 1978). The American Academy of Neurology has published the practice parameters for the diagnosis of Dementia, and in the current standards of clinical practice the use of neuroimaging in the diagnosis and treatment of AD is not required. But the present knowledge about this disease allows physicians to use neuroimaging as a supporting tool in the early diagnosis of AD or in the differential diagnosis to distinguish AD from other pathologies. It is a tool which assists the clinicians to examine structural, functional and biochemical changes in the brain. These methods include: Structural imaging like Magnetic Resonance Imaging (MRI) and Computer Tomography (CT); and functional imaging like functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT).

A study by Chui and Zhang revealed that the use of structural imaging and PET improves the diagnosis of Dementia. In fact the clinical diagnosis changed for 19% of the patients and the clinical management for 15% of the patients, with the conclusion that the clinical evaluation was unable to predict neuroimaging findings (Chui and Zhang, 1997).

Some other authors like Small et al. found that functional neuroimaging can be useful predicting evolution of disease and also following disease progression in people at risk for AD (Small, 2002).

In relation to structural imaging, except in cases where MRI is contraindicated or not

available, there is no reason to prefer CT over MR as an anatomical screening method for Dementia (Petrella et al., 2003).

The clinical course of Dementia begins years before symptoms appear. Functional neuroimaging should be a very useful method for early diagnosis, because it allows the investigation of nerve cell dysfunction (Haxby et al., 1987)

We see some areas of hypometabolism in AD patients before symptoms appear (Johnson et al., 1998; de Leon et al., 2001; Okamura et al., 2002; Chetelat et al., 2003) . Techniques like PET or SPECT, therefore, have the advantage of showing these brain metabolic changes that precede structural brain changes.

It has been thought that MCI is a transitional state between normal aging and AD. It is in fact a kind of catch-all for symptoms that by traditional diagnostic methods can be misunderstood. It represents a heterogeneous group of patients, where some of them develop Dementia or AD, others stabilize, while others revert to normal (Petrella et al., 2003). Functional neuroimaging studies are underway to identify converters from MCI to AD, and also from normal aging to MCI (Johnson et al., 1998; de Leon et al., 2001; Okamura et al., 2002; Chetelat et al., 2003).

For example in the study by Linn et al. the interval between the onset of detectable cognitive impairment and clinical diagnosis in individuals with probable AD (Linn et al., 1995) was evaluated, and they tried to identify the pattern of the earliest changes in cognition in probable AD. Their findings support previous contentions that a "preclinical phase" of detectable cognitive deficits can precede the clinical diagnosis of probable AD. But the question is, how do we reach the most precise and earliest diagnosis. Dysfunctions in people at risk for developing AD may be identified with fMRI years before symptoms appear. By means of fMRI, compensatory strategies developed from people at risk for AD (Apolipoprotein genotype epsilon 4, APOE) can be shown. Before symptoms appear at all, these people require additional cognitive effort to perform tests in comparison to people

without risk (Bondi et al., 2005).

Although there are not so many studies using fMRI to investigate early deficits from patients which may develop AD, it has been shown that fMRI plays a promising role in the preclinical characterization and very early diagnosis of AD (Fleisher et al., 2005). Therefore studies using fMRI need to be extended to the MCI group to further characterize this group of patients and their deficits and to differentiate the MCI patients developing AD from those developing other types of Dementia. An additional benefit of early diagnosis of AD would be higher effectiveness of the currently available treatment options for AD, as it is believed that the available treatment options would be more effective the earlier they would be given to the patients, as the disease process has not led to extensive neuronal and synaptic dysfunction in large areas of the brain.

4. FUNCTIONAL IMAGING

4.1. Neuroimaging of cognitive functions in the human brain: Brain Mapping

The fact that there is a localization of function in the human brain has long been known. It was proved by the cortical stimulation of patients during neurosurgery, in the middle of the 20th century (Savoy, 2001). The disadvantage of these studies was the fact that pathological brains were studied and not healthy ones. During the second half of the 20th century the exploration of cognitive functions in human brains was advanced by means of neuroimaging. Before neuroimaging was established as an exploration method of the brain, almost the whole knowledge of cognitive functions was first obtained from the exploration of patients through neuropsychological methods. And more information was gained later concerning the relationship between different neurostructures, when primates were included in these studies (Krause and Müller-Gärtner, 2005).

The goal of functional neuroimaging is to map the activity of the living brain in space and time. It intends to explore normal and pathological living brains with a non-invasive method. It allows the identification of the functional neuroanatomy of different cognitive functions and to measure how the different brain areas work together by the executions of cognitive exercises. This new field of research is often termed “Brain Mapping”.

There are two different approaches of non-invasive functional neuroimaging:

- **electrophysiological methods**, such as electroencephalography (EEG) and magnetoencephalography (MEG), measure signals which arise as the sum of electrical and magnetic events in individual cells. The main advantage of these methods is their temporal resolution. The main disadvantage is that they rely on sensors located outside of the brain, so that they provide ambiguous spatial information. This information is not sufficient for creating accurate images of function.

- **metabolic/vascular methods**, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These approaches are more indirect

because they measure metabolic correlates of neuronal activity, but not activity itself. FMRI measures blood oxygenation level, which changes with the metabolic demands of active neurons. The technique that forms the basis for nearly all fMRI studies is blood-oxygenation-level dependent (BOLD) contrast. The metabolic/vascular methods have very good spatial resolution, good delineation of the spatial extent of an activated area and precise matching to anatomical structures.

4.1.1. Physiological changes during brain activation:

The fundamental element for the processing of information in the brain is the neuron, which has two primary roles, integration and signalling. Changes in cell membrane potential and release of neurotransmitters are the basis for the activity of neurons. These functions are made possible by the movements of ions across neural membranes. The restoration of concentration gradients following neuronal activities requires an energy supply. This energy supply comes from the molecule ATP. The process of formation of the ATP molecule requires glucose and oxygen consumption. These metabolites are supplied by the vascular system.

Changes in the vascular system may occur in response to neural activity. Roy and Sherrington postulated that the increase in neural activity in one region also means an increase in cerebral blood flow and oxidative metabolism (Friedland and Iadecola, 1991). The regional cerebral blood flow (rCBF) increase brings glucose and oxygen to the activated brain areas. That is the physiological basis of fMRI and PET (see Table 2).

-Translation of Brain Activity into a Functional image:

To understand how functional images are obtained with these methods, it is important to know:

-the relationship between local brain activity and the physiological parameters which

are measured

-the relationship between these physiological parameters and the obtained functional image.

Brain activity can be mapped in two ways, metabolic and vascular, creating two kinds of functional images (Moonen and Bandettini, 2000). This can be represented:

Brain Activity	→	Metabolic Response	→	Functional Image
f(x,t)		g(f(x,t))		h(g(f(x,t)))

Brain Activity	→	Vascular Response	→	Functional Image
f(x,t)		i(f(x,t))		k(i(f(x,t)))

where: x means location, t means time, f(x,t) means functional convolution of brain cell activity, g(f(x,t)) means change in metabolism and i(f(x,t)) means change in Cerebral Blood Flow (CBF) or neurovascular coupling.

We obtain maps of metabolic [h(g(f(x,t)))] and vascular [k(i(f(x,t)))] events associated with changes in brain activity. At this point there is always a loss of information which occurs on at least three levels:

-qualitative reduction of many different types of brain cell activity into just one dimension of brain activity: increase of cerebral blood flow and local cerebral glucose utilization reflects different facets of brain activity like synaptic and presynaptic activity (excitation / inhibition), action potential of the neuron soma and subthreshold depolarization. But more than 85% of cerebral glucose is used in the presynaptic axon terminal of neurons (Jueptner and Weiller, 1995). This means that the maps of metabolism and blood flow are principally ambiguous with respect to the underlying neurophysiological event.

-a loss of spatial resolution: it is possible that the spatial error for the vascular response is quite significant, because the spatial relationship to brain activity is given by the smallest theoretically possible functional unit in the vascular system. This is probably a single

capillary. Some authors say that the opening and closing of capillaries produces changes in capillary blood volume, and this should represent a major mechanism of blood flow adjustment in the brain (capillary recruitment hypothesis) (Shockley and LaManna, 1988). Although this question is not definitely clear, there seems to be no convincing argument that the smallest functional unit of vascular regulation in the brain is in fact the feeding arteriole.

-a loss of temporal resolution: neuronal events occur on a time scale of milliseconds and vascular events occur on a time scale of seconds. This sets limits on the temporal resolution of functional neuroimaging approaches based on metabolic/vascular imaging.

4.2. Functional MRI

4.2.1. MRI principles

Magnetic Resonance Imaging (MRI) is a non-invasive technology for creating pictures of the soft tissues of the human body. MRI is useful in Neuroscience for the study of multiple brain tissues related to brain anatomy and has two very important benefits:

1) The images have high spatial resolution and contrast.

2) The technology does not use ionizing radiation. It is a tool that can be used safely and repeatedly on adult and children volunteers, as well as patients.

The physical principle underlying MRI is nuclear magnetic resonance (NMR). It permits the detection of the hydrogen nuclei of water molecules in the body by their interaction with a magnetic field. Hydrogen nuclei have an odd number of nucleons (protons + neutrons) so that they posses a magnetic moment and a spin (angular momentum). In the presence of an external magnetic field these particles reorganize themselves and spin with a movement called precessing. Some of them go to the position requiring the least energy. In this position their magnetic moments are parallel to the external field. Other particles precess with a magnetic moment which is antiparallel to the external field, the position requiring high energy. The rate of precession is proportional to the local magnetic field strength.

Excitation of the hydrogen nuclei can be reached by the application of a pulse of magnetic energy at the resonant frequency of the precession. Some of the low energy nuclei absorb energy from the pulse and will change to a high energy state. After the energy source is removed the nuclei return to the low energy position and give off the absorbed energy. Measurement of this emitted energy (NMR signal) provides the data which create the images.

The application of the pulse of magnetic energy (rf-pulse) makes hydrogen nuclei change orientation. If we control the power and duration of the rf-pulses we can change the main magnetization vector by an angle θ, called the flip angle. This angle can be 45°, 90° or 180° away from the least energy position.

By systematically varying the strength of the externally applied magnetic field across the three dimensions of space, and measuring the NMR signal as this is done, it is possible to generate images based on the differences of NMR signals at each point in space. MRI allows us to see differences in the physical properties of tissues.

4.2.2. Physiological basis of Blood-oxygenation-level dependent (BOLD) fMRI: What does fMRI tell us about neural activity?

It is also possible to obtain functional images of the brain under the influence of a magnetic field by measuring blood flow and changes in blood characteristics in the brain. The most common functional MRI technique is the BOLD-fMRI (Blood-Oxygenation-Level-Dependent fMRI). It is based on the different magnetic properties of deoxy- and oxy-haemoglobin, and also on the coupling of oxygenated blood flow and neuronal activity. It does create images of physiological activity that is correlated with neural activity.

The work of the American chemist and Nobel Laureate Linus Pauling and his student Charles Coryell showed in 1936 that the magnetic properties of the haemoglobin molecule are different depending on whether or not it is bound to oxygen. Oxygenated haemoglobin is

diamagnetic (zero magnetic moment) and deoxygenated haemoglobin is paramagnetic (significant magnetic moment).

In the early 1980s Thulborn and colleagues found that the decay of transverse magnetization is dependent on the proportion of oxygenated haemoglobin within a test tube of blood (Thulborn et al., 1982). These results provided a theoretical basis for the measurement of blood oxygenation changes using MRI. In the late 1980s Seiji Ogawa investigated the possibility of examining brain physiology using MRI techniques. Based on the previous findings that deoxyhaemoglobin decreases the T2* weighted value of blood, Ogawa and his colleagues made some experiments using both test tube and animal models. Their findings showed that the blood-oxygenated-level dependent (BOLD) contrast could enable measurement of functional changes in the brain, because the BOLD contrast was found to depend upon the total amount of deoxygenated haemoglobin present in a brain region, which in turn depended upon oxygen consumption and oxygen supply (Ogawa et al., 1992; Ogawa et al., 1993).

The coupling of Oxygen comsumption and Blood Flow

Fox and Raichle (Fox and Raichle, 1986) postulated that there exists a disparity between oxygen consumption and oxygen delivery in an activated brain; more oxygen is supplied to the brain than is consumed. This is due to an increase in the velocity in the cerebral blood flow. The capability of the capillary system to deliver oxygen to tissue is less when the transit time decreases. It means that in the venous system (after the oxygen exchange has been done) the oxygen concentration is higher than before neural activity in one region started.

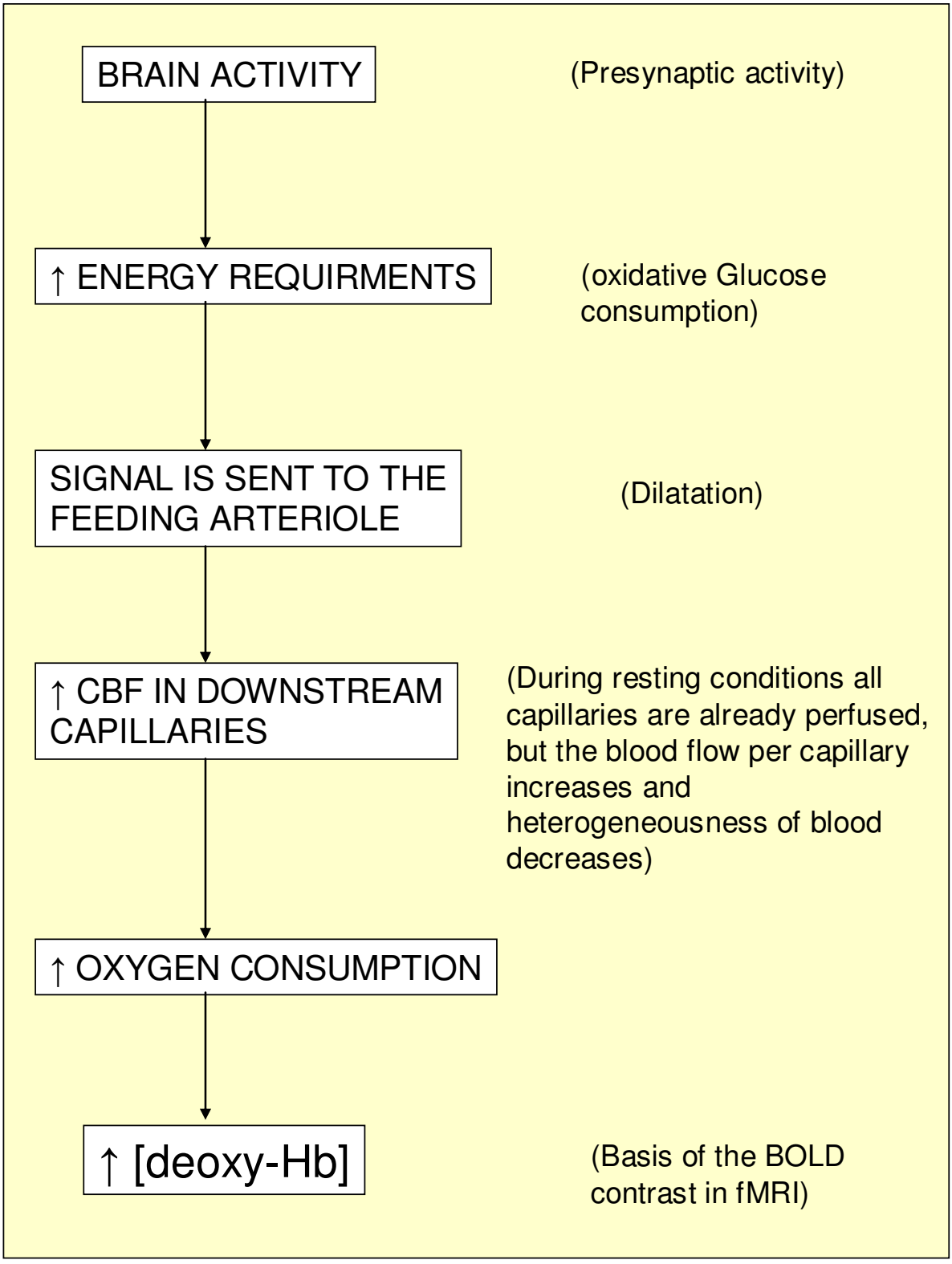
BOLD contrast following neuronal activity occurs not because oxygenated haemoglobin increases in the NMR signal but because it displaces the deoxyhaemoglobin. Neuronal activation produces local hemodynamic changes, as Roy and Sherringtong

postulated. It means that there is an increase in local blood flow and local blood volume. But there is relatively little change in oxygen consumption, so oxygen concentration in venous blood increases, and deoxy haemoglobin concentration decreases. This effect can be measured in the scanner because there is less magnetic substance in the venous blood and the signal increases on T2* weighted images.

Components of the BOLD Hemodynamic Response

The change in the NMR signal triggered by neuronal activity is known as the hemodynamic response (HDR). Cortical neuronal responses occur within tens of milliseconds following a sensory stimulus, but the first observable HDR first occurs 1 to 2 seconds later. BOLD signal in a voxel reflects the amount of deoxyhaemoglobin (which is contained in the voxel) and also noise, coming from different sources. It is known that there is an initial dip of 1 to 2 sec. in the signal, which is attributed to the transient increase in oxyhaemoglobin in blood flow at the beginning of the neuronal activity increase. After this 2 sec., the signal increases up to a maximum value (peak of the hemodynamic response) at about 5 sec., for a short duration. But if the neuronal activity is extended across a block of time, the peak may be similarly extended onto a plateau. After reaching this peak, the BOLD signal decreases to a below-baseline level (undershoot) and remains so for an interval of time.

Table 2. Changes in cell metabolism and blood flow during functional activation



5. VISUAL SYSTEM

5.1. Anatomy of the visual system

Vision provides the largest part of the sensory information we receive from our environment. Vision occurs when light falls on the retina where it is transformed into electrical potentials which are transmitted via Thalamus (Lateral Geniculate Nucleus) to the Cerebral Cortex.

The Lateral Geniculate Nucleus (LGN) is composed of six layers: two of which have a ventral localization and are composed of big neurons. They are called magnocellular neurons. The rest are in a dorsal localization and are little neurons, they are called parvocellular neurons. They have different functions in the visual system. Both of them send their axons to the primary visual cortex in the Calcarine Fissure (Brodmann area 17), which integrate the Radiatio Optica. The magnocellular neurons are the part of the visual system which process location and movement information of objects. Color and shape information of objects are processed by parvocellular neurons. The neurons in the LGN send their axons directly to V1 (primary visual cortex, striate cortex, area17) via the optic radiations. This highway of visual information courses through the white matter of the temporal and parietal lobes.

The primary visual cortex, V1, is located around the Calcarine Fissure in the occipital lobe. It is the best studied visual area of the brain. It is the part of the visual cortex that is responsible for processing visual stimuli. The primary visual cortex is divided into six functionally distinct layers, labeled 1 through 6. Layer 4 receives most visual input from the LNG.

There are three more association visual areas: the V2, V3 and MT (V5). V2 is the second major area in the visual cortex, and first region within the visual association area. It receives strong feedforward connections from V1 and sends strong connections to V3, V4 and V5, and also strong feedback conexions to the V1.

The multiple visual cortical areas are organized into processing streams. According to

the model originally proposed by Ungerleider and Mishkin 1982 (Ungerleider and Mishkin, 1982), there are two major processing streams. The origin of both of them is the primary visual cortex (striate cortex), V1. Both of them consist of different visual areas beyond the V1 (extrastriate areas). The ventral stream goes through visual area V4 into the temporal lobe and is responsible for visual recognition of objects. The dorsal stream goes through visual areas V2, V3 and MT into the parietal lobe and is responsible for the spatial relationships of the objects (see Figure 1). It can be expressed in terms of "what versus where" (Ungerleider and Haxby, 1994; Ungerleider and Desimone, 1986a; Ungerleider and Desimone, 1986b).

The Ventral Stream

The visual information impinging on the retina is a two dimensional projection of a three dimensional world. This projection varies in order to the position, distance, illumination, and orientation relative to the viewer. The function of the ventral stream can be described as determining and encoding these features which are so important for the object recognition. The neurons which compound the ventral stream have sensitivity to the shape, color or texture of visual stimuli, it is a parvocellullar dominated stream. In the progression along the pathway, the neurons can process more complex stimulus features or combination of features.

The Dorsal Stream

One of the more prominent features of the neurons in the dorsal stream is selectivity for the direction of visual motion. But the properties like sensitivity to binocular disparity and the property believed to underlie depth perception are characteristic of many neurons in the dorsal stream. And many properties of these neurons point to their role in the processing of location information in active observers. It is a magnocellular dominated stream.

Beyond Visual Processing Streams

In order to execute visually guided behaviours successfully, the information carried by

the two streams must be integrated. It seems that some kind of integration occurs within the stream, but this is only partial. The question where this definitely integration occurs is already not answered, but it must be in areas outside of the visual system.

Some studies have shown that projections from areas in the dorsal stream terminate mainly in and around Brodmann area (BA) 46 of dorsolateral prefrontal cortex (Ungerleider and Desimone, 1986b). The projections from the ventral stream terminate mainly in the BA 12 and 45 of ventrolateral prefrontal cortex (Ungerleider et al., 1989). Although the inputs to prefrontal cortex from the two streams are anatomically segregated, there is evidence of the existence of individual prefrontal neurons that process information about an object's identity and its location (Rao et al., 1997), in this way this information may be integrated.

In studies in which diverse cognitive demands were performed (like response conflict, task novelty, working memory or perceptual difficulty), it was shown that there are three common regions which are always activated, mid-dorsolateral, mid-ventrolateral, extending along the frontal operculum to the anterior insula and the dorsal part of the anterior cingulated (Duncan and Owen, 2000). This common network of active regions seems to be activated in demands as diverse as response selection, working memory maintenance and stimulus recognition.

5.2. Visual Attention and Perception

Attention is a critical determinant of what we perceive. It makes the difference between looking and seeing. It may alter the cortical representation of the visual scene in a way that is equivalent to increasing the contrast of those stimuli that currently have behavioural relevance.

Since the mid-70s experiments have demonstrated that the organization patterns of neurons in primary visual cortex are not genetically fixed, but develop from visual experience. Connexions among neurons are initially more or less randomly scattered. With

visual experience, the neurons appear to divide their work: some neurons reinforce each other and some unnecessary connexions are eliminated. Such filtering allows the brain to efficiently process the massive amounts of visual information impinging on the retinas.

The possibility to see things is a process much more complex than the result of the light fall on the retina. Visual scenes are usually in a different way considered by different viewers. It depends on which aspect of the scene is being analyzed from the viewer, in other words where he is putting his attention. A very important factor by seeing is the knowledge and experiences the person had before. Many of the processes with influence on seeing and perceiving, take place without attention. Visual perception can be modulated through learning and knowing.

It is well established that response in neurons from the ventral stream are modulated by visual attention. Early studies identified the area V4 and the ventral stream as one of the main sites of attentional influences on visual processing. Recent studies have demonstrated similar influences in visual cortical areas within the dorsal stream. The source of these attentional modulatory influences likely arises from a network of frontal and parietal areas.

5.3. Changes in Visual System in AD

There is clear evidence that AD involves a processing disorder that has his origins in the visual sensory pathway (Gilmore et al., 1994; Hof et al., 1990b; Hof and Morrison, 1990). The memory dysfunction is the hallmark of the AD Disease but before it appears there are other systems which already suffer from the neurodegeneration, like the visual system (Mendola et al., 1995). The sensory problems add to and exacerbate the memory problems.

Neuropathological alterations in AD precede cognitive impairment by several years. Functional changes occur before clinical symptoms appear and the visual system is very early involved in the pathological process. It is demonstrated in several studies with different tasks and different population groups.

In the study of Cronin-Golomb et al. (Cronin-Golomb et al., 1991) visual deficits in the following functions were observed: color, stereoacuity and contrast sensitivity. They received a neuro-ophtalmological examination, and no abnormalities were found. These findings made the authors suggest that the widespread visual dysfunction reported were more likely to be related to known pathological changes in primary visual and association cortex in AD than to changes in the retina or optic nerve.

Sadun may have been the first to suggest that AD may involve a deficit in the magnocellular pathway neural system.(Sadun, 1989). It would mean that the magnocellular neurons of the dorsal pathway are more susceptible to degeneration than the parvocellular neurons of the ventral pathway. For some authors there is evidence for the fact that the magnocellular pathway is the part of the visual system more impaired (Gilmore et al., 1994; Mentis et al., 1996; Mentis et al., 1998). But there are other studies in which deficits in the magnocellular but also in the parvocellular pathway were shown (Cronin-Golomb et al., 1991; Rizzo et al., 2000b; Rizzo et al., 2000a).

Mentis et al. (Mentis et al., 1996) demonstrated that the magnocellular visual system suffers a greater dysfunction than the parvocellular, so that the visuospatial evaluation of AD patients could be very useful for the characterization of the disease

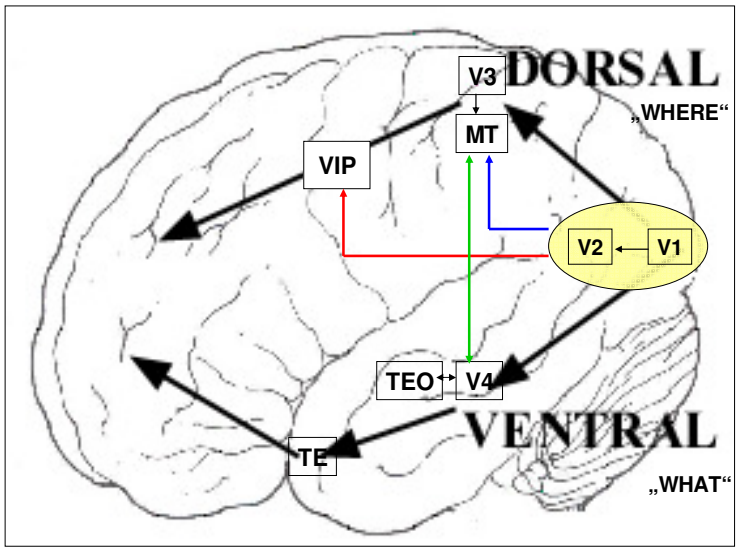
In the investigation of individuals at risk for AD, like the study of Smith et al. (Smith et al., 1999), the authors demonstrate that cognitively normal individuals at a high risk for AD had a decreased brain activation in key areas engaged during naming and fluency tasks. They concluded that it may be a consequence of the presence of subclinical neuropathology in the inferotemporal region or in the inputs to that region. Thulborn et al. (Thulborn et al., 2000) in the same way studied a group of patients with probably AD and a control group using fMRI. The task was a visuospatial cognition task with an eye movement paradigm. The results obtained from the study, showed that a left dominant activation pattern and enhanced prefrontal cortical activation were observed in most of the patients in comparison with the

control group. So the reduction in right parietal activation producing the left-dominant pattern may reflect the progressive dysfunction in spatial attention associated with AD.

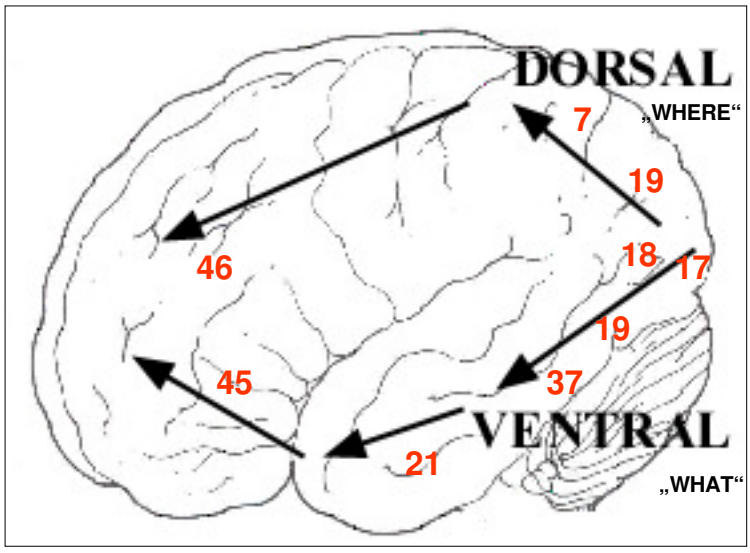
In conclusion, in the majority of the studies diminished intensity and/or extent of activation has been demonstrated in the frontal and temporal regions in patients with AD. Studies with "at-risk" populations showed mixed results with increased or decreased activation patterns. Some of the authors from all these studies explain their findings in terms of a compensatory-recruitment hypothesis, in which greater cognitive effort is required from the patients to perform the same task (Petrella et al., 2003).

According to all these studies, fMRI has proved to be a powerful research technique for analyzing deficits in the very early stage of the pathological process of AD. When memory complains appear, the disease is already in an advanced stadium and some of the functional deficits (like in the visual system) appeared years before.

Figure 1. The primary Visual Cortex and the two Cortical Visual Systems



Anatomical connections of visual areas in the ventral and dorsal streams.
The blue line indicates connexions between the early visual areas V1 and V2 to the middle temporal visual area MT. The red line indicates direct inputs from the peripheral field representations of V1 and V2, bypassing MT (they may provide rapid activation of regions mediating spatial attention). The green line indicates projections “intermediate-type” (they link areas between dorsal and ventral stream).
MT-motion-sensitive area of the sup. temporal sulcus
VIP-ventral intraparietal area
TEO and TE- inferior temporal. They comprise together the inferior temporal (IT) cortex.
(Adapted from Ungerleider, 1995 (Ungerleider, 1995))



Anatomical connections of Brodman areas in the ventral and dorsal streams.
Shown are some of the greater regions of each stream (Brodman areas). Area 17 in the occipital lobe is the primary visual cortex. Area 18 and 19 are located in the occipital cortex as well. In the ventral pathway area 37 and 21 are located in the inferior temporal cortex and area 45 is located in the frontal cortex.
In the dorsal pathway the area 7 is located in the parietal cortex and area 46 is located in the prefrontal cortex.
Take note that nomenclature of Brodman areas is still approximate.
(Adapted from B.J.Krause and H.-W. Müller-Gärtner (Krause and Müller-Gärtner, 2005))

6. OBJECTIVE OF THE WORK

Accurate visual function facilitates memory, attention and executive functions, so that perceptual dysfunction contributes to the severity of cognitive impairment (Rizzo et al., 2000b). Visual system deficits due to the Alzheimer's pathology have already been investigated and it is shown that AD involves disorders in the visual sensory pathways.

The objective of the work is to measure changes in activation in the visual system between MCI patients and old HC subjects using fMRI. This is the first study which makes such a comparison between MCI and old HC using fMRI.

For the study, two different visual processing tasks have been designed in a manner that they activate selectively the ventral and dorsal pathway in healthy people. This work seeks to identify abnormalities in visual system in MCI subjects due to the pathological changes in brain before behavioral performance is impaired, thereby providing the possibility of an earlier diagnosis of AD.

7. SUBJECTS AND METHODS

7.1. The patient group

7.1.1. Inclusion and Exclusion Criteria

Inclusion Criteria

-Age less than 80 years

-MMST over 20

-Diagnosis of MCI with amnestic component (Petersen et al., 1999): the patient must be neither normal nor demented (does not meet criteria (DSM IV, ICD 10) for a Dementia syndrome). There must be a marked cognitive decline (reported by the patient and/or informant) and impairment in objective cognitive tasks and/or evidence of decline over time in objective cognitive tasks. Basic activities of daily living must be preserved and minimal impairment in complex instrumental functions is necessary for the diagnosis.

Exclusion Criteria

-Brain vascular damage (as a risk of Vascular Dementia)

-Arterial hypertension (as defined by consistent blood pressure values over 160/95)

-Diabetes mellitus (as defined by fasting glucose levels over 140 mg/dl with or without therapy)

-Depression (as defined by Hamilton Depression Rating Scale over 12)

-Any other neurological or psychiatric pathology

-Metal implants and/or pacemaker.

7.1.2. Description of the Group

Sixteen patients were included in the study. All patients received an explanation of the study and gave their written consent. The study was approved by the Ethics Committee of the Medical Faculty of Ludwig Maximilian University. The Group was composed of 8 women with an average age (standard deviation) of 68.38 (8.535) and 8 men with an average age

(standard deviation) of 71.50 (7.25).

The average (standard deviation) of the MMST was 27.88 (1.63) for the whole group. Age and gender distribution was matched between groups. There were statistically significant differences between healthy control and MCI group in the MMST Score at the $p<0.05$ level.

7.2. The old healthy people group

7.2.1. Inclusion and Exclusion Criteria

Inclusion Criteria

-Age less than 80 years

-MMST over 20

-Healthy people status is determined by different means to reject medical, neurological, psychiatric and Dementia illness: history, physical and neurological examinations, mental status examination and neuropsychological evaluation.

Exclusion Criteria

The exclusion criteria for the old healthy group were the same as for the patient group.

7.2.2. Description of the Group

There were 19 old healthy people (OH) included in the study. All of them gave written consent to participate as well. The group was composed of 11 women with an average age (standard deviation) of 68.18 (5.29) and 8 men with an average age (standard deviation) of 66.00 (3.46). The average (standard deviation) of the MMST was 29.16 (1.015) for the whole group.

7.3. Physical and Neuropsychological Examination

a) History

To investigate predisposing factors, personal and family medical histories were required. The subjects received particular attention when the history suggested the presence of cardiovascular disease, hypertension, diabetes, inflammatory disease, or Dementia in the family history.

b) Physical and neurological examinations

Vital signs were examined to determine the presence of systemic or neurological abnormalities.

Elemental neurological examination: cranial nerve abnormalities (including visual fields), motor (voluntary and extrapyramidal), sensory signs, impairments of gait or coordination and abnormal and asymmetric reflexes.

c) Mental status examination

The mental status examination is a systematic assessment of an individual's quality of mental functioning. It is the primary clinical tool for examining and understanding cognition, emotion and behaviour. Because of some patients demonstrating abnormalities of mental function without clear abnormalities in general physical or neurological condition, mental status examination is one part of a more comprehensive clinical examination.

The essential elements of the mental status examination are:

-General: appearance and behaviour, speech, thought process and content, emotion

-Cognitive: arousal, attention, language, memory, recognition

d) Laboratory examination

-Electroencephalography (EEG): slowing on the EEG tends to increase in proportion

to the degree of cognitive impairment. It can be useful for the differential diagnosis between Delirium and Dementia.

-Battery of standard Tests to identify a suspected underlying etiology: complete blood count, serum chemistries (creatinine and blood urea nitrogen, liver function tests), vitamin B12, folate, thyroid stimulating hormone (TSH), and serum syphilis serology.

-Structural Neuroimaging study: Magnetic Resonance Imaging (MRI) can provide definitive information on the cause of a Dementia

-Lumbar puncture

e) Neuropsychological evaluation tests

It is necessary when additional information on the pattern and extent of cognitive impairments is needed to clarify the diagnosis and to guide treatment planning.

-MMSE: This is a test which lasts about 10 min, it is used to evaluate grade of Dementia (Folstein et al., 1975). It includes merely cognitive aspects but not mood state or psychotic symptoms. The scores vary between 0 and 30 points, where 0-11 points represents severe Dementia, 12-18 middle-severe Dementia, 19-23 mild Dementia, 24-26 cognitive impairment, and 27-30 unimpaired efficiency. The test includes orientation, attention, memory and language exercises from daily living

-CERAD (Consortium to Establish a Registry for Alzheimer's disease): a battery of clinical and neuropsychological tests for patients with Alzheimer's disease which lasts about 40 min. These tests measure the primary cognitive manifestations of AD across a range of severity, and discriminate between normal subjects and those with mild and severe Dementia (Morris et al., 1989a). It is composed of seven tests:

1) Verbal fluency

2) Boston Naming Test: 15 words from one category must be given

3) MMSE

4) 10 words have to be memorized in three passages

5) Constructive praxis

6) Unprompted recall of the memorised 10 words

7) Identification of the memorized words from a larger list of words.

This battery is scored by the individual test. There is no cumulative score.

For detailed patient characteristic see tables 3 and 4.

Table 3. CERAD scores for the OHC group

Controls	sex	MMSE	Word List 1	Word List 2	Word List 3	Word List 1-3
1	man	30	7	8	10	25
2	Man	28	7	8	8	23
3	woman	29	6	10	10	26
4	man	30	8	9	10	27
5	man	29	4	7	8	19
6	woman	30	8	10	10	28
7	man	29	6	9	9	24
8	woman	29	9	9	10	28
9	man	30	7	8	10	25
10	woman	26	5	8	10	23
11	woman	28	7	8	10	25
12	man	30	6	7	8	21
13	woman	30	5	7	6	18
14	man	30	8	9	10	27
15	woman	30	7	8	9	24
16	woman	29	6	7	9	22
17	woman	29	4	7	8	19
18	woman	30	7	8	10	25
19	woman	29	7	8	10	25

Table 3. continued

Controls	sex	Word Recall	Word Recognition	Word Flow	Name	Drawing
1	man	10	10	23	15	11
2	Man	8	9	25	13	11
3	woman	10	10	37	14	10
4	man	10	10	36	15	11
5	man	6	10	13	13	11
6	woman	10	10	24	15	10
7	man	6	10	21	15	10
8	woman	10	10	29	15	8
9	man	8	10	19	15	11
10	woman	9	10	20	15	11
11	woman	9	10	30	15	11
12	man	8	10	21	15	11
13	woman	6	10	24	14	10
14	man	10	10	22	15	11
15	woman	8	10	15	14	11
16	woman	7	10	13	15	9
17	woman	4	10	23	14	10
18	woman	9	10	30	15	11
19	woman	9	10	33	15	11

Table 4. CERAD scores for the MCI group

Controls	Sex	MMSE	Word List 1	Word List 2	Word List 3	Word List 1-3
1	woman	29	4	7	7	18
2	woman	26	4	5	5	14
3	woman	25	2	3	4	9
4	man	27	5	6	6	17
5	man	28	4	3	7	14
6	man	29	4	5	7	16
7	man	25	4	5	6	15
8	woman	24	4	5	6	15
9	woman	28	7	8	6	21
10	man	27	3	6	7	16
11	woman	27				18
12	man	28	2	3	4	9
13	woman	27	4	8	9	21
14	woman	29				19
15	man	28	4	4	6	14
16	man	28	4	6	8	18

Table 4. continued

Controls	Sex	Word Recall	Word Recognition	Word Flow	Name	Drawing
1	woman	2	7	15	15	11
2	woman	2	10	17	13	11
3	woman	0	4	12	14	10
4	man	5	8	17	15	11
5	man	5	9	17	13	11
6	man	5	7	17	15	10
7	man	4	9	12	15	10
8	woman	4	7	9	15	8
9	woman	4	8	18	15	11
1	man	4	9	18	15	11
1	woman	0	8	18	15	11
12	man	2	10	26	15	11
13	woman	5	10	16	14	10
14	woman	7	9	25	15	11
15	man	5	10	15	14	11
16	man	6	10	15	15	9

7.4. Stimuli and Tasks

Two different tasks were used: face matching (for form discrimination) and location matching (for spatial location). In each the subjects gave their responses by pressing a button.

Face matching + Perception:

Two types of stimulus displays were used.

In the first task (Perception), a series of pairs of identical abstract images appear and disappear continually. The subjects were asked to press the button every time the pictures appeared. This task was used as a control task.

In the second task (face matching), the subjects were shown pairs of faces. The subjects were asked to identify the pair of faces that were identical by pressing the button. Unmatched pairs required no response (see Figure 2). The faces were grey scale stimuli and they were from the Max Planck Institute for Biological Cybernetics database.

Location matching + Perception:

Two types of stimulus displays were used.

The first task was also a control, the same as the previously described perception task. In the second task, pairs of identical abstract images were shown positioned inside larger squares (see Figure 3). The subjects were asked to identify those pairs in which the images are in the same position relative to the larger squares. These were identified by pressing the button. Pairs with mismatched positions required no response.

The presentation of each trial lasted 2.8 sec, and the intervals between them were 0.318 sec. All stimuli were presented in grey scale. There were 8 trials per block and there were 3 blocks in each scan.

Because the instructions for each trial were shown at the beginning of each block,

appearing for 7.2 sec., the subjects always knew which trial came as next. The different conditions were counter-balanced across subjects.

In the control task there were 4 blocks with the same length as the task of interest. The parameters of presentation of the images were identical to the task of interest.

Performance was monitored during the task, counting correct answers and reaction time.

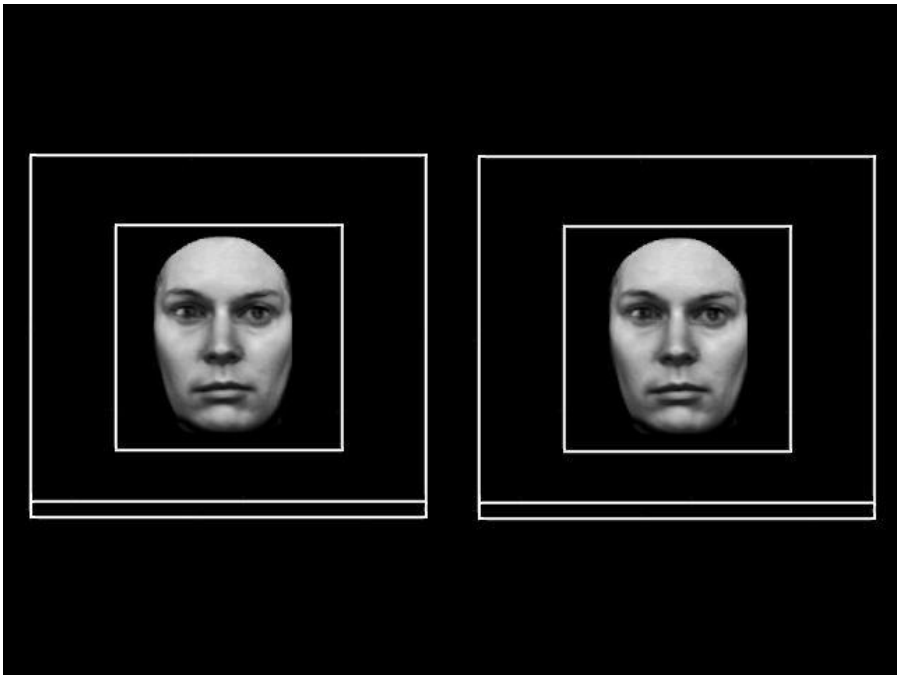
The test was a block design, beginning with a red cross as a fixation point (4 volumes). Control task and the Task of interest (7 volumes each) alternated. Every part was preceded by an instruction (2 volumes).

Checkerboard

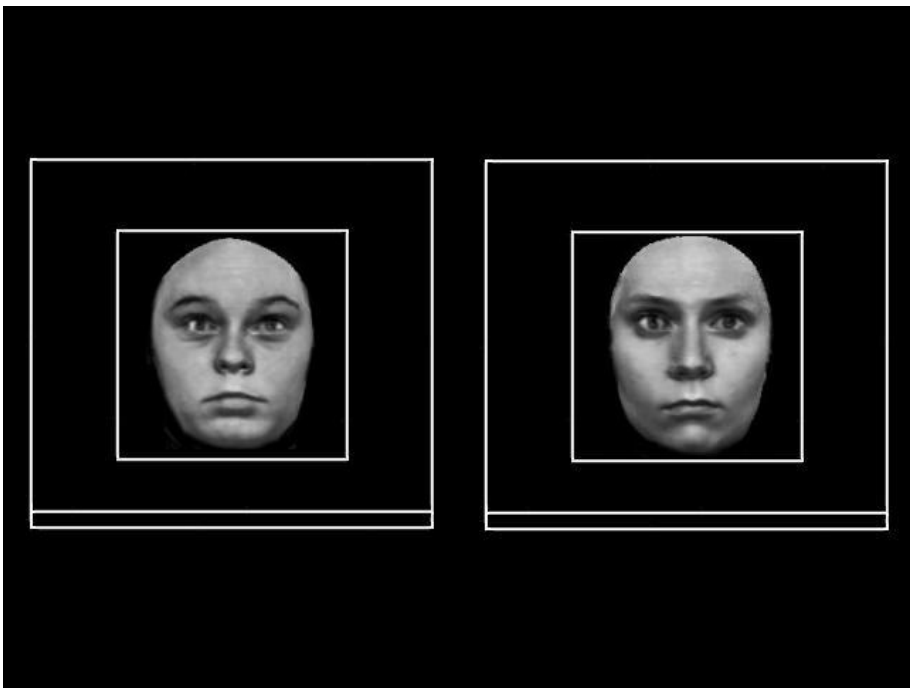
A visual sensory paradigm was developed to assess differences in response of the blood oxygenation level dependent (BOLD) signal to a visual stimulus between the two groups. It was compound by a red cross as a fixation point and a flashing checkerboard.
The third task was a passive sensory stimulation paradigm, block design, with alternating blocks of fixation or a flashing checkerboard at 8 Hz. The blocks were 20 seconds long with the three blocks of stimulus and 4 blocks of fixation. The sensory task was performed in the same session as the object and location matching task.

The subjects were asked just to look at both visual stimuli. They did not need to give any response.

Figure 2. Face Matching Task

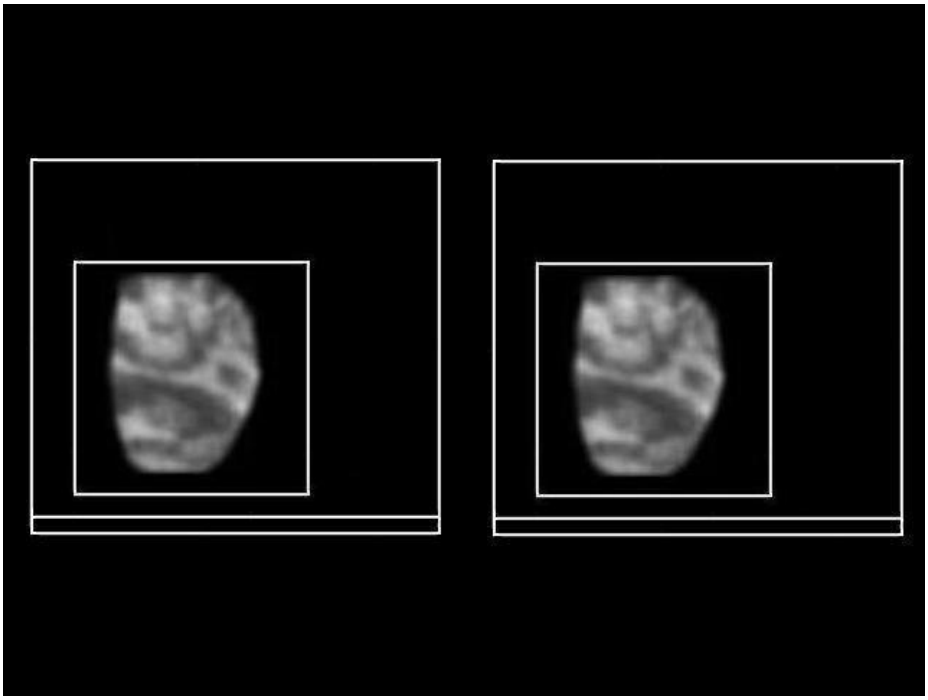


Trial with identical faces

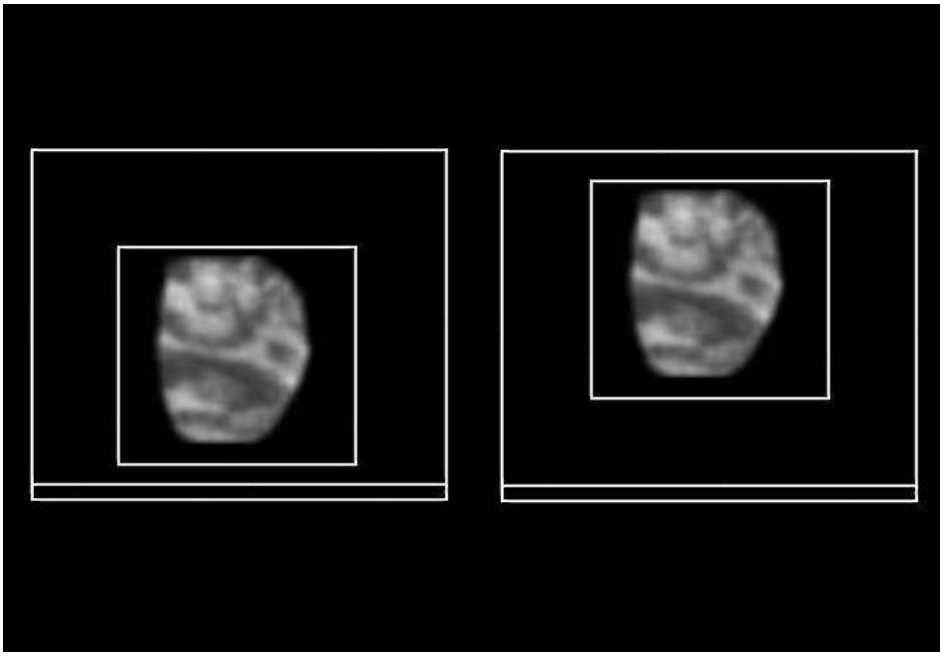


Trial with different faces

Figure 3. Location Matching Task



Trial with the same position



Trial with different positions

7.5. MRI scanning

The goal of fMRI is to map physiological changes in the brain over time related to an experimental stimuli presentation. Looking at a single image does not provide information about brain activity. We need to examine changes over time to isolate the effects caused by the stimuli.

The data are collected in time series, a large number of images of the brain collected in temporal order, so that they can be correlated to stimuli presentation. Each experimental session includes the collection of anatomical images and a number of runs of functional images. Every run lasts for 5 to 10 min. and includes the sequence of the stimuli presentation. It is necessary to break the stimuli presentation into short runs because otherwise the subjects would become very quickly tired. The acquisition of the data within each run occurs as a time series of volumes. Every volume includes all number of slices what we measure in our TR (repetition time). One volume can include the whole brain or a part of it (if we are interested in one specific region, we do not need to get data from the whole brain). Every volume is composed of a number of slices of the brain and the whole number of slices, which are included in one volume, are collected during the TR. Every slice image is taken at a different time point within the TR, but the information within a slice corresponds to the same time point. Each slice contains thousands of voxels ($2^n \times 2^n$ matrix of voxels). All voxels from all slices together compose the image of the brain. When we acquire our data, we can think about our data like a four dimensional matrix (x, y, z, time).

When we examine changes in voxel activation, it may reveal if the increase or decrease of their activation is correlated to the presentation of the stimulus. Functional MRI analysis attempts to detect the small changes in MR signal associated with the BOLD effect, but to ignore the effect of noise.

7.5.1. Data acquisition

The subjects were scanned on a 1.5 Tesla Siemens Magnetom Vision Scanner (Erlangen, Germany) (see Figure 4).

Vacuum mattresses and bandages around the forehead were used to reduce head movements. The subjects were asked to try do not move at all.

The stimuli were projected on a screen located in front of the scanner at about five meters away from a mirror mounted on the head coil. The visual stimuli projected on the screen were reflected on the mirror, so that the subjects were able to see them while lying in the scanner. The answers were giving pressing a button (see Figure 4).

The imaging sequence was an intervaled T2* weighted echo planar sequence with 28 axial slices (4 mm slice thickness and slice gap = 1mm, repetition time (TR) = 60 ms, echo time (TE) = 60 ms, flip angle = 90°, filed of view = 240 mm. Matrix 64 × 64) and 69 frames acquired per scan. For anatomical reference in each subject, a T1 weighted sequence with 28 slices was acquired in the same orientation as the EPI (echo planar imaging) sequence (TR = 620 ms, TE = 12 ms, flip angle = 90°, FOV = 270 mm, matrix = 224 × 256, Rect. FOV = 7/8, Effective Thickness = 1.25 mm).

7.6. Analysis of fMRI data

7.6.1. Analysis tools

Preprocessing of fMRI Data:

fMRI data contains not only brain activation information, but may also contain information due to subject head motion, physiological factors like heart beats and respiration, lack of homogeneities in the magnetic static field and differences in the image acquisition. To have a high detection power in our experiment, we need to correct for all these factors.

Preprocessing of the fMRI data consist of following image reconstruction and it prepares our data before statistical analysis. All the factors not due to the experiment are

removed and signal-to-noise-ratio (SNR) is increased.

a) Slice acquisition Time Correction: the data acquisition occurs usually in a two dimensional pulse sequence, so that one slice will be acquired at a time. A typical pulse sequence acquires 24 slices covering the whole brain within a TR of 1.5 to 3.0 sec. (depending on the capability of the scanner). The acquisition of the slices may be sequential or interwoven. For the interwoven acquisition, the most common one, the odd slices are acquired first, and then the even slices to avoid cross-slice excitation. Every slice is collected at a different time point. We use temporal interpolation to correct this effect. The information of the nearby time points is used to estimate the value of the signal at a time point that was not originally collected. Some different techniques can be used: linear, spline and sinc functions; but none of them can recover the whole information lost. There are two factors which influence the accuracy of interpolation: the variability in the experimental data and the TR.

b) Head motion correction: the most common problem for fMRI studies are head movements. The basic problem with head motion is that in the analysis process of fMRI data every voxel is considered as a unique part of the brain. If the subject moves his head about 5 mm, the information related to one voxel will be derived from two parts of the brain which are separated 5 mm of each other. Head motion is more easily prevented than corrected for, so the use of head restraints avoids much of the possible movement.

If some head movements occur during the experiment, the activation will be located in the wrong place. Motion correction is used to align the brain in every time series so that the position is staying constant. The process to align two image volumes in the time series is called coregistration. The goal of having the brain in the same position at all times can be achieved by the coregistration of successive volume images to a single reference volume. We use a rigid body transformation which assumes that the size and shape of two objects to be coregistrated are identical and that the one can be superposed to the other by the combination of three translations and three rotations.

To determine the amount of head movement, the translation and rotations during the experiment are computed, it allows matching the data with the reference volume. For that, we do a spatial interpolation which considers points in two or three dimensions. We have three methods which fit our desired results: linear interpolation, sinc interpolation and spline interpolation.

c) Distortion correction

Functional images often suffer from intensity and geometric distortions. They are due to the magnetic field inhomogeneities. One approach to correct this distortion is called magnetic field mapping. It provides information about the static magnetic field, so that we can correct our data.

d) Functional-Structural Coregistration and Normalization

The objective is an optimal match between the functional data and the anatomical data. To reach this goal we need:

-functional-structural coregistration: computational processes to match functional and structural images. It is needed for example because of image distortion, because some pulse sequences used to acquire functional images may introduce subtle geometric distortions.

-spatial normalization: every brain is unique in his structure, so when we want to make comparisons between subjects we need to have the anatomical structures located in the same place. The goal of normalization is to compensate for differences by stretching, and warping the images of the brain. In this way, it is possible for us to find the three-dimensional coordinates in a stereotaxic space. There are two standard brain structure templates we use. The most common one is the Talaraich space, which was created from one single brain. The other is the Montreal Neurological Institute template (MNI), which consists of an average 152-T1 weighted brain images.

e) Spatial and Temporal Filtering

In neuroimaging filters are used to remove uninteresting variation in the data that can

be attributed to noise, and to preserve signals of interest, so that filtering can be used to increase functional Signal-Noise Ratio (SNR).

By temporal filtering we try to keep changes which occur at the task frequency and to reduce changes in the data which occurs at other frequencies. It depends on our test, the facility to remove selective noise components, such as those introduced by the physiological processes. If we have a slow stimuli presentation frequency, it should be easy to separate this frequencies from those due to physiological process, like respiration. But if we have for example a fast event-related design it can be more difficult.

Spatial filtering can increase the functional SNR, at a cost of reduced spatial resolution. SNR varies across space because the signal is greater in these voxels associated with the task than in voxels with little to no no task-related activity. Noise varies over space, as well.

Statistical analysis of the Data

fMRI studies try to find a weak signal in the presence of substantial noise, so careful statistical analysis are necessary.

The goal of the fMRI statistical analysis method is to determine if every voxel is consistent with the null hypotheses. Experiments are designed to discriminate between two possible hypotheses: the research hypothesis (H_1) and the null hypothesis (H_0). When the statistical results from all voxels in the brain are combined, we obtain a statistical map of brain activity, which is colour-coded according to the probability value for each voxel. The association between the probability values and the colours that label them, is known as color map.

We use the General Linear Model to treat our data. We assume with this model that the experimental data are a linear combination of a number of factors plus noise. The equation for a univariate multiple regression model, which represents fMRI data is:

$$y = a_0 + a_1x_1 + a_2x_2 + \ldots\ldots + a_nx_n + \varepsilon$$

where a_i are the parameter weights, x_i are the model factors, ε is the additive error and y are the observed data. We can extend it to have a large number of dependent variables so that we reach the general linear model.

In the general linear model we create a **design matrix** (n time points × M model factors) with the factors of interest and the other factors, which introduce variability in the data but are not relevant to our results (nuisance factors). We construct the design matrix based on the study design and explain in it how the model factors change over time. In our model we also have the **parameter matrix** (M model factors × V voxels) and the **error matrix** (n time points × V voxels), which are calculated in the analysis. The empirical data (fMRI data) are obtained experimentally (see Table 5).

7.6.2. Analysis process

The Data was analyzed on a computer with an Intel Pentium CPU (San Jose, California, USA) running LINUX (Red Hat version 7.0, Red Hat Inc Rayleigh, North Carolina, USA) using AFNI (Cox, 1996) (available at afni.nimh.nih.gov/afni/) and FSL (FMRIB Software Library-available at www.fmrib.ox.ac.uk/fsl) as analysing software.

The first step was to delete the first 4 volumes of each scan corresponding to the fixation point (Red Cross). The remaining data was corrected for the timing differences between each slice using Fourier interpolation. After that the data was corrected for motion effects (6-parameter rigid body), where the reference volume was in the middle of the run.

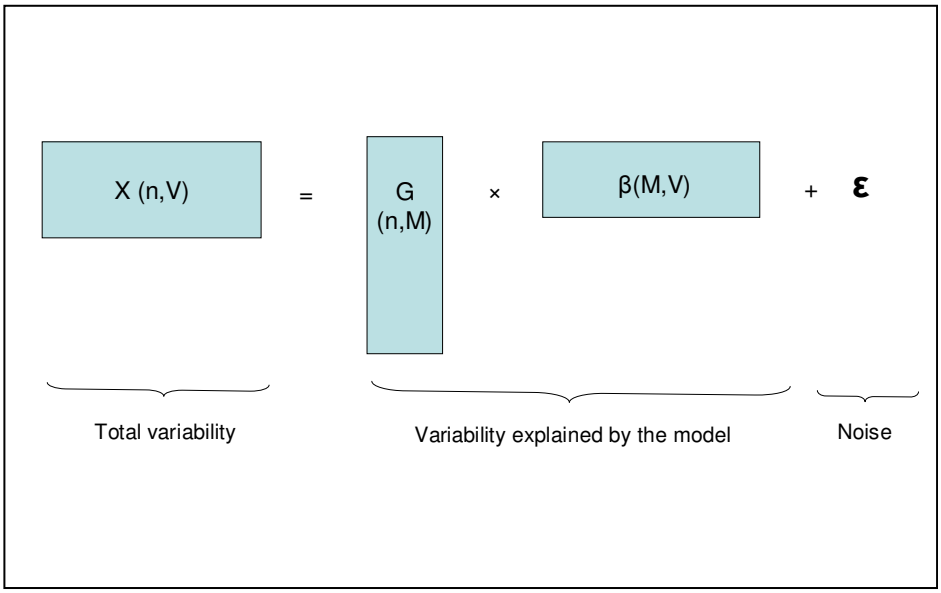
Using FSL, every run was analyzed using a fixed effects general linear model. Each model was composed of the following regressors: the one indicating the task of interest, one for the instructions (the time derivates of the two previous regressors), and regressors for motion during the run. The task and instructions were square waveform models (on-off). The regressors for the task of interest and instructions were convolved with a standard double

gamma hemodynamic response function. The data were smoothed (Gaussian filter at full width at half maximum = 8×8×8 mm) and high pass filter with a cutoff at (1/100) Hz. The normalization was made according to the Montreal Neurological Institute/International Consortium for Brain Mapping 152 standard (MNI/ICBM). The location of activation areas in the brain was done in reference to the Talaraich and Tournoux template (Talaraich and Tournoux, 1988). To transform coordinates from one template to another, a non-linear transformation developed by M. Brett was used (http//:www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The group statistical analysis was based on a random effects model with a statistical threshold of $Z = 2.33$ ($p< 0.01$) and each cluster was corrected for multiple comparisons at the $p<0.05$ level.

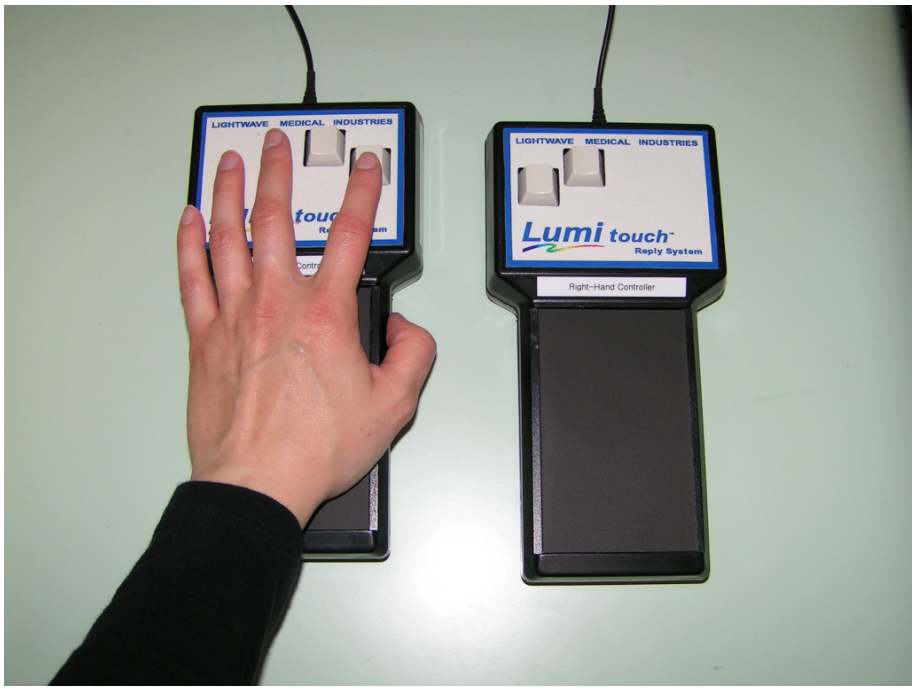
The structural images of the non-brain tissue were edited out using BET and manually edited for any remaining non-brain tissue on the images. The EPI images were first co-registered to the 28-slice T1 weighted image (7-parameter rigid body), the 28-slice T1 weighted image was registered to the MPRAGE image, and the MPRAGE image was registered to the MNI/ICBM template (12 parameter). The statistical results from each subject were transformed into the MNI/ICBM stereotaxic space for group analysis.

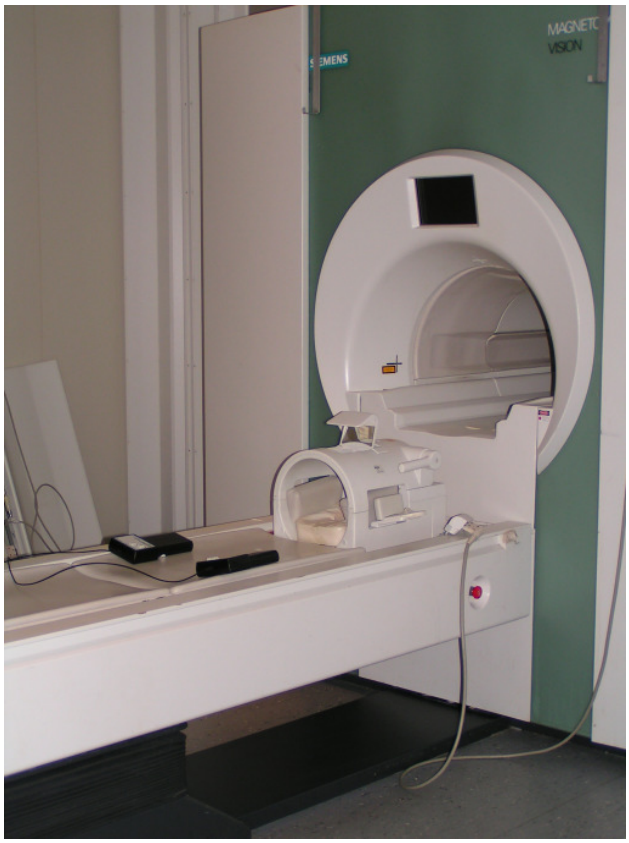
Table 5. Basic principles of the general linear model



Basic principles of the general linear model.
X represents the fMRI data, G is the design matrix, ß is the parameter matrix and ε the error matrix.
Adapted from Huettel at al. (Huettel et al., 2004)

Figure 4 .fMRI buttons and scanner





8. RESULTS

The description of the brain activation patterns for both tests (object and location matching) in the old healthy control group and in the patient group are explained in this chapter. The differences in brain activation patterns between tasks and between groups were analyzed as well.

The tables of activation peaks include the highest 10 statistically significant peaks (as a function of the Z value).

In addition, behavioural performance (percent of correct answers and mean response time) was also recorded, and it is described in this chapter.

8.1. Behavioural Performance

The mean value (standard deviation) in performance of the MCI group in face matching was 87.76 (11.33) and for location matching 91.14 (8.85), showing that the patients were able to resolve the exercises and were paying attention during the task (see Table 6). The mean value (standard deviation) for the response time during the face matching task was 1.46 (0.32) and for the location matching task was 1.55 (0.40).

In the HC group the performance results in the face matching task were 91.67 (7.21) and for location matching 92.98 (10.21).

The mean response time was 1.53 (0.32) for face matching and 1.36 (0.36) for location matching (see Table 7).

Performance in face matching and location matching were not significantly different between the groups. There is no statistically significant difference between the two tasks within each group.

8.2. Task activation in the Healthy Control Group

a) Object Matching

The highest 10 statistically significant activation peaks shown in Table 8 and Figure 5 are the results of the contrast made between the brain images recorded during the object matching task compared to those of the control task.

The healthy control group showed brain activation in the following areas of the right hemisphere: Fusiform Gyrus and Precuneus (Occipital Lobe), Inferior Parietal Lobe, Inferior and Middle Frontal Gyrus, and Anterior Cingulate Gyrus (Frontal Lobe). In left hemisphere the activated areas were located: in the Inferior Occipital Gyrus and Fusiform Gyrus (Occipital Lobe), as well as in the Inferior Frontal Gyrus.

b) Location Matching

The network recruited during location matching compared to the control condition for the group is shown in Table 9 and Figure 7. In the right hemisphere activation was found in the Middle Occipital Gyrus and Precuneus (Occipital Lobe), in the Inferior Parietal Lobulus (Parietal Lobe), and in the Inferior Frontal Gyrus (Frontal Lobe). In the left hemisphere the activation peaks were found in the Inferior and Middle Occipital Gyrus, and Precuneus (Occipital Lobe), in the Inferior Parietal Lobulus (Parietal Lobe).

8.3. Task activation in the Mild Cognitive Impaired group

a) Face Matching

The highest statistically significant activation peaks shown in Table 10 and Figure 6 are the results of the contrast made between the brain images recorded during the object matching task compared to those of the control task

In the right hemisphere: in the Inferior Occipital Lobe and Fusifom Gyrus (Occipital Lobe), in the Inferior Temporal Gyrus, Inferior Parietal Lobulus, in the Inferior and Middle

Frontal Gyrus (Frontal Lobe). In the left hemisphere, the activation in the Occipital Lobe took place in the Inferior and Middle Occipital Lobe, and in the Frontal Lobe in the Inferior Frontal Gyrus.

b) Location Matching

In the contrast between location matching compared to the control condition for the group, there were some activation peaks, which are shown in Table 11 and Figure 8. In the right hemisphere we found activation peaks in Precuneus, Middle Occipital Gyrus and Occipital Gyrus (Occipital Lobe), in the Superior Parietal Lobulus, and in the Inferior Frontal Gyrus. In the left hemisphere the activation in the Occipital Lobe took place in the Precuneus and Occipital Gyrus, in the Temporal Lobe in the Hippocampal Gyrus, in the Parietal Lobe in the Superior Parietal Lobulus, in the Frontal Lobe the activation peaks were found in the Inferior, Middle and Frontal Gyrus.

8.4. Differences in activation between task within groups

8.4.1. Healthy Control Group

a) Face matching versus location matching

The differences in activation peaks in the HC group by the contrast face matching versus location matching are listed in the Table 12. In the right hemisphere the activation peaks found were located: in Cuneus, Lingual Gyrus, Inferior Occipital Gyrus and Fusiform Gyrus (Occipital Lobe), in the Inferior and Superior Temporal Gyrus (Temporal Lobe), in the Medial, Inferior and Superior Frontal Gyrus, as well as the Anterior Cingulate Gyrus (Frontal Lobe). The Basal Ganglia also had an activation peak in the Thalamus.

In the left hemisphere the activation peaks were found: in the Lingual Gyrus (Occipital Gyrus), in the Parahippocampal Gyrus (Temporal Lobe), and in the Inferior, Middle and Superior Frontal Gyrus, as well as in the Anterior Cingulate Gyrus (Frontal Gyrus).

b) Location matching versus face matching

The activation peaks in the HC group for the contrast location matching versus face matching are shown in the Table 13. The activation in the right hemisphere was located in the Occipital Gyrus. In the Parietal Lobe the activation was bilateral.

8.4.2. Mild Cognitive Impaired Group

Within the MCI group, there were no regions that were more activated in the face matching task compared to the location matching task and vice versa.

8.5. Differences in activation between groups

a) Face matching

In the face matching task there were no differences in activation in the contrast between groups compared to the other group.

b) Location matching

In the location matching task the contrast of higher activation of HC compared to MCI showed no statistically significant differences.

The activation peaks in Table 15 and Figure 10 shows the differences in the contrast of higher activation in MCI compared to HC. The activation peaks were found in the Medial Frontal Gyrus bilateral. In the left hemisphere activation peaks were found in the Inferior, Middle and Superior Frontal Gyrus.

8.6. Passive Sensory Task

Both groups activated the primary visual areas of the brain during the passive stimulation paradigm. The contrast comparing differences in activation between both groups showed no statistically significant differences.

Table 6 . Behavioural Performance of the MCI group

	N	Minimum	Maximum	Mean	Standard deviation
Face Performance	16	58,33	100,00	87,7577	11,33011
Face Response Time	16	1,0407	2,1990	1,458744	,3179030
Location Performance	16	66,67	100,00	91,1438	8,85287
Location Response Time	16	,9812	2,1558	1,547031	,3951710
	16				

Performance is given in % correct answers.
The response time units are seconds.

Table 7. Behavioural Performance of the HC Group

	N	Minimum	Maximum	Mean	Standard deviation
Face Performance	19	75,00	100,00	91,6667	7,21560
Face Response Time	19	,9658	2,2414	1,530695	,3227906
Location Performance	19	62,50	100,00	92,9795	10,21287
Location Response Time	19	,8022	2,0735	1,364053	,3649103
	19				

Performance is given in % correct answers.
The response time units are seconds.

Table 8. Main Activation Peaks during Object Matching Task in Healthy Controls

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Z value
Occipital Lobe					
Fusiform Gyrus	19	36	-71	-12	5.37
Precuneus	19	28	-60	40	5.27
Parietal Lobe					
Inferior Parietal Lobulus	40	38	-43	41	5.16
Frontal Lobe					
Inferior Frontal Gyrus	44	44	15	23	5.94
Middle Frontal Gyrus	46	48	23	25	5.96
Anterior Cingulate Gyrus	32	8	21	32	5.36

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Inferior Occipital Gyrus	18	-30	-92	-6	4.57
	18	-48	-86	-9	4.81
Fusiform Gyrus	37	-46	-51	-18	5.02
Frontal Lobe					
Inferior Frontal Gyrus	44	-44	5	31	4.67

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 9. Main Activation Peaks During Location Matching in Healthy Controls.

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Middle Occipital Gyrus	19	32	-81	10	4.98
Precuneus	7	14	-70	35	4.95
	7	16	-60	52	4.73
Parietal Lobe					
Inferior Parietal Lobulus	40	28	-58	42	5.25
Frontal Lobe					
Inferior Frontal Gyrus	44	42	11	30	4.50

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Inferior Occipital Gyrus	18	-36	-84	-9	4.39
Middle Occipital Gyrus	19	-32	-81	15	5.34
Precuneus	7	-12	-62	47	4.73
	18	-18	-70	29	5.36
Parietal Lobe					
Inferior Parietal Lobulus	40	-38	-39	31	4.47

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 10. Main Activation Peaks During Object Matching in Mild Cognitive Impaired Subjects.

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Inferior Occipital Lobe	19	34	-92	12	4.82
Fusiform Gyrus	18	40	-75	-13	5.09
Temporal Lobe					
Inferior Temporal Gyrus	19	50	-74	-1	4.54
Parietal Lobe					
Inferior Parietal Lobulus	40	40	-54	56	4.78
Frontal Lobe					
Inferior Frontal Gyrus	45	38	30	8	4.81
Middle Frontal Gyrus	9	48	11	34	4.75

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Inferior Occipital Lobe	18	-36	-92	-6	4.97
Middle Occipital Lobe	19	-46	-76	-5	4.68
Fusiform Gyrus	19	-50	-70	-12	4.86
Frontal Lobe					
Inferior Frontal Gyrus	44	-46	15	25	4.88

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 11. Main Activation Peaks During Location Matching in Mild Cognitive Impaired Subjects.

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Fusiform Gyrus	37	54	-59	-14	4.21
Middle Occipital Gyrus	19	44	-85	15	4.59
Occipital Gyrus	19	34	-76	30	4.36
Parietal Lobe					
Superior Parietal Lobulus	7	32	-54	54	4.38
Frontal Lobe					
Inferior Frontal Gyrus	46	46	38	11	4.28

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Precuneus	7	-18	-77	48	4.41
Occipital Gyrus	19	-32	-84	28	4.35
Temporal Lobe					
Hippocampal Gyrus	36	-18	-22	-21	4.85
Parietal Lobe					
Superior Parietal Lobulus	7	-32	-59	58	4.08
Frontal Lobe					
Inferior Frontal Gyrus	47	-50	27	-1	3.49
Middle Frontal Gyrus	9	-54	18	-15	3.81
Superior Frontal Gyrus	6	-32	7	59	3.45

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 12. Location of Statistically Significant Higher Activation Peaks During Face Matching Compared to Location Matching Task in Healthy Control Subjects.

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Cuneus	17	20	-75	8	2.97
	31	14	-64	7	3.76
Lingual Gyrus	19	16	-58	-4	3.19
	18	22	-101	-5	4.15
		36	-70	-7	4.65
Inferior Occipital Gyrus	18	38	-82	-4	4.26
Fusiform Gyrus	37	40	-49	-16	5.52
Temporal Lobe					
Inferior Temporal Gyrus	20	30	-6	-38	4.21
		32	-8	-33	3.97
		31	-5	-27	3.62
		44	2	-37	3.39
Superior Temporal Gyrus	38	22	9	-24	3.53
Frontal Lobe					
Medial Frontal Gyrus	8	0	28	52	2.80
	9	8	42	24	2.94
Anterior Cingulate Gyrus	32	6	23	34	3.30
Inferior Frontal Gyrus	47	37	19	-13	3.56
Superior Frontal Gyrus	9	10	58	34	3.19
		10	60	28	3.29
Basal Ganglia					
Thalamus		6	-17	3	3.19

Table 12. continued

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Lingual Gyrus	19	-12	-57	-6	4.71
Temporal Lobe					
Parahippocampal Gyrus	28	-16	-10	-13	3.65
	34	-20	1	-10	3.50
Frontal Lobe					
Inferior Frontal Gyrus	45	-53	27	2	3.06
		-44	30	17	3.15
	46	-55	35	9	2.83
	47	-40	29	-10	3.42
Middle Frontal Gyrus	9	-55	27	27	3.81
	46	-48	48	18	2.82
Superior Frontal Gyrus	10	-22	56	25	3.08
Anterior Cingulate Gyrus	32	-14	21	30	2.67

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 13. Peaks of significantly Higher Activation for Location Matching compared to Object Matching in the Healthy Control Subjects.

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Occipital Lobe					
Occipital Gyrus	19	28	-76	28	3.63
Parietal Lobe					
Precuneus	7	10	-47	61	4.34
		14	-68	49	4.62

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Parietal Lobe					
Precuneus	7	-10	-64	47	4.38
Superior Parietal Lobulus	7	-6	-68	55	4.50

The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Table 14. Peaks of Significantly Higher Activation in MCI compared to HC during Location Matching Task

RIGHT HEMISPHERE

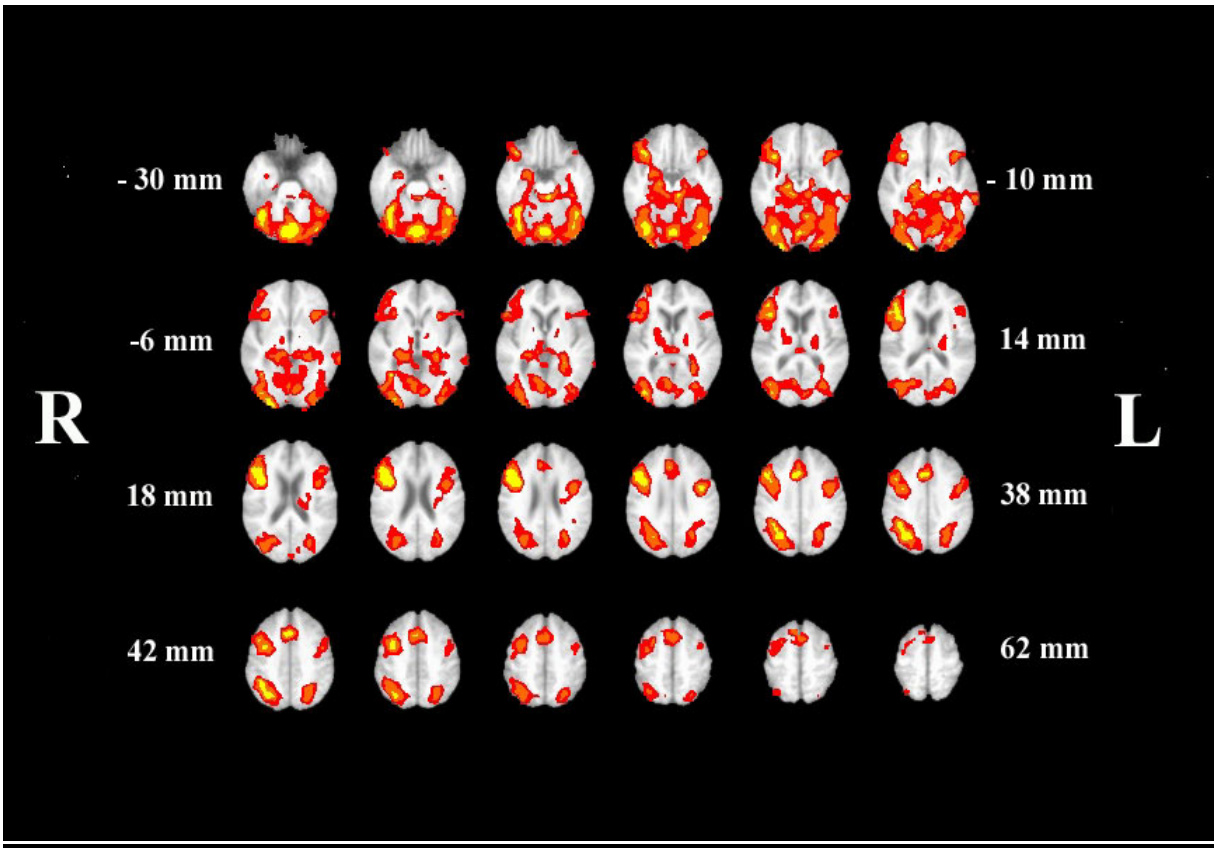
Region	Brodmann Area	x	y	z	Zvalue
Frontal Lobe					
Medial Frontal Gyrus	8	2	45	42	2.75
	9	0	58	27	3.30
	10	4	61	14	2.69

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	Zvalue
Frontal Lobe					
Inferior Frontal Gyrus	46	-46	46	20	3.59
Middle Frontal Gyrus	46/9	-36	46	27	4.57
	8	-34	28	47	3.34
Superior Frontal Gyrus	10	-24	58	25	3.97
	8	-18	45	38	3.90
	8	-10	28	52	3.11
Medial Frontal Gyrus	9	-57	23	34	4.04
	9	-42	55	14	3.36
	10	-38	64	6	3.18
		-36	47	3	2.62
	8	-8	31	41	2.54
	9	-8	42	33	2.97
	10	-8	55	7	2.75

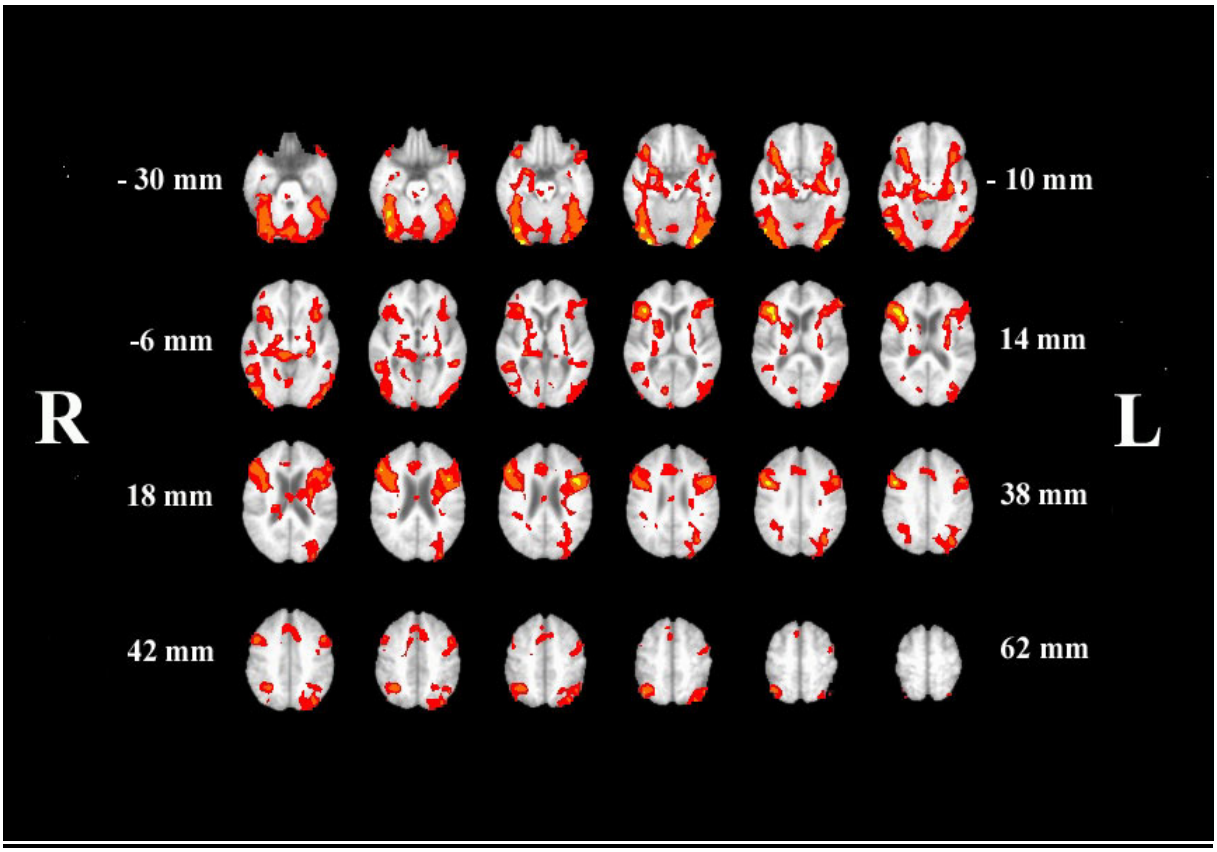
The location of the activation peaks are located with reference to the Talaraich und Tourneaux stereotaxic template. The coordinates x+ are located in the right hemisphere. The coordinates y+ are located anterior to the anterior comisure, and the coordinates z+ are located superior to the AC-PC plane.
The distances are given in mm.

Figure 5. Object Matching activation pattern in the Healthy Control Group



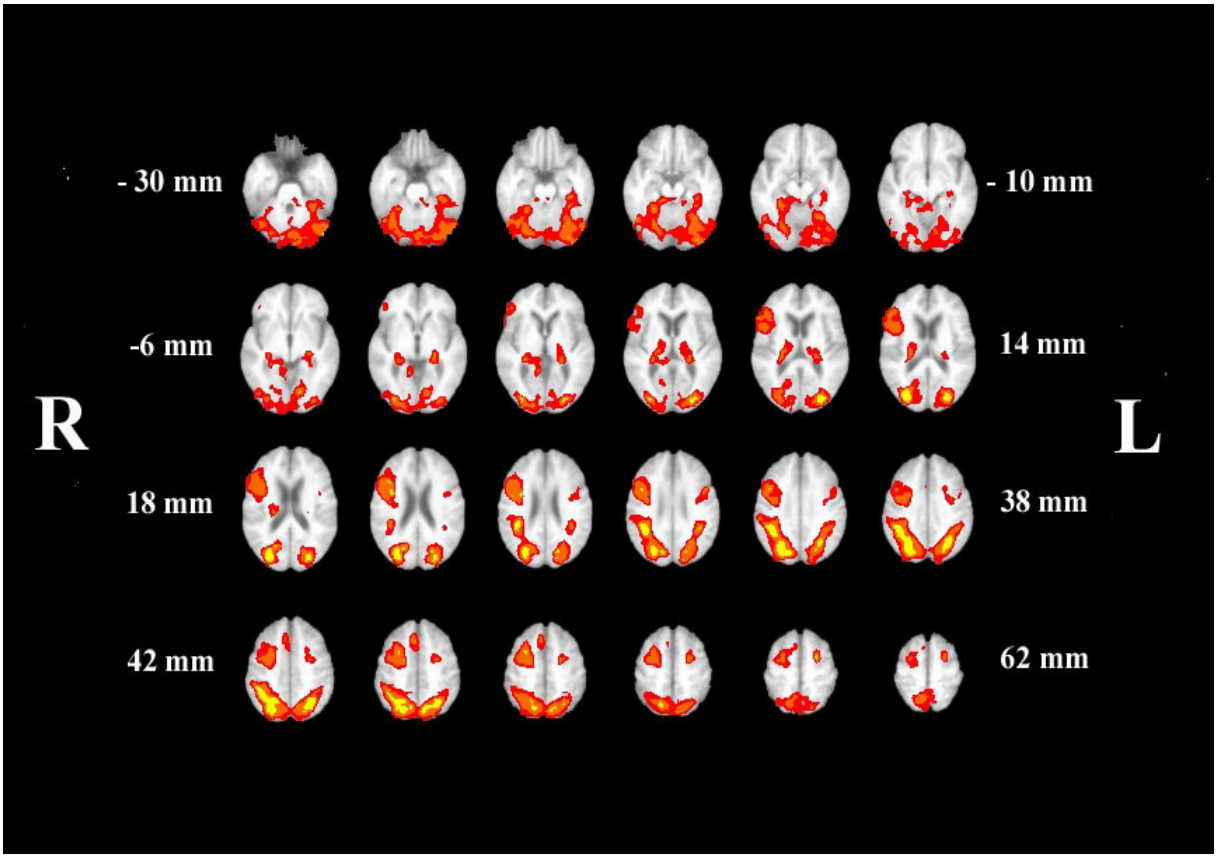
The presentation of the results is divided in 24 planes of the brain. From left to right in every row, the planes are ascendant, and from bottom to top.
The number in mm shows the distance to the AC-PC plane.
The right hand side of the picture shows the left hand side of the brain, and the left hand side of the picture shows the right hand side of the brain.
The activated areas are showed in red and yellow; red means activation intensities between 0.31-0.62 and yellow between 0.62-1.0.

Figure 6. Object Matching activation pattern in the MCI group



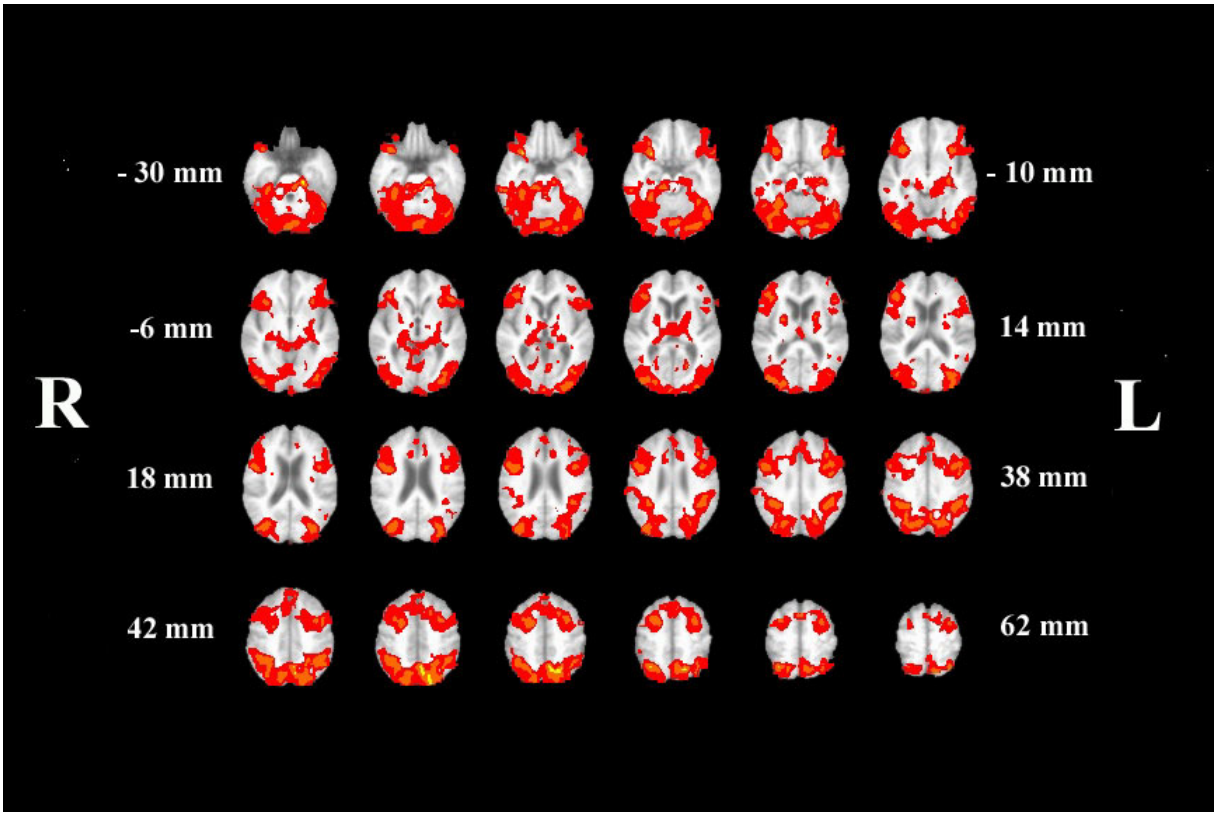
The presentation of the results is divided in 24 planes of the brain. From left to right in every row, the planes are ascendant, and from bottom to top.
The number in mm shows the distance to the AC-PC plane.
The right hand side of the picture shows the left hand side of the brain, and the left hand side of the picture shows the right hand side of the brain.
The activated areas are showed in red and yellow; red means activation intensities between 0.31-0.62 and yellow between 0.62-1.0.

Figure 7. Location Matching activation pattern in the Healthy Control Group



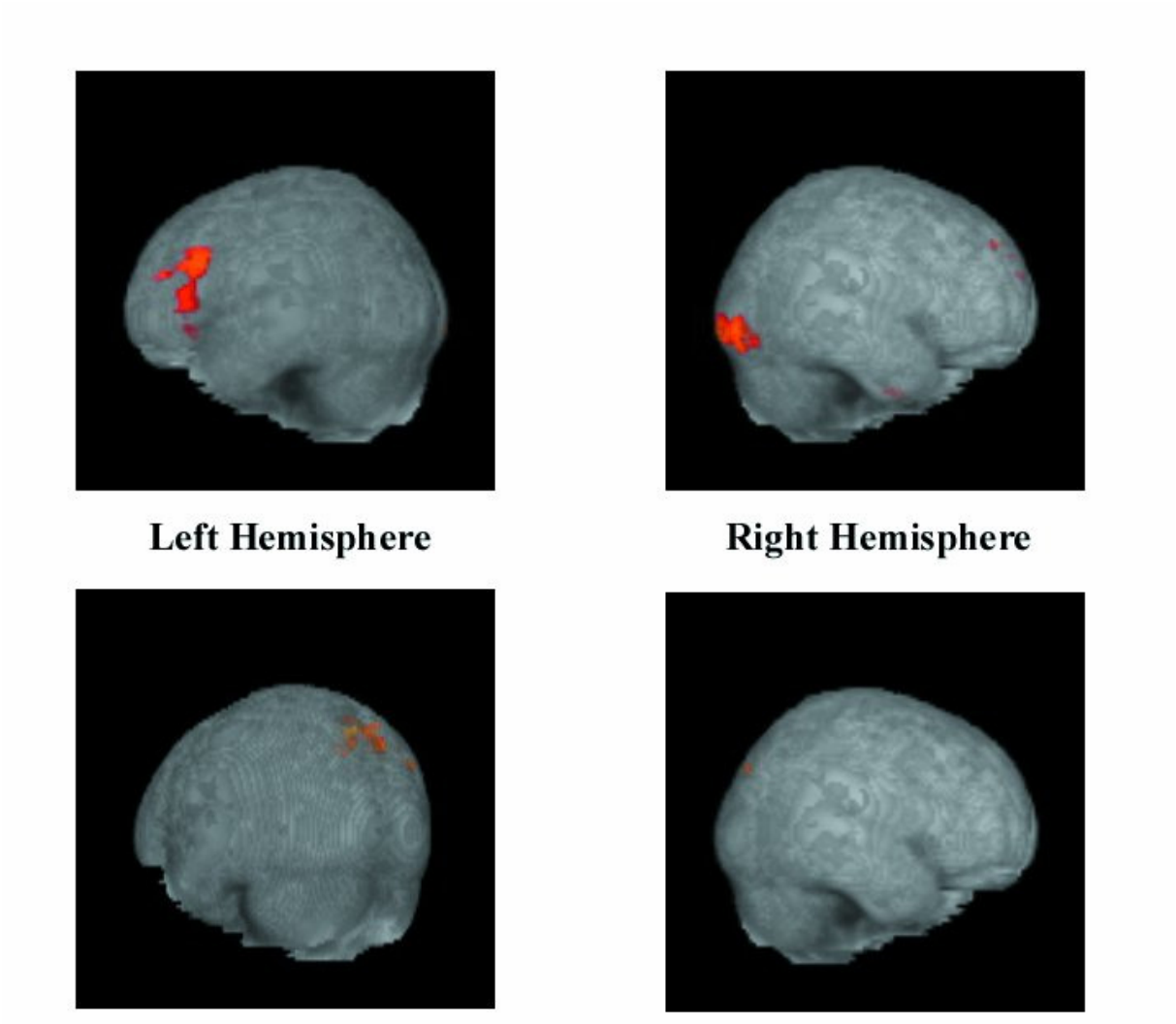
The presentation of the results is divided in 24 planes of the brain. From left to right in every row, the planes are ascendant, and from bottom to top.
The number in mm shows the distance to the AC-PC plane.
The right hand side of the picture shows the left hand side of the brain, and the left hand side of the picture shows the right hand side of the brain.
The activated areas are showed in red and yellow; red means activation intensities between 0.31-0.62 and yellow between 0.62-1.0.

Figure 8. Location Matching activation pattern in the MCI group



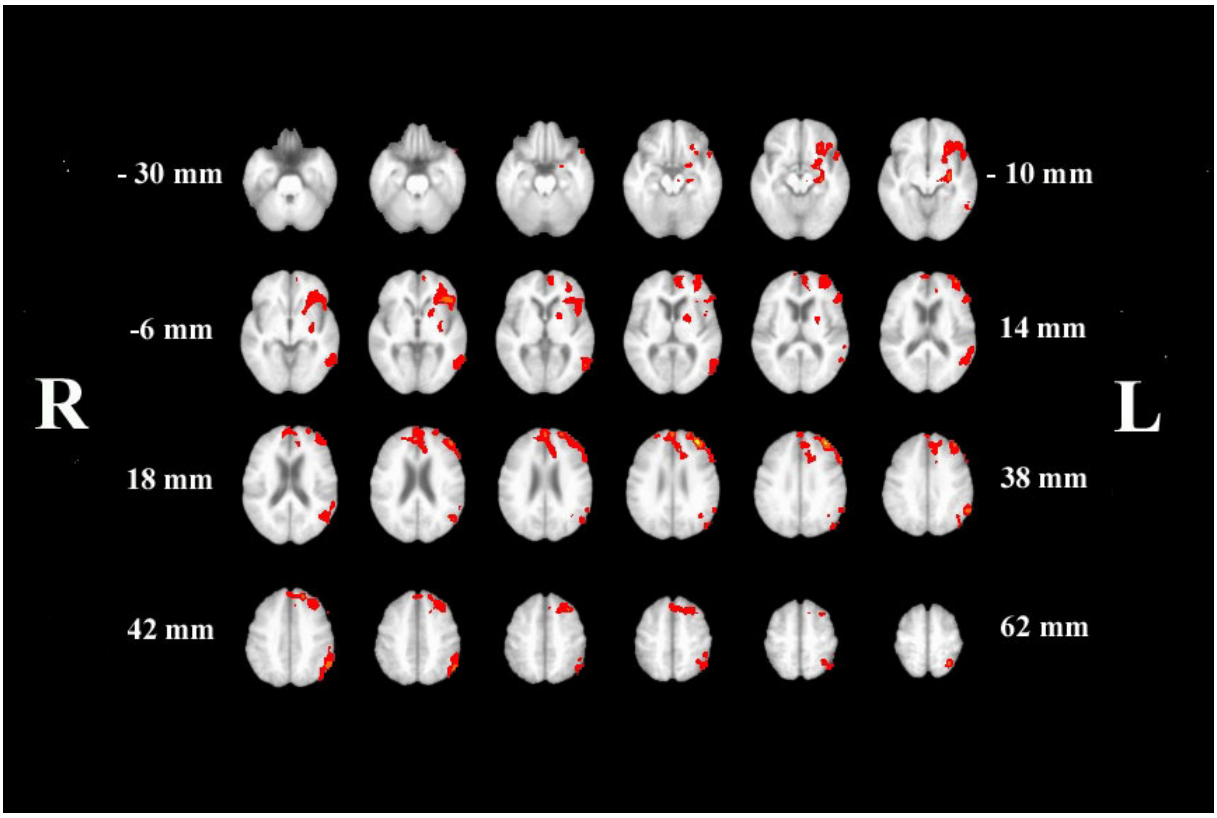
The presentation of the results is divided in 24 planes of the brain. From left to right in every row, the planes are ascendant, and from bottom to top.
The number in mm shows the distance to the AC-PC plane.
The right hand side of the picture shows the left hand side of the brain, and the left hand side of the picture shows the right hand side of the brain.
The activated areas are showed in red and yellow; red means activation intensities between 0.31-0.62 and yellow between 0.62-1.0.

Figure 9. The contrast Face matching versus Location Matching and Location Matching versus Face matching in the Healthy Controls



The presentation of the results is three dimensional. In the first row are shown the activated areas for the contrast face matching > location matching, on the left hand side left hemisphere, on the right hand side right hemisphere. In the second row are shown the results for the contrast location matching > face matching, on the left hand side left hemisphere, on the right hand side right hemisphere.

Figure 10. Location Matching activation patterns for the contrast MCI > HC



The presentation of the results is divided in 24 planes of the brain. From left to right in every row, the planes are ascendant, and from bottom to top.
The number in mm shows the distance to the AC-PC plane.
The right hand side of the picture shows the left hand side of the brain, and the left hand side of the picture shows the right hand side of the brain.
The activated areas are showed in red and yellow; red means activation intensities between 0.31-0.62 and yellow between 0.62-1.0.

9. DISCUSSION

9.1. Discussion of the Method

Challenges of fMRI

Functional MRI is a powerful method for investigating brain function but it is also a challenging method that needs to be utilized appropriately (Savoy, 2005). For appropriate use it is necessary to have knowledge of different areas:

- physics and engineering underlying the imaging device
- temporal and spatial properties of the hemodynamic response that we measure using fMRI
- functional and structural anatomy of the human brain
- the analysis steps which conduct from a collection of MR data to a statistically map of brain activation
- the way all these factors interact by interpreting the results obtained

In spite of the difficulty, research using fMRI is growing very fast. The power of the method is based on the analysis of many different brain images to see the differences between brain states (or between population groups). The results obtained with this method are very reliable.

Advantages and limitations of fMRI

FMRI has great advantages as a method of functional neuroimaging comparing to others. It is indeed a powerful and flexible tool, but it has also some experimental weaknesses.

FMRI was the first technology that promised non-invasive, high spatial resolution, volumetric images of brain activity in normal human subjects, with the opportunity to do repeated studies on the same subject. It is due to the advantages of the method:

-Potential for high temporal and spatial resolution. The spatial resolution allows us to find changes in a map across different spatial localisations, and the temporal resolution allows finding changes at a single location over the time. Neuroscience techniques differ in their spatial and temporal resolution, for example EEG and MEG have a very good temporal resolution, but the spatial resolution is poor. PET techniques has not such a good balance between temporal and spatial resolution like fMRT.

-Lack of radioactivity: the magnetic field does not produce any kind of adversary effects, so the experiments can be repeated multiple times on the same subject. SPECT and PET give excellent functional results as well, but carry the burden of radiation.

-Non invasive technology, there are no secondary effects for the subjects.

-Can be performed on increasingly common state-of-the art MRI scanners

The experimental weaknesses of the method are associated with its disadvantages:

-Extreme sensitivity to head movement. Head movement produce distortion in the results, which are obtained from the scanner. It is very important that the subjects do not move while performing the scanning. Thousands of images are collected during the scanning and it is necessary that they are aligned. Most of the young people scans do not show head movement. It can turn difficult for older people, to lie quite for longer time so that not all the data from scanned subjects can be used. In particular with MCI subjects the percent of data which could not be used because of head movement was very high. We carried out scanning of more than 30 MCI Patients, but we could only include the data from 16 of them because of the artefacts which were present in the data.

-There are some contraindications, where it is not possible at all to perform fMRI: the

presence of irremovable magnetic devices (like pacemaker, metal implantation, tattoos, permanent make-up, etc.), pregnancy and susceptibility to extreme claustrophobia. Subjects with these characteristics can not be scanned.

Safety considerations

FMRI is a very safe method but it has also some risks. Bringing a magnetic object inside the room, in which the scanner is situated, can have disastrous consequences. The magnetic field has a very strong gradient near the scanner, and every kind of magnetic object could be “pulled” into the scanner.

The high-speed sequences which are used for fMRI studies generate a great acoustical noise. The subjects need to use earplugs, to not suffer some damage in the ears.

9.2. Discussion of the Results

9.2.1 The Healthy Control Group

Object Matching in the Healthy Controls

The HC group activated for the object matching task (Table 8, Figure 5) in the right hemisphere the Fusiform Gyrus and Precuneus (Occipital Lobe), Inferior Parietal Lobe, Inferior and Middle Frontal Gyrus, and Anterior Cingulate Gyrus (Frontal Lobe). In left hemisphere, they activated areas located in the Inferior Occipital Gyrus and Fusiform Gyrus (Occipital Lobe), as well as in the Inferior Frontal Gyrus.

The activation found involves some of the areas of the ventral pathway for the object matching task, and they are in concordance with the results from Ungerleider, Mishkin, Haxby and collegues (Ungerleider and Mishkin, 1982; Ungerleider and Desimone, 1986a; Ungerleider and Desimone, 1986b; Ungerleider and Haxby, 1994). Very interesting in our results is the fact that beside the activation of some of the areas of the ventral pathway we also found activation in the Fusiform Gyrus in the right and in the left hemisphere. The PET study from Haxby and Collegues (Haxby et al., 1994) had a similar design to ours, with a face matching task and a location matching task in a group of healthy young people. They measured changes in regional cerebral blood flow associated to the perception of faces and locations. They found strong activation in the Fusiform Gyrus during the face matching task as well. This area is responsible for face recognition; it allows the perception of the face as a unique entity. In their conclusion Haxby and colleagues argued that there is lack of activation of more anterior temporal cortices associated with the face matching task, because the Fusiform Gyrus is more involved in this object recognition. The face matching task is a special kind of object matching task (Sergent et al., 1992), where the objects to be recognized are faces. It seems that the ventral pathway in this case has less activation in the temporal lobe and instead there is a strong activation in the Fusiform Gyrus. Our results for the HC

group are consistent with those from Haxby and colleagues.

Location Matching in the Healthy Controls

The HC group activated for the location matching task (Table 9, Figure 7) areas in the right hemisphere that were located in the Middle Occipital Gyrus and Precuneus (Occipital Lobe), in the Inferior Parietal Lobe (Parietal Lobe), and in the Inferior Frontal Gyrus (Frontal Lobe). In the left hemisphere the activation peaks were found in the Inferior and Middle Occipital Gyrus, and Precuneus (Occipital Lobe), in the Inferior Parietal Lobulus (Parietal Lobe).

According to the results of Haxby and collegues (Haxby et al., 1994), we found activated areas in the location matching task which belong to the dorsal pathway.

The contrast Object Matching versus Location Matching in the Healthy Controls

Comparison between the object and location matching tasks showed that the activated regions in the visual system varied depending on the task they performed.

In the contrast object matching versus location matching (Table 12, Figure 9) there were activations found in the right hemisphere in Cuneus, Lingual Gyrus, Inferior Occipital Gyrus and Fusiform Gyrus; in the Inferior and Superior Temporal Gyrus; in the Medial, Inferior and Superior Frontal Gyrus, as well as the Anterior Cingulate Gyrus. In the left hemisphere the activations found were located in the Lingual Gyrus, in the Parahippocampal, and in the Inferior, Middle and Superior Frontal Gyrus, as well as in the Anterior Cingulate Gyrus.

In the object matching task they had to attend to the characteristics of the object, so there was more activation in the parvocellular dominated ventral pathway. These results are

consistent with those of Corbetta and Haxby and collegues (Corbetta et al., 1991a; Corbetta et al., 1991b; Haxby et al., 1991; Haxby et al., 1994); they showed that the attention to one specific aspect of a visual stimulus increases selectively activation for the network that processes the specific type of stimulus. Corbetta et al. (Corbetta et al., 1991a) showed that the neural systems involved in discriminating between the shape, color and speed of a visual stimulus involves different regions of the extrastriate cortex depending on the selected feature processed. In a similar form, Haxby et al. (Haxby et al., 1994) showed that the selective attention to faces is associated with increased activity in those cortical areas that process the attended information, it means ventral pathway for object matching.

Our results are consistent with those from Haxby and Corbetta, for the selectively activation of the visual system depending on the test performed. So in this case the stronger activation due to object matching in contrast with location matching in healthy controls shows selective activation in the ventral pathway (parvocellular).

We also found increased activation of frontal cortical areas during face matching than during location matching tasks. This findings are consistent with the data from Grady et al. (Grady et al., 1994), which showed greater activation of frontal areas during a face and a location matching task in older adults as compared to young adults. It has been suggested that greater engagement of frontal areas in older (healthy) adults indicate that there is an age-related increase in the reliance on frontally-mediated strategic monitoring of low-level processes (Anderson and Grady, 2004; Grady et al., 1994). Our results show the effects of normal aging in the healthy group, consistent with the data from Grady and colleagues of age-realted differences in face processing (Grady, 2002), where they found that an increased prefrontal activity in old healthy adults is a more general response to increased cognitive effort or need for resources.

The contrast Location Matching versus Object Matching in the Healthy Controls

This contrast shows activations due to the location matching task in comparison with the face matching task. It was showed again that the activated regions in the visual system varied depending on the task they performed.

In the contrast location matching versus face matching (Table 13, Figure 9) the activations found were located in the right hemisphere in the occipital lobe. In the left hemisphere the activation was located in the Superior Parietal Lobulus. In Precuneus the activation was bilateral.

In the location matching task they had to attend to the spatial location of the objects; that produced activation along the magnocellular dominated dorsal pathway. These results are consistent with those of Corbetta and Haxby again (Corbetta et al., 1991a; Corbetta et al., 1991b; Haxby et al., 1991; Haxby et al., 1994). Haxby et al. (Haxby et al., 1994) showed that the selective attention to locations is associated with increased activity in those cortical areas that process the attended information, it means dorsal pathway for location matching.

When the subjects performed the location matching task compared to the face matching task, they showed regions of higher activation within the dorsal visual pathway (magnocellular). In this case, we did not find increase activation of frontal cortical areas in the location matching task compared to the face matching task. According with the results from Grady (Grady, 2002), face processing in older adults requires more effort than young people. This effect seems not to appear in the location matching task.

9.2.2. The Mild Cognitive Impaired Group

Object Matching in the MCI Group

The activated areas while performing face matching for the MCI group (Table 10 and Figure 6) were found in the right hemisphere in the Inferior Occipital Lobe and Fusiform

Gyrus, in the Inferior Temporal Gyrus, Inferior Parietal Lobulus, in the Inferior and Middle Frontal Gyrus; and in the left hemisphere, the activation in the Occipital Lobe took place in the Inferior and Middle Occipital Lobe, and in the Frontal Lobe in the Inferior Frontal Gyrus.

We see here again strong activation of the Fusiform Gyrus. Frontal areas are activated as well. The differences between this activation pattern and the one of the old healthy group are determined by activation of the areas which belong to the dorsal pathway and to the ventral pathway. It means that the subjects were using some areas of the magnocellular pathway of the visual system while performing an object matching task.

Location Matching in the MCI Group

The network of activated areas while performing the location matching task for the MCI group (Table 11 and Figure 8), were found in the right hemisphere in Precuneus, Middle Occipital Gyrus, in the Superior Parietal Lobulus, and in the Inferior Frontal Gyrus. In the left hemisphere the activation took place in the Precuneus and Occipital Gyrus, in the Hippocampal Gyrus, in the Superior Parietal Lobulus, and in the Inferior, Middle and Frontal Gyrus.

Like in the face matching task the MCI group recruited for the location matching task not only areas from the dorsal pathway but also some areas from the ventral pathway. It means that the subjects were using some areas of the parvocellular pathway of the ventral system while performing a location matching task.

During the location matching task the MCI group recruited also frontal areas, in contrast to the HC. It would mean for the MCI group the need of higher activation areas to perform the task.

The contrast Object Matching versus Location Matching

Within the MCI group there were no regions that were more activated in the face matching task compared to the location matching task.

As shown in the activation pattern of the MCI group for face matching, together with ventral areas, there were some areas of the dorsal pathway activated while performing the face matching task, so that there was no selective activation of the ventral pathway for performing the task. In the contrast object matching versus location matching, it is shown the lack of selectivity in the activation of the parvocellular pathway of the visual system.

The contrast Location Matching versus Object Matching

Within the MCI group there were no regions that were more activated in the location matching task compared to the face matching task.

It is also shown in the activation pattern of the MCI group for location matching, that some areas of the ventral pathway were activated while performing the location matching task, so that in this case a lack of selective activation of the dorsal pathway was also present.

No selective activation of the Visual System in Mild Cognitive Impaired Subjects

Unlike the HC group, the MCI group did not selectively activate the dorsal and ventral attention pathways; MCI showed activation of some regions of both of the pathways in every task, as indicated in Tables 11 and 12 and Figures 6 and 8. In addition, the contrast comparing object matching to location matching did not show any regions of greater activation for one task compared to the other task.

It seemed that in the MCI group both pathways were activated irrespective of the visual task. One explanation for these findings could be that the subjects were attending to relevant and irrelevant information during the task; it means that they were attending to the

spatial information and characteristics of the objects at the same time. But the fact is that the performance of the task and the response time for both groups did not show statistically differences. Both groups performed the task, but the network recruited was different for the MCI group.

There are different hypotheses as to why there was no selective activation of the visual pathways during the tasks. One reason may be that the MCI group was recruiting regions along both pathways as a compensatory strategy for performing the task. Another hypothesis is that the subjects were performing the task using a different strategy, which led to activation in both pathways. The last possibility is that MCI subjects used a similar strategy as the HC group but they invoked a different neural network for performing the task.

The lack of selective activation in the face and location matching tasks (as shown by the HC) would indicate that the underpinning neuropathology (even in preclinical stages) has an effect on the areas activated for performing a task.

The finding that there was no frontal activation in the contrast face matching versus location matching in MCI patients is very interesting because it seems to be somewhat unexpected taking in mind the results for the contrast object matching versus location matching for HC. But this result might indeed reflect the fact that the frontal areas as compensatory strategy are more recruited during location matching in MCI patients than in HC maybe because the dorsal pathway necessary for location matching is more susceptible for early subclinical impairment in MCI. Thereby a greater activation of frontal areas in the contrast face matching versus location matching as shown before for older adults is not longer visible.

9.2.3. MCI subjects compared to Healthy controls

Face Matching Task activation in MCI subjects compared to Healthy Controls

In this contrast, we wanted to examine if the activation in the MCI group was different compared to the HC group. We expected that a higher activation in the ventral pathway in the MCI group would indicate a compensatory process of the group.

When we made the contrast of the activation of the face matching task between the MCI group and the HC group, we found no areas that had statistically significant higher activation in the MCI group compared to the HC group.

These results are consistent with those from Sperling et al. (Sperling et al., 2003), where no differences in extrastriate activity between mild AD patients and age-matched control participants on a task of face name encoding.

Location Matching Task activation in MCI subjects compared to Healthy Controls

We found that there was increased activation in the dorsal pathway in the MCI group compared to the HC group in the location matching task. The activation peaks (table 14 and Figure 10) for the contrast MCI versus HC in the location matching task were found in the Medial Frontal Gyrus bilateral. In addition in the left hemisphere activation peaks were found in the Inferior, Middle and Superior Frontal Gyrus.

In addition to non-selective activation of the pathways, the differences that we found between groups were increased activation in the frontal lobes in performing the location matching task (Table 14 and Figure 10). We did find increased frontal activity in the contrast face versus location matching for HC but did not find such a difference for MCI. This fits into the picture that there was a stronger frontal activation pattern in the contrast MCI versus HC for location object matching because of the impairment of the dorsal pathway due to the pathology. Frontal areas in location matching tasks may have been activated more as a

compensatory mechanism by MCI patients. This finding would be consistent with the study from Pfefferbaum et al. (Pfefferbaum et al., 2001). In this study a group of alcoholics were studied, and they showed a recruitment of activation in the dorsal pathway and increased activation in the frontal lobes during a visuo-spatial working memory task despite equivalence in behavioural performance as a compensatory mechanism. In the same way, in our study the MCI group may need to compensate for inefficient or altered processing in earlier regions along the dorsal pathway by additional neural regions in the frontal lobe.

The compensatory process could have involved various processes: (a) inefficient processing along the occipital-parietal regions, (b) MCI subject use a different strategy, (c) MCI subjects use the same strategy but recruited different brain regions, (d) the MCI subjects were attending to information non-germane to the task. Even though it was activation in the dorsal pathway, the recruitment of the Frontal Lobe for processing the data indicates that the processing of the stimuli was inefficient compared to HC. Other possibility is the utilization of a different strategy to perform the task. The fact that Frontal Lobe areas were recruited may indicate that the patients needed higher order functions to solve the task. For example, it would have been possible, that patients used a verbal strategy to perform the task, but we found no activation in Wernicke's area. The lack of selective activation along the ventral and dorsal pathways suggest the possibility that the MCI group was not selectively attending to the germane information needed to perform the task, but overall task performance was equivalent in both groups.

The hypothesis that increased activation in the Frontal Lobe in the MCI group occurs as a compensatory process for the dysfunction from the dorsal pathway is supported by the fact that compensatory processes are not only present in patient populations but also in groups of cognitively normal subjects that have a high risk for AD. Smith et al. (Smith et al., 1999) found in a group of women with a high risk for developing AD, that the activation patterns using fMRI for a visual naming and letter fluency task were different than in the

control group, although their performances were identical. Decreased activation along the Inferior Temporal cortex but increased activation in Left Parietal Lobe was found. This may be a consequence of the presence of subclinical neuropathology. Bookheimer et al.(Bookheimer et al., 2000) studied a group of 30 subject who were carriers of the APOE epsilon4 (high risk group) allele and APOE epsilon3 allele (low risk group). The activation patterns using fMRI were determined while subjects memorized and recalled unrelated pairs of words. The patterns found were different for both groups, a network comprising of the Parietal and Frontal Lobe, and hippocampus had higher activation in the high risk group compared to the low risk group. So the differences were depending on the genetic risk of Alzheimer's disease and may predict a decline in memory. The functional re-organization as shown in these studies is heterogeneous with respect to the functional changes dependent on the cognitive paradigm, the risk group, the severity of the disease, and the various possible mechanisms that exist as a compensatory mechanism.

Magnocellular Deficit Hypothesis

The activation pattern that we found in our study was increased activation in the Frontal Lobe in the MCI group for the location matching task compared to the HC group and no differences in activation between groups for the object matching task. This would support the hypothesis that the magnocellular dominated pathway has increased susceptibility to neurodegenerative damage than the ventral pathway.

Sadun may have been the first to suggest that AD may involve a deficit in the magnocellular pathway neural system (Sadun, 1989). But there are other studies in which deficits in the magnocellular but also parvocellular pathway were shown (Cronin-Golomb et al., 1991; Rizzo et al., 2000b; Rizzo et al., 2000a). One suggestion is that the deficits may be expressed more strongly in some patients, indicating that it may be some subtypes of AD

with vivid visual problems. One example would be the AD patients presenting a major impairment of visuospatial skills referred to as Balint's syndrome. Mendez found significant hypometabolism in the posterior dorsal visual stream in AD patients with Balint's Syndrom compared to both without Balint's syndrome and to HC (Mendez et al., 1990). Hof and colleagues found by the evaluation of a large autopsy population of brains that the visual areas of the occipital and posterior parietal regions were more damage than temporal and prefrontal cortex (Hof et al., 1990a). The present study did not have any patients with Balint's syndrome.

In the same way, Mentis et al.(Mentis et al., 1996; Mentis et al., 1998) showed the abnormal visual cortical function in AD patients as an expression of the impairment of the magnocellular visual system. Our work extends these results to a group of MCI subjects using a cognitive task that selectively activates either visual pathway in HC. Comparing the activation patterns within both groups of subjects for both tasks (object and location matching tasks), we could show the differences in impairment of the pathways for the MCI group.

Our results show more impairment of the magnocellular pathway than the parvocellular in our MCI group. It would indicate that the visual dysfunction already occurs in such early stadium of the disease, and could be used as a diagnostic feature for a preclinical diagnosis. Because visual deficits of AD patients are typically undiagnosed, it would be necessary to pay more attention to these kinds of deficits, because these symptoms have profound effects on the ability of the patients to interact with their environment. It is likely that the differences in brain activity seen in older adults and in MCI subjects (as well as it is shown in other studies with AD patients) develop gradually over time, but it is not known at what point these changes begin. Finally the relation between activation differences in visual and prefrontal regions, or other brain areas, is not known (Anderson and Grady, 2004).

Further work on the determination of visual dysfunction in aging as well as people at risk for AD and MCI, and how these changes are expressed in terms of cognitive difficulties, would be a way to better understand this disease.

9.1.4. Hemodynamic Response Function

The passive stimulus task was a control experiment to assess if the two groups had a difference in the BOLD signal magnitude in response to a stimulus. Lack of differences between groups indicate that the differences in the activation patterns for the object and location matching task within the groups is not due to a global difference in BOLD magnitude between groups. Thus the increased activation in the location matching task in the MCI group compared to HC group is due to the cognitive task and not to non-specific difference of the BOLD signal.

The difference in activation in the location matching task between groups is unlikely due to brain atrophy. The areas of increased activation of the MCI group compared to the HC group were in the Frontal Lobes. If grey matter atrophy had affected our results, we would have expected the MCI group to have had lower activation in parietal end temporal areas compared to the HC.

9.1.5. Heterogeneousness of the MCI group

Even thought the initial diagnosis of the MCI group was limited to a single memory dysfunction the group of participants in the study was probably a heterogeneous group composed of:

- those who will convert to AD in the future
- those who may convert to other types of dementia or neurodegenerative syndromes that cause cognitive dysfunction

- those that may remain classified as MCI

Based on previous studies it can be expected that between 50 to 80 % will convert to AD in 5 years (Petersen et al., 1999; Geslani et al., 2005). If the subjects would be followed in the clinical development, it could be possible to better elucidate in the future the difference in activation between those MCI subjects that convert to AD and those that convert to other neurological or psychiatric diseases and those subjects that do not suffer cognitive decline.

10. CONCLUSIONS

The results show that the HC group selectively activated the ventral pathways for the object matching task and the dorsal pathway for the location matching task. In contrast, the MCI subjects did not show selective activation along the ventral and dorsal pathways, and they had higher activation in the left frontal lobe compared to the HC when performing the location matching task. The HC group did not show areas of significantly greater activation compared to the MCI group in any task. Changes in the neural substrate underpinning visual attention function in the comparison between both groups are detailed within both visual pathways.

This work identifies abnormalities in the visual system in both visual pathways in MCI subjects consistent with previous reports of visual attention abnormalities in AD patients. The present results using the visual tasks suggest that even when behavioural performance between groups is the same, the neural systems that support performance may differ. The differences in activation pattern that we found may happen when the ideal network (as defined by the healthy control group) is compromised by disease. This may occur so long the brain is able to compensate for the impairment suffered. In the case of the MCI subjects the compensatory mechanism helps the subjects to maintain the performance as well as in HC.

It has already been shown that AD involves also a processing disorder in the visual sensory pathways. This pathological property of the illness exacerbates memory symptoms (hallmark of the disease). The results from our study extended the results from previous studies with AD patients to a group of MCI patients. In addition, it extended the results by utilizing cognitive tasks that activated selectively either visual pathway in HC.

Visual deficits of AD patients are typically undiagnosed. Mild or subclinical changes in performance may go undetected unless brain imaging techniques are used to measure brain activation during performance of the task. This demonstrates the usability of brain imaging techniques to better understand the underlying pathology of AD and to better differentiate subtypes of MCI.

To better understand the changes occurring within the visual cortex in the process of AD, it would be necessary to follow up the MCI group, investigating which of the subjects have develop a mild AD. Following the clinical development of the subjects will allow us to better elucidate in the future the difference in activation among those MCI subjects that convert to AD and those that convert to other neurological or psychiatric diseases, and those subjects that do not suffer cognitive decline. This would further illuminate the changes along the ventral and dorsal pathways due to AD.

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„Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment" Bokde, A.; Lopez-Bayo, P.; Meindl, T.; Pechler, S.; Born, C.; Faltraco, F.; Teipel, S.; Möller, H.-J. and Hampel, H.; Brain (2006), 129, 1113-1124