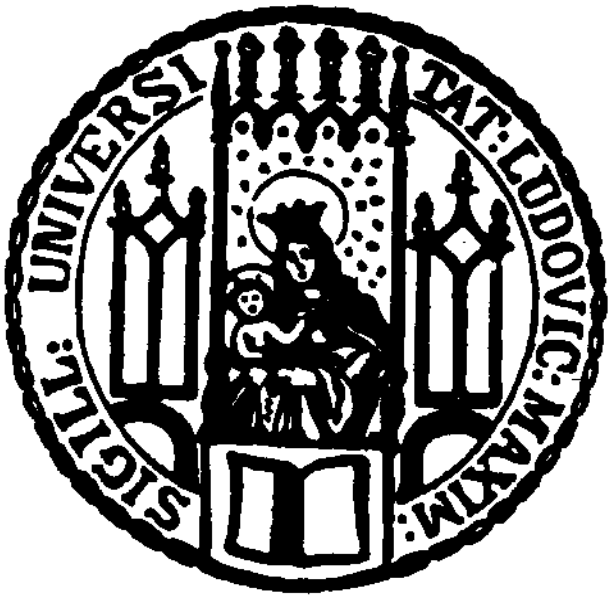
Differences in brain activation between mild cognitive impairment patients and healthy controls during a verbal working memory task: a functional magnetic resonance imaging (fMRI) study



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Preface

The work for this dissertation was done at the Alzheimer Memorial Centre of the Department of Psychiatry of the Ludwig-Maximilians-University.

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Very special thanks go to my parents for their patience and understanding, for pushing me when it was necessary, and for always believing in me. I am most thankful for their support and for always being there for me.

Abstract

Background:

This study was performed to see what differences of brain activation there are between two groups of mild cognitive impairment (MCI) patients and healthy controls (HC) during a working memory task. MCI is a prodromal stage of Alzheimer's disease (AD). In order to make early diagnosis of dementia possible, it is important to find diagnostic markers for AD and MCI.

Methods:

Eight MCI patients and eight HC underwent functional magnetic resonance imaging (fMRI) while performing a verbal working memory task. They were shown five letters, and had to memorize these letters, while a fixation cross appeared on the screen. After this delay the subjects were shown a single letter, and they had to decide whether this letter was among the previously shown group of letters. The answer was given by response buttons, which the subjects held in their right and left hands.
Statistical parametric maps of brain activation were obtained in each group, and group activation difference maps were generated.

Objective:

The goals of this study were to examine brain activation in patients with MCI and HC while performing a verbal working memory task and to find differences in brain activation between the two groups.

Results:

Activation was observed in dorsolateral-prefrontal, parietal, and temporal regions in the HC, with left-lateralization, wich is typical for verbal materials. However, there were also active regions in the right hemisphere, which indicates a certain level of delateralization, which is typical in normal aging. The MCI group showed activation in the same regions, but with less prominent delateralization. Interhemispherical and interregional differences between the groups were found. The HC had higher acitvation in frontal lobe regions, while the MCI group had higher activation in temporal lobe regions. Areas were found in both groups that show higher activation during the resting state compared to the task, the default mode network. The MCI group showed higher deactivation compared to the HC during the delay stage, and lower deactivation during the decision period.

Conclusion:

For each group, the brain activation during the different parts of the task were in areas that were expected to show activation during a verbal working memory task. Differences in activation patterns between the two groups could be shown. The main difference was that the MCI group showed higher activation than the HC, which could be due to compensation for neural degeneration and cognitive decline. The compensatory process is present in all stages of the working memory task.

Deutsche Übersetzung der Zusammenfassung

Hintergrund:
Diese Studie wurde durchgeführt, um Unterschiede in der zerebralen Aktivierung zwischen zwei Gruppen von einerseits Patienten mit leichten kognitiven Störungen (LKS) und andererseits gesunden Kontrollpersonen (GK) während eines verbalen Arbeitsgedächtnistests zu untersuchen. LKS wird als Vorstufe der Alzheimer Demenz angesehen. Um eine frühe Diagnose der Demenz zu ermöglichen, ist es wichtig, diagnostische Marker für LSK und AD zu etablieren.

Methoden:
Acht Personen mit LKS und acht GK haben sich einer funktionellen Magnetresonanztomographie unterzogen, während sie einen verbalen Arbeitsgedächtnistest durchführten. Sie bekamen fünf Buchstaben gezeigt, die sie sich nach der Einprägungsphase sechs Sekunden lang merken mussten, währenddessen sie ein Fixierungskreuz sahen. Nach dieser Verzögerung wurde den Probanden ein einzelner Buchstabe gezeigt, und sie mussten entscheiden, ob dieser Buchstabe in der vorher gezeigten Gruppe von Buchstaben enthalten war. Die Antwort erfolgte über Tasten in der rechten und linken Hand. Statistische parametrische Karten des Gehirns, die die Gehirnaktivität für die jeweiligen Gruppen zeigen, und Karten, die die Unterschiede zwischen beiden Gruppen zeigen, wurden für beide Gruppen erstellt.

Ziele:
Ziele der Studie waren, die Gehirnaktivierung von Patienten mit LKS und einer Gruppe von GK während eines verbalen Arbeitsgedächtnistests zu untersuchen, und Unterschiede in der Aktivierung zwischen den beiden Gruppen zu finden.

Ergebnisse:
Gehirnaktivierung in der GK-Gruppe wurde in dorsolateral-präfrontalen, parietalen und temporalen Gegenden beobachtet. Diese Aktivierungen wießen linksseitige Lateralisierung auf, was für verbale Aufgaben typisch ist. Trotzdem gab es auch aktive Regionen in der rechten Hemisphäre, was einen gewissen Grad von Delateralisierung bedeutet. Dies wiederum ist ein typischer Prozess der normalen Alterung. Die LKS-Gruppe wies Aktivierung in den gleichen Regionen auf, allerdings mit einem geringeren Grad an Delateralisierung. Es gab sowohl interhemisphärische wie auch interregionale Unterschiede in der Aktivierung zwischen den Gruppen. Die GK-Gruppe zeigte höhere Aktivierung in Regionen des Frontallappens, während die LKS-Gruppe höhere Aktivierung in Regionen des Termporallappens aufwies.
In beiden Gruppen fanden sich Regionen, die höhere Aktivierung während der Ruhe-Phase des Tests im Vergleich zu der tatsächlichen Aufgabe zeigten. Diese Regionen werden ‚Default'-Netzwerk genannt. Die LKS-Gruppe hatte eine ausgeprägtere ‚Deaktivierung' als die GK-Gruppe während der Wiederholungs-Phase des Tests, und eine niedrigere ‚Deaktivierung' als die GK-Gruppe während der Entscheidungs-Phase.

Ausblick:
In beiden Gruppen war die Gehirnaktivierung während der verschiedenen Teile der Aufgabe in Gegenden, die während eines verbalen Arbeitsgedächtnistests typischerweise aktiviert werden. Es fanden sich Unterschiede in den Aktivierungsmustern zwischen den beiden Gruppen. Der auffallendste Unterschied war, dass die LKS-Gruppe höhere Aktivierung als die GK-Gruppe hatte, was auf Kompensierung für neurale Degeneration und kognitiven Leistungsabfall zurückgeführt werden kann. Dieser Kompensationsprozess trat während allen Teilen des Arbeitsgedächtnistests auf.

Table of Contents

List of Figures

List of Tables

1 Introduction

1.1 Introduction

Alzheimer's Disease (AD) is the most prevalent cause of dementia in older patients. Life span is increasing and therefore more people will be affected by AD. The prevalence of AD in Germany ranges from 0.9% within the age group of 65 to 74 years up to 30% in women older than 84 years. The incidence gets also higher with age, reaching a maximum of 6.6% within persons of 90 years and older [1].

The demographic development and rising life expectations will lead to a large increase in AD. AD will place a large social and financial burden on society and the families of the patients. The earlier the diganosis is made, the earlier treatment can be started. It is expected that treatment at the early stages of the disease will be more effective and that it will allow patients to maintain a higher level of cognition for longer period of time [2].

Research about early diagnosis of AD has led to the diagnostic entity of Mild Cognitive Impairment (MCI). Subjects with MCI have a higher risk to develop AD. The progression rate from MCI to dementia is reported to be between 6% [3] and 12 % [4] per year. This means after a 6 year follow-up, 50-80% of a group with MCI will have converted to dementia [4].

1.2 Mild Cognitive Impairment (MCI)

MCI refers to a group of individuals who have cognitive deficits and who also present a clinical syndrome that can be utilized to classify persons who do not fulfill a diagnosis of dementia [2, 5]. There are various criteria for defining MCI. The Key Symposium in Stockholm, Sweden, about MCI as a diagnostic entity suggested to proceed as follows: First it has to be determined that the person is neither normal nor demented. MCI involves minimal impairment in functional activities of daily living, but impairment in cognitive functions. After that the next decision involves assessing the decline in cognitive function. If there is no additional impairment in functional activities, the diagnosis of MCI may be entertained [2, 4, 6].
Petersen et al [4] have defined MCI as follows: (i) memory complaint, preferably corroborated by an informant, (ii) objective memory impairment for age, (iii) relatively preserved general cognition for age, (iv) essentially intact activities of daily living, and (v) not demented (see Table 1-1).

There are various subtypes of MCI. The initial cognitive impairment can be of an isolated nature in cognitive domains such as memory, language, attention, executive function or visuospatial skills. If only memory functions are impaired, it is classified as amnestic MCI (a-MCI). Multiple domain MCI (md-MCI) subtype defines various degrees of impairment in multiple domains such as language, executive functions, visuospatial skills. If md-MCI involves memory impairment, it is called md-MCI +a (for amnesia), or if no memory impairment is apparent, it is called md-MCI -a [2, 4].

Petersen et al [4, 7] suggest that especially the amnestic MCI with only one domain (a-MCI) and multiple domain MCI with memory impairment (md-MCI +a) present the earliest clinical manifestation of AD [4, 5, 7]. This is based on the presumption of a-MCI and md-MCI +a resulting from a degenerative aetiology, which would likely represent a prodromal form of AD [4, 5]. A-MCI and md-MCI +a are also discussed to have an underlying depression aetiology [4, 5]. The nonmemory types of MCI emphasizing impairments in executive function and visuospatial skills may have a higher likelihood of progressing to a non-AD dementia such as Lewy body dementia or frontotemporal dementia [4, 8].

In general diagnosis of MCI is met when the subject scores 0.5 in the Clinical Dementia Rating Scale (CDRS) [9], no matter of what sort the deteriorations are. Memory deficits are a significant tool to predict whether a MCI patient will convert to AD. The more similar the cognitive impairments are to AD, the more likely it is for the subject to develop AD later on. This applies particularly for those patients whose caregivers report impaired daily function [10].

Healthy persons, MCI and AD patients differ in the rates of change in diagnostic tests like the Mini-Mental State Exam (MMSE), the Dementia Rating Scale (DRS) and the Global Deterioration Scale (GDS). The scores for Controls remain stable, while for MCI patients the average MMSE score drops by 1 point each year, the average DRS by 2 and the average GDS by 0.4. For AD patients these average drops are higher (3-4 for MMSE, 8 for DRS and 0.8 for GDR) [4].

1.3 Alzheimer's Disease

Diagnosis of dementia is based on an acquired polysymptomatic pattern of impairment of higher psychological functions, including memory and attention, and excluding deteriorations of mind.

Tools for diagnosis of dementia are for example the Diagnostic and Statistical Manual of Mental Disorders (DSM) [11], the GDS [12], the Consortium to Establish a Registry for AD (CERAD) [13] and the MMSE [14]. The shortest one of these is the MMSE, where scores of 30 to 27 indicate no impairment, 26 to 24 mild impairment, 23 to 19 mild dementia, 18 to 12 middle stages of dementia and 11 to 0 severe dementia.

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) established The Work Group on the Diagnosis of Alzheimer's Disease and reported criteria for diagnosis of AD [15]. These are summarized in the report of the NINCDS-ADRDA Work Group under the auspices of the U.S. Department of Health and Human Services Task Force on AD. The group states that the diagnosis of probable AD can be made with confidence if there is a typical onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive deficits. Their criteria for the diagnosis of probable, possible and definite AD are given in Table 1-2 [15].

The Composite International Diagnostic Interview (CIDI) [16] can be used to assess other mental disorders. This is important in excluding other deteriorations, which could cause demential symptoms [1].

In general AD symptoms can be described by a differential impairment of the memory systems. The deficits occur in long-term episodic memory, shown by weak performance in free recall, cued recall and recognition, short-term memory and tasks involving verbal fluency, vocabulary and sentence completion, which represent the semantic memory. However, a high variability exists both in different interindividual cognitive functions and within the same functions themselves [17].

Essentially, the main features of AD diagnosis are (i) memory impairment and (ii) aphasia, and/or apraxia, agnosia or an impairment in executive function. Lately the requirements for apraxia, agnosia and executive dysfunction have been substituted with impairments in relevant cognitive domains such as language, attention/executive function and visuospatial skills. In addition to these deficits there needs to be a concomitant impairment in functioning either socially or occupationally. Other psychiatric disorders or neurological explanations for the decline in function have to be excluded [4].

The central histopathological change in AD is the amyloid plaques. They are extracellular protein sediments, which occur when the transmembranal amyloid precursor protein (APP) is proteolyzed. The product of this proteolysis is Amyloid β (Aβ), 10% of which are not soluble and form the main component of the amyloid plaques [1].

The second histopathological characteristic of AD is hyperphosphorylated Tau-Peptide. The normal Tau-Peptide stabilizes the microtubuli. Hyperphosphorylated Tau accumulates intracellularly and aggregates in paired helical filaments. These are part of the neurofibrillary tangles, which cause neuronal dysfunction and degeneration [1].

Neuronal functions are also altered in beginning AD, namely the loss of cellular homeostasis, caused by a decrease in glucose and oxygen metabolism. This imbalance can be found in all areas of the brain, but mainly in frontal and parietotemporal cortex. Further stages of loss of neuronal functions are loss of synapses and dying of neuronal cells [1].

Another finding in AD was a loss of cortical cholinergic markers and a decreased activity of cholin-acetyltransferase (CAT), especially in temporal cortex, entorhinal region and hippocampus. These findings led to the therapeutic regime of acetylcholine enhancing drugs [1].

Neuronal degeneration begins in entorhinal cortex and hippocampus and spreads to temporal and parietal lobe. Associated with these degenerations are short-term memory deficits and deficits in verbal and visuo constructive abilities. Memory, thinking, language, orientation, attention, visuoconstructive abilities, calculating, practical abilities, recognizing and executive functions are the mainly affected cognitive areas.

Table 1-1. Criteria for amnestic mild cognitive impairment (a-MCI) from [4]

Memory complaint usually corroborated by an informant
Objectice memory impairment for age
Essentially preserved general cognitive function
Largely intact functional activities
Not demented

Table 1-2. Criteria for diagnosis of AD (from [15])

Criteria for the clinical diagnosis of probable Alzheimer's disease

- Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale or some similar examination, and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- Absence of systemic disorders or other brain diseases that in and themselves could account for the progressive deficits in memory and cognition

The diagnosis of probable Alzheimer's disease is supported by

- Progressive deterioration of specific cognitive functions such as language, motor skills, and perception
- Impaired activities of daily living and altered patterns of behaviour
- Family history of similar disorders, particularly if confirmed neuropathologically
- Laboratory results of lumbar puncture as evaluated by standard techniques, normal pattern or nonspecific changes in EEG, and evidence of cerebral atrophy with progression documented by serial observation

Other clinical features consistent with the diagnosis of probable Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease include

- Plateaus in the course of progression of the illness
- Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss
- Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
- Seizures in advanced disease
- CT normal for age

Features that make the diagnosis of probable Alzheimer's disease uncertain or unlikely include:

- Sudden, apoplectic onset
- Focal neurologic findings such as hemiparesis, sensory loss, visual fiels deficits, and incoordination early in the course of the illness
- Seizures or gait disturbances at the onset or very early in the course of illness

Clinical diagnosis of possible Alzheimer's disease:

- May be made on the basis of the dementia syndrome, in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the pesentation or in the clinical course

- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause

Criteria for diagnosis of definite Alzheimer's disease are:

- The clinical criteria for Alzheimer's disease
- Histopathologic evidence obtained from a biobsy or autopsy

Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- Familial occurence
- Onset before age of 65
- Presence of trisomy-21
- Coexistence of other relevant conditions such as Parkinson's disease

2 Brain Mapping and functional magnetic resonance imaging

2.1 Brain Mapping

Functional magnetic resonance imaging (fMRI) is one of the tools to assess and localize human brain function, research that is often termed “Brain Mapping”. Previously research in this field had been limited to examination of brain lesions and resulting deteriorations of cognitive functions. With non-invasive methods like Positron Emission Tomography (PET) and fMRI methods have been established that allow measurement of brain activity during cognitive tests and thus the function of different regions can be investigated.

The basic principle of PET is detection of γ-rays that are emitted by an incorporated radiation source, most commonly ^{18}fluor marked fluor-2-deoxy-2-D-glucose (^{18}FDG). Positrons (β^+) are emitted, which react with electrons (annihilation), and as a result emit two γ-photons. These photons drift away from each other in an 180° angle, and are registered by a PET-scanner only if they hit the scanner at the same time. ^{18}FDG is spread with the blood-flow, and is transported and incorporated into the brain cells like normal glucose. Inside the brain cells, the ^{18}FDG is converted to ^{18}FDG-phosphate, which can’t be catabolized further and stays inside the cells. PET measures the amount of ^{18}FDG that is being accumulated into brain cells over a period of 30 to 45 minutes [18].

The strengths of fMRI in contrast to PET are the substantially higher temporal and spatial resolution, and the ability to measure brain activation without radioactive agents. Limitations of fMRI are the high noise level, which makes it necessary for subjects to wear hearing protection. The radio-frequency magnetic field oscillations are non-ionising, but do generate internal body heat. However, there are guidelines that secure a safe environment for the subject.

2.2 Magnetic Resonance Imaging (MRI)

2.2.1 Physics of MRI

In 1936 Pauling and Coryell discovered the magnetic properties of hemoglobin [19]. In 1990 researchers found in mice and rats that these properties can be used for measuring brain activity without the help of any contrast agents, solely through the change in oxygen concentration [20, 21]. Later, the same researchers were able to apply this method for human studies [22].

Functional Magnetic Resonance Imaging is a special method within the field of Nuclear Magnetic Resonance Imaging. The advantages of MRI are the high spatial resolution and contrast, lack of ionising radiation and its ability to make the images sensitive for blood flow and blood composition, therefore providing a method to measure neural function by virtue of their localized coupling to hemodynamics in brain [23]. Its limitations are that persons with fresh iron implants, cardiac pacemakers, metallic vessel clips or other magnetic acting objects have to be excluded from examination. Also the limited space in the scanner makes it sometimes impossible to examine claustrophobic persons [24].

To get an image based on NMR a large, fixed magnetic field (B_0) needs to be applied. The strength of the field is 1.5 or 3 Tesla (T) in clinical scanners. A fraction of the nuclei in the body of the subject lying in the scanner is lined up in the same orientation of the large magnetic field.

The next step would be to apply an excitation pulse, which is applied by a transmitter coil, to tip the magnetization vector downward from the longitudinal direction to the transverse (see Figure 2-2) and change the net magnetization. Over the time the direction of the magnetization rotates around the longitudinal axis, changes in the magnetic field occur, which can be measured by an external receiver coil (see Figure 2-3). This detector acquires changes in the magnetic flux caused by the preccession of the magnetization around the longitudinal axis [25].

The changes in magnetization generally only last a few seconds. The main mechanisms for the relaxation are longitudinal and transverse relaxation (see Figure 2-4). When the transverse magnetization is gradually going back to the longitudinal direction, the signal received by the coil decreases. The time constant that is associated with the longitudinal relaxation process is called T_1, and the process itself is called T_1 recovery. The relaxation time generally ranges around 1 second [23, 25, 26].

The transverse relaxation results from the initially coherent spins, which are precessing around the main field vector at about the same phase in the beginning, losing their coherence and becoming out of phase. This loss of coherence is caused by spin-spin interaction. The time constant associated with this transverse relaxation is called T_2, and the signal-loss that is caused by this mechanism is called the T_2 decay. This type of relaxation takes only fractions of a second (up to around 100ms) [23, 25, 26].

The third mechanism of relaxation is caused by external field inhomogenities. These inhomogenities affect the spin precession frequencies at their different spatial locations. Those inhomogenity effects combined with spin-spin interactions lead to a signal loss known as T_2* decay, which is characterized by the time constant T_2*. It is always faster than the T_2 decay alone, because the additional factor of field inhomogenity causes the T_2* time constant to be smaller than T_2 [23, 25, 26].

The T_1 and T_2 time constants are affected by tissue type and T_2* by blood flow changes. The T_1 and T_2 contrasts are based on the number of protons in a voxel, which differs across different tissue types [23, 26].

For a T_1-weighted image, the TR has to be chosen at an intermediate repetition time (TR). At a very short TR, there is no time for longitudinal relaxation, while at a very long TR all kinds of tissue have recovered longitudinal magnetization. To minimize the T_2 contrast, a very short echo time (TE) is needed. For an illustration see Figure 2-5 [23, 25, 26].

For a T_2-weighted image, data acquisition is at an intermediate TE, to maximize the difference in transverse magnetization. The TR is chosen to be very long, so that the longitudinal recovery is almost complete and T_1 contrast is minimal. Figure 2-6 shows an illustration of how TR and TE are chosen for a T_2 contrast [23, 25, 26].

Examples of these effects are shown in Figure 2-7, and a graph that explains how the different tissues show different rates of longitudinal magnetization recovery (TR of 200, 600, 1200 and 2400msec) in Figure 2-8. In Figure 2-7 short TR (200 msec) lead to little signal intensity and little contrast between the different tissues. For the TR of 600 msec substantial T_1 contrast between grey and white matter and cerebral fluid is apparent. For longer TR (1200 and 2400 msec), the overall intensity increases, at the cost of contrast decrease [27].

By applying a spin-echo pulse frequency we can get rid of the nuisance signal, which can be caused by the equipment (an imperfect external field). After the excitation pulse, at a defined point of time another echo-generating pulse is applied. This reverses the dephasing and that part of it, which is caused by external field inhomogenities, is cancelled out [23, 26].

2.2.2 Functional MRI (fMRI)

Functional MRI (fMRI) can create images, which reveal localized neural activity in human brains during sensory, motor, and cognitive activity. It is based on local blood flow changes and blood oxygenation changes in response to neural activity. MRI can detect these hemodynamic changes [23, 28, 29].

When neurons are processing information, their metabolic requirements increase. Energy is provided through glucose and oxygen, the oxygen bound to hemoglobin molecules. The differential magnetic properties of deoxygenated and oxygenated hemoglobin can be used to measure images on blood-oxygenation-level dependent (BOLD) contrast. This contrast is a consequence of a series of indirect effects. It results from changes in the magnetic properties of water molecules, which in turn reflect the influence of paramagnetic deoxyhemoglobin. The deoxyhemoglobin is the physiological correlate of oxygen consumption, which itself is a correlate of a change in neuronal activity evoked by cognitive processes [23, 25, 26].

The increase of blood flow and oxygen delivery flushes deoxyhemoglobin from blood vessels. These deoxyhemoglobin have magnetic field gradients that alter the spins of nearby diffusing hydrogen nuclei. When paramagnetic deoxyhemoglobin is present, the MR signal intensity of the hydrogen nuclei decreases, caused by less dephasing of hydrogen. The T_2* decay changes allow the spin alterations caused by changes in the composition of the local blood supply to be measured. When the deoxyhemoglobin is displaced with oxygenated hemoglobin through increased blood flow, a local increase in the T_2* MR signal can be observed [23, 25, 26]. The increase in cerebral blood flow overcompensates for the decrease in oxygen caused by oxygen comsumption in neurons, delivering an oversupply of oxygenated blood. So indirectly neural activity can be measured by T_2* changes [23, 26].

To summarize, the BOLD response provides unprecedented visibility of the neural activity in human brain. The BOLD signal has been shown to be correlated to the presynaptic activity and local neuronal activity [30-32].

An fMRI experiment needs a series of anatomical scans, which are later on used to relate the functional findings to known anatomical landmarks in the brain. The anatomical scans provide the information to better localize the place of the activation due to cognitive tasks [23].

FMRI differs from conventional MRI by rapidly variating magnetic field gradients. By applying a gradient of magnetic field across one spatial dimension, the resonant frequency will change with position. Thus the NRM signal becomes a mixture of signals of different temporal frequencies, which can be analyzed independently and interpreted as functions of position. A three dimensional image can be created by repeatedly applying magnetic field gradients in all three dimensions. This permits a much more rapid acquisition of whole-brain volumes than in conventional MRI [25, 33].

There are two major design formats for fMRI experiments. The design of the task can be block design, where a “steady state” of neuronal and hemodynamic change is set up, and event-related design, where the hemodynamic response to each stimulus is measured. The design has to include other tasks or a resting period as activation results are based on comparing between two cognitive states [25, 33].

The signal modulation in fMRI is typically 0.5-5%. It is very important to minimize head motion to be able to detect the actual signal. Applications of fMRI can be retinotopy, modulatory effects of attention, emotional affects, cognitive processing and clinical and preoperative use, for example to better understand neurological and psychiatric disorders [33].

2.3 Analysis tools of fMRI data

2.3.1 High and low pass filtering

Using temporal filters, frequency components due to noise sources that are present in the fMRI signal can be removed. The removal of those frequencies improves the signal-to-noise ratio. There are low and high frequency components to the noise signal. These components are due to physiological sources as breathing and pulse and the scanner sources such as electronic noise. The low frequency components often lead to near linear increases or decreases in absolute signal over the course of a several-minute long experimental run. Thus the noise signal can be removed using low and high pass filters, or by modeling the noise signal using linear regression [25].

2.3.2 Slice time correction

The fMRI data from the brain is acquired in many slices over the TR period. All slices are not acquired simultaneously, but there is a time difference in acquisition of each slice. This sampling delay can influence the strength of the association between the measured data and the experimental hypothesis. For the correction, temporal interpolation was used. This method uses information from the entire time series to estimate the amplitude of the MR signal at the onset of the TR. The time shift is usually done with reference to the initial slice acquired [25].

2.3.3 Motion correction

Even though the subjects were requested to lay still during the scanning, and there was padding to prevent head motion, movement did occur. Even if the movement is a fraction of a millimeter, this causes additional variance in the fMRI-data. Therefore it is necessary to correct the images for motion effects. To correct for motion effects, a single image in the run is chosen as a reference image and all other images are corrected for differences in position relative to the reference image. The second step is to calculate the new images with the estimated motion parameters.

2.3.4 Smoothing

The measured signal is composed of the neurophysiological effects in response to the cognitive task and of noise signal. The noise signal is composed of neuropsychological effects such as motion due to breathing and heart rate and due to electrical noise from the scanner. Spatial smoothing of the data improves the signal to noise ratio. The disadvantage of spatial smoothing is that the spatial specifity of the signal is decreased relative to the original measurement. This is a small disadvantage relative to the advantage of increased signal to noise ratio from spatial smoothing. Another effect of smoothing is that anatomical differences between subjects are reduced.

2.3.5 Spatial Normalization

Due to differences in anatomy between subject, it is necessary to transform the data into a standard reference frame. Through spatial normalization the data of the single subjects were transferred into a standardized space defined by the MNI/ICBM template [34]. This step assures compensation of individual differences of brain size and geometry. This makes it possible to average the data across groups of subjects.

2.3.6 Classification of cortical areas

The brain can be subdivided into different anatomical regions. Anatomical regions may be defined by the various lobes or gyri. In addition, the regions may be defined on the basis of the cortical thickness, packing density and composition and size of neuronal vells to distinguish between regions. These differences in cytoarchitecture are mapped with the hope of differentiating function on the basis of structure. A common cytoarchitectural map used in brain imaging is one developed by Brodmann, who divided the cortex into 47 regions. These regions are now called Brodmann areas (BA) and numbered from 1 to 47 [35]. An overview of the anatomical regions is given in Figure 2-9.

2.3.7 Extraction of brain structures

This step removed all non-brain structures like bone and other tissues from the MRI images. It was performed by the AFNI-programm 3DAutomask. Both in the structural MPRAGE data as well as the functional data the non-brain structures were removed to assure the co-registration of structural and functional data could be performed correctly.

2.3.8 Statistical Analysis

The analysis of fMRI data is based on the General Linear Model (GLM). It is a class of statistical test that assume that the experimental data are composed of the linear combination of different model factors, along with uncorrelated noise [25]. The linear model assumes that the observed data is equal to a weighted combination of several model factors plus an additive error term. The model factors are a set of hypothesized changes in BOLD activity associated with the manipulations of the independent variables. There are also parameter weights that indicate how much each factor contributes to the overall data. Calculating what combination of weights serves to minimize the error term [25].

The linear model calculations with only one dependent variable can be extended to include a larger number of dependent variables, through the general linear model. The basic components are the empirical data, the design matrix, which is constructed by the experimenter based on the study design, the parameter weights, and the residual error, the latter two being calculated during the analysis [25].

For fMRI analysis, the experimental data are represented as a two-dimensional matrix that consists of the time points and the voxels. There is an independent calculation for the values of the parameter weights and error term in each voxel. A design matrix is created, which specifies how the model factors change over time. The columns that are entered in the matrix should represent a prediction about how hemodynamic activity would change should a voxel be associated with that factor. The general linear model then calculates how much this hypothetical time course contributed to the real data [25].

In general, the general linear model assumes that raw fMRI data can be modeled as the sum of several separate factors, which may each vary independently across voxels, along with additive noise that is also independently and identically distributed [25].

There are two types of experimental factors, the covariates, which can take any of a continuous range of values, where the value of the factor represents the amount of some known quantity, and the indicators, factors that have integral values that indicate a qualitative level, for example demographic conditions [25].

The ANCOVA (analysis of covariance) is a special case of the general linear model. It is used to assess interaction between variables, to correct for confounding variables, and to increase the precision when estimating the association of interest. An ANCOVA analysis is conducted by fitting a regression model that contains not only the study factors of interest, but also extraneous variables considered to be important as independent variables. The goal of an ANCOVA is to determine what effects the study factors have on the responsible variable, which has been adjusted for the presence of the control variable [36-41].

The ANCOVA procedure for regression modeling involves a multiple regression model. In this model the study factors of interest are all treated as nominal variables, whereas the variables that are being controlled (the covariates, in this study age), can be measurements on any measurement scale. The nominal variables are incorporated into the regression models by means of dummy variables [41].

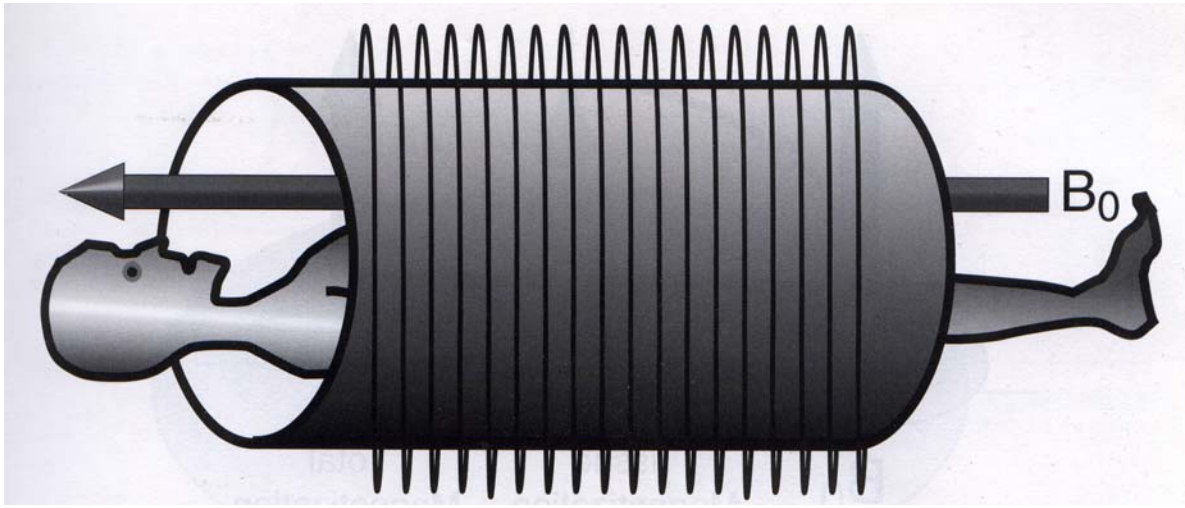

Figure 2-1: Main magnetic field (B_0) oriented along the axis of a resistive or superconducting magnetic bore (from [27])

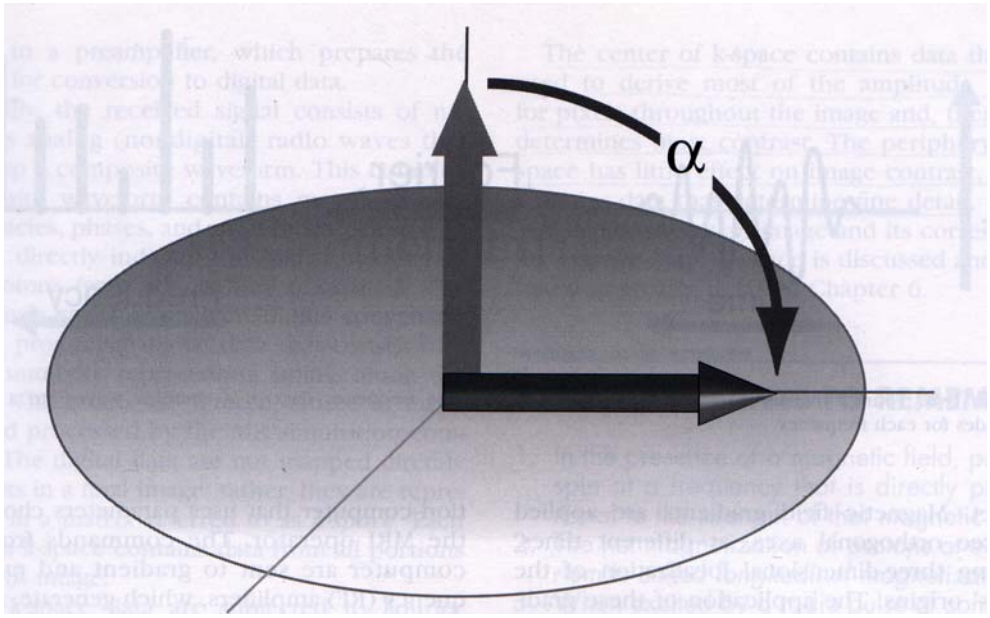

Figure 2-2: A 90° excitation pulse (α) rotates longitudinal magnetization into the transverse plane, allowing it to be measured (from [27])

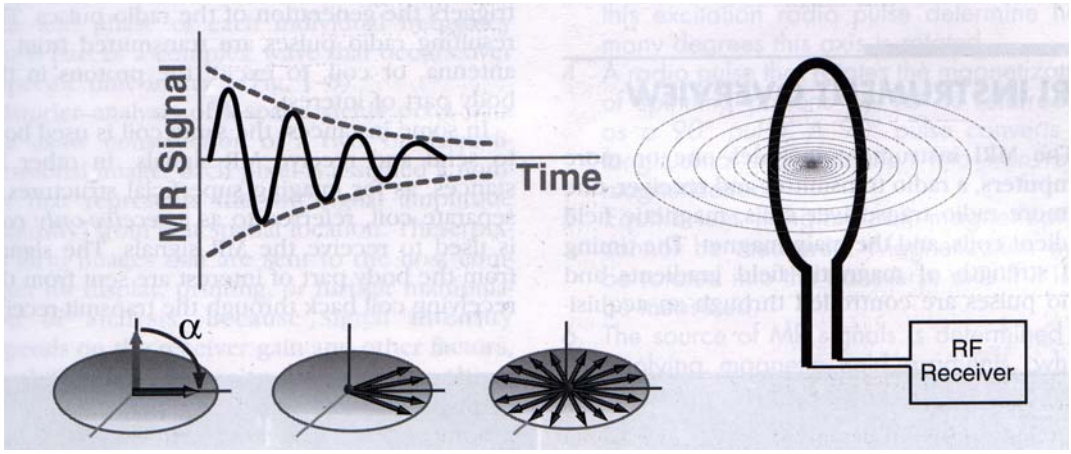

Figure 2-3: Rapidly decaying transverse magnetization and its measurement (from [27])

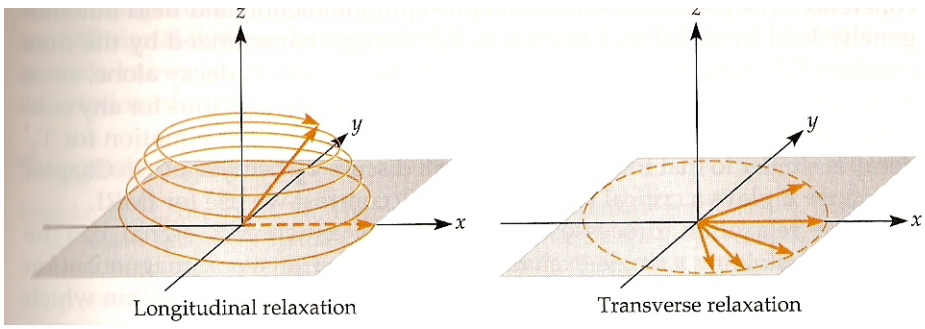

Figure 2-4: Longitudinal and transversal spin relaxation (from [25])

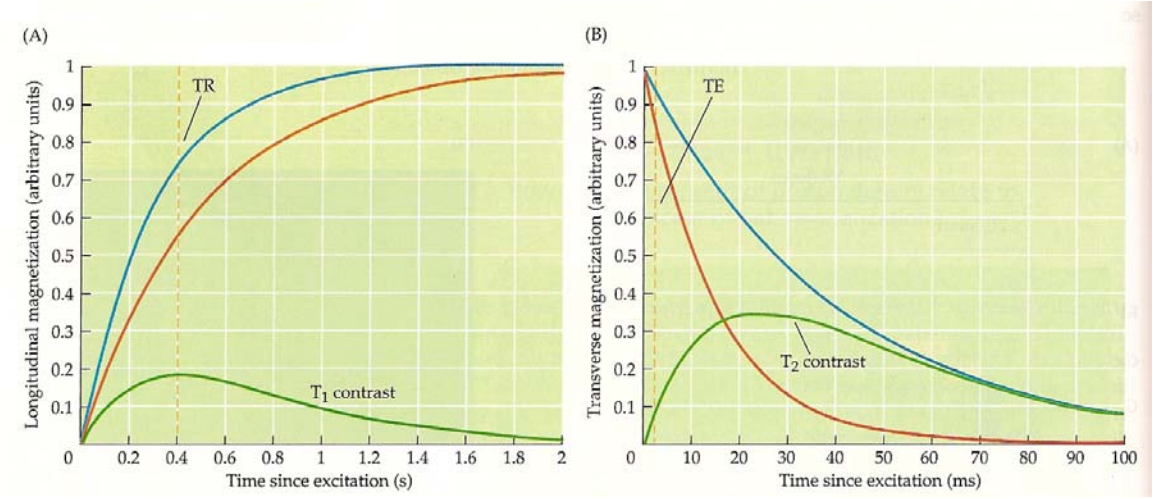

Figure 2-5: Selection of TR and TE values for T1 contrast (from [25])

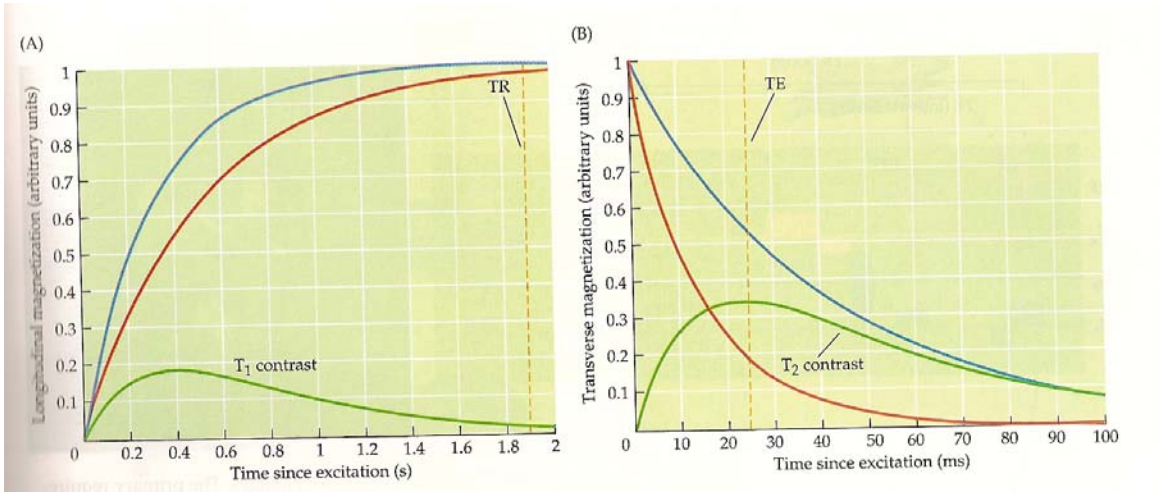

Figure 2-6: Selection of TR and TE values for T2 contrast (from [25])

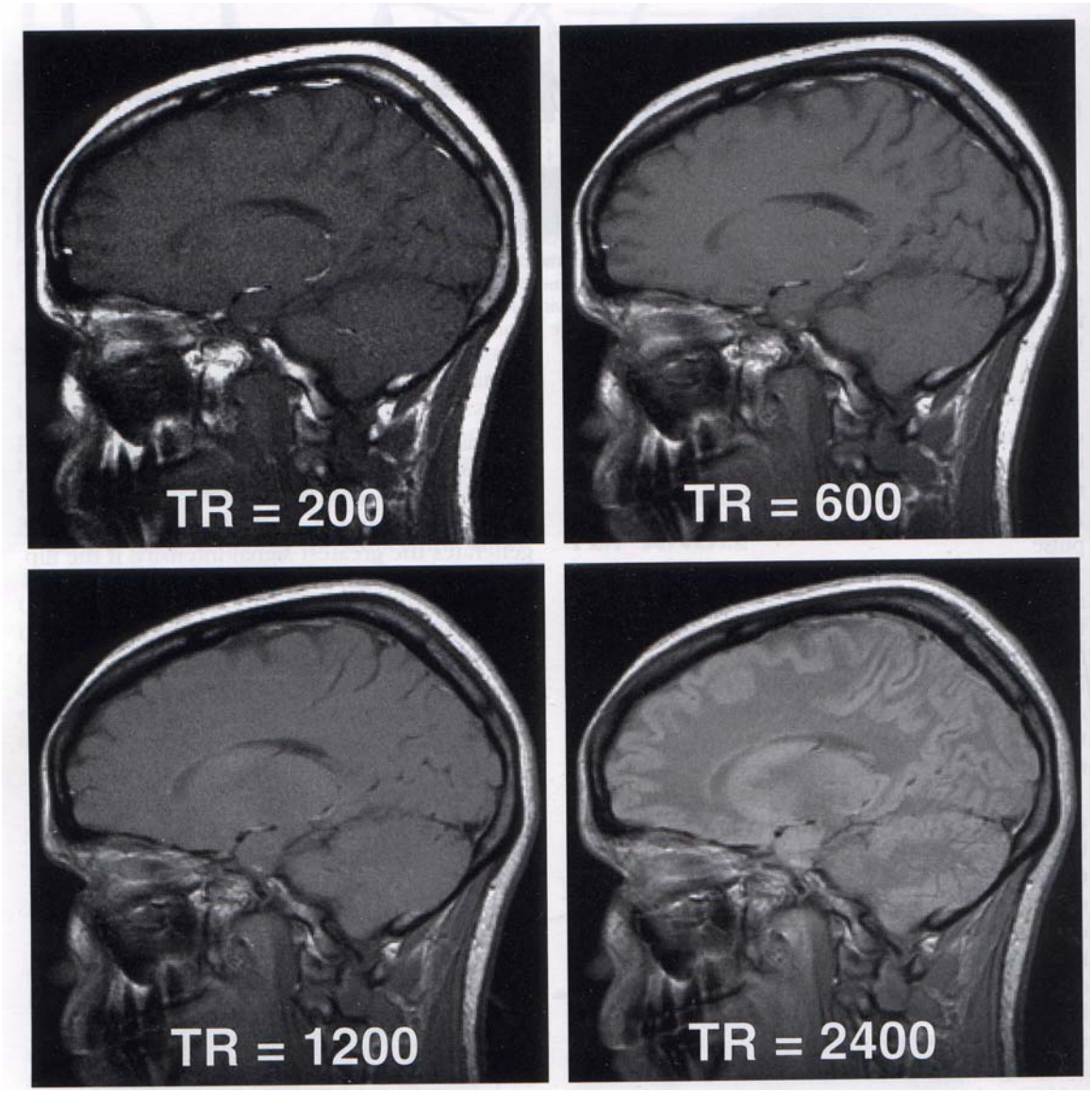

Figure 2-7: Effect of varying TR on tissue contrast (from [27])

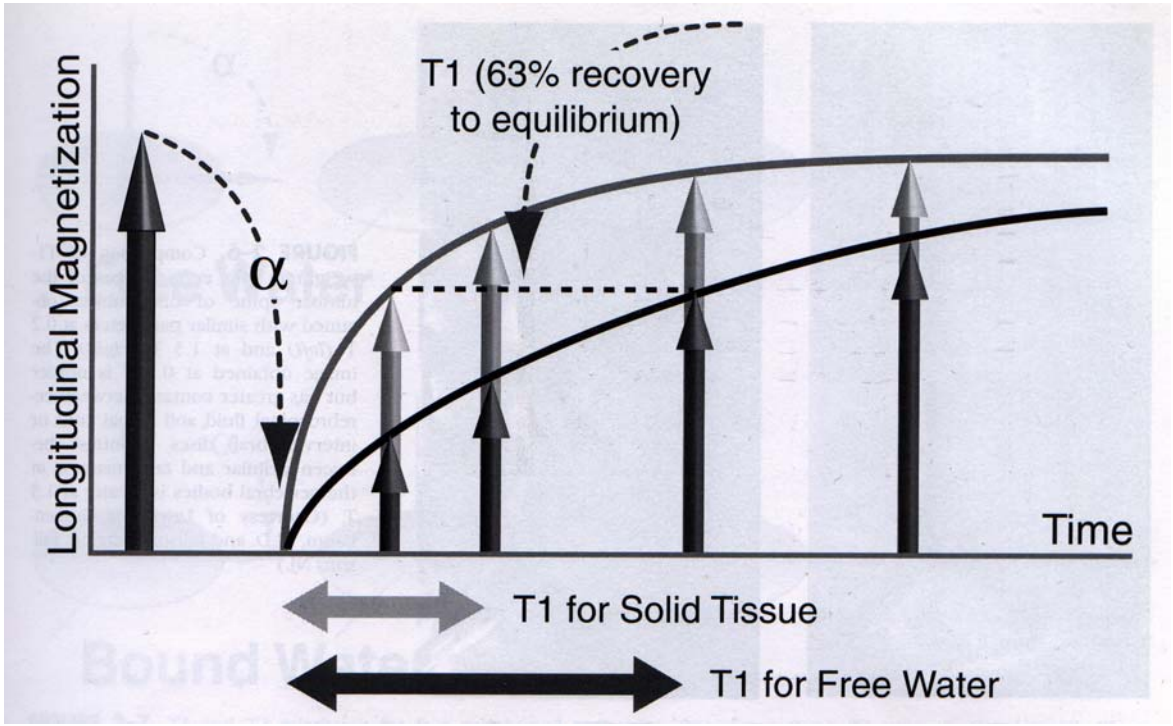

Figure 2-8: Recovering times for different tissues (from [27])

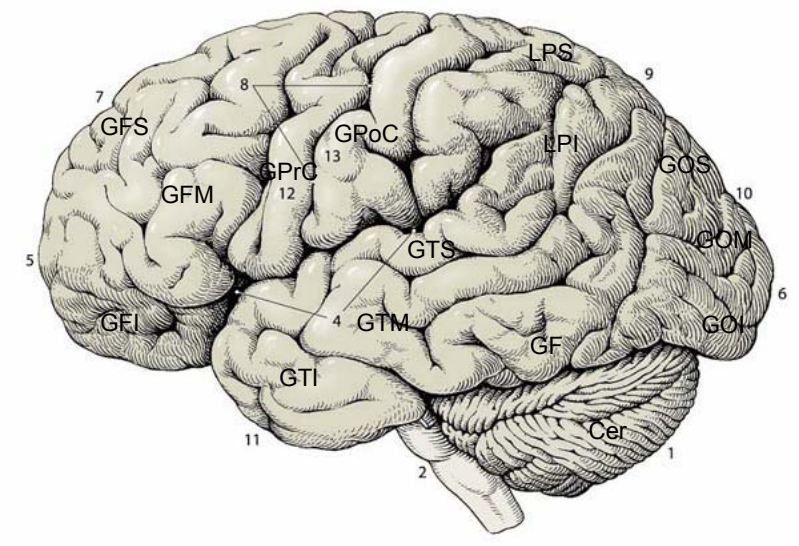

Figure 2-9: Cortical Regions (from [42])

3 Literature Review

FMRI along with PET have been extensively used to explore the functional neuroanatomy of cognitive functions. These methods have been utilized for finding which cortical regions are being activated when performing cognitive tasks. Various studies have been conducted to assess the different types of memory, such as explicit and implicit memory, long-term memory, short-term memory, and working memory (WM). In addition, the different phases of memory tasks were also examined: encoding, delay and retrieval.

Another utilization of fMRI and PET is to find differences in activation due to aging and neurodegenerative diseases such as AD. One goal of this research is to find patterns of activation that might indicate early stages of Alzheimer's disease (AD). These patterns might serve as markers for AD of also its discussed prodromal stages like mild cognitive impairment (MCI).

3.1 Activation Patterns for Working Memory Tasks

Working memory refers to temporary storage and processing information while cognitive tasks are performed. It consists of a limited capacity system responsible for the storage and processing. Several studies have examined activation patterns in healthy subjects who were performing WM tasks. WM is typically assessed through delayed response tasks, *N*-back tasks and self-ordered response. During the delayed response tasks, subjects are presented with items, which they hold in short-term memory for a few seconds, and then respond to a probe. Tasks like this require primarily maintenance operations, and the short-term memory store is emptied after each trial [43]. This type of WM was examined in our study.

In the *N*-back tasks, subjects see a continuous stream of items and have to indicate for each item if it matches an item that occured one, two, or more items back in the series. These tasks involve short-term memory, but also constant updating, which is an operation attributed to the central executive [43, 44].

In self-ordered response tasks, subjects generate verbal or motor responses following a rule (for example, response alternation) or avoiding repetition (for example, self-order pointing, random generation) [43, 45].

WM is typically associated with increased activity in the prefrontal cortex, specifically in left-lateralized Brodmann area (BA) 44 for verbal and numeric stimuli and in right-lateralized BA 44 for spatial tasks. Verbal and spatial tasks have also been associated with activity in BA 6, which is also in prefrontal cortex, for verbal and spatial tasks. BA 6 is likely to be related to general WM operations. BA 9 and 46 in the prefrontal cortex seem to be active only for certain kinds of WM like tasks that require manipulation of WM contents, but not others [46]. Broca's area was attributed with two functions in another study that stated dorsal Broca's area was sensitive for performance, while ventral Broca's area was sensitive to lexical status [47].

Other areas typically involved in WM tasks are parietal regions, particularily BA 7 and 40. Again, for verbal/numeric tasks, they show left-lateralization, suggesting they are involved in linguistic operations. Parietal activation is thought to represent the phonological store, while Broca's area (BA 44) represents the rehearsal process [48, 49]. Anterior cingulate is also associated with WM, often activated in BA 32. However, it seems to be related to task difficulty rather than to WM itself [47]. Cerebellar activation is common during verbal WM tasks that involve processing (for example, holding letters) and that engaged Broca's area [43]. Parahippocampal regions, superior, middle, and inferior frontal gyri, parietal regions, anterior and posterior cingulate gyrus, fusiform gyrus and basal ganglia have been found to be activated during a visual WM task [50].

In a study examining the encoding and retrieval of pictures in long term memory, activity was found for encoding in left hippocampal area, right dorsolateral and inferior frontal regions. The more activity was found in these regions, the deeper the encoding was, and the better the regions that support effective encoding and successful retrieval could be identified. For retrieval, anterior middle temporal lobe and prefrontal regions had greater involvement than for encoding [51].

Clark et al. [52] showed in their study that verbal WM was associated with dorsolateral-prefrontal and inferior parietal activation. They found that prefrontal regions act as the executive control, linking the posterior representations of anticipated target stimulus fo anterior representation of planned response. Their proposal is, that updating the stimulus is mediated through a connection of middle frontal gyrus and supramarginal gyrus. The supramarginal gyrus is seen as an amodal region binding modal representations in posterior association cortex of the word being retained [52].

The prefrontal cortex has been the interest of a study that examined the prefrontal contributions to WM. The lateral prefrontal cortex is connected with those types of cognitive operations that one performs when attempting to temporarily maintain and manipulate information. It is also involved in encoding- and response-related processes as well as memory and non-memory processes that are engaged during the temporary maintenance of information. Lateral prefrontal cortex can therefore not be described as a single, unitary cognitive domain, but contributes to working memory through different paths [53].

3.2 Changes in lateralization patterns in aging

Changes in frontal lobe function, which seem particularly vulnerable to the effects of aging, are often hypothesized to be the source of various cognitive deficits that occur in older adults [54]. Dysfunctions in frontal lobe have been associated with age-related impairments in long-term memory, attention and inhibitory processes [55]. Prefrontal cortex (PFC) is behaviourally engaged for a variety of cognitive operations (for example, WM, episodic memory, inhibition, monitoring, strategic organization and planning). In working memory, the dorsolateral prefrontal cortex had been identified with executive processes [43, 56].

A variety of PFC regions showed both increases and decreases in activation during WM and episodic memory in older subjects. The subjects' performance is often weaker when these changes occur [57-59]. Those PFC changes are suspected to be compensatory, reflecting the recruitment of additional brain regions to augment the task performance [60].

It has been found that age-related deficits in WM and also episodic memory abilities are related to changes in PFC. With age, reduction in the hemispheric specialization of cognitive function in the frontal lobes occurs. Causes of this could be dedifferentiation of function and/or reorganization and compensation [57].

Reduced lateralization in PFC has been found across WM and episodic memory tasks with age. These laterality effects could result from functional compensation, primary deficits in function, dedifferentiation, or a combination of these mechanisms. Deficits in brain function with age are thought to result in decreases or absences in activation in older subjects compared to young subjects. The successful or attempted compensation of these deficits is reflected by the concomitant increases in activation. The dedifferentiation theory explains the age-related changes in functional activation by deficits in neurotransmission [61], which in turn cause decreases in signal-to-noise ratio and less distinct neural representations. Increases in activity reflect generalized spreading of activity, caused by reduced specialization of function. It is possible, that this results form compensatory efforts, but not necessarily [57].

Age differences in frontal lateralization of verbal and spatial WM have been investigated in another study. In the younger subjects, activation for verbal WM was predominantly found in left hemisphere, and for spatial WM in right hemisphere. The older subjects revealed a global pattern of anterior bilateral activation for both verbal and spatial WM rehearsal. These effects have been explained by compensation for neural declines in age [60].

A study about the age effects on neural correlates of successful memory encoding also yielded differences in activation patterns in younger and older subjects. The subsequent memory effect of the two groups was compared. This refers to activation found for items that were later on in a recall test remembered by the subjects. The younger subjects showed left lateralized activation in prefrontal cortex, hippocampal formation, and inferior temporal cortex for the subsequently remembered words. The older subjects in contrast showed bilateral activation in prefrontal cortex and hippocampal formation [62].

3.3 Changes in activation patterns in MCI and AD

An important subject of functional brain research over the past years has been the investigation of typical activation patterns of mild cognitive impairment (MCI) patients and Alzheimer's disease (AD) patients. Memory impairment is the most characteristic hallmark of both MCI and AD. Therefore, a lot of emphasis has been put on examining alterations in brain functions during memory tasks of MCI and AD patients in comparison to older healthy subjects.

During a face encoding task that compared the BOLD signals of HC, MCI and AD, differences in occipital regions could be shown. These differences could significantly distinct between the three groups, when regressors of the early phase of the BOLD phase were applied. The HC showed diminished BOLD signal compared to the MCI, and the MCI showed diminished BOLD signal compared to the AD. The decreased BOLD signal was restricted to occipital regions in MCI, while in AD it occured in more widespread regions. This might be consistent with the idea that MCI is a transitional state between healthy aging and dementia. Single standard hemodynamic response [63].

Yetkin et al. [50] examined differences in healthy controls (HC), MCI and AD subjects. For visual WM several regions have been identified that reveal activation differences: AD and MCI subjects had greater activation than older healthy controls (OHC) sujects in right superior frontal gyrus, bilateral middle temporal gyrus, middle frontal gyrus, anterior cingulate gyrus, and fusiform gyrus. Within this, the MCI group had greater activation than the AD groups in right parahippocampal gyrus, left inferior frontal gyrus, bilateral cingulate gyrus, lingual gyrus, lentiform nucleus, right fusiform gyrus, and left supramarginal gyrus. Both MCI and AD patients had shown an increased extent of activation and recruitment of additional areas compared to OHC [50].

The cingulate gyrus was another region that revealed different activation patterns in healthy subjects and patients in a visual working memory task. It revealed activation in YC and in AD patients, but the temporal profile was different. In YC, the response quickly reversed, while it maintained active throughout the task for the AD patients [64]. A group of MCI patients and also a group of AD patients had greater activity in bilateral anterior cingulate during a visual WM task than OHC subjects. The activation in the MCI group was higher in the MCI group than in the AD group [50].

MCI subjects showed different patterns of activation in several studies. Visual memory has been observed to activate parahippocampal, frontal and parietal regions and cingulate gyri to a greater extent in the MCI group compared to the AD group. The AD groups showed higher activity in temporal and parietal regions and in anterior cingulate. The changes in activation were hypothesized to be compensatory for neural loss and loss of synapses or neurotransmitters. The observed differences in activation may result from a reserve of healthy tissue, which is available for recruitment to compensate for decreased neural capabilities [50].

Medial temporal lobe was also an area of investigations' interest. MCI and AD groups showed lower activation in medial temporal lobe than an OHC group during a memory encoding task [65].

Differences in activation of AD patients and older healthy controls (OHC) have been found during performance of a face-name encoding and retrieval task. The OHC group had greater activation in hippocampal region, while the AD group had higher activation in medial parietal regions (precuneus), right posterior cingulate, and right superior frontal cortex. The decline in hippocampal region in the AD subjects was attributed to neuronal loss. The alterations in frontal and perietal regions was thought to be caused by age-related changes in memory, as well as compensation for impairments in other regions. The parietal regions in particular have been reported to show decreased resting state metabolism and perfusion in AD, but increased activation [66].

In a study about intentional encoding in early stage AD patients and OHC, the AD group had an activation deficit in medial temporal lobe and also fusiform gyrus. The medial temporal lobe was being associated with explicit memory, which was said to be impaired. The implicit memory in contrast, which is being assessed by priming functions in lateral occipital, parietal, and frontal cortices, areas that haven't been showing decreased activity in this study, was thought to be intact in this early AD stage patients [67].

Differences in hippocampal activation were found during visual encoding. This was connected with better performance in those MCI patients compared to MCI subjects with lower activation and weaker performance. Patients with greater clinical impairment also showed a larger extent parahippocampal activations, probably based on a compensatory mechanism [68].

The group of Bookheimer et al. [69] examined if there were differences in activation for persons at risk for AD. The group with the risk for AD were carriers of the apolipoproteine E allele ε4 (APOE ε4). This group showed higher activation in hippocampal, parietal, and prefrontal regions during memory activation tasks, and higher activation hippocampal region and a greater mean number of activated regions for recall [69].

These studies provide evidence that it might be possible to use changes in activation patterns while performing cognitive tasks. One group established an index of synchrony in hippocampus for subjects that underwent a resting-state fMRI for measurement of functional synchrony in the hippocampus. This index cross-correlated spontaneous low frequency components between possible pairs of voxel times courses in a brain region. This index of MCI subjects was significantly higher than in AD patients, and significantly lower than in OHC [70].

An increased extent of activation and recruitment of additional areas could also potentially be used as marking OHC from MCI (increased activation) and AD (activation higher than OCH, but lower than MCI) [50]. The results of [65] suggest the extent of decrease in medial temporal lobe activation as specific marker of limbic dysfunction due to neurodegenerative changes in AD [65]. Extent of prefrontal activation has been suggested as a marker for differentiating between healthy older subjects at high or low risk for AD: High risk subjects were those who reported subjective memory impairment, in contrast to low risk subjects who did not have subjective memory complaints. Both encoding and retrieval of an episodic memory task yielded increased activation in prefrontal brain regions relative to a baseline condition in the low-risk group. The high-risk group, in contrast, did not significantly activate any prefrontal regions. This activation pattern might predict a subsequent disease in persons with subjective memory complaint [71].

4 Materials and Methods

4.1 Subjects

The two groups of subjects were MCI (mild cognitive impairment) patients and healthy control (HC). The eight MCI subjects were all in-patients at ward D2 of the Psychiatric Clinic of Ludwig-Maximilians-University. Diagnosis of MCI was performed by physicians of the ward using the criteria of Petersen et al. [4, 5]. Only patients with a-MCI-single domain were included in our study. The age range of the patient group was between 63 and 76 years with a mean age of 70.8 years and a standard deviation of 5.23 years. There were 6 men and 2 women in the MCI group. The CERAD scores of the MCI subjects are in Table 4-1.

The healthy volunteers for this study were recruited from Volkshochschule München Seniorenprogramm, a local education programm for older, and also from acquaintances of patients and others involved in this study. The CERAD was performed with every subject, as well as an intensive discussion about their state of memory to assure they did not have memory impairment themselves.

If depression in the HC was suspected, the Hamilton Test was performed. Subjects who had a score of 9 or higher in the Hamilton Test were excluded from the study, because of possible depression in the subject. Exclusion of subjects with suspected depression was necessary because of possible overlapping symptoms between depression and dementia. MCI patients that were diagnosed with depression were also excluded from the study.

The age of the healthy control group ranged from 60 to 71 with a mean age of 66.6 years and a standard deviation of 3.89 years. Five of the healthy control subjects were male, 3 female. The CERAD scores for this group are shown in Table 4-2. Only subjects without fresh metallic implants or cardiac pacemakers, without other psychiatric and neurological conditions and with normal vision or corrected to normal were included in the study.

The test was explained to all subjects prior to the examination. For that purpose each subject was handed a standardized form, which explained the goals and process of the study. All subjects gave their written informed consent to being a participant in the study. The study was approved by the Ethics Commission of the Medical Faculty of Ludwig-Maximilians-University Munich.

4.1.1 CERAD

The cognitive profiles of the subjects were established with the CERAD Battery Test [13]. The CERAD (The Consortium to establish a registry for Alzheimer's Disease) is a neuropsychological test battery to assess a subject's cognitive impairment. It was developed to standardize the assessment of AD, using brief and reliable clinical and neuropsychological measures. Its advantages are the little time needed to perform the test (about 30-40 minutes for patients, for healthy controls less), and also its high reliability. It has a high consistency in administration and scoring of the neuropsychological tasks [72, 73].

The CERAD adresses several cognitive aspects:

Verbal fluency – This test measures impairment in verbal production, semantic memory, and language.

Boston Naming Test (modified) – The subjects are asked to name 15 objects presented as line drawings.

MMSE – This is a well-known brief general cognitive battery that measures orientation, immediate and delayed memory, concentration, language and praxis.

Word List Memory – This free recall task with 3 trials of learning words assesses the ability to remember newly learned information.

Constructional Praxis – Four line drawings of figures of increasing complexity are presented to the subject for copying.

Word List Recall – In this delayed memory test the subjects are asked to name the ten words they previously had learned during the Word List Memory task.

Word List Recognition – This tests the recognition of the 10 words of the Word List Memory task when presented among 10 distractor words.

4.2 Working Memory Paradigm

The task was explained to the subjects using examples on a paper and once understood they were shown a short demonstration version of the task on a computer.

In the working memory task the subjects were presented simultaneously 5 capital letters for 4 seconds, followed by a 6 second period in which they were required to remember the 5 letters and could see a white fixation cross on the screen. After 6 seconds one single lower case letter appeared, for which the subjects were to decide if it was among the 5 letters they had seen. If the letter was in the group of 5 letters, the subject pushed a button with their right hand, if it was not in the group, he/she pushed a button with their left hand. The exact design of the working memory paradigm is shown in Figure 4-1.

Each subject performed three runs of the working memory task. Each run contained 3 blocks of working memory (50 seconds per block) and each block had 3 trials. Each subject performed 27 trials. The working memory trials alternated with four resting state blocks (20 seconds per block). Before each block, the subjects saw a short instruction for 10 seconds.

4.3 Test procedure

The subjects were scanned in a 1.5T Siemens Vision System scanner (Siemens, Erlangen, Germany). While lying in the scanner, the subjects saw a 1.5 x 1.5 meter screen through a mirror that was attached to the head coil. The stimuli were projected on this screen by a video projector. A computer equipped with VAPP (Visual and Auditory Presentation Package, [74]) software for displaying visual images for psychological studies was connected to the video projector. An illustration of the scanning environment can be seen in Figure 4-2.

The subjects were instructed to press a button with the index finger of the right hand (for letters that have been among the previously seen ones) or left hand (for letters that have not been among the 5 previously seen ones). A picture of the response device they utilized is in Figure 4-3.

4.4 Group Matching

The subjects in the two groups were matched for performance. For each pair of subjects, the number of runs and performance in each run were matched. The difference in age was adjusted by including a covariate for age when comparing differences between groups. All subjects performed three runs of the task. Some runs have been excluded from the analysis, because the subjects' performance in those runs was not above chance (55.6 % or higher percentage of correct answers). Some runs showed motion artefacts and also had to be excluded from the analysis. The number of runs and performance for each group are shown in Table 4-3 and Table 4-4.

4.5 Data acquisition

Structural images were acquired first using a sagittal T_1 weighted MPRAGE (3D Magnetization Prepared Rapid Gradient Echo) sequence (repetition time [TR] = 620ms, echo time [TE] = 60ms, flip angle *a* = 90°, inversion time [TI] = 12ms, voxel size = 0.9375 x 0.9375 x 5mm, field of view = 240 mm, matrix = 224 x 256, rectangular field of view = 7/8, effective thickness = 1.25mm).

The acquisition of the functional data was conducted by an interleaved T_2* weighted echo-planar sequence (repetition time [TR] = 3.6 sec, echo-time [ET] = 60ms, flip angle a = 90°, voxel size = 3.75 x 3.75 mm in-plane resolution) during which 87 sets of 28 4-mm-thick axial images were acquired parallel to the anterior posterior commissure plane. There was a 1mm gap between slices. Each functional run lasted about 5.3 minutes.

4.6 Data Analysis

The data was analyzed off line on a computer with an Intel Pentium III CPU (San Jose, California, USA) running Linux (Red Hat version 7.0, Red Hat Inc, Raleigh, North Carolina, USA). AFNI [75] (http://afni.nimh.nih.gov/afni) and FSL (FMRIB Software Library – http://www.fmrib.ox.ac.uk/fsl) software were used to analyze the data.

The analysis of the data was performed through an event-related design [38, 76-81], which is able to extract only activity that is transient and associated with the event of interest. The three different parts that were analyzed in this fashion were the letter period, the delay period and the retrieval period. This design is in contrast to the block design, which would have compared overall activity during the whole block when the subjects performed the working memory task to overall activity during a block when the subjects were in the resting state [82].

The initial step was to remove the initial T1 magnetic transients in the data by deleting the first 4 volumes of each scan. Then the data were corrected for the timing differences between each slice. The data were then corrected for motion effects, with the reference volume being in the center of the run. The motion corrected data were normalized to the Montreal Neurological Institute/International Consortium for Brain Mapping 152 (MNI/ICBM) standard stereotaxic space using the MRI template [34], as contained within the FSL software package. The data were then high pass filtered with a cutoff at (1/100) Hz and smoothed (Gaussian filter at full width at half maximum = 6 x 6 x 6 mm).

Each run for each subject was analyzed using a fixed effects general linear model. Each model consisted of several regressors for each part of the task, the letter period, the delay stage, and the retrieval period. For each part of the task, there were regressors for the correct trials, regressors for incorrect trials. Additional regressors were added for the instruction periods and the resting periods. The task and instruction models were square wave-forms (on-off). They were convolved with a standard double gamma hemodynamic response function.

Before comparing the cortical activities of both groups, a mask was created of only those areas, which showed significant activation for either or both of the groups. This makes sure only areas that have been significantly active in either group are compared for differences.

The group statistical analyses were done using a mixed effects model with a voxel wise threshold of $Z = 2.9$ ($p < 0.01$) and each cluster was corrected for multiple comparisons at the $p < 0.05$ level using Monte Carlo simulations. ANCOVA model was used to determine the statistical significant differences in activation between both groups. Because of the age difference of both groups, it was necessary to examine what effect age had to either group had on the activation results that. Thus the subjects' age was added as an extra variable. The ANCOVA analysis consisted of three parts: An analysis of linear correlation of the activation with age was performed, which shows where significant activity was correlated with subjects' age; the actual analysis of differences in activation of HC and MCI patients; the analysis of interaction between the age effect and the difference between the two groups.

The Talairach and Tournoux template [83] was used as reference for locating the activation in the brain. The MNI/ICBM coordinates were converted to the Talairach and Tournoux coordinates using a non-linear transformation developed by M. Brett for transforming coordinate location between both stereotaxic spaces (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The structural images were first edited of non-brain tissue using BET [84]. Remaining non-brain tissue were edited manually.

Table 4-1. CERAD scores of MCI patients

Subject	MMSE [0-30]	Word List Memory [0-30]	Word List Recall [0-30]	Word List Recognition [0-10]	Verbal fluency	Boston Naming Test [0-15]	Constructive Praxis [0-11]
1	27	15	4	10	20	15	11
2	26	13	4	9	13	14	11
3	28	19	7	10	20	15	11
4	29	22	8	10	19	13	11
5	26	13	1	8	18	15	11
6	25	14	1	8	24	15	11
7	26	17	3	4	18	14	11
8	26	14	2	6	16	13	11
Ø±SD	26.6±1.3	15.9±3.2	3.75±2.6	8.1±2.2	18.5±3.2	14.2±0.9	11±0

Table 4-2. CERAD scores of healthy control group

Subject	MMSE [0-30]	Word List Memory [0-30]	Word List Recall [0-10]	Word List Recognition [0-10]	Verbal Fluency	Boston Naming Test [0-15]	Constructive Praxis [0-11]
1	30	19	8	10	18	14	9
2	30	21	9	10	18	15	11
3	30	26	9	10	19	15	11
4	30	26	9	10	25	14	11
5	30	26	10	10	16	15	11
6	30	24	9	10	22	15	11
7	30	23	8	10	19	14	10
8	30	19	6	10	21	15	11
Ø±SD	30±0	23±3.0	8.5±1.2	10±0	19.75±2.8	14.6±0.5	10.6±0.7

Table 4-3: Task performance of OHC subjects

OHC Subject	Run No.	Adjusted Performance [% correct of 9 trials]	Average Response Time [sec]	Standard Deviation Response Time [sec]
2	01	77.8	1.97	0.29
3	01	66.7	1.63	0.13
	02	66.7	1.58	0.21
	03	77.8	2.33	0.73
5	01	77.8	1.59	0.46
	02	100	1.60	0.29
	03	100	2.10	0.40
1	01	88.9	1.62	0.50
	02	88.9	1.44	0.31
6	01	77.8	1.51	0.46
	02	77.8	1.51	0.35
7	01	88.9	1.44	0.66
	02	77.8	1.34	0.47
4	01	100	1.54	0.44
	02	88.9	1.46	0.50
	03	100	1.39	0.48
8	01	88.9	1.50	0.32
	02	88.9	1.41	0.23
	03	77.8	1.36	0.21
Ø		84.8	1.60	0.39

Table 4-4: Task performance of MCI Patients

MCI Subject	Run No.	Adjusted Performance [% correct of 9 trials]	Average Response Time [sec]	Standard Deviation Response Time [sec]
1	01	77.8	1.41	0.29
2	01	66.7	3.41	0.58
	02	66.7	4.49	1.43
	03	77.8	2.89	0.86
3	01	77.8	1.78	0.49
	02	100	1.47	0.33
	03	100	1.60	0.55
4	01	88.9	1.82	0.32
	02	88.9	1.60	0.25
5	01	77.8	1.31	0.13
	02	77.8	1.40	0.29
6	01	88.9	1.63	0.68
	02	77.8	1.38	0.34
7	01	100	1.48	0.17
	02	88.9	1.51	0.46
	03	100	1.51	0.35
8	01	88.9	1.43	0.25
	02	88.9	1.76	0.62
	03	77.8	2.86	3.22
Ø		84.8	1.93	0.61

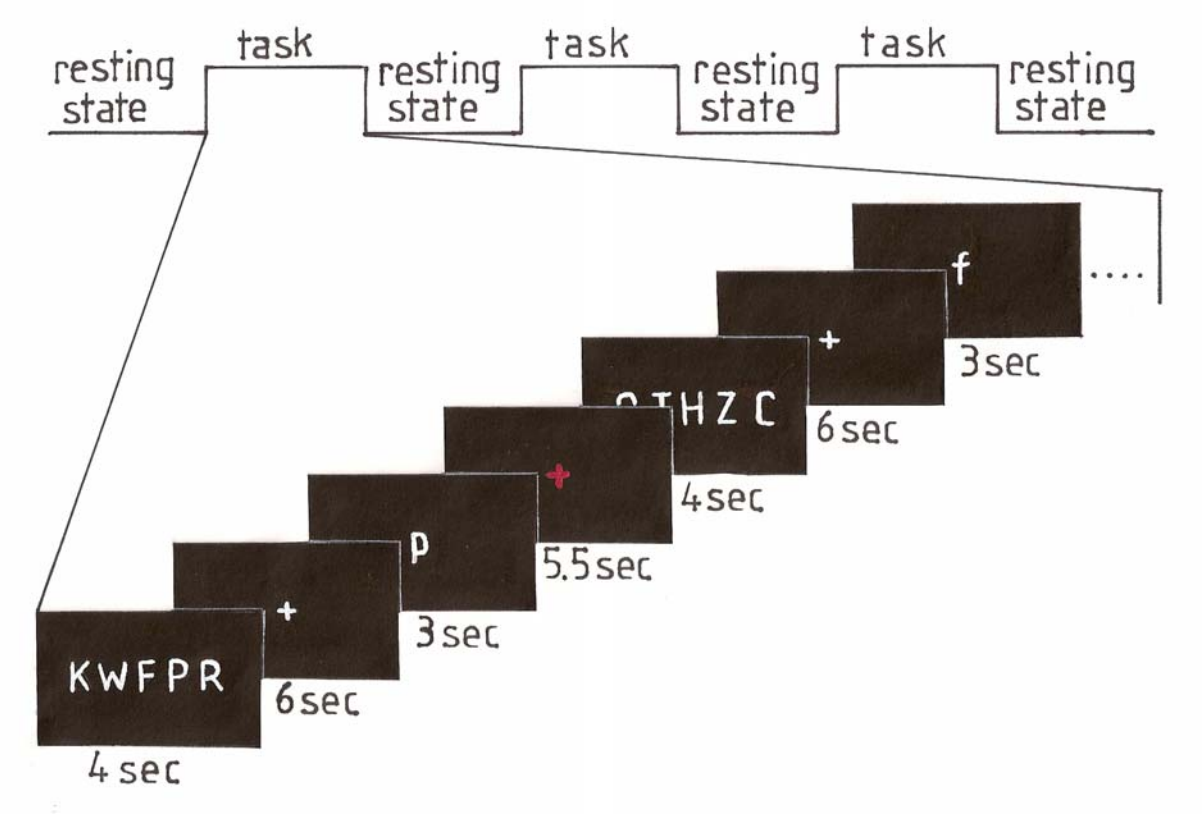

Figure 4-1: Scheme of Working Memory Paradigm

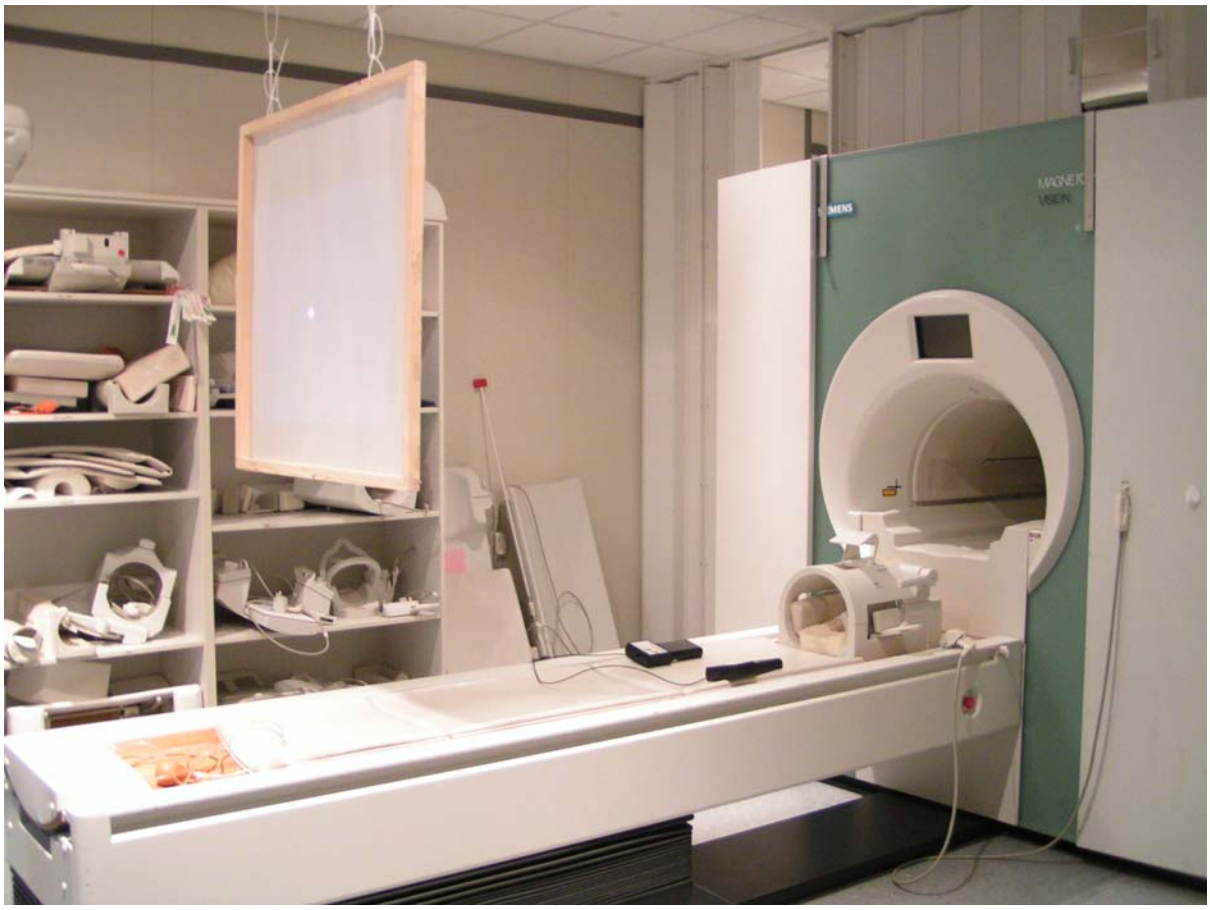

Figure 4-2: Setup for functional scanning

Figure 4-3: Response buttons

5 Results

5.1 Task Performance

The performance had been matched for both groups. The response time showed no statistically significant difference between both groups (t-test, p = 0.1).

5.2 Localization of positive cerebral activation for Healthy Control Group

5.2.1 Cerebral Activation during Letter Period

The main cortical areas of the left hemisphere with statistically significant higher activation during the letter period compared to the resting state were found in inferior (BA 18) and middle occipital gyrus (BA 18, 37), fusiform gyrus (BA 19), superior parietal lobule (BA 7), superior (BA 38, 22), inferior (BA 45) and medial frontal gyrus (BA 6) as well as in the cerebellum, and in right hemisphere's inferior frontal gyrus (BA 46) and also cerebellum. An overview of the activation is shown in Table 5-1 and Figure 5-1.

5.2.2 Cerebral Activation during Working Memory Period

During the working memory period for HC both statistically significant positive and negative activation were found. The positive activation indicated activation during the task compared to rest while the negative activation refered to higher activation during the rest period compared to task period.

The positive activation peaks in the left hemisphere were in fusiform gyrus (BA 37), supramarginal gyrus (BA 40), inferior parietal lobule (BA 40), postcentral gyrus (BA 2), paracentral lobule (BA 6), precentral gyrus (BA 4, 6), inferior frontal gyrus (BA 44) and cingulate gyrus (BA 32).

The activation peaks in the right hemisphere were in fusiform gyrus (BA 37), supramarginal gyrus (BA 40), inferior parietal lobule (BA 40), postcentral gyrus (BA 40, 4), paracentral lobule (BA 6), superior temporal gyrus (BA 38), precentral gyrus (BA 4), medial frontal gyrus (BA 6), cingulate gyrus (BA 32), and cerebellum. Table 5-2 and Figure 5-2 show these peaks.

5.2.3 Cerebral Activation during Decision Period

The analysis of statistically significant activation for HC during the decision period also yielded positive and negative peaks.

The most significant positive peaks are listed in Table 5-3 and shown in Figure 5-3. The main peaks were in left hemisphere's middle occipital gyrus (BA 37), supramarginal gyrus (BA 40), inferior parietal lobule (BA 5, 40), postcentral gyrus (BA 40), paracentral lobule (BA 4), middle (BA 21) and superior temporal gyrus (BA 22), inferior (BA 44, 47) and middle frontal gyrus (BA 9), and in right hemisphere's supramarginal gyrus (BA 40), postcentral gyrus (BA 2), middle temporal gyrus (BA 21), and middle frontal gyrus (BA 8).

5.3 Localization of cerebral activation for Mild Cognitive Impairment Patients

For the MCI group, positive activation peaks that present higher activation during the task than during the resting state as well as negative activation peaks that present lower activation during the task than during the resting state were found for all the parts of the task.

5.3.1 Cerebral Activation during Letter Period

Table 5-4 and Figure 5-4 show the main peaks of statistically significant activation for MCI patients during the letter period.

The main positive peaks in the left hemisphere were in inferior (BA 18) and middle occipital gyrus (BA 37, 19), inferior parietal lobule (BA 40), postcentral gyrus (BA 3, 43), precentral gyrus (BA 4), middle frontal gyrus (BA 9, 46), medial frontal gyrus (BA 6), and cerebellum.

In the right hemisphere the significant positive peaks were in inferior frontal gyrus (BA 44) and cerebellum.

5.3.2 Cerebral Activation during Working Memory Period

The peaks found for the working memory period are shown in Table 5-5 and Figure 5-5.

For the left hemisphere the main positive peaks were located in superior parietal lobule (BA 7), postcentral gyrus (BA 40, 1), precuneus (BA 7), middle (BA 21, 42) and superior (BA 22) temporal gyrus, precentral gyrus (BA 44), inferior (BA 45, 47), middle (BA 6, 9), superior (BA 6) and medial (BA 6) frontal gyrus, and cerebellum.

The right hemisphere's main positive peaks were in middle frontal gyrus (BA 4, 46), and cerebellum.

5.3.3 Cerebral Activation during Decision Period

The statistically most significant positive activation peaks for the MCI patients while performing the Decision period of the Working Memory task are listed in Table 5-6 and shown in Figure 5-6.

The statistically significant positive peaks of the left hemisphere were found in middle (BA 21, 22) and superior (BA 22, 38) temporal gyrus, inferior (BA 44), middle (BA 6, 9, 46), superior (BA 6, 8) and medial (BA 6) frontal gyrus, and cerebellum.

The right hemisphere's highest positive peaks were in postcentral gyrus (BA 40), middle (BA 21) and superior temporal gyrus (BA 22, 38), inferior (BA 44, 47), middle (BA 9), and superior (BA 8) frontal gyrus, and thalamus.

5.4 Differences in cerebral activation during the delay stage

5.4.1 Difference between groups

The analysis of the difference between the two groups during the working memory period gave the following clusters with higher activation in MCI compared to HC: lingual gyrus (BA 17), superior parietal lobule (BA 7), postcentral gyrus (BA 40), precuneus (BA 7), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22), medial frontal gyrus (BA 6), inferior frontal gyrus (BA 45), middle frontal gyrus (BA 9), and cerebellum of the left hemisphere; cuneus (BA 19), postcentral gyrus (BA 4), medial frontal gyrus (BA 8), cingulate gyrus (BA 32), and cerebellum of the right hemisphere. Table 5-7 and Figure 5-7 show these clusters.

There were no statistically significant clusters found with higher activation in HC compared to MCI.

5.4.2 Age Effect

Left hemisphere's clusters with significant negative correlation for age effect during the working memory period were in postcentral gyrus (BA 2), middle temporal gyrus (BA 20), parahippocampal gyrus (BA 36), and inferior frontal gyrus (BA 47). These clusters are listed in Table 5-8 and shown in Figure 5-8.

Clusters with positive correlation were found in left hemisphere's middle occipital gyrus (BA 18), cuneus (BA 19), supramarginal gyrus (BA 40), middle temporal gyrus (BA 21, 39), and in right hemisphere's cuneus (BA 19), lingual gyrus (BA 40), inferior parietal lobule (BA 40), middle temporal gyrus (BA 39), superior temporal gyrus (BA 22), and cingulate gyrus (BA 24). They are listed in Table 5-9 and shown in Figure 5-9.

5.4.3 Interaction

Negative interaction was found in clusters in left hemisphere's inferior parietal lobule (BA 18), precuneus (BA 7), medial frontal gyrus (BA 6), and right hemisphere's lingual gyrus (BA 18), postcentral gyrus (BA 40), precuneus (BA 7), middle frontal gyrus (BA 10), cingulate gyrus (BA 29), and cerebellum. These clusters can be viewed in Table 5-10 and Figure 5-10.

Positive interaction clusters were located in middle temporal gyrus (BA 21), and inferior frontal gyrus (BA 47) of the left hemisphere. They are listed in Table 5-11 and shown in Figure 5-11.

5.5 Differences in cerebral activation during letter periods

5.5.1 Difference between groups

There was higher activation in MCI compared to HC in superior temporal gyrus (BA 22, 42) of the left hemisphere and in cuneus (BA 18) and cingulate gyrus (BA 30) of the right hemisphere. See Table 5-12 and Figure 5-12 for a detailed listing.

Table 5-13 and Figure 5-13 display the statistically significant clusters of higher activation in HC compared to MCI during the letter period. The main cortical areas are precentral gyrus (BA 6), cingulate gyrus (BA 32) and cerebellum of the left hemishpere and superior temporal gyrus (BA 38), and cerebellum of the right hemisphere.

5.5.2 Age Effect

There was statistically significant negative correlation of activation with age in left hemisphere's postcentral gyrus(BA 43) and superior temporal gyrus (BA 21), and in right hemisphere's postcentral gyrus (BA 43) and cerebellum. The values can be viewed in Table 5-14 and Figure 5-14.

There was statistically significant positive correlation of activation with age in left hemisphere's inferior parietal lobule (BA 40) and precentral gyrus (BA 6), and in right hemisphere's precuneus (BA 7), middle temporal gyrus (BA 21), precentral gyrus (BA 6) and inferior frontal gyrus (BA 47). These results are also shown in Table 5-15 and Figure 5-15.

5.5.3 Interaction

The clusters with statistically significant negative interaction between age and activation were located in left hemisphere's precentral gyrus (BA 6), and in right hemisphere's fusiform gyrus (BA 37), supramarginal gyrus (BA 40), superior parietal lobule (BA 7), precentral gyrus (BA 4), middle frontal gyrus (BA 10) and in superior frontal gyrus (BA 6). These clusters are listed in Table 5-16 and shown in Figure 5-16.

Statistically significant positive interaction between age and activation was found in clusters in middle temporal gyrus (BA 21) and middle frontal gyrus (BA 11) in the left hemisphere. The clusters are shown in Table 5-17 and Figure 5-17.

5.6 Differences in cerebral activation during Decision period

5.6.1 Difference between groups

There were no statistically significant activation clusters with greater activation for MCI compared to HC in the decision period.

Clusters with statistically significant higher activation in HC than in MCI as results of the analysis of the difference between the two groups were in left hemisphere's cuneus (BA 19), superior temporal gyrus (BA 42), medial frontal gyrus (BA 10) and cerebellum, as well as in right hemisphere's lingual gyrus (BA 18), inferior parietal lobule (BA 40), transversal temporal gyri (BA 41), superior temporal gyrus (BA 38), superior frontal gyrus (BA 11), medial frontal gyrus (BA 6), and cerebellum. These clusters are listed in Table 5-18 and shown in Figure 5-18.

5.6.2 Age Effect

During the Decision period, clusters with statistically significant negative age effect were located in left middle temporal gyrus (BA 21), inferior frontal gyrus (BA 47), medial frontal gyrus (BA 10), cingulate gyrus (BA 24, 32), and cerebellum, and right cuneus (BA 18), inferior parietal lobule (BA 40), and postcentral gyrus (BA 2). Table 5-19 and Figure 5-19 show these clusters.

No clusters with statistically significant positive correlation with age were found for the decision period.

5.6.3 Interaction

There were no statistically significant interactions between age and differences in activation during the decision period.

5.7 Localization of 'negative' cerebral activation for Healthy Control Group

The term 'negative activation' is used to describe activation that was higher during the resting state than during the task.

5.7.1 Working Memory Period

Statistically significant negative peaks were located in left hemisphere middle occipital gyrus (BA 19), cuneus (BA 17, 18, 19), lingual gyrus (BA 18, 19), inferior parietal lobule (BA 19), middle temporal gyrus (BA 39), middle (BA 10) and medial frontal gyrus (BA 9), cingulate gyrus (BA 32, 30) and cerebellum.

The right hemisphere statistically significant negative peaks were in cuneus (BA 18), lingual gyrus (BA 18), middle (BA 21) and superior (BA 22) temporal gyrus, medial frontal gyrus (BA 9, 10, 11), cingulate gyrus (BA 23, 24), and cerebellum. These peaks are listed in Table 5-20 and shown in Figure 5-20.

5.7.2 Decision Period

Peaks with statistically significant negative activation for HC subjects were located in fusiform gyrus (BA 37), medial frontal gyrus (BA 11), and cerebellum of the left hemisphere and superior frontal gyrus (BA 11), and medial frontal gyrus (BA 10) of the right hemisphere. These peaks are shown in Table 5-21 and Figure 5-21.

5.8 Localization of negative cerebral activation for MCI Group

5.8.1 Letter Period

Statistically significant negative peaks of activation in MCI were found in left hemisphere medial frontal gyrus (BA 10), cingulate gyrus (BA 32), and in right hemisphere superior temporal gyrus (BA 38), medial frontal gyrus (BA 11), and cingulate gyrus (BA 32). These peaks can be viewed in Table 5-22 and Figure 5-22.

5.8.2 Working Memory Period

The statistically significant negative peaks in the left hemisphere were located in medial frontal gyrus (BA 11), and in cingulate gyrus (BA 32), while the right hemisphere statistically significant negative peaks were in superior temporal gyrus (BA 38), inferior frontal gyrus (BA 47), and medial frontal gyrus (BA 11). Table 5-23 and Figure 5-23 show these peaks.

5.8.3 Decision Period

The highest statistically significant negative peaks in the left hemisphere for MCI patients during the decision period were identified in cuneus (BA 19, 29, 17), lingual Gyrus (BA 18), fusiform gyrus (BA 19), medial frontal gyrus (BA 9, 10), cingulate gyrus (BA 32), and cerebellum. These peaks are listed in Table 5-24 and shown in Figure 5-24.

Statistically significant negative peaks of activation in the right hemisphere were located in cuneus (BA 17, 18), lingual gyrus (BA 17, 18), middle (BA 21), superior (BA 38) temporal gyrus, inferior (BA 47), middle (BA 11) and superior (BA 10) frontal gyrus, cingulate gyrus (BA 32), hippocampus and cerebellum. The main negative peaks are also presented in Table 5-24 and Figure 5-24.

Table 5-1: Statistically significant activation peaks in HC during the letter period compared to the rest period

Region	Side	BA	X	Y	Z	Z-Value
Inferior Occipital Gyrus	L	18	-38	-88	-9	9.51
Middle Occipital Gyrus	L	18	-42	-85	10	9.68
	L	37	-52	-66	-7	9.56
Fusiform Gyrus	L	19	-48	-74	-11	9.54
Superior Parietal Lobule	L	7	-26	-61	60	10.14
	L	7	-36	-50	50	9.64
Superior Temporal Gyrus	L	38	-50	10	-18	9.98
	L	22	-65	-23	3	9.23
Inferior Frontal Gyrus	R	46	40	41	7	9.69
	L	45	-52	14	5	9.86
Medial Frontal Gyrus	L	6	-4	1	57	9.97
Cerebellum	R					11.43
	R					11.34
	R					9.27
	L					9.33

Table 5-2: Statistically significant activation peaks in HC during the delay stage compared to the rest period

Region	Side	BA	X	Y	Z	Z-Value
Fusiform Gyrus	R	37	52	-63	-12	5.93
	L	37	-46	-53	-12	6.77
Supramarginal Gyrus	R	40	54	-47	28	4.74
	L	40	-57	-50	28	7.04
Inferior Parietal Lobule	R	40	59	-37	37	5.05
	L	40	-40	-52	45	7.58
	L	40	-57	-41	40	7.49
	L	40	-46	-37	39	5.57
Postcentral Gyrus	R	40	54	-22	18	6.09
	R	4	63	-16	34	4.78
	L	2	-50	-23	49	6.62
	L	2	-34	-19	45	5.95
Paracentral Lobule	R	6	8	-13	47	5.25
	L	6	-2	-11	50	5.61
Superior Temporal Gyrus	R	38	46	9	-6	5.49
Precentral Gyrus	R	4	42	-2	43	4.86
	L	4	-36	-19	54	5.87
	L	6	-50	2	35	5.12
	L	4	-52	-2	43	4.86
Inferior Frontal Gyrus	L	44	-42	3	22	5.50
Medial Frontal Gyrus	R	6	6	-13	58	5.99
	R	6	10	5	51	4.81
Cingulate Gyrus	R	32	8	12	38	5.87
	L	32	-6	12	38	5.14
Cerebellum	R		6	-41	-43	5.13

Table 5-3: Statistically significant activation peaks in HC during the decision period compared to rest period

Region	Side	BA	X	Y	Z	Z-Value
Middle Occipital Gyrus	L	37	-46	-65	-10	6.15
Supramarginal Gyrus	R	40	61	-43	37	6.94
	L	40	-60	-43	30	8.36
Inferior Parietal Lobule	L	5	-44	-40	59	6.77
	L	40	-40	-54	43	6.35
	L	40	-50	-50	50	6.28
Postcentral Gyrus	R	2	57	-19	45	6.64
	R	2	61	-20	23	6.62
	L	40	-65	-24	20	6.96
Paracentral Lobule	L	4	-6	-33	72	6.28
Middle Temporal Gyrus	R	21	59	-50	10	6.91
	L	21	-57	-54	8	6.31
Superior Temporal Gyrus	L	22	-65	-44	17	7.99
Inferior Frontal Gyrus	L	47	-48	21	-10	7.09
	L	44	-50	13	23	6.10
Middle Frontal Gyrus	L	9	-52	10	36	6.75
Medial Frontal Gyrus	R	8	4	33	39	6.05
Cerebellum	R		32	-83	-25	8.15
	R		30	-65	25	7.53
	R		28	-46	-21	7.51
	R		4	-53	-14	7.37
	R		26	-51	-46	6.87
	R		32	-56	-39	6.40
	L		-38	-46	-26	8.78
	L		-22	-42	-25	8.23
	L		-22	-60	-24	7.31

Table 5-4: Statistically significant activation peaks in MCI during the letter period compared to rest period

Region	Side	BA	X	Y	Z	Z-Value
Inferior Occipital Gyrus	L	18	-28	-92	-4	8.33
Middle Occipital Gyrus	L	37	-54	-70	-10	7.90
	L	19	-38	-89	38	7.52
Inferior Parietal Lobule	L	40	-46	-45	39	8.19
	L	40	-46	-44	54	8.14
Postcentral Gyrus	L	3	-48	-11	53	11.47
	L	43	-53	3	15	8.85
Precentral Gyrus	L	4	-54	-10	37	9.30
	L	4	-46	-14	30	8.85
Inferior Frontal Gyrus	R	44	40	5	26	8.66
Middle Frontal Gyrus	L	9	-50	6	35	9.35
	L	46	-40	-46	-21	8.66
	L	9	-52	2	40	8.28
Medial Frontal Gyrus	L	6	-6	-3	61	8.65
	L	6	-4	3	53	8.46
Cerebellum	R		18	-63	-20	16.33
	R		36	-67	-25	11.36
	R		38	-57	-21	10.96
	R		32	-62	-29	10.48
	R		48	-64	-31	8.53
	L		-40	-46	-21	8.66
	L		-30	-83	-19	8.66

Table 5-5: Statistically significant activationpeaks in MCI during the delay stage compared to rest period

Region	Side	BA	X	Y	Z	Z-Value
Superior Parietal Lobule	L	7	-38	-58	49	9.72
Postcentral Gyrus	L	40	-59	-24	25	7.68
	L	1	-54	-15	45	7.44
Precuneus	L	7	-2	-72	46	7.54
	L	7	-6	-62	51	7.28
Middle Temporal Gyrus	L	21	-54	-31	-2	7.70
	L	42	-46	37	6	7.59
Superior Temporal Gyrus	L	22	-57	10	1	7.80
Precentral Gyrus	L	44	-48	14	7	10.31
Inferior Frontal Gyrus	L	45	-54	20	19	8.99
	L	47	-28	23	1	8.31
	L	47	-55	8	-4	7.34
	L	47	-46	-61	-5	7.30
Middle Frontal Gyrus	R	46	42	36	22	7.64
	R	4	44	4	39	7.14
	L	9	-50	4	37	14.45
	L	6	-40	6	48	8.88
	L	9	-48	19	30	8.04
	L	6	-32	-5	53	7.65
Superior Frontal Gyrus	L	6	-4	6	48	8.80
Medial Frontal Gyrus	L	6	-10	5	55	9.90
	L	6	-4	-3	59	9.35
	L	6	-2	20	43	8.01
Cerebellum	R		30	-69	-25	8.68
	R		12	-81	-21	8.27

Table 5-6: Statistically significant activation peaks in MCI during the decision period compared to rest period

Region	Side	BA	X	Y	Z	Z-Value
Postcentral Gyrus	R	40	38	-15	19	4.79
Middle Temporal Gyrus	R	21	63	3	-10	3.71
	L	21	-57	4	-7	4.09
	L	21	-67	-27	-4	3.72
	L	22	-63	-6	64	2.98
Superior Temporal Gyrus	R	38	42	11	-7	4.63
	R	22	57	13	-4	4.07
	R	38	52	21	-16	3.99
	L	38	-54	15	-11	5.75
	L	22	-63	-6	2	3.63
	L	38	-36	20	-20	3.19
Inferior Frontal Gyrus	R	44	48	22	6	4.08
	R	47	36	25	-6	3.36
	L	44	-52	23	25	5.82
Middle Frontal Gyrus	R	9	50	32	26	3.80
	L	9	-46	21	32	3.99
	L	9	-46	6	38	3.92
	L	6	-48	6	46	3.28
	L	46	-54	25	25	3.27
Superior Frontal Gyrus	R	8	4	37	48	4.08
	L	8	-2	28	52	5.15
	L	6	-2	7	55	3.23
Medial Frontal Gyrus	L	6	-4	16	45	4.23
Thalamus	R		4	-13	12	5.24
Cerebellum	L		-48	-63	-20	5.78
	L		-42	-46	-20	4.04
	L		-46	-79	-18	3.23

Table 5-7: Statistically significant clusters of lower activation in HC compared to MCI during the delay stage

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Cuneus	R	336	19	4	-82	28	3.27
Lingual Gyrus	L	1528	17	-2	-92	-12	3.88
Superior Parietal Lobule	L	560	7	-30	-44	61	3.99
Postcentral Gyrus	L	25464	40	-61	-24	25	6.37
Superior Parietal Lobule	*L*		*7*	*-38*	*-58*	*49*	*5.89*
Postcentral Gyrus	R	656	4	20	-34	61	3.95
Precuneus	L	224	7	-0	-49	61	2.68
Middle Temporal Gyrus	L	1008	21	-52	-43	2	4.95
Superior Temporal Gyrus	L	1032	22	-52	-57	18	4.35
Medial Frontal Gyrus	L	51696	6	-6	18	43	6.48
Inferior Frontal Gyrus	*L*		*45*	*-46*	*37*	*6*	*5.97*
			45	*-57*	*8*	*3*	*5.68*
			45	*-34*	*26*	*4*	*4.70*
Middle Frontal Gyrus	*L*		*9*	*-48*	*8*	*35*	*5.61*
Medial Frontal Gyrus	R	296	8	12	56	34	3.80
Cingulate Gyrus	R	3120	32	12	-43	-1	5.18
Cerebellum	L	4648		-40	-61	-17	6.45
Cerebellum	*L*			*-40*	*-50*	*-23*	*5.34*
Cerebellum	L	712		-34	-84	-16	3.89
	R	800		32	-39	-32	5.47
	R	1040		12	-81	-21	5.21
	R	2712		28	-71	-25	5.14

Table 5-8: Statistically significant clusters of negative correlation with age during the delay stage

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Postcentral Gyrus	L	352	2	-30	-41	67	5.14
Middle Temporal Gyrus	L	512	20	-54	-34	-12	4.88
Parahippocampal Gyrus	L	1128	36	-28	30	-15	4.33
Inferior Frontal Gyrus	L	248	47	-24	15	-21	3.69

Table 5-9: Statistically significant clusters of positive correlation with age during the delay stage

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Middle Occipital Gyrus	L	248	18	-16	-81	15	4.37
Cuneus	L	856	19	-10	-92	29	4.12
	R	1160	19	18	-88	25	3.71
Lingual Gyrus	R	912	17	6	-85	3	3.90
Supramarginal Gyrus	L	944	40	-63	-47	26	3.68
Inferior Parietal Lobule	R	224	40	50	-58	42	3.87
Middle Temporal Gyrus	L	432	21	-63	-47	-4	3.86
		208	39	-52	-65	25	2.91
	R	272	39	36	-57	21	3.89
Superior Temporal Gyrus	R	1320	22	65	-44	19	4.88
Cingulate Gyrus	R	800	24	2	17	27	4.29

Table 5-10: Statistically significant clusters with negative interaction of age and activation difference during the delay stage

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Lingual Gyrus	R	328	18	10	-64	5	3.34
Inferior Parietal Lobule	L	376	40	-61	-53	25	4.52
Postcentral Gyrus	R	368	40	63	-24	22	3.81
Precuneus	L	424	7	-2	-74	44	3.63
	R	624	7	18	-70	51	4.41
Medial Frontal Gyrus	L	360	6	-8	-16	65	3.94
Middle Frontal Gyrus	R	264	10	36	55	16	3.04
Cingulate Gyrus	R	208	29	4	-46	13	3.49
Cerebellum	R	472		6	-75	-15	3.44

Table 5-11: Statistically significant clusters with positive interaction of age and activation difference during the delay stage

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Middle Temporal Gyrus	L	400	21	-55	-34	-10	4.10
Inferior Frontal Gyrus	L	8096	47	-24	28	-15	5.26

Table 5-12: Statistically significant clusters of lower activation in HC compared to MCI during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Cuneus	R	504	18	3	-101	32	4.40
Superior Temporal Gyrus	L	2184	22	7	-37	61	4.69
		2408	42	8	-9	59	4.10
Cingulate Gyrus	R	1144	30	12	-50	6	3.74

Table 5-13: Statistically significant clusters of higher activation in HC compared to MCI during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-value
Superior Temporal Gyrus	R	720	38	26	6	-34	5.06
Precentral Gyrus	L	1544	6	-52	1	26	4.14
Cingulate Gyrus	L	7864	32	-12	41	-2	4.89
Cerebellum	L	1256		-38	-81	-26	4.47
	R	1192		42	-63	-47	3.78

Table 5-14: Statistically significant clusters of negative correlation with age during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Postcentral Gyrus	R	736	43	57	-11	17	4.83
	L	616	5	-30	-43	69	5.38
Superior Temporal Gyrus	L	1120	21	-61	-23	-1	5.24
Cerebellum	R	944		38	-79	-25	4.25

Table 5-15: Statistically significant clusters of positive correlation with age during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Inferior Parietal Lobule	L	1072	40	-42	-56	43	4.90
Precuneus	R	1000	7	10	-65	59	3.93
Middle Temporal Gyrus	R	560	21	69	-10	-13	4.24
Precentral Gyrus	R	784	6	61	0	31	5.25
	L	1144	6	-40	4	35	4.41
Inferior Frontal Gyrus	R	240	47	24	27	-11	3.61

Table 5-16: Statistically significant clusters with negative interaction of age and activation difference during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Fusiform Gyrus	R	232	37	60	-59	-16	5.00
Supramarginal Gyrus	R	384	40	57	-45	35	3.45
Superior Parietal Lobule	R	1032	7	2	-67	53	3.70
Precentral Gyrus	L	560	6	-40	4	35	4.19
	R	1240	4	28	54	-5	5.07
Middle Frontal Gyrus	R	760	10	34	59	12	3.85
Superior Frontal Gyrus	R	384	6	28	5	62	4.83

Table 5-17: Statistically significant clusters of positive interaction of age and activation difference during the letter period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Middle Temporal Gyrus	L	720	21	-1	-10	-61	4.28
		976	21	2	-37	-54	3.86
Middle Frontal Gyrus	L	456	11	-24	36	-17	3.60

Table 5-18: Statistically significant clusters of higher activation in HC compared to MCI during the decision period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Cuneus	L	680	19	-10	-76	30	3.52
Lingual Gyrus	R	968	18	4	-87	1	4.23
Inferior Parietal Lobule	R	480	40	59	-36	28	4.35
Transversal Temporal Gyri	R	1032	41	42	-27	11	3.80
Superior Temporal Gyrus	L	296	42	-44	-21	7	3.89
		432	42	-52	-28	18	3.87
	R	464	38	48	16	-29	3.69
Superior Frontal Gyrus	R	696	11	20	48	-14	3.81
Medial Frontal Gyrus	L	1056	10	-6	48	-9	3.39
		1072	10	-0	60	21	3.28
	R	688	6	2	-13	52	5.42
Cerebellum	L	7816		-4	-70	-5	3.92
		768		-18	-36	-22	3.81
	R	2712		30	-69	-15	3.81
		1272		4	-51	-18	3.75
		416		20	-49	-14	3.58

Table 5-19: Statistically significant clusters of negative correlation with age during the decision period

Region	Side	Volume [µl]	BA	X	Y	Z	Z-Value
Cuneus	R	408	18	8	-101	11	4.60
Inferior Parietal Lobule	R	272	40	52	-34	29	2.89
Postcentral Gyrus	R	264	2	55	-22	23	4.30
Middle Temporal Gyrus	L	344	21	-48	-58	5	3.51
Inferior Frontal Gyrus	L	256	47	-30	30	-17	3.53
Medial Frontal Gyrus	L	408	10	-24	37	-9	3.14
Cingulate Gyrus	L	448	24	-4	34	17	3.90
		1704	32	-2	43	-2	3.63
Cerebellum	L	1168		-16	-56	-29	4.33
		360		-18	-64	-37	3.72

Table 5-20: Statistically significant peaks in HC of higher activation in the rest period compared to the delay stage

Region	Side	BA	X	Y	Z	Z-Value
Middle Occipital Gyrus	L	19	-24	-81	15	7.90
	L	19	-22	-93	16	5.57
Cuneus	R	18	20	-97	10	5.28
	L	18	-24	-95	8	6.18
	L	17	-18	-99	0	6.03
	L	18	-4	-83	17	5.74
	L	19	-8	-82	26	5.67
	L	19	-26	-88	28	5.40
	L	18	-16	-99	5	5.28
Lingual Gyrus	R	18	72	-72	-8	7.07
	L	19	-12	-60	-5	5.41
	L	18	-18	-80	-9	5.37
Inferior Parietal Lobule	L	19	-22	-74	42	6.35
Middle Temporal Gyrus	R	21	44	6	-32	5.16
	L	39	-52	-65	24	5.40
Superior Temporal Gyrus	R	22	50	-6	-5	5.60
Middle Frontal Gyrus	L	10	-18	50	-6	6.33
	L	10	-20	31	-10	5.21
Medial Frontal Gyrus	R	10	14	52	-6	6.32
	R	9	2	55	14	5.37
	R	11	2	48	-11	5.21
	L	9	-12	36	28	5.22
Cingulate Gyrus	R	24	4	39	9	6.73
	R	23	2	-42	24	6.06
	L	30	-6	-53	21	8.27
	L	32	-2	41	-5	5.46

Table 5-21: Statistically significant peaks of higher activation in HC in the rest period compared to the decision period

Region	Side	BA	X	Y	Z	Z-Value
Fusiform Gyrus	L	37	-20	40	-12	4.69
Superior Frontal Gyrus	R	11	12	48	-16	4.06
Medial Frontal Gyrus	R	10	22	-37	-9	6.24
	R	10	4	46	-8	4.61
	L	11	-2	50	-16	5.13
Cingulate Gyrus	L	24	-6	37	-4	4.70

Table 5-22: Statistically significant peaks of higher activation in MCI in the rest period compared to the letter period

Region	Side	BA	X	Y	Z	Z-Value
Superior Temporal Gyrus	R	38	32	16	-33	4.53
Medial Frontal Gyrus	R	11	8	52	-11	5.37
	L	10	-4	48	-9	5.85
Cingulate Gyrus	R	32	6	41	4	4.90
	L	32	-10	41	-2	6.71

Table 5-23: Statistically significant peaks in MCI of higher activation during the rest period compared to the delay stage

Region	Side	BA	X	Y	Z	Z-Value
Superior Temporal Gyrus	R	38	38	18	-36	4.89
	R	38	34	20	-31	4.78
	R	38	28	8	-32	4.61
Inferior Frontal Gyrus	R	47	26	24	-16	5.59
Medial Frontal Gyrus	R	11	10	56	-16	4.68
	L	11	-10	48	-13	4.94
Cingulate Gyrus	L	32	-2	43	3	6.10

Table 5-24: Statistically significant peaks in MCI of higher activation during the rest period compared to the decision period

Region	Side	BA	X	Y	Z	Z-Value
Cuneus	R	17	6	-83	8	4.09
	R	18	8	-79	12	3.78
	L	19	-24	-94	25	3.82
	L	29	-14	-90	30	3.68
Gyrus Lingualis	R	17	8	-91	-1	4.39
	R	18	20	-103	-5	2.72
	L	18	-12	-80	-4	4.54
Fusiform Gyrus	L	19	-30	-49	-6	3.76
Middle Temporal Gyrus	R	21	40	6	-32	4.75
Superior Temporal Gyrus	R	38	36	21	-38	4.53
	R	38	48	12	-29	4.35
	R	38	34	18	-31	4.11
Inferior Frontal Gyrus	R	47	26	24	-18	4.66
Middle Frontal Gyrus	R	11	22	31	-12	4.95
Superior Frontal Gyrus	R	10	20	44	-12	5.51
	R	10	22	49	-1	5.47
	R	10	10	62	-8	4.75
Medial Frontal Gyrus	L	10	-6	48	-9	5.16
Cingulate Gyrus	R	32	6	40	-7	5.85
	R	32	2	45	5	4.38
	L	32	-16	43	5	4.31
Hippocampus	R		30	-10	-15	3.65
Cerebellum	R		6	-52	-28	3.99
	L		-20	-75	-13	3.91

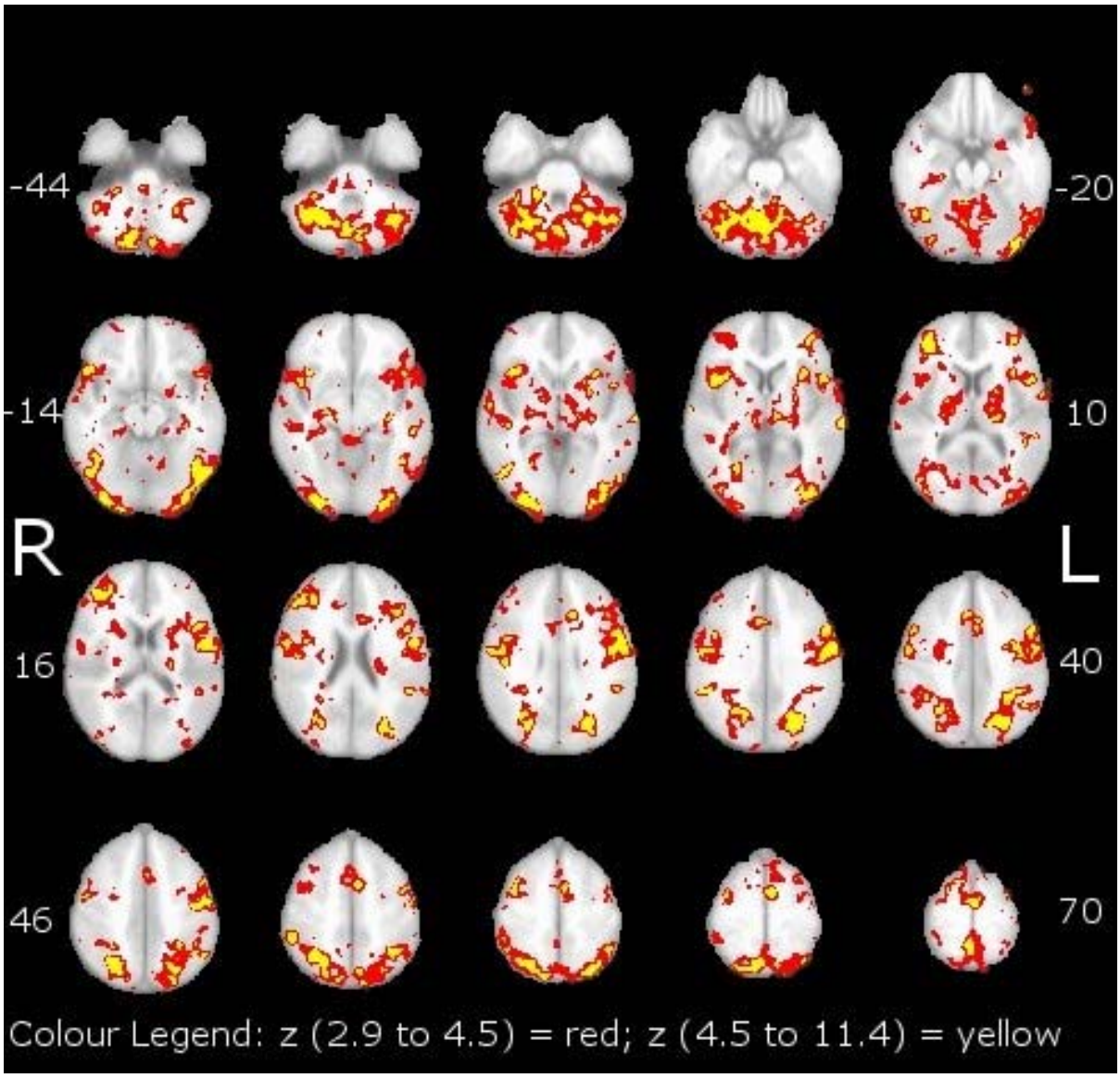

Figure 5-1: Statistically significant activation peaks in HC during the letter period compared to rest period

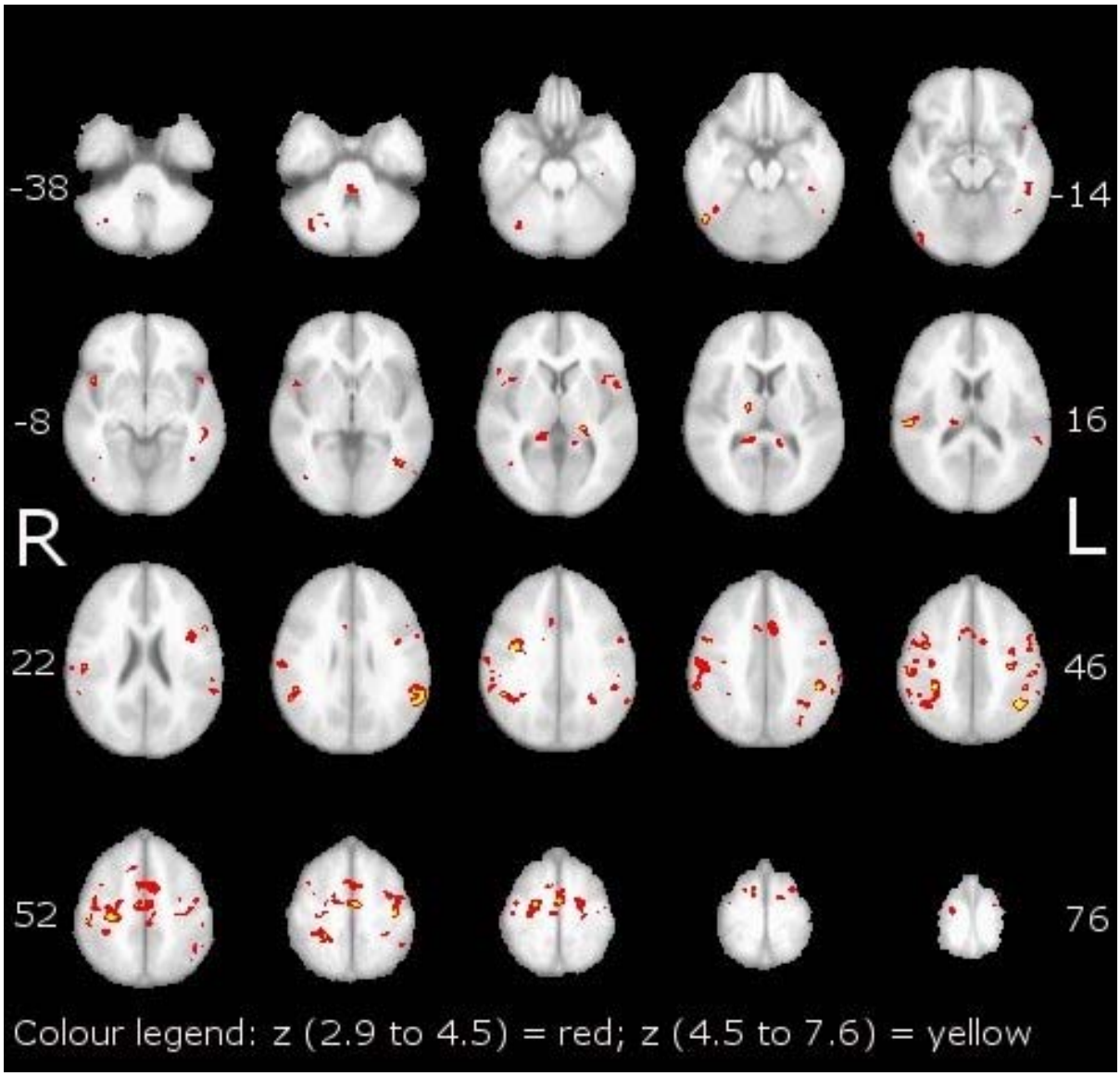

Figure 5-2: Statistically significant activation peaks in HC during the delay stage compared to rest period

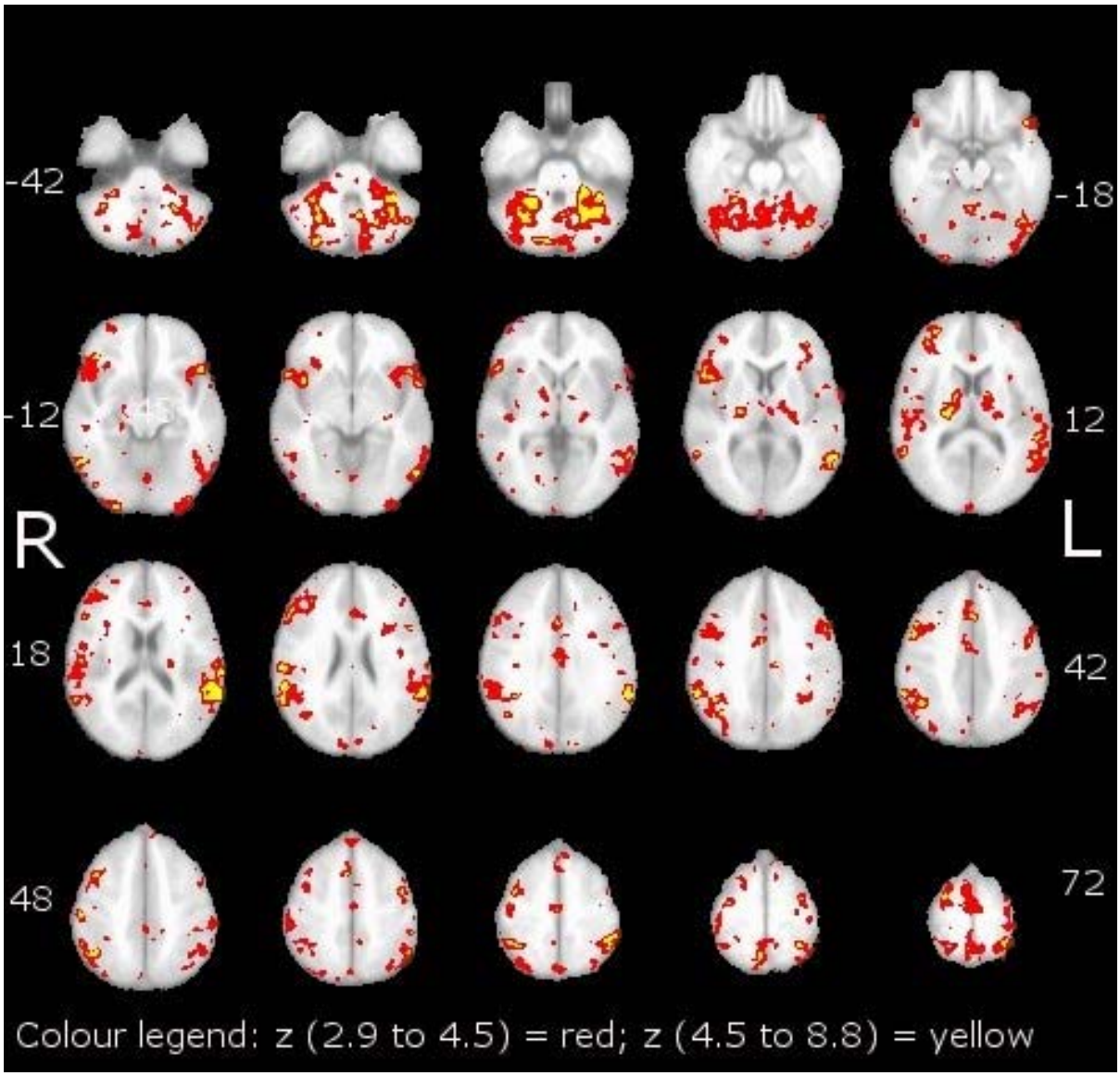

Figure 5-3: Statistically significant activation peaks in HC during the decision period compared to rest period

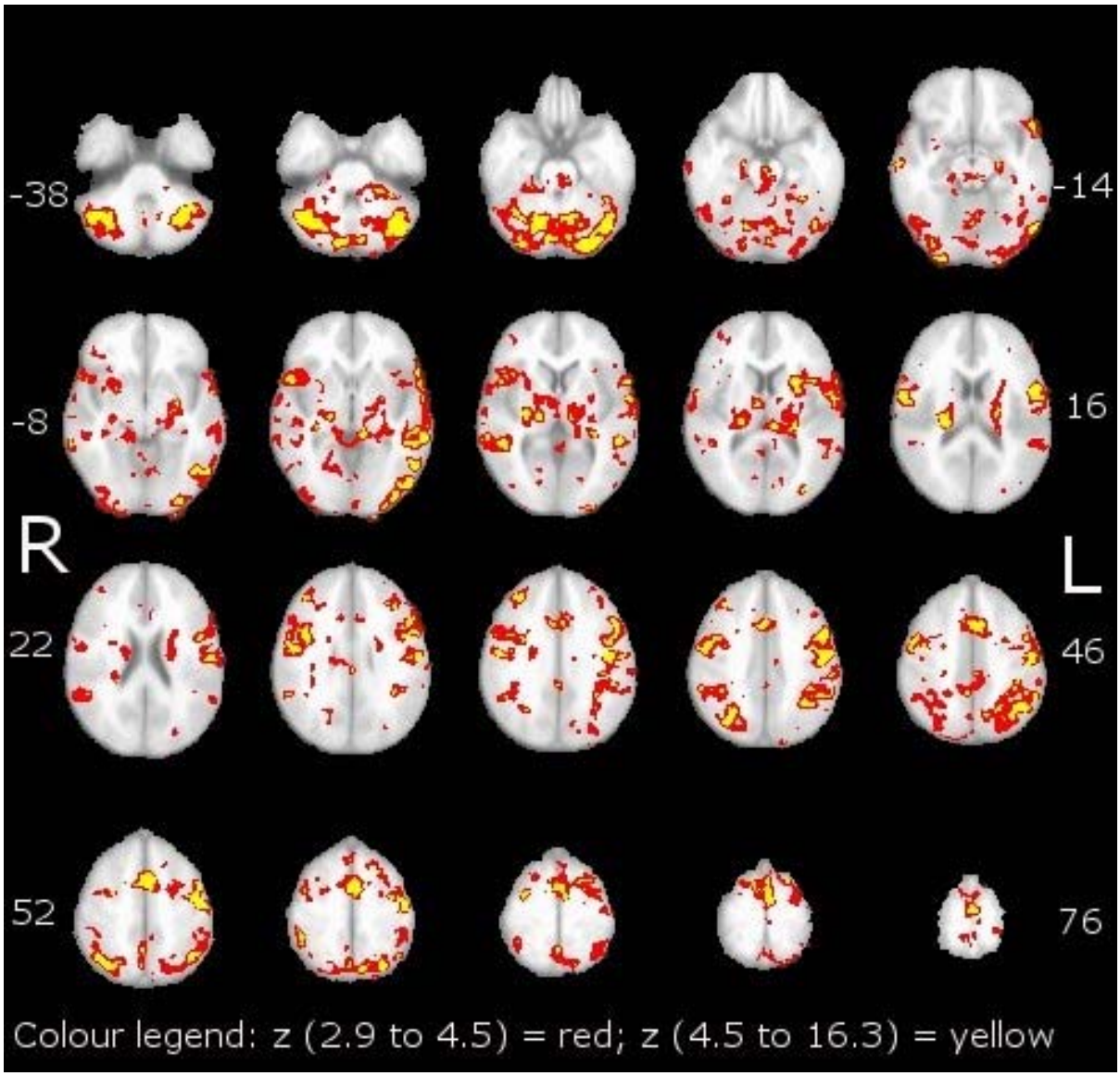

Figure 5-4: Statistically significant activation peaks in MCI during the letter period compared to rest period

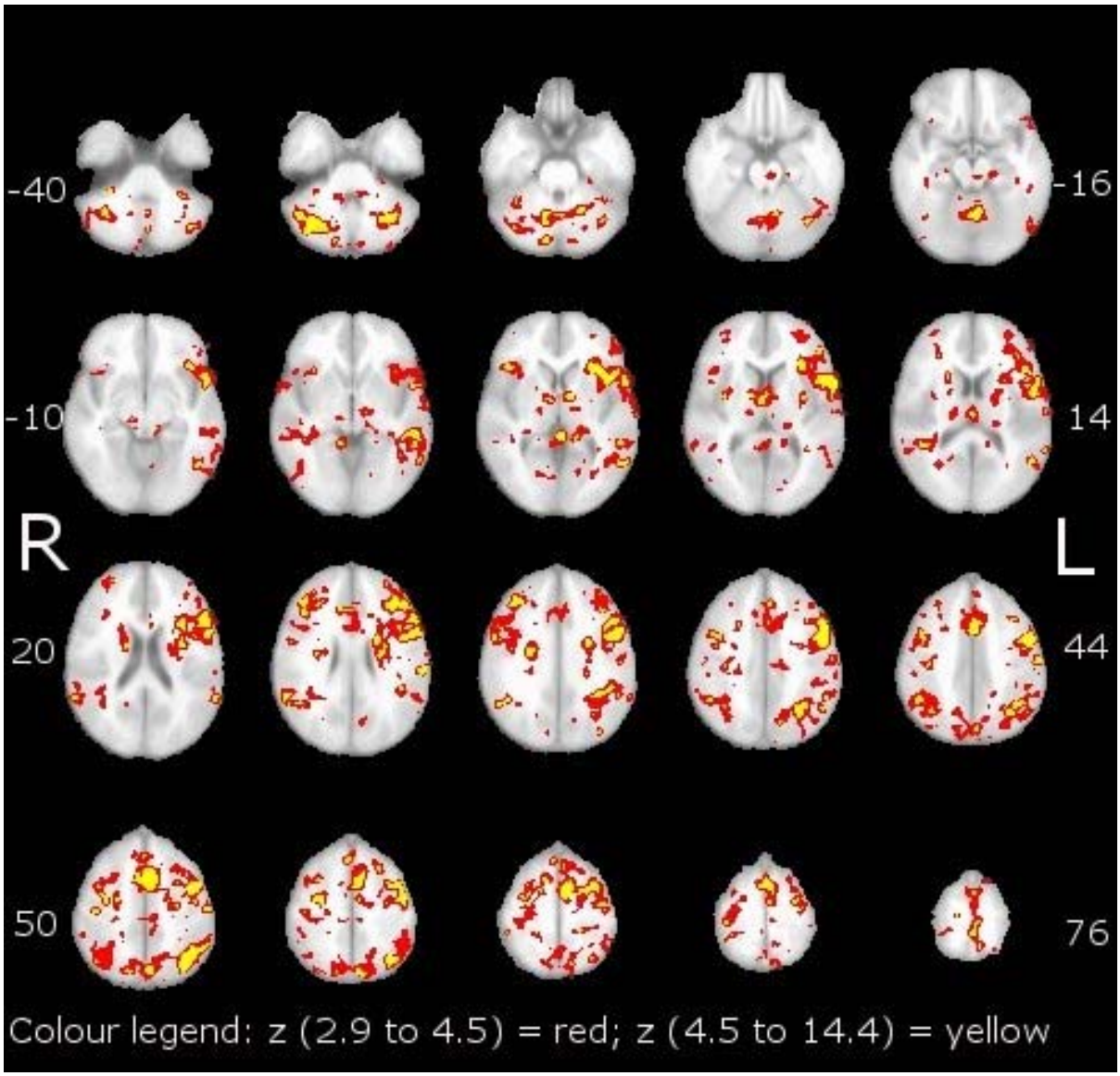

Figure 5-5: Statistically significant activation peaks in MCI during the delay stage compared to rest period

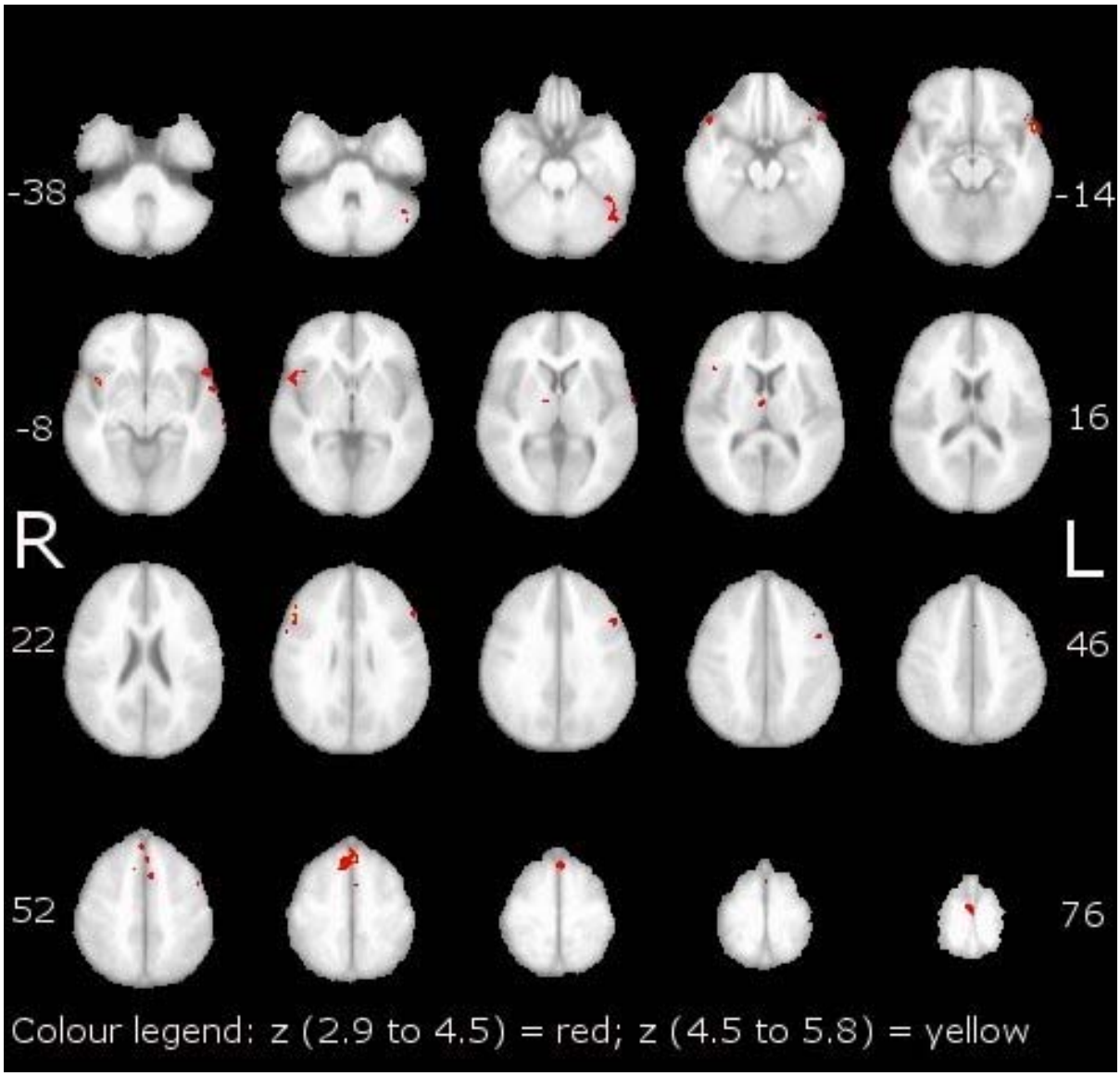

Figure 5-6: Statistically significant activation peaks in MCI during the decision period compared to rest period

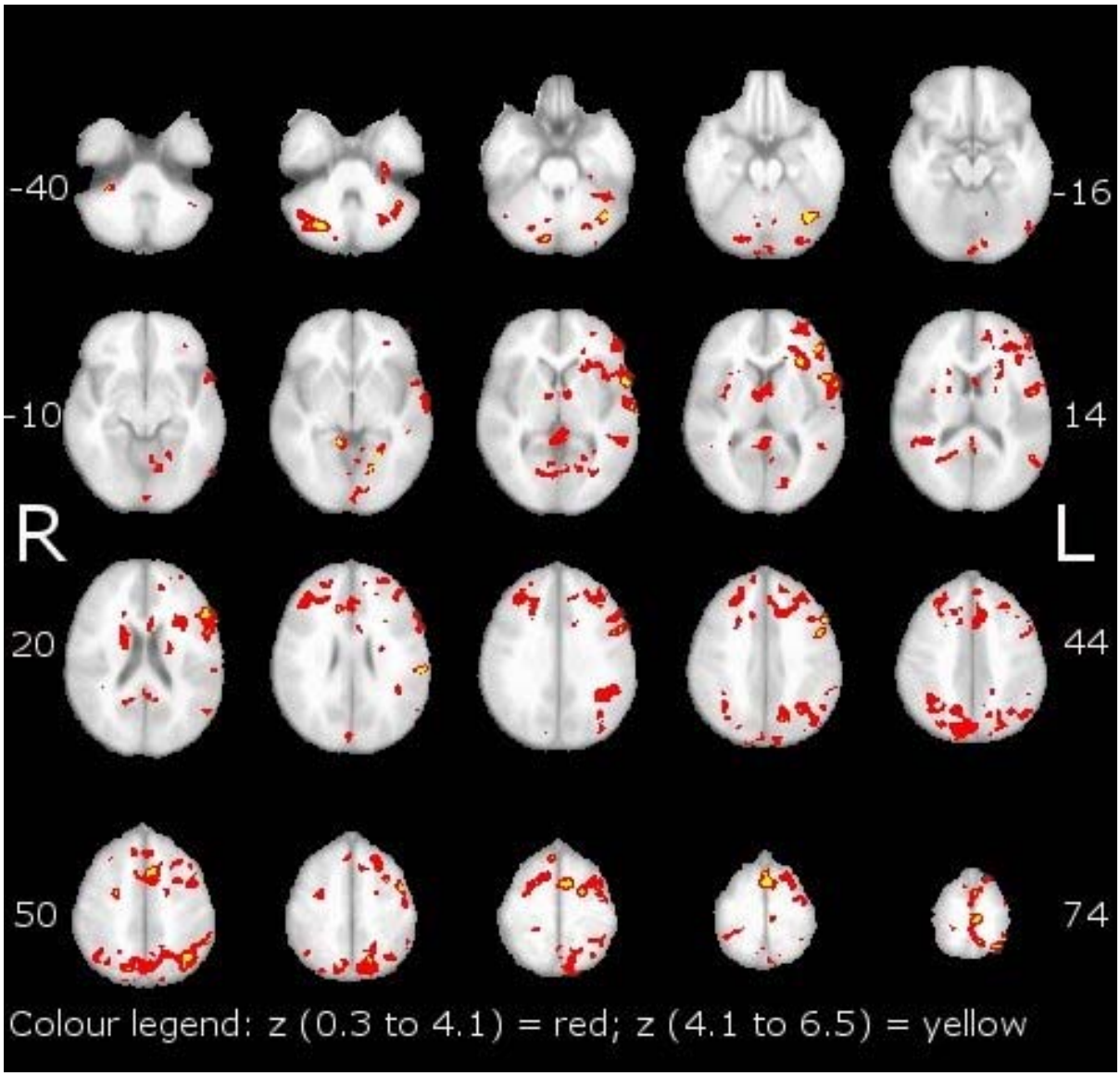

Figure 5-7: Statistically significant clusters of higher activation in MCI compared to HC during the delay stage

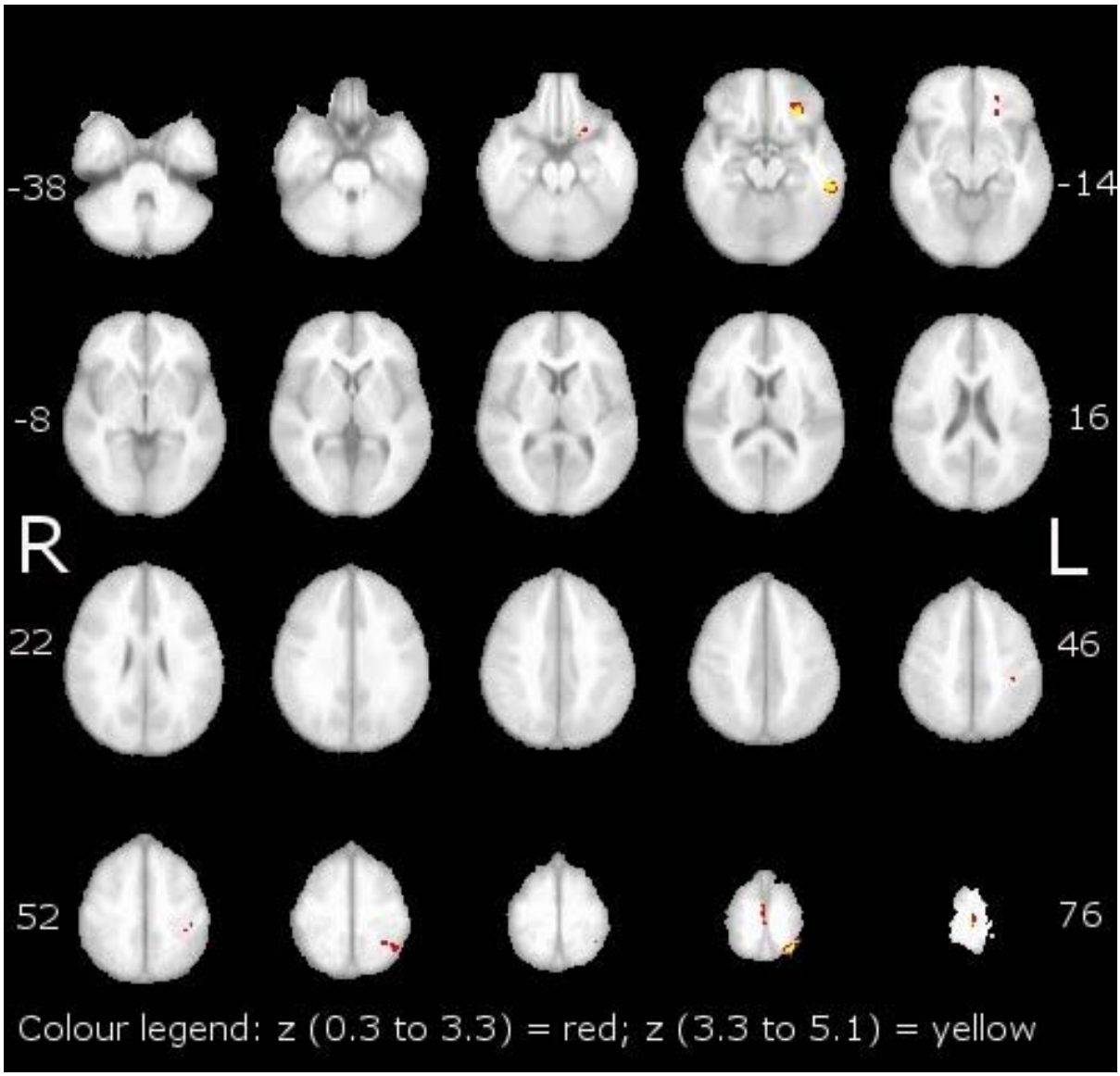

Figure 5-8: Statistically significant clusters with negative correlation with age during the delay stage

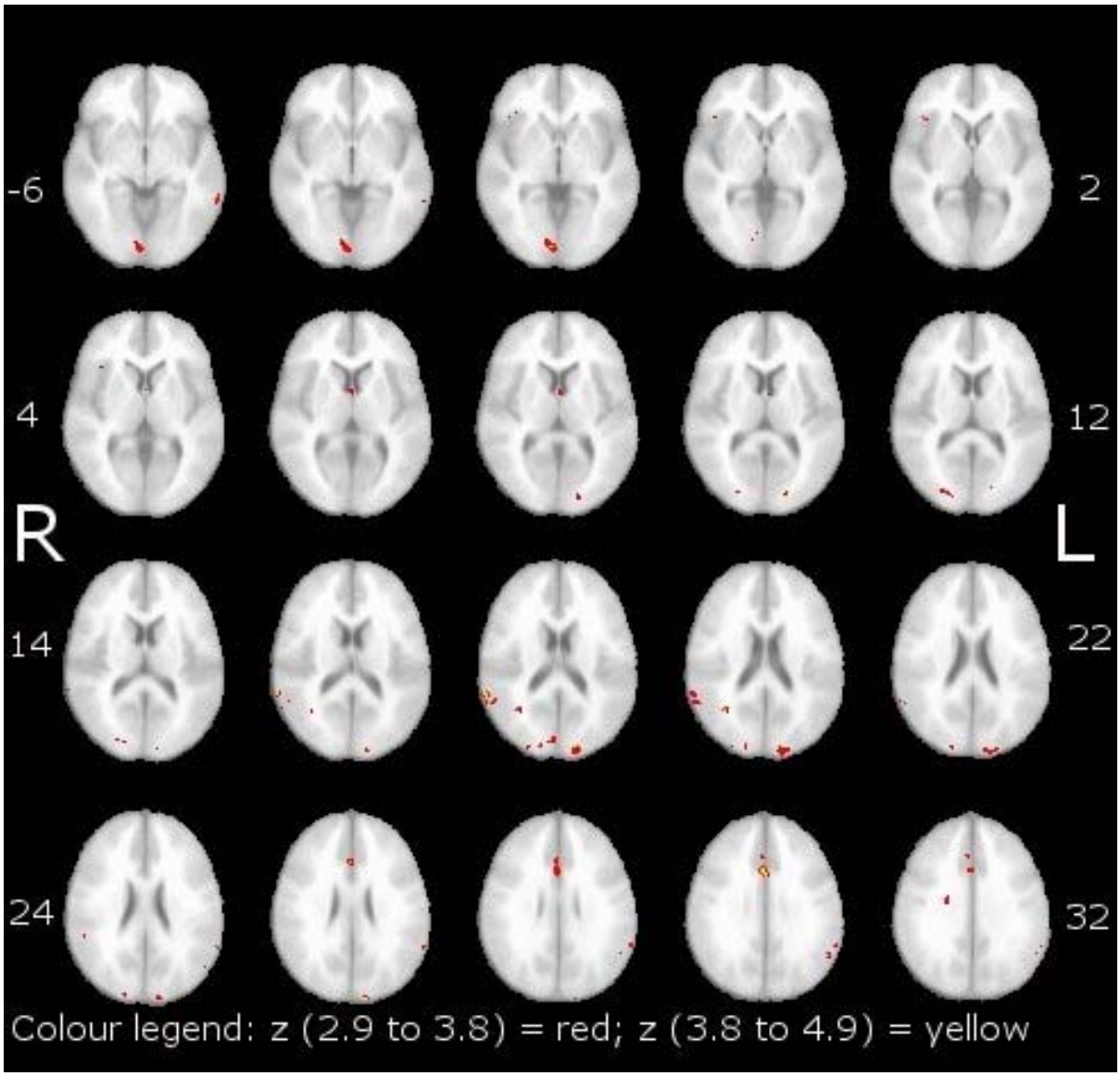

Figure 5-9: Statistically significant clusters with positive correlation with age during the delay stage

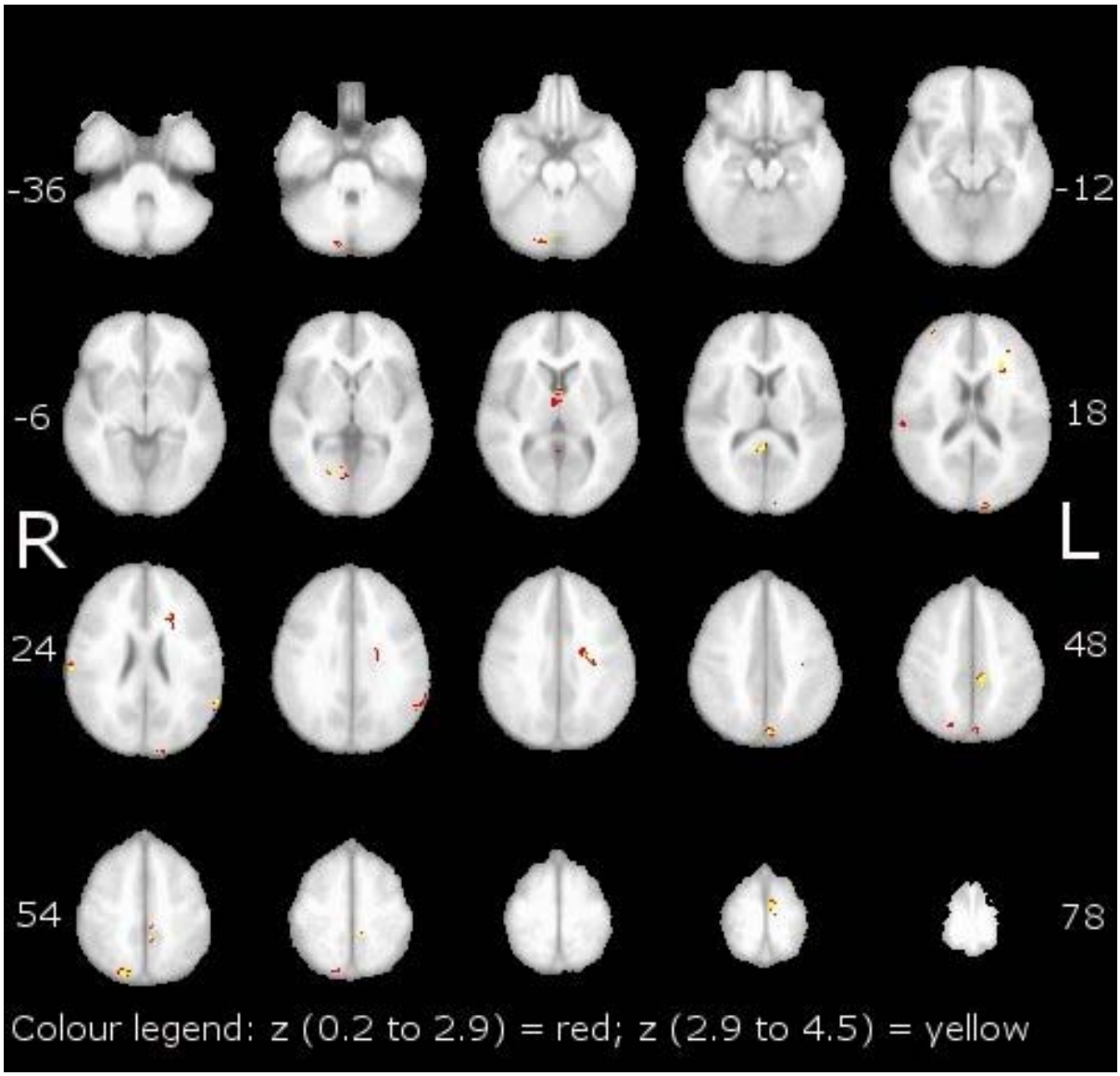

Figure 5-10: Statistically significant clusters with negative interaction of age and activation difference during the delay stage

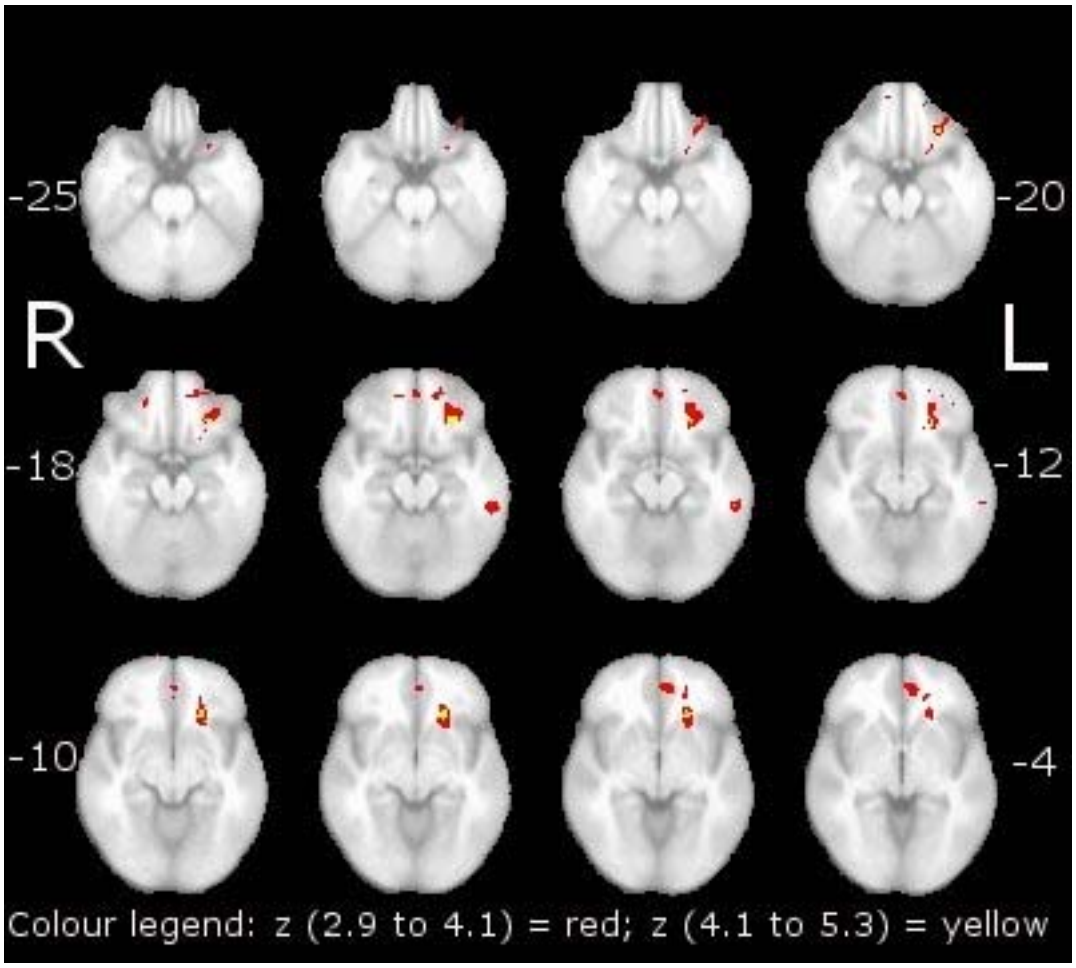

Figure 5-11: Statistically significant clusters with positive interaction of age and activation difference during the delay stage

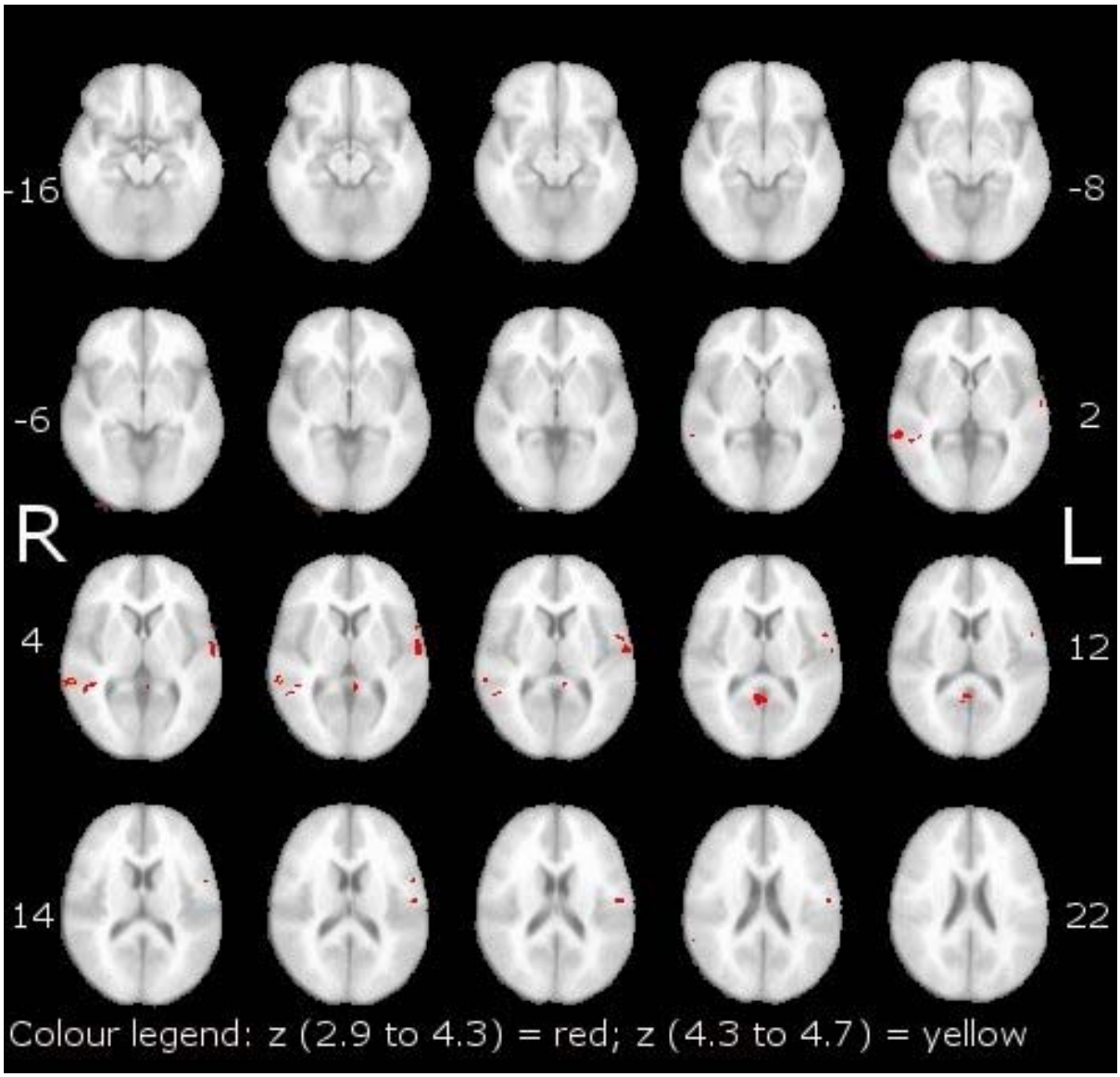

Figure 5-12: Statistically significant clusters of higher activation in MCI compared to HC during the letter period

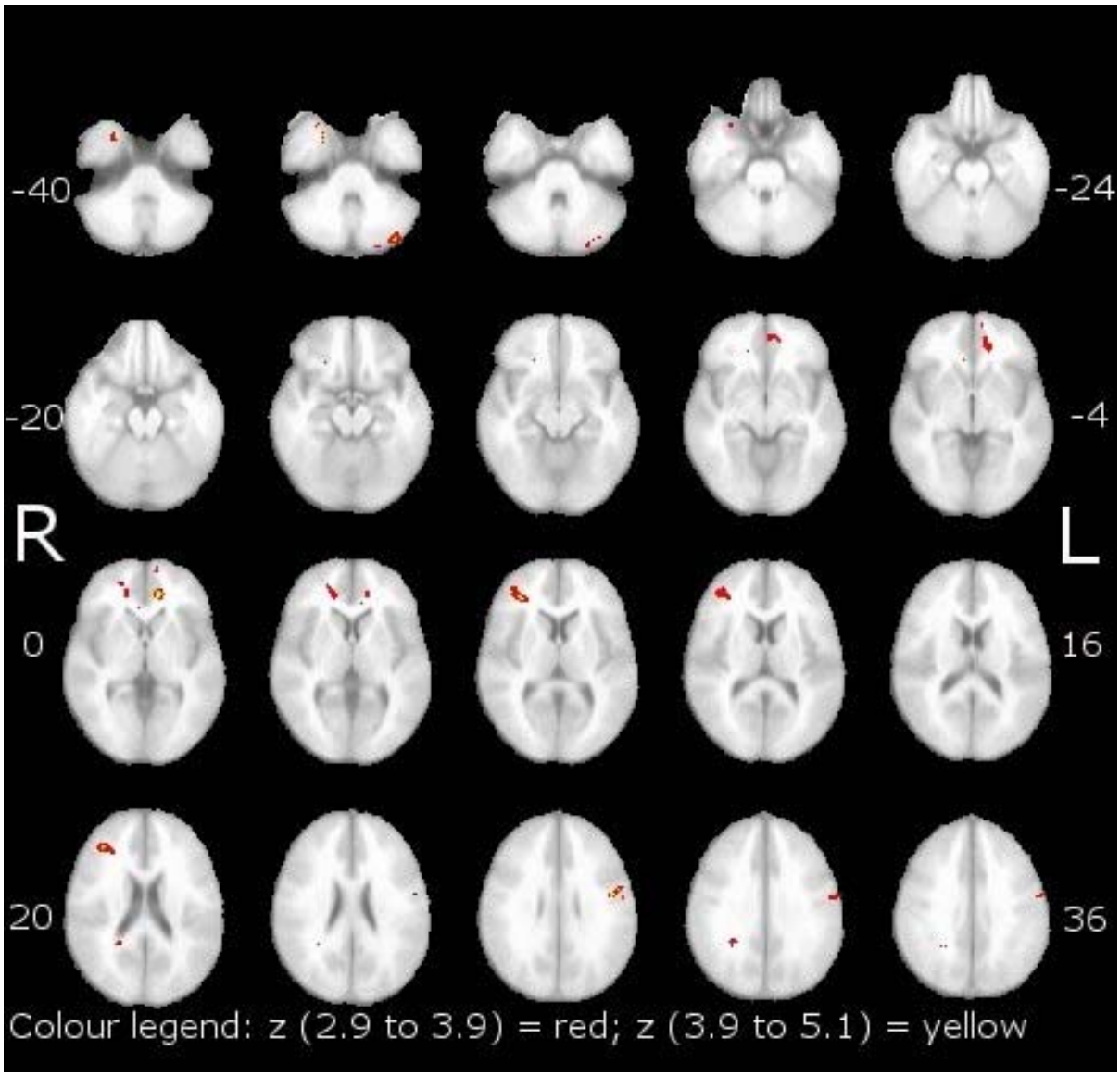

Figure 5-13: Statistically significant clusters of higher activation in HC compared to MCI during the letter period

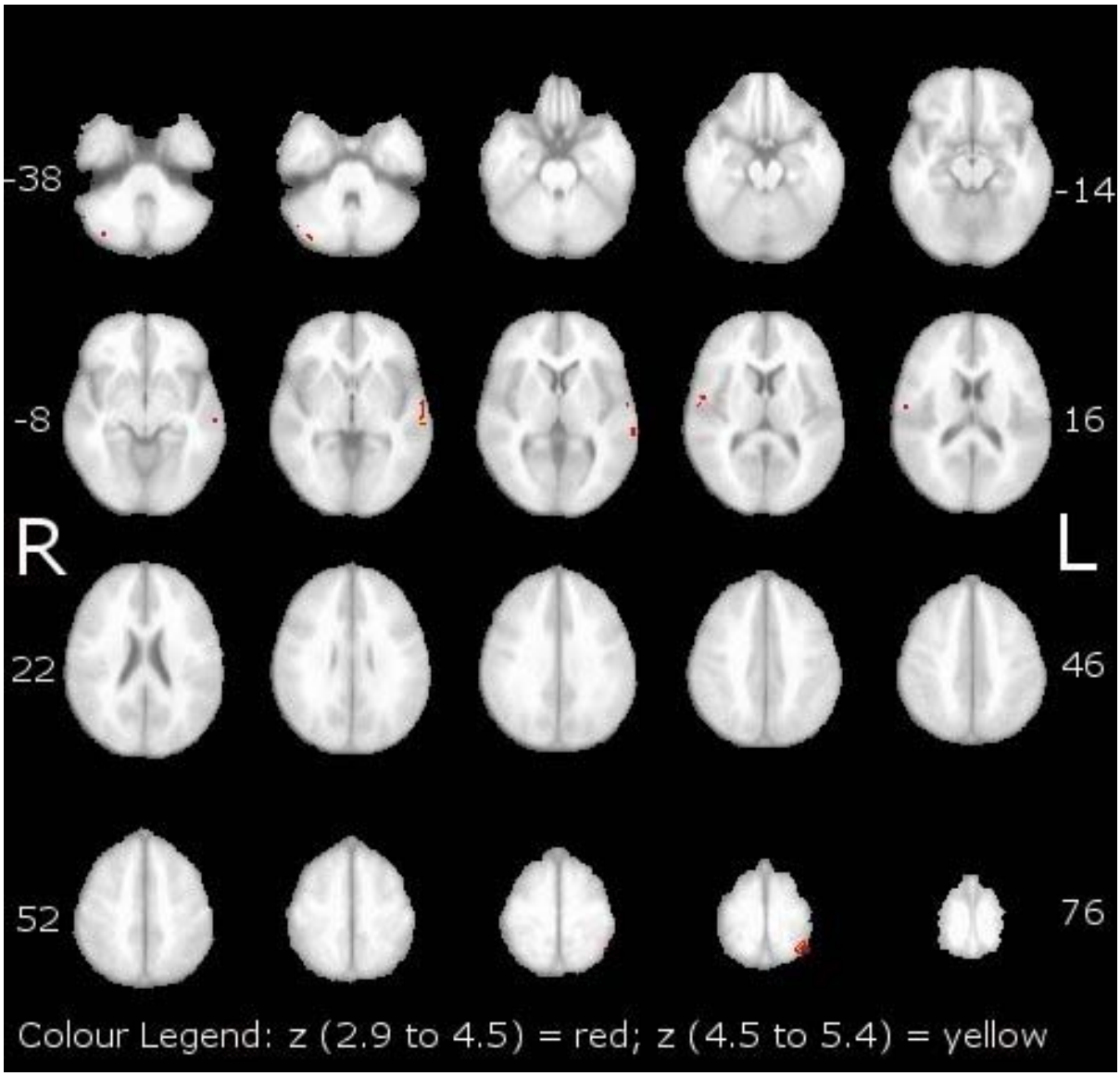

Figure 5-14: Statistically significant clusters with negative correlation with age during the letter period

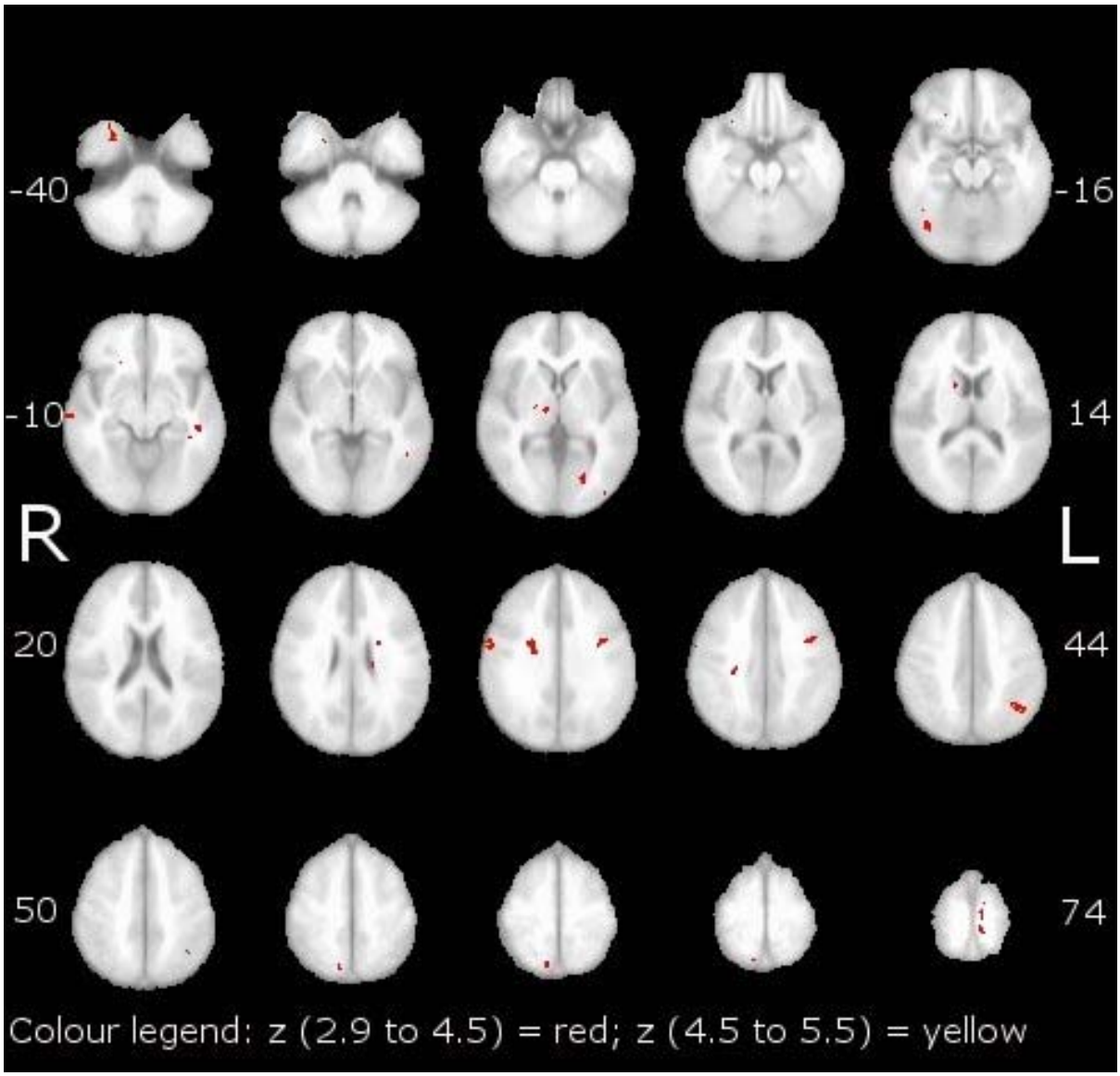

Figure 5-15: Statistically significant clusters of positive correlation with age during the letter period

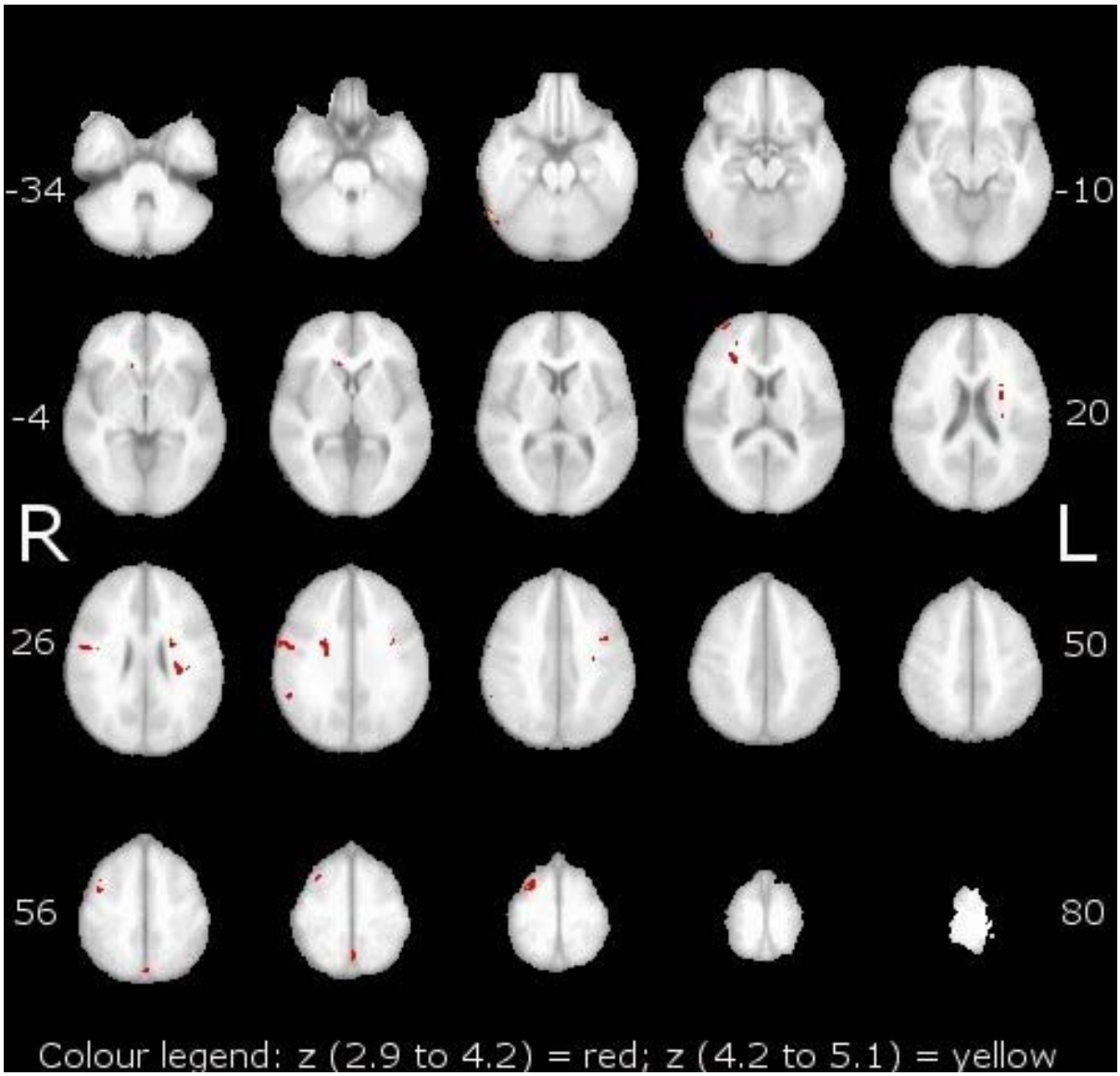

Figure 5-16: Statistically significant clusters with negative interaction of age and activation difference during the letter period

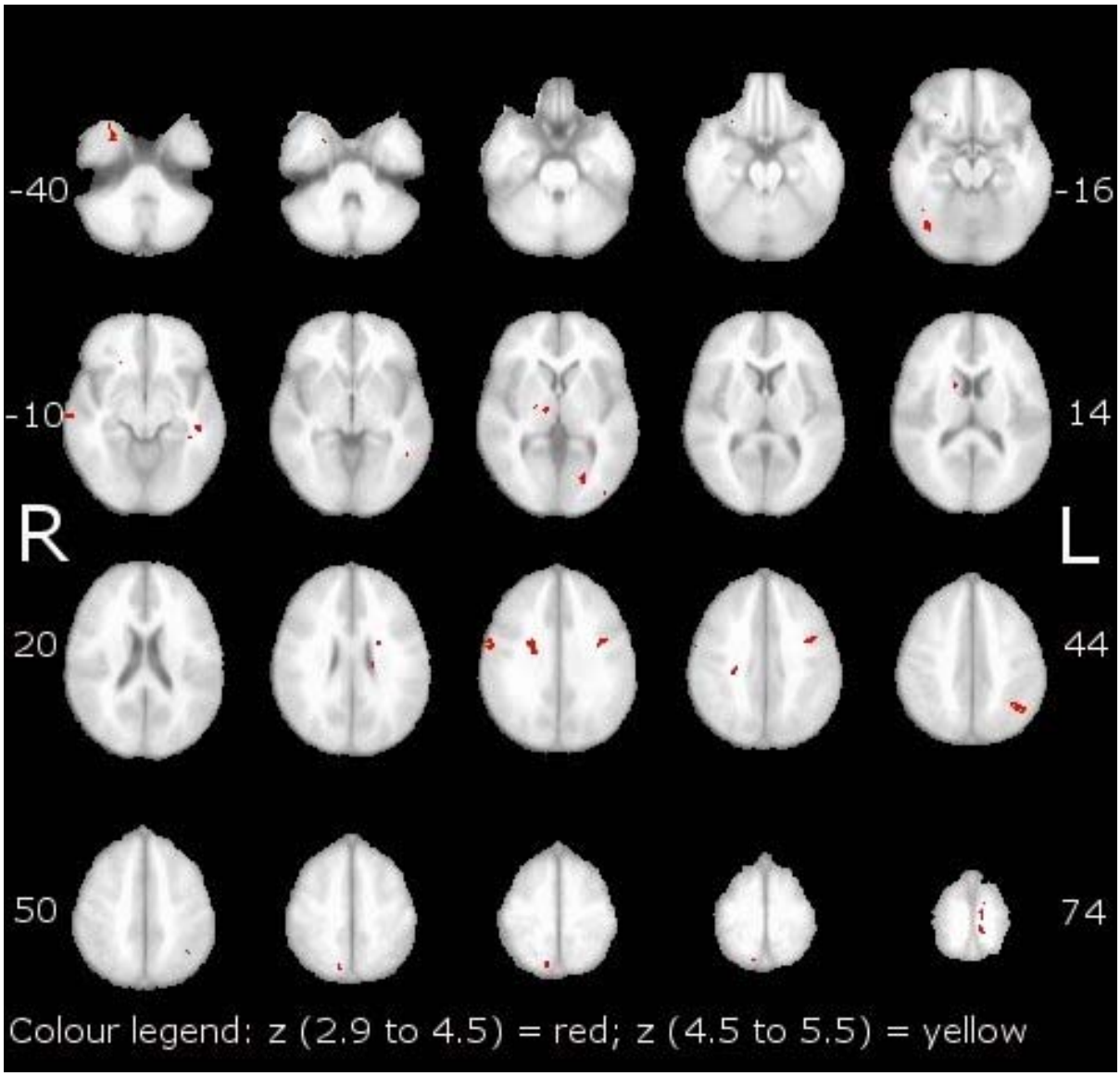

Figure 5-17: Statistically significant clusters of positive correlation with age during the decision period

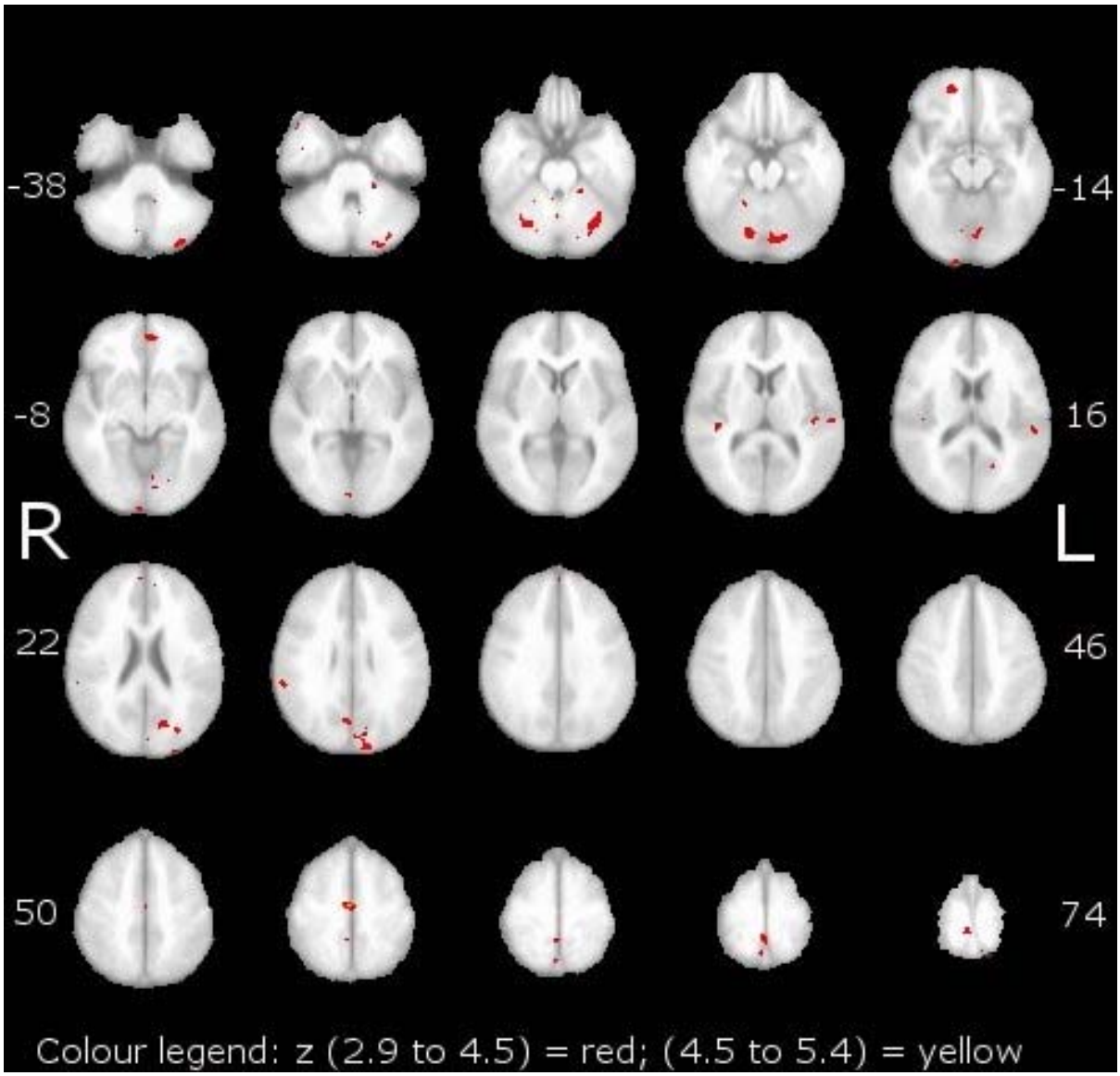

Figure 5-18: Statistically significant clusters of higher activation in HC compared to MCI during the decision period

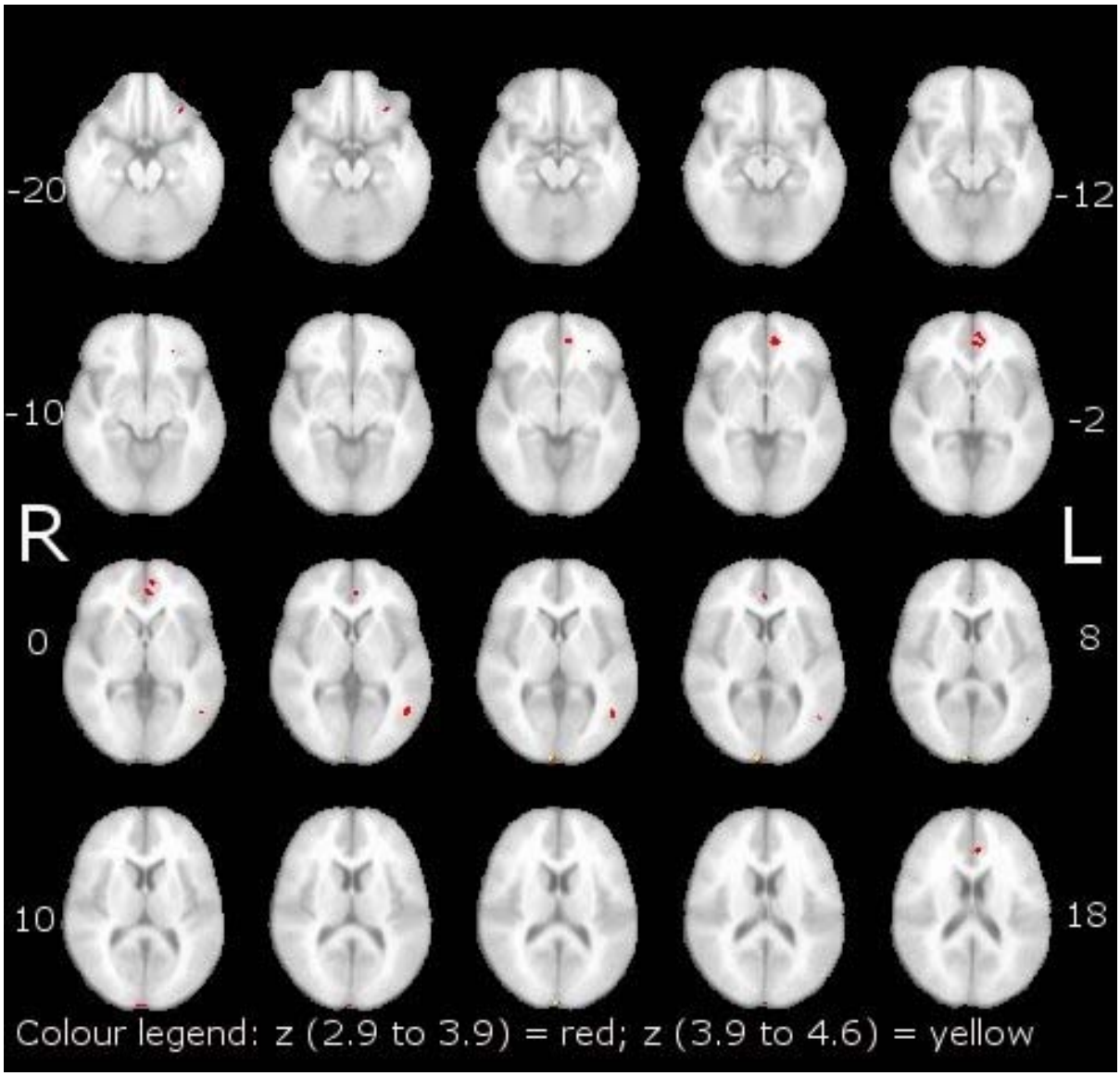

Figure 5-19: Statistically significant clusters with negative correlation with age during the decision period

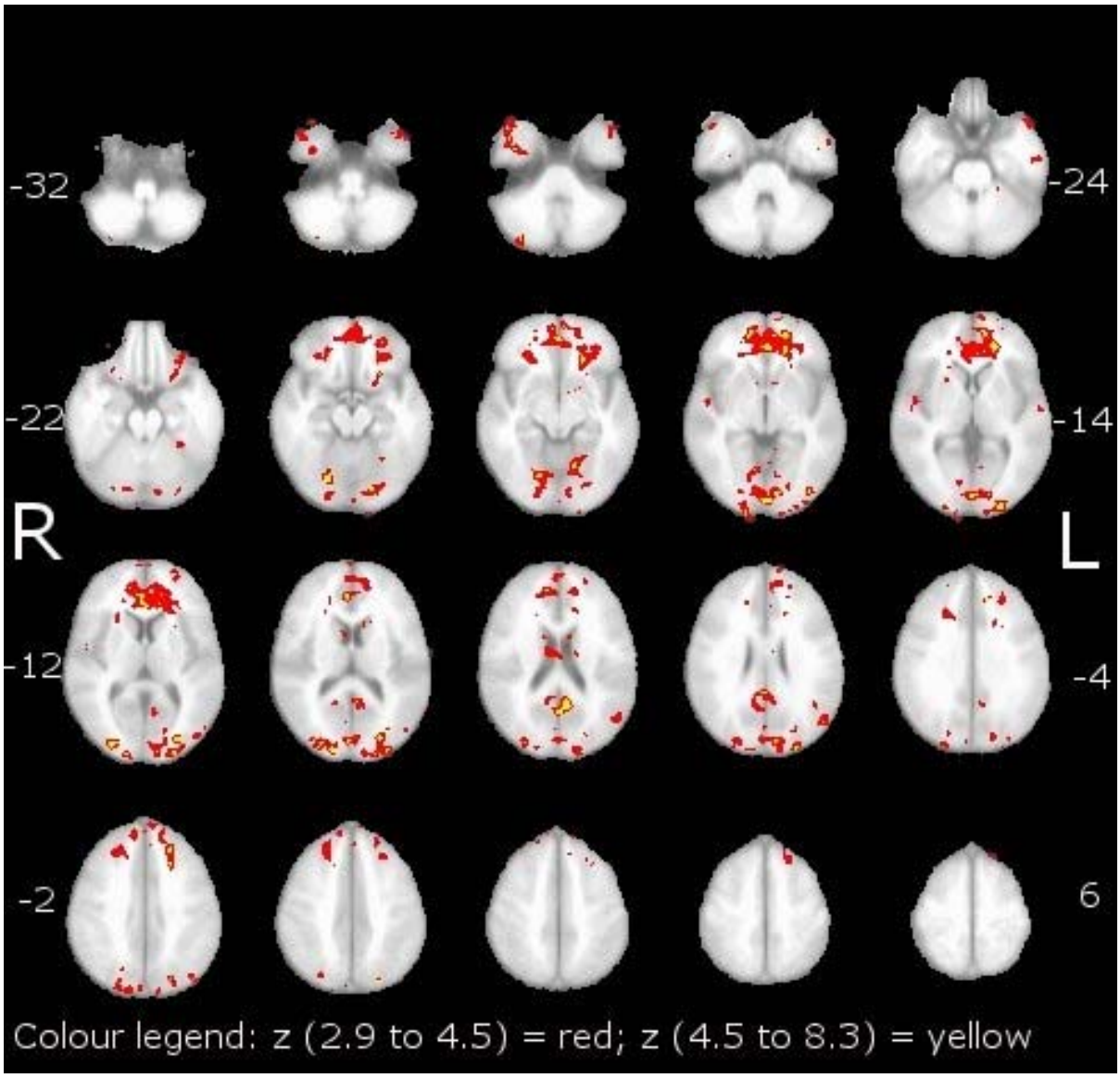

Figure 5-20: Statistically significant peaks in HC of higher activation during the rest period compared to the delay stage

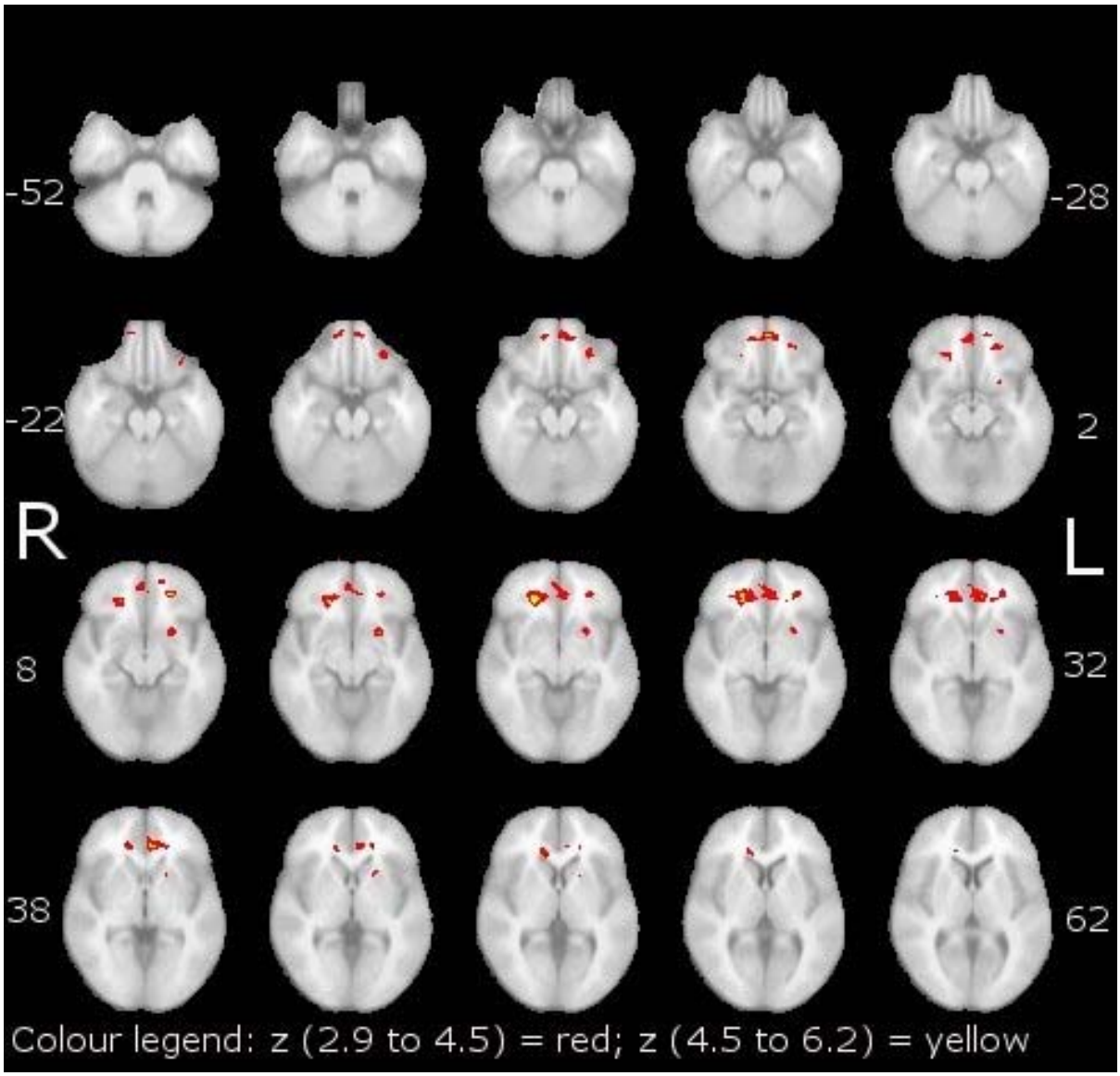

Figure 5-21: Statistically significant peaks in HC of higher activation during the rest period compared to the decision period

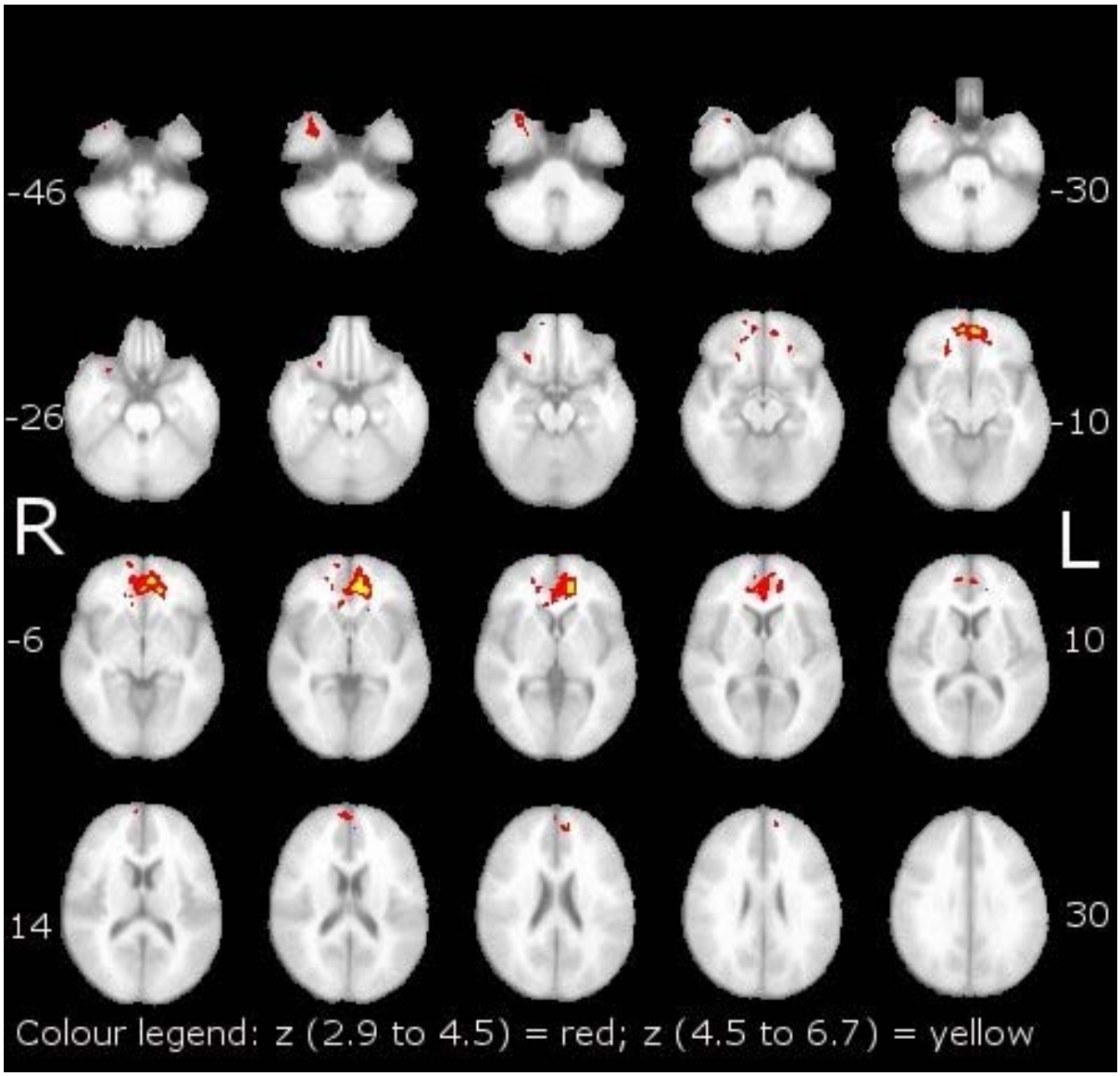

Figure 5-22: Statistically significant peaks in MCI of higher activation during the rest period compared to the letter period

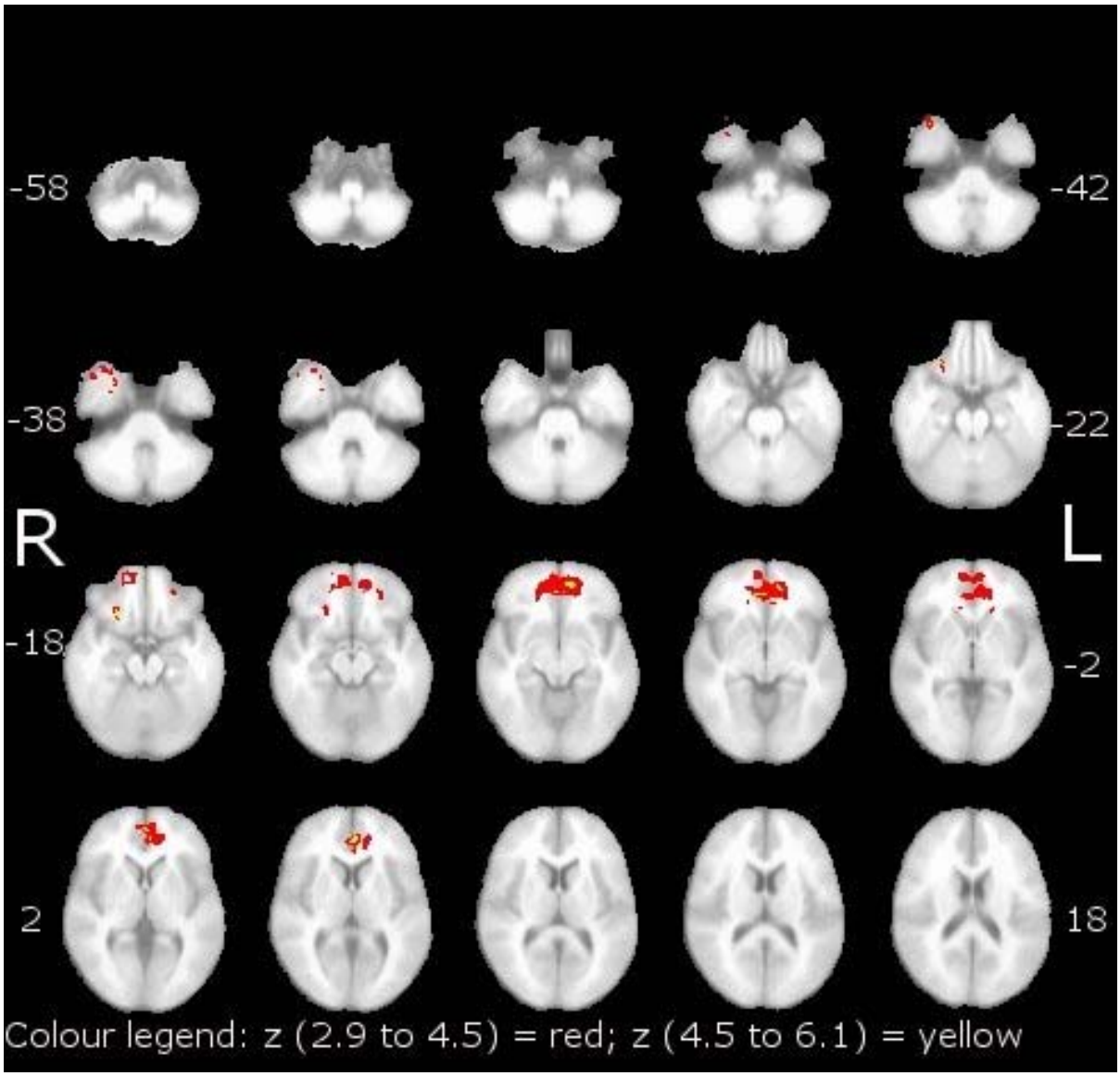

Figure 5-23: Statistically significant peaks in MCI of higher activation during the rest period compared to the delay stage

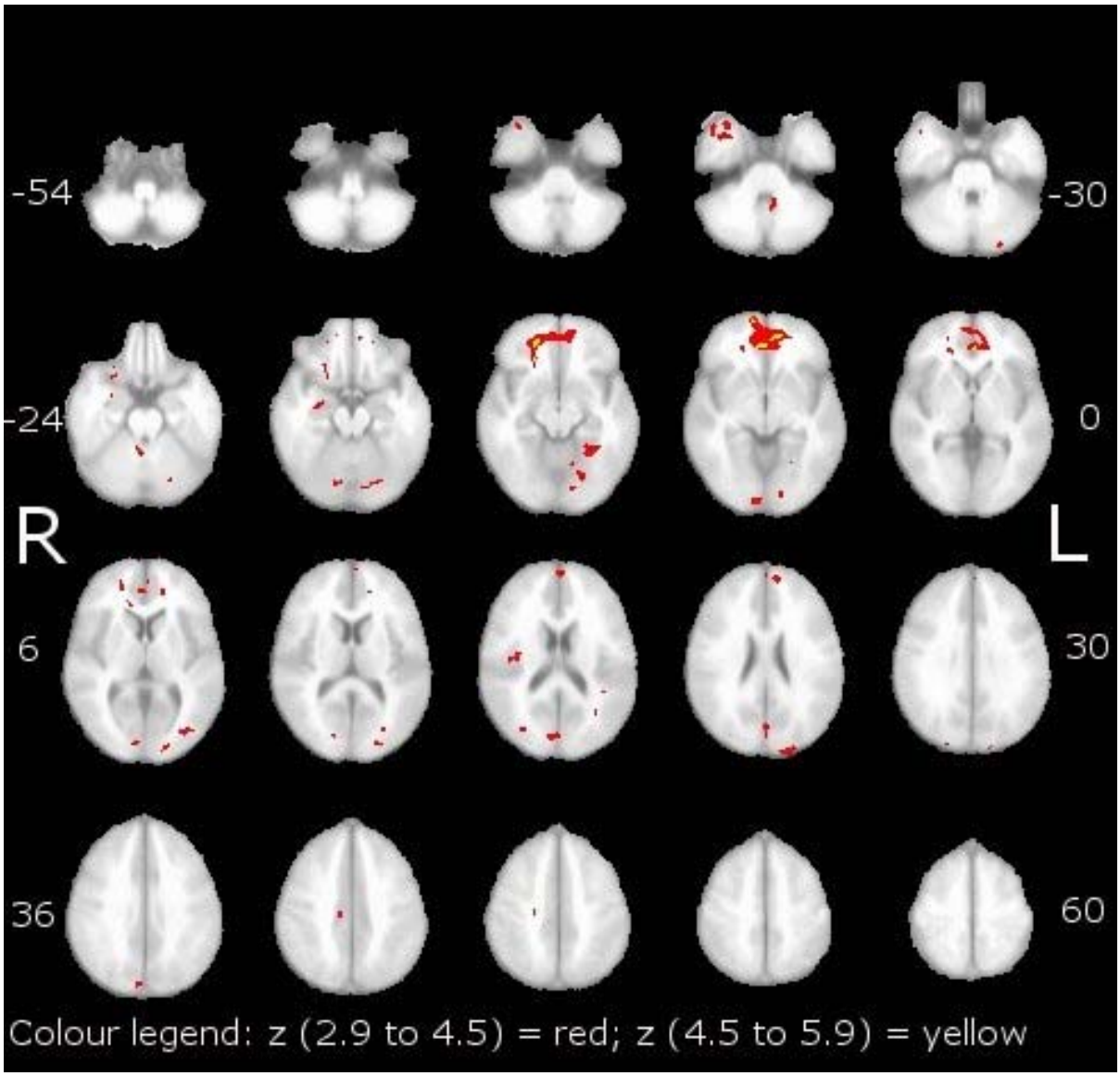

Figure 5-24: Statistically significant peaks in MCI of higher activation during the rest period compared to the decision period

6 Discussion

6.1 Overview

Our study revealed active regions during the working memory task that were consistent with our expectations. A wide network of regions including inferior parietal and dorsolateral-prefrontal regions and cingulate gyrus was activated in the healthy controls (HC) and also in the mild cognitive impairment (MCI) patients during the task. These regions are typically engaged in working memory.

The comparison of both groups for difference in their activation yielded to higher activation in the MCI group during the delay period, mainly in dorsolateral prefrontal regions, but also in parietal and temporal regions. This is according to compensation theories, which say that patients with cognitive impairment need to recruit additional brain areas for task performance.

Another aspect we found in our analysis was the presence of a so-called default-mode network, areas that were more active during the resting state than during the task performance. In both HC and MCI mainly prefrontal regions and the cingulate gyrus showed higher activation during the resting state than the task. In comparison to the MCI group the control group in our study exhibited greater negative activation during the delay part, but less negative activation during the retrieval period.

6.2 Working memory activation in HC

In HC, the strongest activity over the whole task was in dorsolateral-prefrontal cortex, inferior parietal, and temporal regions. These regions form the typical network for modality-independent working memory tasks [85].

The HC group did not show strong left-lateralization as it was expected for a verbal working memory task [57, 60, 61]. Activation was found in both hemispheres. However, the clusters of activation were larger and had greater intensity values in the left hemisphere. Activation in right hemisphere did occur in the same regions as in the left hemisphere. Other studies have also found a general delateralization of activity during working memory tasks for older subjects [57, 61]. This may be a compensatory mechanism in older HC. The aging brain undergoes deleterious changes in grey and white matter, such as atrophy, synaptic degeneration, blood flow reductions, and neurochemical alterations [60, 86]. This loss of cognitive reserve leads to the need of recruiting other cortical regions to be able to perform cognitive tasks [87]. There is strong evidence that brain activity in old adults shows reduced lateralization during cognitive processes. In verbal working memory, young adults generally show left-lateralization, while old adults show activity in both hemispheres [60]. In addition, Cabeza et al [87] found that high-performing older adults showed a greater extent of delateralization than in low-performing older adults. The low-performing older adults showed a lower extent of delateralization, and had activation in additional areas of the left hemisphere.

The dorsolateral prefrontal cortex, which includes the inferior and middle frontal gyri, is involved in the executive components of the WM task [88]. The dorsolateral prefrontal cortex is thought responsible for initiating the controlled processing of verbal working memory material [89-91]. They were active in all parts of this task, to a higher extent during the letter period and the decision period than during the delay stage.

We found that the anterior cingulate was activated in both groups. It is thought that anterior cingulate gyrus and lateral prefrontal cortex operate together during tasks that involve high levels of mental effort and control. Activation in extensive parts of the posterior medial frontal cortex are discussed to be elicited when detection of unfavourable outcomes, response errors, response conflicts, and decision uncertainty occur during a task. These areas are thought to be involved in monitoring of ongoing actions and performance outcomes, and subsequent adjustments of behaviour and learning. The posterior medial frontal cortex is also interacting with the lateral prefrontal cortex. Activity in posterior medial frontal lobe areas might serve as a signal that engages regulatory processes in the lateral prefrontal cortex. This connectivity is thought to be responsible for performance adjustments [92].

Parietal regions and supramarginal gyrus that showed activity in all parts of our task, with the highest extent during the letter period, reflect the stores affected by the working memory updating process [52, 93-95]. Temporal regions in this study showed mainly activity during the letter period, which indicates again, that the HC started maintaining the letters already during the encoding period.

In addition to the previously mentioned regions there was also activity in occipital regions, predominantly during the letter period. This was the part of the task with the most visual stimulus. Other studies have also found occipital regions to be active during memory tasks, although this activity has not been connected with the task itself, but with the visual stimulation [54, 60, 88, 96, 97] as in the current study.

6.3 Working memory activation in MCI

In MCI, the dominating activity over the whole task was in dorsolateral-prefrontal cortex, inferior parietal, and temporal regions. These regions form the typical network for modality-independent working memory tasks [85]. The decision period showed relatively little activation compared to the other parts of the task.

The working memory network of parietal, prefrontal and temporal regions [48, 50, 88, 97, 98] was active during the delay stage. The MCI group also showed activity of the working memory network during the letter period, indicating that the subjects began with maintaining the letters already during the encoding phase.

The delateraliztion in MCI was not as distinct as in the HC group. Especially in the dorsolateral prefrontal area, which is considered responsible for storing tasks in working memory and for updating processes, shows less delateralization in the MCI. This can be due to neuronal changes, which prevent effective compensation in the right hemisphere. As Cabeza et al [87] showed, high extent of delateralization is associated with successful compensation for aging declines. The MCI group might be at a stage of decline where this sort of compensation cannot be executed as effectively anymore.

The dorsolateral prefrontal cortex, which is involved in executive components [88] and initiating controlled processing [89-91], was more active during the letter period than the delay stage. Activity in frontal areas during the decision stage was relatively little, which means that the executive component added only to a minor part to the activation during this stage.

The anterior cingulate gyrus, which is considered to be involved in monitoring ongoing actions and in subsequent adjusting of behaviour and responses [92], shows no activity in the MCI group. This might indicate that MCI subjects have been utilizing a different strategy or the same strategy as the HC group but partly using a different network. The use of a different strategy is also a compensatory mechanism.

Parietal lobe regions and supramarginal gyrus showed activity in the MCI as well, reflecting the stores that are affected by the memory updating process [52, 93-95]. Temporal lobe activity only occured during the delay stage and the decision period. While the HC also had activity in temporal lobe regions in the letter period, the MCI did not.

Occipital regions only had statistically significant activity in MCI during the letter period. This again is due to visual stimulation and not connected to the working memory process [54, 60, 88, 96, 97].

6.4 Difference in activation of OHC and MCI

6.4.1 Comparison of both groups' activation

We found significant changes in brain activation across several regions after performing statistical parametric mapping. The HC group had higher activation than the MCI group during the letter period predominantly in frontal lobe regions. Areas with higher activation in the MCI group were mainly in temporal lobe regions.

For the delay part of the task, there were no regions that revealed higher activation in the HC, but only areas where the activation was greater in the MCI group: dorsolateral prefrontal, inferior parietal regions, and cingulate gyrus. The greater activation in MCI might reflect greater effort by the MCI group in maintaining the group of letters in WM.

The retrieval part yielded only areas, which were more active in the HC than in the healthy control group: dorsolateral prefrontal and inferior parietal regions.

The areas with different activation in both groups varied both interhemispherically as well as intraregionally. These findings might reflect a process of reorganization due to the decline in the brain reserve of the MCI group. Volumetric measurements of the brain have not been conducted in our study, there was no evidence of significant atrophy, infarcts or chronic microvascular changes was identified. However, subtle atrophy might have been present at the early stage of our MCI subjects.

Neuropathological changes in Alzheimer's disease initially start in the entorhinal cortex at early stages of the disease. From there the declines spread to association cortices. The middle temporal lobe has strong neural projections to all these areas [99, 100]. The association cortices in the parietal, temporal, and frontal lobes are connected to attention to complex stimuli, identification of relevant features of such stimuli, recognition of related objects and planning of appropriate responses [101]. These areas predominantly have shown higher activity in our MCI group than in the control group. The region that had the largest volume of higher activation in the MCI group was the middle frontal gyrus, which is closely linked to the other regions of the association cortices. Alzheimer's disease's early neuropsychological manifestation begins with episodic memory impairment, and is followed by the development of other cognitive deficits [102]. Changes possibly result from reduced metabolic and functional activity in these areas. In early stages like in our MCI subjects, the increases in activation are suggested to result from compensation for decreased neural efficiency [50].

6.4.2 Age effect and interaction with activated regions

Because the healthy control group and the MCI group showed significant difference in age, we analyzed the data to see if and where there was activation correlated with age. With these results, we could also detect if there was an interaction between the age effect activation and the results of the group comparison. This is important for proving that none of the activation in the group comparison was because of age effect.

The regions with positive are effect activation were in frontal, parietal, and temporal regions for the encoding period, and in parietal and occipital regions as well as cingulate gyrus, for the delay stage.

Age effect activation peaks with negative value during the letter period were located in postcentral and temporal regions, during the delay stage in postcentral and frontal regions, and for the retrieval stage in cingulate gyrus and frontal regions.

Positive age effects mean that those regions are the more active the older the subject is, while negative age effect activation indicates regions that are the more active the younger the subjects are.

There was no overlap between the clusters of activation differences between MCI and OHC and the age effect. The activation peaks in the group comparison indeed resulted from the subjects performing the working memory task and not from the age effect.

6.5 Default mode network

Regions that show less activation during cognitive tasks than during the resting state have been interpreted as belonging to a default-mode network.

The MCI group of our study had negative activation predominantly in cingulate gyrus and frontal regions during all parts of the task.

The HC group had no regions that had negative activation during the encoding part. Regions with negative activation during the delay period were occipital and frontal regions and cingulate gyrus. The retrieval stage yielded in negative activation of mainly frontal regions and cingulate gyrus.

The default-mode network is thought to be active during the resting state. This network is suppressed when the subject performs a goal oriented task. Its function could be attending to external environmental stimuli, attending to internal state and emotions and retrieval of past memories [103-106]. The deactivation in the default-mode network is likely to be based on reallocating processing resources to areas involved in active task performance, and also due to suspension of spontaneous semantic processing during a task that occur during resting state [107].

It has been found that the more difficult a task is, the more is the default network deactivated. The amount of deactivation during a task in the default-mode network is dependent on the amount of attention the task requires and of the amount of activity present during the resting state [63].

The regions involved in default-mode network are middle frontal cortex, and cingulate cortex [63, 106, 108], areas that had negative activation in our study as well.

The more extensive negative activation in our healthy control group during the delay stage could result from more available cognitive capacity. As previously described, the healthy control group exhibits less positive activation during the delay part, which indicates that the control group utilizes the respective areas performing the task more effectively than the MCI group does. This again results in stronger suppression of the default-mode network.

The retrieval part yielded different results. Here, the negative activation of the default-mode network included more regions in the MCI group than in the healthy control group, while contrary to the delay part, the OHC showed positive activation in more regions than the MCI group.

7 Conclusion

Differences in brain activation have been found between the healthy control group and the mild cognitive impairment group. These differences predominantly occured in dorsolateral prefrontal, parietal, and temporal regions. There were also differences between both groups regarding the default mode network. These findings suggest that it is possible to distinguish between HC and MCI using working memory paradigms. This is the first study that compares differences in activation patterns in HC and MCI during the different stages of a verbal working memory task.

A further goal of research could be the extending this study to other groups of subjects, such as vascular dementia patients. If certain characteristic specific changes in activation patterns in the MCI group could be found, those activation patterns could eventually be used as a diagnostic marker for MCI. It is important to find clinical markers for MCI, as MCI is currently considered a prodromal stage of Alzheimer's disease.

FMRI results, especially during memory tasks, might be of important use in early diagnosis of dementia. Memory impairment is one of the earliest symptoms of AD. These memory changes are associated with functional changes, which precede the anatomical changes.

In this study, the subjects performed a working memory task. Another possibility for further research would be to compare the brain activation in HC and MCI during both working memory and long term memory tasks. This will show if the compensatory activation patterns in MCI differ in WM and long term memory. Specific changes in long term memory could also be used as a diagnostic marker.

The comparison of activation in working memory and long term memory, particularily in MCI, could also give insight in how these two are connected. Especially when using similar materials for the two types of tasks, the results might show, if similar compensatory mechanisms are used. It also might be shown if the activation patterns in MCI during working memory and long term memory and the compensation patterns are similar.

Differences of the DMN between HC and MCI could be shown in our study. To possibly use those changes as a diagnostic marker, it is necessary to examine a larger number of subjects. The default network is very interesting, because it is involved in retrieval and manipulation of episodic memory and semantic knowledge. It might be possible to detect changes in memory associated with early stages of dementia through changes in the default mode network.

The results of this study are very promising to contribute to the early diagnosis of dementia in general, and specifically Alzheimer's dementia.

8 Bibliography

1. Hampel, H., F. Padberg, and H.-J. Möller, *Alzheimer Demenz*. 2003, Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH.
2. Winblad, B., K. Palmer, M. Kivipelto, V. Jelic, L. Fratiglioni, L.-O. Wahlund, A. Nordberg, L. Bäckman, M. Albert, O. Almkvist, H. Arai, H. Basun, K. Blennow, M. De Leon, C. DeCarli, T. Erkinjuntti, E. Giacobini, C. Graff, J. Hardy, C. Jack, A. Jorm, K. Ritchie, C. Van Duijn, M, P. Visser, and R. Petersen, P, *Mild cognitive impairment - beyond controversies, towards a consensun: report of the International Working Group on Mild Cognitive Impairment.* Journal of Internal Medicine, 2004. **256**: p. 140-146.
3. Daly, E., D. Zaitchik, M. Copeland, J. Schmahmann, J. Gunther, and M. Albert, *Predicting conversion to Alzheimer disease using standardized clinical information.* Arch Neurol, 2000. **57**: p. 675-680.
4. Petersen, R., C, *Mild cognitive impairment as a diagnostic entity.* Journal of Internal Medicine, 2004. **256**: p. 183-194.
5. Petersen, R., C, R. Doody, A. Kurz, R. Mohs, C, J. Morris, C, P. Rabins, V, K. Ritchie, M. Rossor, L.J. Thal, and B. Winblad, *Current concepts in mild cognitive impairment.* Arch Neurol, 2001. **58**(12): p. 1985-1992.
6. Petersen, R., C, G. Smith, E, S. Waring, C, R. Ivnik, J, E. Tangalos, G, and E. Kokmen, *Mild Cognitive Impairment.* Archives of Neurology, 1999. **56**: p. 303-308.
7. Petersen, R., C, R. Ivnik, J, B. Boeve, F, D. Knopman, G. Smith, E, and E. Tangalos, G, *Outcome of clinical subtypes of mild cognitive impairment.* Neurology, 2004. **62**: p. A29S.
8. Boeve, B., F, T. Ferman, J, and G. Smith, E, *Mild cognitive impairment preceding dementia with Lewy bodies.* Neurology, 2004. **62**: p. A86.
9. Hughes, C.P., L. Berg, W.L. Danziger, L.A. Coben, and R.L. Martin, *A new clinical scale for the staging of dementia.* Br J Psychiatry, 1982. **140**: p. 566-572.
10. DeCarli, C., D. Mungas, D. Harvey, B. Reed, M. Weiner, H. Chui, and W. Jagust, *Memory impairment, but not cerebrovascular diseas, predicts progression of MCI to dementia.* Journal of Neurology, 2004. **63**: p. 220-227.
11. *Diagnostic and Statistical Manual of Mental Disorders*. 4 ed. 1994, Washington DC: American Psychiatric Association.
12. Reisberg, B., S. Ferris, H, M. De Leon, and T. Crook, *The Global Deterioration Scale for assessment of primary degenerative dementia.* American Journal of Pychiatry, 1982. **139**: p. 1136-1139.
13. Thalmann, B. and A. Monsch, U, *CERAD. The Consortium to Establish a Registry for Alzheimer's disease. A neuropsychological test battery*. 1997: Basel, Memory Clinic.
14. Kukull, W., A, E. Larson, B, L. Teri, J. Bowen, W. McCormick, and M. Pfanschmidt, L, *The Mini-Mental State Examination and the clinical diagnosis of dementia.* Journal of Clinical Epidemiology, 1994. **48**: p. 1061-1067.
15. McKhann, G., D. Drachman, M. Folstein, R. Katzmann, D. Price, and E. Stadlan, M, *Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ARDRA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease.* Journal of Neurology, 1984. **34**: p. 934-944.
16. *The Composite International Diagnostic Iinterview (CIDI)*, in *World Health Organization*. 1997: Geneva, Switzerland.
17. Desgranges, B., F. Eustache, P. Rioux, V. de La Sayette, and B. Lechevalier, *Memory Disorders in Alzheimer's Disease and the Organization of Human Memory.* Cortex, 1996. **32**: p. 387-412.
18. Senda, M., Y. Kimura, and P. Herscovitch, *Brain Imaging Using PET*. 2002, San Diego, California, USA: Academic Press.

19. Pauling, L. and C. Coryell, *The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbon monooxyhemoglobin.* Proc. Natl. Acad. Sci. USA, 1936. **22**: p. 210-216.
20. Ogawa, S. and T.M. Lee, *Magnetic Resonance Imaging of Blood Vessels at High Fields: In vivo and in vitro Measurements and Image Simulation.* Magn. Reson. Medicine, 1990. **16**: p. 9-18.
21. Ogawa, S., T.M. Lee, A.S. Nayak, and P. Glynn, *Oxygenation-sensitive Contrast in Magnetic Resonance Image of Rodent Brain at high Magnetic Fields.* Magn. Reson. Medicine, 1990. **14**: p. 68-78.
22. Ogawa, S., D.W. Tank, R. Menon, J.M. Ellermann, S.G. Kim, H. Merkle, and K. Ugurbil, *Intrinsic Signal Changes accompanying Sensory Stimulation: Functional Brain Mapping with Magnetic Resonance Imaging.* Proc. Natl. Acad. Sci. USA, 1992: p. 5951-5955.
23. Savoy, R., *Basics of NRM and MRI*, in *fMRI Visiting Fellowship Classes*. 2004: Charlestown, MA, USA.
24. Budinger, T.F., *Emerging Nuclear Magnetic Resonance Technologies. Health and Safety.* Ann. N. Y. Acad. Sci., 1992. **649**: p. 1-8.
25. Huettel, S.A., A.W. Song, and G. McCarthy, *Functional Magnetic Resonance Imaging*. 2004, Sunderland, Massachusetts, USA: Sinauer Associates, Inc.
26. Wolbarst, A., B, *Physics of Radiology*, ed. I. Appleton & Lange. 1993, Norwalk.
27. Mitchell, D.G., *MRI Principles*. 1999, Philadelphia: W.B. Saunders Company.
28. Raichle, M.E., *Bildliche Erfassung von kognitiven Prozessen.* Spektrum der Wissenschaft, 1994. **6**: p. 56-63.
29. Villringer, A., *Physiological Changes during Brain Activation*, in *Functional MRI*, C.T.W. Moonen and P.A. Bandetti, Editors. 2000, Springer Verlag: Berlin. p. 3-11.
30. Logothetis, N., K and B. Wandell, A, *Interpreting the BOLD signal.* Annual Review of Psychology, 2004. **66**: p. 735-69.
31. Wald, L., *MR Physics: Signal, Contrast, Imaging Tradeoffs for fMRI, and Safety*, in *fMRI Visiting Fellowship Class*. 2004: Charlestown, MA, USA.
32. Weisskoff, R.M., *Basic theoretical models of BOLD signal change*, in *Functional MRI*, C.T.W. Moonen and P.A. Bandetti, Editors. 2000, Springer Verlag: Berlin. p. 115-123.
33. Savoy, R., *Functional Magnetic Resonance Imaging*, in *Encyclopedia of the Brain*, Ramachandran, Editor. 2002, Academic Press.
34. Evans, A., C, D. Collins, L, S. Mills, R, E. Brown, D, R. Kelly, L, and T. Peters, M. *3D statistical neuroanatomical models from 305 MRI volumes*. in *Proc. IEEE-Nuclear Science Symposium and Medical Imaging Conference*. 1993.
35. Brodmann, K., *Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. 1909, Leipzig: Barth JA.
36. Friston, K.J., P. Jezzard, and R. Turner, *Analysis of functional MRI time-series.* Hum. Brain Mapp., 1994. **1**: p. 153-171.
37. Worsley, K.J. and K.J. Friston, *Analysis of fMRI time-series revisited - again.* NeuroImage, 1995. **2**: p. 173-181.
38. Josephs, O., R. Turner, and K. Friston, *Event-related fMRI.* Hum. Brain Mapp., 1997. **5**: p. 243-248.
39. Zarahn, E., G.K. Aguirre, and M. D'Esposito, *Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions.* NeuroImage, 1997. **5**: p. 179-197.
40. Miezin, F.M., L. Maccotta, J.M. Ollinger, S.E. Petersen, and R.L. Buckner, *Characterizing the hemodynamic response: Effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing.* NeuroImage, 2000. **11**: p. 1-23.
41. Kleinbaum, D.G., L.L. Kupper, K.E. Muller, and A. Nizam, *Applied Regression Analysis and Other Multivariate Methods*. 3 ed. 1998, Pacific Grove, CA, USA: Duxbury Press at Brooks/Cole Publishing Company.
42. Kahle, W. and M. Frotscher, *Nervensystem und Sinnesorgane*. 7 ed. Taschenatlas der Anatomie Band 3. 2000, Stuttgart: Thieme.

43. Cabeza, R. and L. Nyberg, *Imaging Cognition II: An Empirical Review of 275 PET and fMRI Studies.* J Cogn Neurosci, 2000. **12**(1): p. 1-47.
44. Morris, N. and D. Jones, M, *Memory updating in working memory: The role of the central executive.* British Journal of Psychology, 1990. **81**: p. 111-121.
45. D'Esposito, M., J. Detre, A, D. Alsop, C, and R. Shin, K, *The neural basis of the central executive system of working memory.* Nature, 1995. **378**(6554): p. 279-281.
46. D'Esposito, M., G. Aguirre, E. Zarahn, D. Ballard, R. Shin, K, and J. Lease, *Functional MRI studies of spatial and nonspatial-working memory.* Cognitive Brain Research, 1998. **7**: p. 1-13.
47. Barch, D., M, T.S. Braver, L. Nystrom, E, S. Forman, D, D. Noll, C, and J. Cohen, D, *Dissociating working memory from task difficulty in human prefrontal cortex.* Neuropsychologia, 1997. **35**(10): p. 1373-1380.
48. Awh, E., J. Jonides, E.E. Smith, E. Schumacher, R. Koeppe, and S. Katz, *Dissociating of storage and rehearsal in verbal working memory: evidence for positron emission tomography.* Psychological Sci, 1996. **7**: p. 25-31.
49. Paulesu, E., C. Frith, D, and R.J.S. Frackowiak, *The neural correlates of the verbal component of working memory.* Nature, 1993. **362**: p. 342-345.
50. Yetkin, F.Z., R.N. Rosenberg, M.F. Weiner, P.D. Purdy, and C.M. Cullum, *FMRI of working memory in patients with mild cognitive impairment and probably Alzheimer's disease.* Eur Radiol, 2005. **14**.
51. Mandzia, J.L., S.E. Black, M.P. McAndrews, C.L. Grady, and S. Graham, *fMRI Differences in Encoding and Retrieval of Pictures Due to Encoding Strategy in the Elderly.* Hum. Brain Mapp., 2004. **21**: p. 1-14.
52. Clark, C.R., G.F. Egan, A.C. McFarlane, P. Morris, D. Weber, C. Sonkkilla, J. Marcina, and H.J. Tochon-Danguy, *Updating Working Memory for Words: A PET Activation Study.* Hum. Brain Mapp., 2000. **9**: p. 42-54.
53. D'Esposito, M., B.R. Postle, and B. Rypma, *Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies.* Exp Brain Res, 2000. **133**(1): p. 3-11.
54. Moscovitch, M. and G. Winocur, *Frontal lobes, memory and aging: Structure and functions of the frontal lobes.* Annals of the New York Academy of Sciences, 1995. **769**: p. 115-150.
55. Chao, L.L. and R.T. Knight, *Prefrontal deficit in attention and inhibitory control with aging.* Cereb Cortex, 1997. **7**(63-69).
56. Andersen, N., D, T. Iidaka, R. Cabeza, S. Kapur, A.R. McIntosh, and F. Craik, I, *The effects of divided attention on encoding- and retrieval-related brain activity: a PET study of younger and older adults.* J Cogn Neurosci, 2000. **12**: p. 775-792.
57. Rajah, M.N. and M. D'Esposito, *Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory.* Brain, 2005. **128**: p. 1964-1983.
58. Cabeza, R., N.D. Anderson, S. Houle, J. Mangels, A, and L. Nyberg, *Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study.* J Cogn Neurosci, 2000. **12**: p. 197-206.
59. Rypma, B., V. Prabhakaran, J. Desmond, E, and J. Gabrieli, D, *Age differences in prefrontal cortical activity in working memory.* Psychol. Aging, 2001. **16**: p. 371-384.
60. Reuter-Lorenz, P.A., J. Jonides, E.E. Smith, A. Hartley, A. Miller, C. Marshuetz, and R.A. Koeppe, *Age differences in the Frontal Lateralization of Verbal and Spatial Working Memory Revealed by PET.* Journal of Cognitive Neuroscience, 2000. **12**(1): p. 174-187.
61. Li, S., U. Lindenberger, and S. Sikstrom, *Aging cognition: from neuromodulation to representation.* Trends Cogn Sci, 2001. **5**: p. 479-486.
62. Morcom, A.M., C.D. Good, R.J.S. Frackowiak, and M.D. Rugg, *Age effects on the neural correlates of successufl memory encoding.* Brain, 2003. **126**: p. 213-229.

63. Rombouts, S.A.R.B., F. Barkhof, R. Goekopp, C.J. Stam, and P. Scheltens, *Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI studyq.* Hum. Brain Mapp., 2005.
64. Lustig, C., A.Z. Snyder, M. Bhakta, K.C. O'Brien, M.P. McAvoy, M.E. Raichle, J. Morris, C, and R.L. Buckner, *Functional deactivations: Change with age and dementia of the Alzheimer type.* Proc Natl Acad Sci, 2003. **100**(24): p. 14504-14509.
65. Machulda, M., M, H. Ward, A, B. Borowski, J. Gunter, L, R. Cha, H, P. O'Brien, C, R. Petersen, C, B. Boeve, F, D. Knopman, D. Tang-Wai, F, R. Ivnik, J, G. Smith, E, E. Tangalos, G, and C. Jack Jr, R, *Comparison of memory fMRI response among normal, MCI and Alzheimer's patients.* Journal of Neurology, 2003. **61**(2): p. 500-506.
66. Sperling, R., J. Bates, E. Chua, A.J. Cocchiarella, D.M. Rentz, B.R. Rosen, D.L. Schacter, and M. Albert, *fMRI studies of associate encoding in young and elderly controls and mild Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2003. **74**: p. 44-50.
67. Golby, A., G. Silverberg, E. Race, S. Gabrieli, J. O'Shea, K. Knierim, G. Stebbins, and J. Gabrieli, *Memory endocing in Alzheimer's disease: an fMRI study of explicit and implicit memory.* Brain, 2005. **128**: p. 773-787.
68. Dickerson, B.C., D.H. Salat, J.F. Bates, M. Atiya, R.J. Killiany, D.N. Greve, A.M. Dale, C.E. Stern, D. Blacker, M.S. Albert, and R.A. Sperling, *Medial Temporal Lobe Function and Structure in Mild Cognitive Impairment.* Annals of Neurology, 2004. **56**(1): p. 27-35.
69. Bookheimer, S.Y., M.H. Strojwas, M.S. Cohen, A.M. Saunders, M.A. Pericak-Vance, J.C. Mazziotta, and G.W. Small, *Patterns of Brain activation in people at risk for Alzheimer's disease.* New England Journal of Medicine, 2000. **343**(7): p. 450-456.
70. Li, S.-J., Z. Li, G. Wu, M.-J. Zhang, M. Franczak, and P.G. Antuono, *Alzheimer's Disease: Evaluation of a Functional MR Imaging Index as a Marker.* Radiology, 2002. **225**: p. 253-259.
71. Elgh, E., A. Larsson, S. Eriksson, and L. Nyberg, *Altered prefrontal brain activity in persons at risk for Alzheimer's disease: an fMRI study.* Int Psychogeriatr, 2003. **15**(2): p. 121-133.
72. Morris, J., C, A. Heyman, R. Mohs, C, J. Hughes, P, G. van Belle, G. Fillenbaum, E. Mellits, D, C. Clark, and C. investigators, *The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease.* Journal of Neurology, 1989. **39**: p. 1159-1165.
73. Morris, J., C, S. Edland, C. Clark, D. Galasko, E. Koss, R. Mohs, C, G. van Belle, G. Fillenbaum, and A. Heyman, *The Consortium to Establish a Registry for Alzheimer's disease.* Journal of Neurology, 1993. **43**: p. 2457-2465.
74. Kiehl, K. and T. Gray, *Visual and Auditory Presentation Package (VAPP) Home Page*. 2001.
75. Cox, R.W., Z. Saad, R. Reynolds, P. Christidis, R. Hammett, G. Chen, D. Glen, R. Doucette, and A. Clark, *AFNI: software for analysis and visualization of functional magnetic resonance neuroimages*. 2001, Cox, R.
76. Buckner, R.L., P.A. Bandetti, K.M. O'Craven, R.L. Savoy, S.E. Petersen, M.E. Raichle, and B.R. Rosen, *Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging.* Proc. Natl. Acad. Sci. USA, 1996. **93**: p. 14878-14883.
77. Dale, A.M. and R.L. Buckner, *Selective averaging of rapidly presented individual trials using fMRI.* Hum. Brain Mapp., 1997. **5**: p. 329-340.
78. McCarthy, G., M. Luby, M. Gore, and J. Goldman-Rakic, *Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI.* J. Neurophysiol., 1997. **77**: p. 1630-1634.
79. Zarahn, E., G. Aguirre, and M. D'Esposito, *A trial-based experimental design for fMRI.* Neuroimage, 1997. **6**: p. 122-138.
80. Buckner, R.L. and T.S. Braver, *Event-related functional MRI*.

81. Bandetti, P.A. and R.W. Cox, *Event-Related fMRI Contrast When Using Constant Interstimulus Interval: Theory and Experiment.* Magn. Reson. Medicine, 2000. **43**: p. 540-548.
82. Visscher, K.M., F.M. Miezin, J.E. Kelly, R.L. Buckner, D.I. Donaldson, M.P. McAvoy, V.M. Bhalodia, and S.E. Petersen, *Mixed blocked/event-related designs separate transient and sustained activity in fMRI.* NeuroImage, 2003. **19**: p. 1694-1708.
83. Talairach, J. and P. Tournoux, *Co-planar stereotactic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging*. 1988, Stuttgart: Thieme.
84. Bannister, P., C. Beckmann, T. Behrens, S. Clare, M. De Luca, I. Drobnjak, D. Flitney, P. Hansen, M. Jenkinson, H. Johansen-Berg, D. Leibovici, D. Mortimer, R. Niazy, T. Nichols, J. Saunders, S. Smith, J. Vickers, M. Woolrich, and Y. Zhang, *FMRIB Software Library*. 2000.
85. Hautzel, H., F.M. Mottaghy, and D. Schmidt, *Topographic segregation and convergence of verbal, object, shape and spatial working memory in humans.* Neurosci Lett, 2002. **323**(2): p. 156-160.
86. Cabeza, R., J.K. Locantore, and N.D. Anderson, *Lateralization of prefrontal cortex activity during episodic memory retrieval: A positron emission tomography study.* J Cogn Neurosci, 2001.
87. Cabeza, R., N.D. Anderson, J.K. Locantore, and A.R. McIntosh, *Aging gracefully: Compensatory Brain Activity in High-Performing Older Adults.* NeuroImage, 2002. **17**: p. 1394-1402.
88. Mottaghy, F.M., T. Döring, H.-W. Müller-Gärtner, R. Töpper, and B.J. Krause, *Bilateral perieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation (rTMS).* European Journal of Neuroscience, 2002. **16**: p. 1627-1632.
89. Davidson, R.J., D. Pizzagalli, J.B. Nitschke, and K. Putnam, *Depression: perspectives from affective neuroscience.* Annu. Rev. Psychol., 2002. **53**: p. 545-574.
90. Harvey, P.-O., P. Fossati, J.-B. Pochon, R. Levy, G. LeBastard, S. Lehericy, J.-F. Allilaire, and B. Dubois, *Cognitive control and brain resources in major depression: An fMRI study using the n-back task.* NeuroImage, 2005. **26**: p. 860-869.
91. Bush, G., P. Luu, and M.I. Posner, *Cognitive and emotional influences in anterior cingulate cortex.* Trends Cogn Sci, 2000. **4**(6): p. 215-222.
92. Ridderinkhof, K.R., M. Ullsperger, E.A. Crone, and S. Nieuwenhuis, *The role of the medial frontal cortex in cognitive control.* Science, 2004. **396**(5695): p. 12959-12964.
93. Fiez, J.A., E.A. Raife, D.A. Balota, J.P. Schwarz, M.E. Raichle, and S.E. Petersen, *A positron emission tomography study of the short-term maintenance of verbal information.* Journal of Neuroscience, 1996. **16**: p. 808-822.
94. Jonides, J., E. Schumacher, E.E. Smith, R. Koeppe, E. Awh, P.A. Reuter-Lorenz, C. Marshuetz, and C.R. Willis, *The role of parietal cortex in verbal-working memory.* Journal of Neuroscience, 1998. **18**: p. 5026-5034.
95. Schumacher, E., E. Lauber, E. Awh, J. Jonides, E.E. Smith, and R. Koeppe, *PET evidence for an amodal verbal working-memory system.* NeuroImage, 1996. **3**: p. 79-88.
96. Gazzaley, A., J. Rissman, and M. D'Esposito, *Functional connectivity during working memory maintenance.* Cognitive, Affective & Behavioural Neuroscience, 2004. **4**(4): p. 580-599.
97. Smith, E.E. and J. Jonides, *Storage and executive processes of in the frontal lobes.* Science, 1999. **283**: p. 1657-1661.
98. Smith, E.E., J. Jonides, and R. Koeppe, *Dissociating verbal and spatial working memory using PET.* Cereb Cortex, 1996. **6**: p. 11-20.
99. Thal, D.R., U. Rub, M. Orantes, and H. Braak, *Phases of A beta-deposition in the human brain and its relevance for the development of AD.* Neurology, 2002. **58**(12): p. 1791-1800.

100. Braak, H. and E. Braak, *Neuropathological staging of Alzheimer-related changes.* Acta Neuropathol, 1991. **82**: p. 239-259.
101. Purves, D., D. Fitzpatrick, G.J. Augustine, L.C. Katz, S.M. Williams, J.O. McNamara, and A.-S. LaMantia, *Complex Brain Functions*, in *Neuroscience*. 2001, Sinauer Associates, Inc.: Sunderland, Massachusetts, USA.
102. Geula, C., *Abnormalities of neural circuitry in Alzheimer's disease: hippocampus and cortical cholinergic innervation.* Neurology, 1998. **51**(Suppl 1): p. S18-S29.
103. Gusnard, D.A. and M.E. Raichle, *Searching for a baseline: functional imaging and the resting human brain.* Nat Rev Neurosci, 2001. **2**: p. 685-694.
104. Raichle, M.E., A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, and G.L. Shulman, *A default mode of brain function.* Proc Natl Acad Sci, 2001. **98**: p. 676-682.
105. Binder, J.R., J.A. Frost, T.A. Hammeke, P.S. Bellgowan, S.M. Rao, and R.W. Cox, *Conceptual processing during the conscious resting state. A functional MRI study.* J Cogn Neurosci, 1999. **11**: p. 80-95.
106. Greicius, M.D., B. Krasnow, A.L. Reiss, and V. Menon, *Functional connectivity in the resting brain: A network analysis of the default mode hypothesis.* Proc Natl Acad Sci, 2003. **100**(1): p. 253-258.
107. McKiernan, K.A., J.N. Kaufman, J. Kucera-Thompson, and J.R. Binder, *A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging.* J Cogn Neurology, 2003. **15**: p. 394-408.
108. Greicius, M.D., G. Srivastava, A.L. Reiss, and V. Menon, *Default-mode network activity distinguishes Alzheimer's disease from healty aging: Evidence from functional MRI.* Proc Natl Acad Sci, 2004. **101**(13): p. 4637-4642.

9 List of Abbreviations

Aβ	Amyloid β
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADRDA	Alzheimer's Disease and Related Disorders Association
AFNI	Analysis of Functional Neuroimaging
ANCOVA	Analysis of Covariance
APOE ε4	Apolipoproteine E allele ε4
APP	Amyloid Precursor Protein
BA	Brodmann Area
BOLD	Blood-Oxygenation-Level Dependent
CERAD	Consortium to Establish a Registry for AD
CDRS	Clinical Dementia Rating Scale
CIDI	Composite International Diagnostic Interview
CT	Computer Tomography
DMN	Default Mode Network
DRS	Dementia Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogramm
^{18}FDG	^{18}Fluor marked Fluor-2-deoxy-2-D-glucose
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GDS	Global Deterioration Scale
GK	gesunde Kontrollpersonen
GLM	General Linear Model
HC	Healthy Control
LKS	leichte kognitive Störungen
MCI	Mild Cognitive Impairment
a-MCI	Amnestic Mild Cognitive Impairment
md-MCI	Multiple Domain Mild Cognitive Impairment
MMSE	Mini-Mental State Exam
MNI/ICBM	Montreal Neurological Institute/International Consortium for Brain Mapping
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NMR	Nuclear Magnetic Resonance

OHC	Older Healthy Control
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
T	Tesla
TE	Echo Time
TR	Repetition Time
VAPP	Visual and Auditory Presentation Package
WM	Working Memory
YC	Young Control

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