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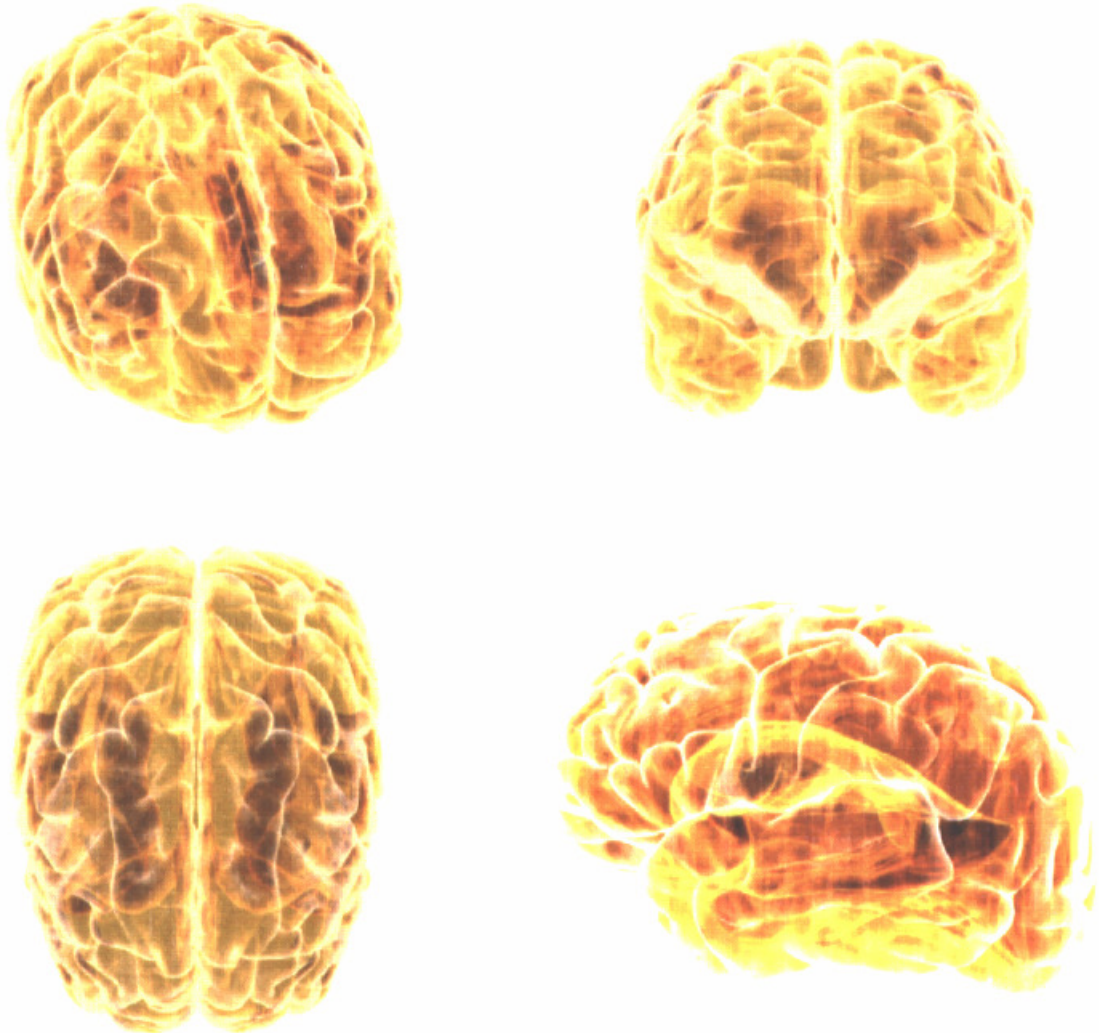
Functional Neurobiology in Normal Aging, Mild Cognitive Impairment and Alzheimer's Disease:

Focus on visuospatial processing using functional Magnetic Resonance Imaging



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FUNCTIONAL NEUROBIOLOGY IN NORMAL AGING, MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE:

Focus on Visuospatial Processing using functional Magnetic Resonance Imaging

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Cover: 3D illustrations of a nearly lucent brain showing its gyri and sulci.
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To my mother and my family with love
In memory of those recently gone

ABSTRACT

With the proportional increase of the aging population in the coming decades as well as a continuously augmenting life expectancy, the effects of neurodegeneration on brain function are a topic of increasing importance. Of special interest are tools that probe the functional consequences of neurodegenerative processes and possible compensatory mechanisms that might emerge. This thesis uses functional magnetic resonance imaging, fMRI to investigate visuospatial processing in early adulthood, old age and during different stages in the course of Alzheimer's disease, AD (including mild cognitive impairment, MCI), with the aim to relate the functional activation changes in aging and dementia to the task demand (assessed by reaction time, RT), and task performance (% correct responses).

Using an angle discrimination task with varying task demand we could demonstrate that all groups engaged a visuospatial network including bilateral core regions in parietal, occipital, and frontal cortex as well as basal ganglia. In these regions a general pattern of a linear relationship (either by using correlation analysis **(study I)** or by incorporating a reaction time dependent hemodynamic response predictor in the statistical model **(study II-V)**) between cortical activation and behavioral performance could be observed, reflecting increased cortical processing due to increased task demand.

However, the processing efficiency or relative contribution of the components in this network differed depending on age and disease. In **study III** we found an age-related task demand dependent change of activation, suggesting that age modulates the utilization of cerebral networks, which has bearing on the behavioral response in the elderly subjects. The results of a weaker relation between task demand and brain activity in several areas of the visuospatial network in elderly compared to young subjects indicate that age-related decrease in processing speed is related to a decline in the neural correlates of processing efficiency. In **study V** we found an enhanced parietal activation (especially left sided) pattern in patient that later progressed to AD compared to patients that remained stable (SMCI) and controls. This could reflect a reduced neuronal efficacy due to accumulating AD pathology, in which the increased activation could serve as a compensatory role for PMCI patients to achieve the same level of behavioral task performance as the controls and SMCI. However, as the pathological changes progress in AD, abnormal brain function was observed in the parietal cortices. A weak and sometimes absent increase in BOLD signal with increasing task demand was demonstrated in **study IV** in several regions in the dorsal visual pathway in AD patients compared to controls, suggesting a failure to modulate the neural response to increased task demand.

Further, it was shown that the groups also differed with respect to the general BOLD signal increase of activation irrespective of task demand. In **study III-IV**, an age- and disease related reduction in occipital activity was discovered. These findings could be due to a decline in sensory processing due to age which is worsening further by the neurodegenerative disease. However, in **study III** we also found an age-related increase in several prefrontal regions, which was interpreted to reflect a compensatory pathway in which older brains may apply a different strategy in order to solve the task with similar task performance as the younger subjects. A similar compensatory effect could be demonstrate in the PMCI patients **(study V)**, reflected as an increase of activation in left precuneus (as compared to SMCI and controls). In **study IV**, AD patients demonstrated a weaker general increase in BOLD signal in these areas (e.g. left precuneus, and prefrontal cortex) suggesting that the above reported compensatory pathways are limited in AD patients. Instead, we found an increased activation in the right

ventral pathway, which might reflect a potential secondary compensatory mechanism for the reduced functional capacity of the parietal regions in AD patients.

A proposed integrative model that applies to the functional activation studies of both healthy aging and Alzheimer's disease and its precursors is presented. This model reveals that alterations in the visuospatial network, independently of its cause, lead to changes in functional activation which seems to follow similar rules in aging and dementia. Thus, the findings presented in this thesis are providing one step in the unraveling of the physiological and pathophysiological mechanisms behind age- and disease related cognitive decline.

Key words: Alzheimer's disease; brain function; functional magnetic resonance imaging; mild cognitive impairment; normal aging; task demand; visuospatial processing

SAMMANFATTNING PÅ SVENSKA

När vi åldras blir vi (förhoppningsvis) klokare, men åldrandet är också förknippat med perceptuella och kognitiva förändringar av olika slag. En av de kognitiva funktioner som förändras med ökad ålder och vid demens är den visuospatiala förmågan. Denna funktion refererar till vår förmåga att processa och tolka information vi får via ögonen om var objekt finns i vår omgivning. Denna funktion är till exempel grunden till att vi kan röra oss runt i olika miljöer och orientera oss riktigt. Den utgör alltså en viktig del av våra kognitiva funktioner och om denna funktion drabbas kan den påverka en stor del av våra dagliga rutiner och individens livskvalitet, inte minst för dem som lever med neurodegenerativ sjukdom som exempelvis Alzheimers sjukdom.

Idag vet vi väldigt lite om orsakerna till hur normalt åldrande påverkar den biologiska basen av kognition och skillnaden mellan normalt till patologisk orsak av de åldersrelaterade kognitiva försämringarna. Av särskilt intresse är därför att hitta tekniker och modeller som kan detektera och göra det möjligt att studera funktionella konsekvenser av neurodegenerativa processer och möjliga *kompensatoriska* mekanismer som kan dyka upp. Utvecklingen av olika hjärnavbildningstekniker har under det senaste årtiondet gett oss möjlighet att *in vivo* observera hur hjärnan arbetar när en person får utföra en uppgift. Dessa tekniker ger oss därmed möjligheten för oss att ”kika in” i hjärnan för att få en inblick av den underliggande neurobiologin som krävs för att individen ska lyckas lösa en uppgift.

Målet med denna avhandling

I denna avhandling har vi använt oss av hjärnavbildningstekniken funktionell magnetresonanstomografi (fMRI från eng. functional magnetic resonance imaging) för att titta på aktiviteten i hjärnan när individer får utföra ett visuospatialt test. För att öka vår kunskap om hur hjärnan arbetar vid ökad ålder samt vid neurodegenerativ sjukdom har vi undersökt individer i olika stadier; från friska unga till friska äldre individer samt personer som lider av Alzheimers sjukdom, inklusive de som är i ett förstadium till demens s.k. mild kognitiv svikt (MCI från eng. mild cognitive impairment).

Huvudmålet med de olika studierna var att undersöka huruvida det är möjligt att kartlägga skillnader i hjärnans aktivitet (vilka delar av hjärnan som aktiveras för att lösa uppgiften samt om den uppmätta signalen (se nedan) är olika) mellan grupperna och relatera dessa skillnader till mängden neuronal skada, svårighetsgraden på uppgiften samt hur bra gruppen presterar på hela testet.

Hjärnans arbete och fMRI

Hjärnans huvudsakliga arbete är att transportera och processera information. Detta gör den med hjälp av hjärnceller eller *neuron* vilka aktiveras genom frisläppandet (och sedan återupptag) av kemiska neurotransmittorer (vanligtvis glutamat) samt genom propagering av en förhöjd membran potential. Båda dessa processer innebär transport av joner över cellmembranet. Man har uppskattat att det i en normalstor vuxen hjärna finns ca 100 miljard neuron! Neuronen är sammankopplade med varandra och bildar ett komplext *nätverk* i hjärnan. För att kunna utföra en fysisk och/eller mental funktion är det nödvändigt att den eller det nätverket som ansvarar för den specifika uppgiften vi vill utföra dels existerar och dels fungerar. När du utför en specifik uppgift kommer ett specifikt nätverk av neuron, ofta spatialt distribuerat i hjärnan, att aktiveras vilka

arbetar tillsammans för att lösa uppgiften. Man skulle faktiskt kunna jämföra hjärnans arbete som en kombination av en dator och en kemisk fabrik.

Funktionell MRI är en teknik som gör det möjligt att mäta och lokalisera vilka delar av hjärnan som blir aktiva när vi utför en uppgift och därmed ge oss en bild av nätverket för den specifika uppgiften. När man utför ett experiment med fMRI får försökspersonen ligga i en så kallad magnetkamera och utför ett test (se bild 1). Som namnet antyder är man omgiven av ett magnetfält (1.5 Tesla vid Karolinska Univesitetssjukhuset i Huddinge) och det är de magnetiska egenskaperna av järn i blodets hemoglobin som gör det möjligt att se bilder av hjärnan när personen utför en uppgift. Tekniken är baserad på det faktum att när ett område blir aktiverat (dvs neuron aktiveras) så kommer blodflöde till detta område också att öka till följd av detta. Det tillströmmande blodet har med sig syre och andra näringsämnen som behövs för att området ska kunna utföra arbetet. Det är detta blodflöde som vi ser som en ökad signal (dessa lyser upp som gulorangea områden) när vi analyserar i våra bilder. Tekniken ger oss därmed ett indirekt mått på hur neuronen arbetar i hjänan. Mängden blod är också kopplat till mängden neuronal aktivitet. I det fall uppgiften blir svårare att lösa behövs fler neuron för att lösa uppgiften, vilket innebär att kravet på mer blod till området också ökar. Denna ökning av blodflöde registreras som en ökad signal med tekniken och har därför kommit att kallas för kvantitativ fMRI då den förlitar sig på att hitta modulering av signalen i hjärnan.

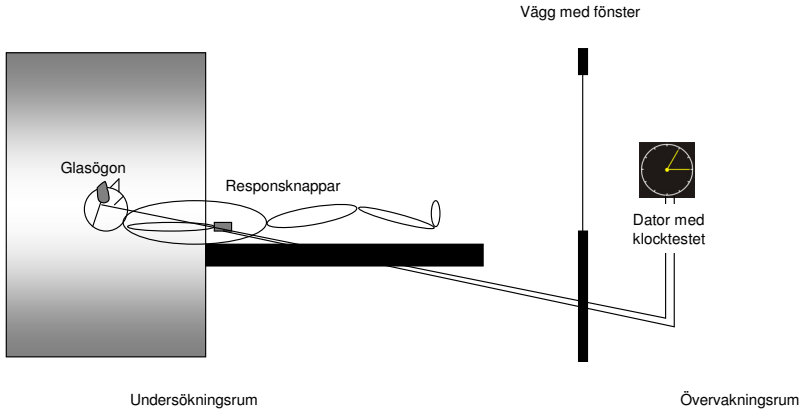

Bild 1. Skiss över experimentuppställningen. I övervakningsrummet, mitt emot undersökningsrummet, finns en bärbar dator där programmet med uppgiften körs. Försökspersonen ligger ned i magnetkameran och får där ha på sig ett par ”video” glasögon samt hålla en knappsats i höger hand vilka båda är kopplade till datorn utanför.

Modulering av hjärnans arbete

För att studera visuospatial funktion har vi konstruerat ett klocktest där uppgiften är att försöka att urskilja graden mellan två (lika långa) visare. Försökspersonen skall sedan indikera med hjälp av två knappar om klockan som visas har 60 grader (10 minuter) mellan visarna eller inte har 60 grader (dvs antigen mindre eller större än 60 grader) mellan visarna. För att göra det lättare och svårare att diskriminera klockans gradtal ändrades visarnas längder.

I vår första **studie (I)** lät vi 10 friska unga individer (medelålder 26 år) utföra testet för att undersöka vilka områden i hjärnan som aktiveras samt om det är möjligt att detektera om signalen i hjärnan ändras beroende på om uppgiften är lättare eller svårare att lösa. Vi kunde i denna studie visa att det främst är områdena i parietal loben (hjässloben) som aktiveras när försökspersonerna utför klocktestet och att signalen i detta område ökar med ökad svårighetsgrad (mätt genom den ökade reaktionstiden).

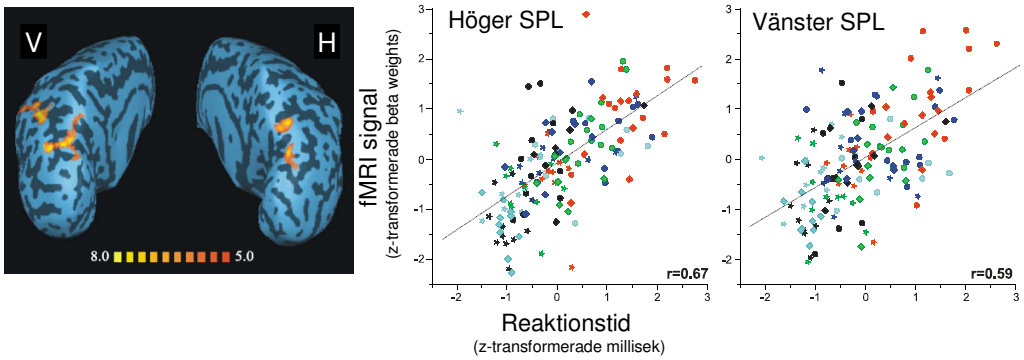

Bild 2. I första delstudien kunde vi visa att vårt klocktest aktiverar parietalloben (se guloreanga områden i den ”uppblåsta” medelhjärnan för unga individer). I dessa områden fanns en positiv korrelation mellan reaktionstid och fMRI signal.

Detta fick vi fram genom att för varje individ ta ut signalen från detta område och korrelera med reaktionstiden för en specifik klocka (se bild 2).

Studera hela visuospatiala nätverket

I den andra **studien (II)** vidareutvecklade vi vår metod att detektera vilka områden som modulerar sin aktivitet med svårighetsgraden ytterliggare genom utveckla en metod och låta analysprogrammet direkt ta hänsyn till individens reaktionstid för varje enskild klocka. Detta visade sig vara en mycket mer tideffektiv och mer sensitiv metod vilket medförde att vi nu kunde studera flera områden i hjärnan som modulerade sin aktivitet med svårighetsgraden i det visuospatiala nätverket. Förutom de tidigare kända områdena i parietal loben kunde vi visa att unga friska individer också använder områden i frontal loben (framhjärnan) samt delar av det limbiska systemet för att lösa uppgiften.

Normalt åldrande

När vi åldras eller vid ett sjukdomstillstånd är det viktigt att också beakta hjärnans förmåga att förändra sitt sätt att arbeta. Detta kan den göra genom att omorganisera vilka områden i hjärnan som ska användas för att lösa uppgiften s.k. plasticitet. För att studera om det finns några åldersrelaterade skillnader i hur man utför och aktiverar hjärnan undersökte vi i **studie III** en grupp friska äldre individer (medelålder 66 år) och jämförde med våra friska unga individer. Vi fann att äldre försökspersonerna tog längre tid på sig att lösa alla uppgifter. Detta resultat stämmer väl överrens med hypotesen att äldre personer tar längre tid på sig att processa uppgiften, vilket ofta uttrycks som att ädre individer upplever sig tänka mer ”långsamt” jämfört med när man var yngre. När vi undersökte korrelationen mellan reaktionstiden och fMRI signalen fann vi att denna var mycket svagare jämfört med de yngre i flera områden i det visuospatiala nätverket (framför allt i parietal loben) Vi fann också att signalen i synkortex var mycket lägre hos de äldre individerna jämfört med de yngre, samt att flera ”extra” områden i frontal loben var aktiverade hos de äldre individerna. Slutsatsen vi drog av dessa resultat var att när vi åldras så minskar vår förmåga att utnyttja alla hjärnresurser, vilket syns tydligt när uppgiften blir svårare eftersom de äldre inte lyckas modulera sitt hjärnsvar lika bra som de yngre. Ytterliggare ett bevis på denna försämring är den lägre aktiviteten i synkortex som registrerades hos de äldre individerna, vilken kan tolkas som att de har en nedsatt perception och därmed svårare att registrera syninformation. Områdena i

frontalloben kan ha aktiverats för att kompensera för denna försämring (plasticitet). Dessa förändringar kan gemensamt ha lett till att de äldre löste uppgiften långsammare men ändå lyckades prestera med samma resultat (lika många rätt).

Alzheimers sjukdom

I **studie IV** ville vi undersöka om vårt klocktest kan ge oss en insikt i den underliggande neuronala mekanismen för försämring av visuospatial funktion vid Alzheimers sjukdom. En grupp patienter med Alzheimers sjukdom i tidig fas fick utföra klocktestet och sedan jämförde vi resultatet med en åldersmatchad kontroll grupp. Vi fann att trots att både grupperna hade samma reaktionstider för att lösa uppgifterna så hade Alzheimer patienterna mer fel än kontrollerna. När vi sedan tittade på hjärnaktiviteten fann vi att korrelationen mellan reaktionstid och fMRI signal i flera områden i det visuospatiala nätverket var mycket svagare och ibland inte signifikant alls hos patienterna. Liksom i studie III fann vi att Alzheimer patienterna inte lyckats aktivera synkortex jämfört med kontrollerna, vilket skulle kunna tolkas på samma sätt som ovan att patienterna har nedsatt perception och inte kan integrera syninformationen lika bra. Alzheimer patienterna hade dock ett område i mediala temporal loben som uppvisade högre signal jämfört med kontrollerna. Sammantaget tyder dessa resultat på att Alzheimer patienterna inte lyckas aktivera det visuospatial nätverket för att kunna lösa uppgiften korrekt och detta skulle kunna bero på att sjukdomen har förstört de neuronala resurser som behövs för att aktivera det visuospatial nätverket. Trots detta försöker hjärnan att kompensera denna förlust genom att utnyttja andra områden i hjärnan vars huvuduppgift inte är att lösa visuospatiala uppgiften (temporal loben).

Mild kognitiv svikt – preklinisk Alzheimers sjukdom

I den sista **studien (V)** ville vi undersöka hur tidigt vi kan se skillnader i hjärnan hos individer som lider av Alzheimers sjukdom och om det är möjligt att identifiera dessa skillnader innan en klinisk diagnos av Alzheimers sjukdom har fastställts. För att undersöka detta studerade vi en grupp individer som lider av MCI och följde sedan denna grupp i ungefär 3 år. Vissa av dessa individer försämrades under dessa år och blev omdiagnosticerade till Alzheimers sjukdom och andra förblev stabila efter uppföljningen. Med denna information kunde vi därför gruppera individerna i en preklinisk grupp (PMCI efter eng. progressive MCI) och en stabil grupp (SMCI av eng. stable MCI). När vi jämförde PMCI gruppen mot en grupp matchade friska kontroller och SMCI fann vi att dessa individer aktiverade områden i visuospatiala nätverket mycket mer än dessa, (vilket kan jämföras med Alzheimer patienterna som uppvisade en lägre och ickesignifikant aktivitet i dessa områden). Detta tolkade vi som att individer i ett förstadium (prekliniskt stadium) av Alzheimers sjukdom måste utnyttja mer hjärnresurser för att kunna lösa uppgiften lika bra som friska kontroller, vilket kan bero på att området redan är skadat av Alzheimer patologi.

Integrerad modell för åldrande och sjukdom

Genom att skapa en integrerad modell, kunde vi visa att de redovisade funktionella förändringar, oberoende av dess orsak, alla leder till förändringar i den funktionella aktiviteten vilka verkar följa samma regler vid åldrande och vid sjukdom. Fynden i denna avhandling kan därför ses om ett steg i försöket att hitta de fysiologiska och patofysiologiska mekanismerna bakom ålders och sjukdomsrelaterad kognitiv försämring.

LIST OF PUBLICATIONS

This thesis consists of two parts. The first part serves to put the contents of the second part into a broader context by giving a background to how fMRI can be used to measure brain function, an outline of visuospatial processing and a description of the current understanding of the aging brain and Alzheimer's disease.The second part consists of the following publications, which are referred to in the text by their Roman numerals:

I. **P. Vannini,** O. Almkvist, A. Franck, T. Jonsson, U. Volpe, M. Kristoffersen-Wiberg, L-O. Wahlund, T. Dierks.
Task demand modulations of visuospatial processing measured with functional magnetic resonance imaging.
NeuroImage **21,** 58-68, (2004).

II. C. Lehmann, **P. Vannini,** L-O. Wahlund, O. Almkvist, T. Dierks.
Increased sensitivity in mapping task demand in visuospatial processing using reaction-time-dependent hemodynamic response predictors in rapid event-related fMRI.
NeuroImage **31**, 505-512, (2006).

III. **P. Vannini,** C. Lehmann, O. Almkvist, T. Jonsson, C. Kiefer, C. Menzi, L-O.Wahlund, T. Dierks.
When things are getting difficult: Brain basis of age-related slowing in visuospatial processing.
Submitted.

IV. **P. Vannini,** C. Lehmann, T. Dierks, M. Viitanen, L-O. Wahlund, O. Almkvist.
Failure to modulate neural response to increased task demand in mild Alzheimer's disease: fMRI study of visuospatial processing.
Submitted.

V. **P. Vannini,** O. Almkvist, T. Dierks, C. Lehmann, L-O. Wahlund
Reduced neuronal efficacy in progressive mild cognitive impairment: A prospective fMRI study on visuospatial processing
Psychiatry Research: Neuroimaging, In press.

LIST OF ABBREVIATIONS

A	Anterior
AC	Anterior commissure
ACC	Anterior cingulate cortex
AD	Alzheimer's disease
ADL	Activities of daily living
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
APOE	Apolipoprotein E (gene)
BA	Brodmann area
BOLD	Blood oxygen level dependent
(r)CBF	(regional) cerebral blood flow
(r)CBV	(regional) cerebral blood volume
CDR	Clinical dementia rating scale
(r)$CMRO_2$	(regional) cerebral metabolic rate of oxygen utilization
(r)CMR_{glu}	(regional) cerebral metabolic rate of glucose
CSF	Cerebrospinal fluid
DLPC	Dorsolateral prefrontal cortex
DSM	Diagnostic and statistical manual of mental disorders
E.g.	For example, Lat. *exempli gratia*
EPI	Echo planar imaging
FIR	Finite impulse response
FOV	Field of view
FSIQ	Full scale intelligence quotient
FTD	Frontotemporal dementia
FWHM	Full width half maximum
GLM	General linear model
GPrC	Precentral gyrus
HAROLD	Hemispheric asymmetry reductions in old adults
HDR	Hemodynamic response
HERA	Hemispheric encoding/retrieval asymmetry
HRF	Hemodynamic response function
I	Inferior
ICD	International classification of diseases
I.e.	That is, Lat. *Id est*
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
IT	Inferior temporal cortex
K	Koniocellular
L	Left
LGN	Lateral geniculate nucleus
LR	Likelihood ratio
M	Magnocellular
MCI	Mild cognitive impairment

MeFG	Medial frontal gyrus
MFG	Middle frontal gyrus
mm	Millimeter
MMSE	Mini mental state examination
MOG	Middle occipital gyrus
MP-RAGE	Magnetization-prepared rapid acquisition gradient echo
(f)MRI	(Functional) magnetic resonance imaging
MT	Middle temporal area
MTG	Middle temporal gyrus
N	Listing of numbers
Na^+	Sodium ion
NFT	Neurofibrillary tangle
NMCI	Normalized mild cognitive impairment
NP	Neuritic plaque
P	Parvocellular
PC	Posterior commissure
PET	Positron emission tomography
PFC	Prefrontal cortex
PMCI	Progressive mild cognitive impairment
PP(C)	Posterior parietal cortex
R	Right
RT	Reaction time
ROI	Region of interest
SE	Standard error
s	Second
S	Superior
SD	Standard deviation
SCM	Stimulus convolution matrix
SC	Superior colliculus
SFG	Superior frontal gyrus
SMCI	Stable mild cognitive impairment
SOA	Stimulus onset asynchrony
SOG	Superior occipital gyrus
SPECT	Single photon emission computed tomography
SPL	Superior parietal lobule
T	Tesla
TE	Echo-time
(r)TMS	(repetitive) transcranial magnetic stimulation
TR	Repetition time
V1	Visual area 1, striate cortex
WAIS-R	Wechsler adult intelligent scale, revised
WMH	White matter hyperintensity

CONTENTS

The great tragedy of Science – the slaying of a beautiful hypothesis by an ugly fact.
[Thomas H. Huxley]

1 PROBING THE SECRETS OF THE BRAIN

1.1 GENERAL BACKGROUND TO THE THESIS

Understanding how the brain functions is key to understanding its malfunctions, such as neurodegenerative disorders. Thus, this requires not only the comprehension of the physiological working of neurons and glia cells, but it also demands a description of the networks that underlie a certain behavior. *In vivo* imaging is one tool for such observations since it has the opportunity to investigate the neurobiological correlates of behavior by identifying the brain region(s) that become "active" during the execution of a specific task. As the brain is aging or in the event of brain damage (e.g. neurodegenerative diseases), it's important to also take into account the brain's functional plasticity (or the lack of it) which is reflected in the capacity for anatomical reorganization or redistribution of cerebral resources. One way of increasing the knowledge about the underlying mechanisms of functional activation changes in aging and dementia is to examine individuals in early adulthood, old age, and during different stages in the course of dementia (including mild cognitive impairment, MCI). This thesis attempts to integrate the findings from such studies using a technique called functional magnetic resonance imaging (fMRI) and relate the functional activation changes during visuospatial processing in aging and dementia to the task demand (assessed with reaction time, RT), and task performance (assessed with accuracy, % correct responses).

This thesis starts with a general introduction to the art of mapping brain functions and subsequently the field of cognitive neuroscience in order to put the rest of the text in a wider context. It can also be read as a short background of the different studies included in the thesis.

1.1.1 The quest to understand the brain

The history of our quest to understand the brain is certainly as long as human history itself. For centuries, scientists and philosophers have pondered the relationship between memory, emotion, behavior, thought, consciousness, and the physical body[1]. The history of "mapping" brain functions begins in the last century when many scientists (the most prominent ones being Karl Spencer Lashley and Marie-Jean-Pierre Flourens) argued that the brain operated by the principle of *mass action*[2], also known as *equipotential* view (Finger, 2000). An even earlier view, known as *localizationist* view believed that there is substantial localization of many functions in the neural tissue of the brain, i.e. that specific types of brain functions are associated with a particular region of the brain[3]. This latter theory gave way to studies which sought to map out the primitive processes that are engaged when particular regions of the brain are active. In the 18th century the *phrenology* school of the German anatomist Franz Joseph Gall

[1] The first known writing on the brain is actually found in ancient Sumerian records (4000 B.C.), when an anonymous writer described the euphoric mind-altering sensations caused by ingesting the common poppy plant.

[2] A theory which states that areas of the brain work together for every task without much regional functional specialization.

[3] That the regions in the brain would act as specific functional modules.

formed the foundation for the concept of discreet cortical localizations, as the practitioners tried to read individual personality traits from bumps on their subjects' skulls. They believed that a lump at a certain place on the head corresponded with a particular personality trait and the larger the lump, the more of the trait (Zola-Morgan, 1995). Most of the theories in phrenology however proved to be incorrect. Nonetheless, the notion of cortical functional localisation still remains supported by current science, although today it is assumed that complex psychological processes is performed by a network of neuronal assemblies, often widely distributed, which forms specific types of *computational processes* that act together. The study of brain function progressed in the late 19th century, where the most progress in the study of brain function came from patients with neurological disorders or from electrode measurements on animals. This approach tried to map brain functions based on lesion studies, in that they observed how damage to a specific part of the brain could produce relatively specific deficits in the patients.

1.1.1.1 First step towards probing brain functions

To probe brain function, the most widely used technique has been to measure the cerebral blood flow (CBF) changes that are induced by neural activity. In fact, as we will see later also fMRI is depending on this relationship. This concept clearly lay behind the experiment performed in the 19th century by Angelo Mosso, an Italian physiologist who mainly studied patients with skull defects to monitor the changes in brain volume or temperature that are produced by brain activity (Mosso, 1880; Mosso, 1881; Mosso, 1894). He is also acknowledged for being the first to perform a functional "brain imaging" experiment[4], recounted by William James (1890) in his book The Principles of Psychology:

"[In Mosso´s experiment] the subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either the end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in the system."

By current standards of blood flow measurements, this experiment is quaintly crude, but it indicates that the idea of inferring neural activity in the brain from measurements of changes in local blood flow long preceded the ability to do such measurements (Raichle, 1998). However, although this robust empirical relationship has fascinated scientists for well over hundred years, its cellular basis remains largely unexplained despite considerable research (Raichle, 1998).

1.1.2 Pictures of the mind

A whole new appreciation of the neurobiological correlates behind our behavior (rather than just observing the consequences of these effects) arises in the last decade with the development of brain imaging techniques, like positron emission tomography (PET) in the 1980s and fMRI in the 1990s. Subsequently, the field of cognitive

[4] Which was probably the cheapest one too!

neuroscience (Gazzaniga, 1995; 1999)[5] emerged as an attempt for scientists to combine the experimental strategies of cognitive neuropsychology with these various techniques to examine how brain function supports mental activities.

1.1.2.1 Functional magnetic resonance imaging

Thus fMRI has proved to be a powerful non-invasive technique for studying brain function, with both good spatial (~4-6 mm) and good temporal (~6-8 s) resolution. The technique also offers considerable potential in early identification of patients with prodromal Alzheimer's disease (AD). Because fMRI does not use ionizing radiation (as used in PET) it can be applied repeatedly over the course of a year in the same subjects without risk (with appropriate precautions). This means that fMRI can measure longitudinal changes during the course of the disease and improve assessment of declines in brain integrity in patients with AD. Also, because the measure of brain functioning is more direct than inferences based on behavior or other systemic indicators such as cerebrospinal fluid (CSF) metabolites (e.g. Tau concentrations), fMRI is the most likely candidate to enable this improved assessment. If subtle brain changes predict which older adults are on the verge of converting to AD, and medications successfully slowed down or halted disease progression, then the disorder would cause fewer years of disability (Rosen et al., 2002).

However, fMRI also has potential hazards and discomforts. Although with careful subject selection and avoidance of known risks, fMRI is relatively safe (Rosen et al., 2002). For example, the enclosed nature of the MRI environment makes it difficult to tolerate for claustrophobic people. Also, the fMRI is particularly noisy, making it difficult to conduct studies with auditory stimuli and there is the potential for sensory stimulation such as minor muscle twitches, particularly at higher field strength than the standard clinical 1.5 Tesla (T) MRI. None of these issues with MRI are believed to be a danger. The truly dangerous situations arise from the fact that the MRI is a powerful magnet that can cause ferromagnetic implants to become projectiles and disrupt function of electrochemical devices like pacemakers (Rosen et al., 2002).

1.1.2.2 Study modulation of brain response

One main aim of neuroimaging studies (using fMRI) of the brain is to localize or "map" different brain functions (Matthews, 2003). That is, to identify which brain regions that is involved in the neural networks subserving a specific cognitive function. On the other hand if you are interested to gain a better understanding of how the different areas of the network for that cognitive process interact, one approach is to study modulation of brain responses. This specific application of fMRI has been termed *quantitative fMRI*, since it relies primarily on detection of changes in signal intensity (Matthews, 2003). The underlying hypothesis for this approach is based on the fact that the neuronal activity that is needed to perform a task usually depends on the task demands. Subsequently, when the task demand changes, either in magnitude or in quality, more neuronal activity is needed to solve the task. Relying on the premise that the hemodynamic responses vary with the amount of cortical processing engaged by the task, this increment in neuronal processing can be measured quantitatively in the fMRI signal.

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[5] Cognitive neuroscience is said to be included in the field of neuroscience and emerged 20 years ago.

1.1.3 Investigating normal aging and Alzheimer's disease

In the context of aging and dementia, however, the subjective task demand is additionally influences by the amount of damage to the brain structures that are involved in task processing (Prvulovic et al., 2005). It is therefore conceivable that with increasing regional damage, different compensatory mechanisms such as for example the recruitment of additional areas will be necessary to execute the task (Prvulovic et al., 2005). The interaction of task demand, different levels of neuronal damage and task performance is thus not only complex but also very dynamic as aging- and dementia-related degenerative processes increase over time (Prvulovic et al., 2005). Given that these complex relations have so far not been investigated in detail, the work in this thesis was set out to examine this by focusing on a restricted aspect of cognition, namely visuospatial processing, and to pursue this through a series of studies, tracking subjects from early adulthood to old age and during different stages of AD.

1.1.3.1 How do we discriminate angles?

Visuospatial functioning requires the ability to perceive and subsequently manipulate visual information (Harvey and Mohs, 2001). This is an important aspect of cognitive functioning because it is responsible for a wide range of activities of daily living, as for example, our ability to move around in an environment and orient ourselves appropriately. In a clinical setting, this ability is often measured through either the production or recognition of figures (Harvey and Mohs, 2001). One such test is clock-drawing tasks which have been used for decades to assess the mental status of patients with various neurological or psychiatric disorders, (see Freedman et al., 1994 for an overview). Subsequently, in the search for the neural correlates of visuospatial processing, we have adopted an angle discrimination task with varying task demand. Thus in this task, based on a clock, the subjects were instructed to indicate which angle the hands in a clock face were showing. From previous research, starting with the pioneering work of Ungerleider and Mishkin (1982), but later also from lesion studies (Newcombe et al., 1987) and functional imaging studies (e.g. Cohen et al., 1996), there is a substantial amount of evidence that visuospatial processing is subserved by the parietal lobes in the human brain. Thus, by using an a priori hypothesis the first question that we set out to answer was whether our angle discrimination task also activates these structures in healthy young individuals.

1.1.3.2 Seeing disease before clinical symptoms

Apart from a detailed mapping of the functions of various brain structures during visuospatial processing, we also wanted to elucidate whether our paradigm could reveal brain-activation patterns changes in healthy aging as well as providing further insights in the understanding of the pathophysiological mechanism underlying the impairment of visuospatial processing in AD. In addition, considering that that the early pathogenic process of AD is protracted and may extend several years before the clinical diagnosis can be set, there has been an increasingly interest in studies examining task related brain activity using fMRI in subjects at risk of developing AD, including healthy individuals with genetic risk of developing AD (i.e. APOE ε4 allelle) and individuals with MCI. These groups are considered to reveal a neuropathological burden that has not reached the threshold of clinically manifest AD (Prvulovic et al., 2005). However, considering that the clinical outcome of these individuals is uncertain, i.e. some will

progress to AD and others not, only a subgroup of those affected are supposed to represent preclinical stages of AD. Based on these problems it can therefore be difficult to conduct studies with the aim to correctly describe the clinical characteristics of preclinical AD and possible predictors of AD. One way of doing this is to conduct a prospective study. In this way, the term preclinical AD is used to describe subjects who have MCI at the baseline assessment and who become demented and have AD during the follow up period. This means that the distinction between subjects with MCI with and without preclinical AD is based on the outcome at follow up. This approach was used in the study in this thesis with the aim to investigate if it was possible to discriminate between a group of individuals that progressed to AD from those that remained stable and controls.

1.2 THE SCOPE OF THE THESIS

The opening of this thesis has been devoted to a detailed description of the history of mapping brain functions as well as outlined the approach used in this thesis to the study of cognitive decline in aging and AD. The next chapters are intended to give the reader a more detailed knowledge about how fMRI can be applied to the study of this as well as giving a general introduction of the current understanding of the aging brain and AD.

In *chapter two*, an overview of the physiological basis of brain function and the general principles underlying neuroimaging signals using fMRI is given.

The *third chapter* is intended to give a background to the theoretical framework and study design used in the study. Also, an outline of visual processing and in particular visuospatial processing including angle discrimination is given.

Chapter four is an introduction to the cognitive neuroscience of aging, which tries to relate age-associated cognitive changes to their neural substrates in order to understand the nature and mechanism of the relationship between behavior and neurobiology. Hence, a short overview of the cerebral changes (including anatomical and physiological characteristics) and the behavioural changes with age (focusing on visuospatial processing and the proposed general mechanism of age-related slowing of processing time) is presented followed by a short review of functional activation studies in healthy aging.

Chapter five contains an overview of the pathophysiology of AD, including the major anatomical and physiological changes occurring over the course of the disease. Also, the cognitive changes with a focus on visuospatial processing is given including a description of MCI and the preclinical phase of the disease as it is used in this thesis. This chapter also presents a short review of previous functional activation studies in MCI and AD.

In *chapter six* the general and specific aims of the study is presented and in *chapter seven* an overview of the subjects and methods used in the studies is presented.

Chapter eight and *nine* is dedicated to the data respectively statistical analysis.

A short outline of the major results from the different studies is presented in *chapter ten*, followed by a general discussion about the work presented in this thesis in *chapter eleven.* In this chapter a model is also proposed that aim to explain the underlying mechanisms of functional activation changes in normal aging and during different stages of dementia.

Chapter twelve summarizes the conclusions made in the thesis and last, expected future developments and suggestions for further research are discussed in *chapter thirteen.*

2 PHYSIOLOGICAL BASIS OF BRAIN FUNCTION

2.1 BRAIN WORK AND BRAIN IMAGING

The major work of the brain is the transfer and processing of information. This is achieved by *neuronal activity* [6] which in turn is linked to subsequent changes in blood flow and energy metabolism. Functional neuroimaging studies (e.g. with fMRI), can be used to map these regional changes in brain activity. This chapter will give a short introduction of how the brain works and how we can see these changes in the images acquired with fMRI.

2.1.1 How the brain works

The *neuron* is the basic functional unit of the brain. From the neuron's cell body (the central command centre), short processes called *dendrites* are projected. These receive message inputs from other neurons and then relay the information back to the cell body. Other long processes called *axons* conducts electrical impulses away from the cell body towards the dendrites of other neurons. This is done via propagation of electrical signals (action potentials), generated by exploiting the electrically excitable membrane in the axons (i.e. voltage gated sodium (Na^+) channels in the neuron membrane open due to an excitatory stimulus and causes Na^+ to diffuse in through the channels along their electrochemical gradient). Information is transferred between neurons by release of neurotransmitter molecules (glutamate being the most excitatory neurotransmitter) at *synapses*[7] (at the presynaptic terminal) and their subsequent interaction with specific receptors on target (postsynaptic) neurons, typically on a dendrite, cell body or any other part of the cell. These neurotransmitter-receptor interactions lead to changes in the membrane current flow, changing the postsynaptic neuronal membrane potential (and the accompanying extracellular electrical field). If the membrane potential reaches a certain threshold level, an action potential will be produced carrying the information further. Although the most interactions are *excitatory*, some synapses are *inhibitory* and limit subsequent neuronal excitation.

It has been estimated that the adult human brain has about 100 billion (10^{11}) neurons and 100 trillion (10^{14}) synapses. These neurons connect with one another through the synapses to form interconnected neural circuits. Furthermore, the contact of neurotransmitter with these receptors may then trigger the transmission of a nerve impulse down the second neuron and then onto further neurons until that a large number are activated coherently in a *functional network*. The establishment and maintenance of these networks are crucial to the biological computations that underlie perception and thought.

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[6] Neuronal activity is difficult to define properly. It includes several complex functional processes within the brain, both biochemical events (release/uptake of neurotransmitters) and electrophysiological processes (excitatory/inhibitory post synaptic processes, evoked potentials). See also section 2.1.1.

[7] Called chemical synapses and is the most common biological synapse in the brain.

2.1.1.1 Producing energy for brain work

Continuous neural activity and maintenance of homeostasis of the cerebral microenvironment are dependent on active processes (such as restoration of ionic gradients and repacking of neurotransmitter molecules) requiring energy. Most of this energy is used at or around the synapses. The primary energy "currency" in the brain is the hydrolysis of adenosine triphosphate (ATP) (Gjedde, 2001). In that sense, ATP is the link between energy utilizing and energy producing processes and several biochemical pathways are responsible for ATP synthesis in which the aim is to keep a constant concentration of this metabolite through different factors that are related to changes in its rate of utilization. Hence, there are several mechanisms for maintaining ATP concentration, in which the vast majority of the energy consumed by the brain is provided by the metabolism of glucose to carbon dioxide and water (i.e. *oxidative phosphorylation*) (Siesjo, 1978). Following this, with increased synaptic activity there is a greater local demand for delivery of oxygen. To meet this increased metabolic demand, neuronal activation is accompanied by increased local CBF.

2.1.2 Brain activation regulates cerebral perfusion

It is these behaviorally evoked changes in blood flow that are at the heart of most functional brain imaging signals. Beginning with the experiments performed by Angelo Mosso (1881) (see chapter 1) and later by the neurosurgeon John Fulton (1928) we now know that when the activity of a brain region increases, CBF to that region also increases. This mechanism, termed *functional hyperaemia*, is based on the concept of a coupling of neuronal functioning with both local brain energy demand and local brain metabolic variations and CBF variations. This important physiological principle was first evoked by Roy and Sherrington (1890), who in their famous seminal study concluded that:

"…the chemical products of cerebral metabolism contained in the lymph that bathes the walls of the arterioles of the brain can cause variations of the caliber of cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity".

Since then it has been hypothesized that functional hyperaemia is mediated by the release of vasoactive agents that act on local blood vessels to increase flow (Mosso, 1880; Roy and Sherrington, 1890; Iadecola, 1993), (but see Girouard and Iadecola, 2006 for a discussion of the vasoactive mediators known today). Current data indicate that the signals generated by these mediators are processed by vascular cells (endothelial cells, smooth muscle cells and pericytes), which act in concert to initiate the changes in vascular diameter (Iadecola 2004; Girouard and Iadecola, 2006). However, although the basic premise of this conjecture still remains valid, the precise nature of the relationship between neuronal activity and blood flow, termed *neurovascular coupling*[8], remains largely unknown.

[8] Neurovascular coupling refers to the close spatial and temporal relationship between neural activity and CBF.

2.1.2.1 The BOLD contrast mechanism

Functional MRI using the *Blood Oxygenation Level Dependent* (BOLD) method, originally termed by (Ogawa and Lee, 1990), depends on the blood-flow mediated relationship between neural activity and the concentration of deoxygenated hemoglobin across regions in the brain. This is illustrated in figure 2.1. Thus, when a neural event occurs anywhere in the brain, there is a local increase of oxygen usage that is followed within a few seconds by a larger fractional increase in blood flow and blood volume, resulting in a net decrease of the amount of deoxygenated hemoglobin in the microvasculature surrounding the activated region[9] (Fox and Raichle, 1986; Malonek, 1997). It has further been suggested that fMRI is sensitive to deoxygenated haemoglobin in the capillaries and draining venules surrounding synapses. Decrease in the concentration of deoxygenated haemoglobin lead to a small (few percent) BOLD signal intensity increase (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992), since blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility. Hence, the BOLD signal reflects the ratio of non-paramagnetic oxygenated haemoglobin to paramagnetic deoxygenated haemoglobin. In short, fMRI allows one to make inference about the localization of neural activity based on the assumption that neural activity alters this ratio by influencing several factors including CBF, cerebral blood volume (CBV) and cerebral blood oxygen consumption ($CMRO_2$) (Fox and Raichle, 1986; Buxton and Frank, 1997).

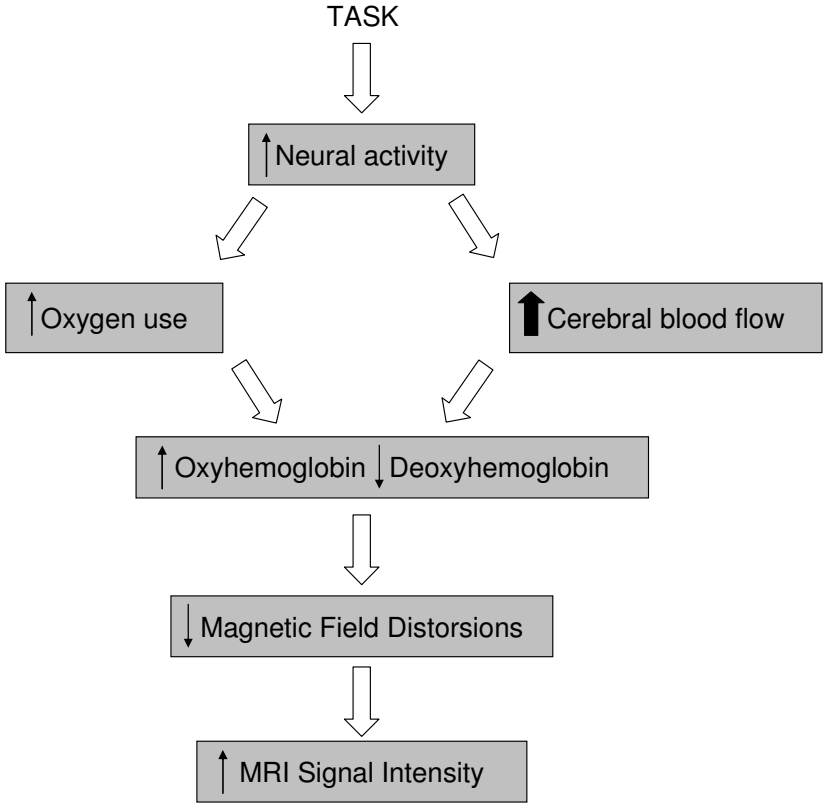


Figure 2.1 A schematic representation describing the connection between the neural activity and the hemodynamic response, giving rise to the measured (BOLD) fMRI signal. See text for a more detailed explanation.

[9] This observed overcompensation for the decrease in oxygen by delivering an oversupply of oxygenated blood is unclear at present.

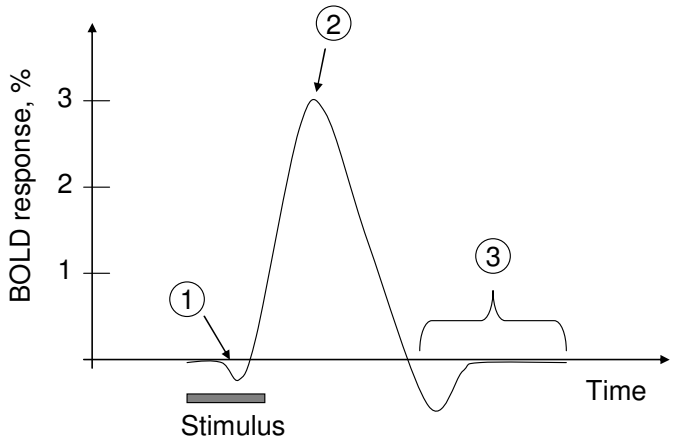


Figure 2.2 Schematic (simplified) representation of the BOLD response during a period of neuronal stimulation. A small negative "initial dip" (1) may be observed immediately after stimulus presentation. Signal begins to rise soon after stimulus begins resulting in "positive BOLD response" (2) which peaks after 5-8 s. Signal is suppressed after stimulus ends and there is a return of signal to baseline accompanied by a "post stimulus undershoot" (3).

2.1.2.2 Features of the BOLD signal

The typical time course of BOLD fMRI signal to a brief stimulus, the temporal impulse response function or *hemodynamic response function* (HRF), can be schematically divided into three epochs (figure 2.2). When the neural activity commences, the first epoch of the BOLD response starts with a very brief (0.5 - 1 second (s)) period during which the MRI signal decreases slightly below baseline (~0.5 %), also known as the "initial dip" (Menon et al., 1993). This subtle feature (observed most easy at higher magnetic field strengths) corresponds to an apparent surge in tissue deoxygenated hemoglobin levels occurring immediately following onset of stimulation, and has been attributed to a stimulus-driven increase in oxygen consumption occurring before the circulatory response. Subsequently, a more robust "positive BOLD response" is observed which peaks 5-8 s after the stimulus onset. This effect is due to the fact that activation-induced reductions in the amount of deoxyhemoglobin lead to an increase in the signal, usually around 2-3 % of the baseline signal level (depending on the magnetic field strength). Last, there is a return of the signal to the baseline, often accompanied by a "post stimulus (negative) undershoot" upon cessation of stimulation, that concludes with an exponential rise back to the pre-stimulation baseline level.

2.2 SUMMARY

This chapter has given a brief description of the physiological basis of brain function and the general principles underlying neuroimaging signals using fMRI. When nerve cells are active they consume oxygen which is carried by hemoglobin in red blood cells from local capillaries. This leads to local changes in the relative concentration of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic) and changes in local CBV in addition to changes in local CBF. The MR signal of blood is therefore slightly different depending on the level of oxygenation, which can be detected using appropriate MR pulse sequence, e.g. BOLD contrast. Higher BOLD signal intensities arise from decrease in the concentration of deoxygenated hemoglobin since the blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility.

3 INVESTIGATING BRAIN FUNCTION – FOCUS ON VISUOSPATIAL PROCESSING

3.1 APPLICATION OF FMRI

One main aim of neurophysiological studies (using BOLD fMRI) of the brain is to localize or *map* different brain functions (Matthews, 2003). That is, to identify which brain regions that are involved in the neural networks subserving a specific cognitive function. Similarly, to gain a better understanding of how the different areas of the network for that cognitive process interact, one approach is to study modulation of brain responses. This specific application of fMRI has been termed *quantitative fMRI*, since it relies primarily on detection of changes in signal intensity (Matthews, 2003). The following chapter provides a short background to the theoretical framework that tries to integrate cognition, such as visuospatial processing, to brain activation patterns using this latter approach, as well as a description of the study design used.

3.1.1 Modulation of brain function

The basis for using quantitative fMRI to study cognitive function is based on several key properties of the cortical system. These have been presented in detail by Just et al. (1999) and thus only a short overview is presented here.

The first basic signature property of cortical function is the fact that *thinking is work.* That is, the computational work underlying thinking and the execution of a given task requires energy and must be accompanied by some resource utilization (Just et al., 1999). As discussed in chapter 2, the work carried out by the brain's neural system subsumes several dimensions, including neurotransmitter function and various metabolic support systems. Thus, in this sense one can consider any brain region to be a sort of resource pool (Just et al., 1999).

The second basic property of cortical function is the notion that *thinking is self-organizing* in that the neural underpinnings underlying the execution of a given task will lead to a certain amount of resource utilization which is relative to the task demand imposed on the system (Just et al., 1999). That is, when the task demand changes either in magnitude or in quality, a physiological response would be expected including both increments in intensity of neural activation and the number of activated neurons to meet that demand. Based on the premise that hemodynamic responses vary with the amount of cortical processing engaged by the task (e.g. Buchel et al., 1996), fMRI can measure this increment quantitatively in the BOLD signal.

The third cortical property is the fact that *thinking is a team sport.* That is, a cognitive task often engages a large-scale cortical network, each brain area with its own set of computational specialization that cooperates to execute that task efficiently (Just et al., 1999). For example, visual perception could be said to be subserved by a network of areas including two main streams (ventral and dorsal) of visual information processing in the brain (see section 3.2). Perception of a certain stimuli will of course generate activity in a number of these different brain areas, which are highly interactive.

However, even though more than one area may be able to process the same information and produce the same or similar results, the precise qualitative nature of the

processing and hence its efficiency (resource use) would generally differ (Just et al., 1999). Similarly, the fact that a broad network of activation is brought into action by a cognitive task could reflect the fact that the functions of these areas are believed to be so fundamental to the performance of the cognitive task that they cannot be separated from the task (Podzebenko et al., 2002). Following this, the notion that one region increasingly responds to increasing task demand may enhance, in the same pattern, the workload of other regions (Carpenter et al., 1999; Podzebenko et al., 2002).

In sum, under normal conditions, when brain function is not altered by neurodegeneration or aging, these basic properties outlined above will give us an opportunity to study the network that is needed for successful execution of a given task such as visuospatial processing. Similarly, these basic properties may account for altered functional activation patterns responses in patients with declining brain function (i.e. aging, or during different stages Alzheimer's disease), where the task demand is influenced not only by parametric variations in the task at hand but also by the level of neurodegeneration.

3.1.2 Using reaction time as an index of task demand

The fact that increasing task demand yields to stronger cortical processing and consequently increased BOLD signal (as presented above) can therefore be used for identification of regions involved in the task under investigation. An operationalization of the task demand is only required, e.g., by measuring *reaction times* (RT). There are several reasons for using RT (such as choice RT with visual stimuli and manual keypress responses) as an index of performance and subsequent provide an indication of the imposed task demand for each subject. First, in the psychology literature, RT has traditionally been associated with the time at which mental processes, or computations, are continuously occurring in the components of an information processing system (e.g. (McClelland, 1979). Second, it is a continuous variable and hence does not have a ceiling effect. Also, it takes into account individual differences, both within the tasks to be performed and also between the subjects. Last, there is a well-documented relationship between RT and accuracy (see Salthouse, 2000 for a review), giving further proof of using RT as an index of the imposed task demand on the subject.

3.1.2.1 Event-related parametric design

Considering the above mentioned reasons for using RT as an index of task demand and based on the assumption that the magnitude of the hemodynamic response changes as a function of task demand, it has further been proposed that the relationship between these two variables can be used to study the functional involvement of a given brain region (Owen et al., 2003). Thus, using this approach termed *correlational/parametric design*, we hypothesized that what makes a brain region with a significant (linear) relationship between brain activation and RT critical is their association with *processing efficiency* on the task. A prerequisite for adopting this design is the use of an *event-related* approach when collecting the fMRI data (see also method). That is, for each single task stimulus, data is collected which permits not only spatial resolution but also temporal correlation information. Next, the application of this approach to visuospatial processing will be given.

3.2 VISUOSPATIAL PROCESSING

Visuospatial processing refers to our ability to process and interpret visual information about where objects are in space. This is an important aspect of cognitive functioning because it is responsible for a wide range of activities of daily living. For instance, it underlies our ability to move around in an environment and orient ourselves appropriately. Visuospatial perception is also involved in our ability to accurately reach for objects in our visual field and our ability to shift our gaze to different points in space[10]. The field of visuospatial thinking is a relatively diverse interdisciplinary research enterprise. However, an understanding of visuospatial thinking, and in particular how people represent and process visual and spatial information, is relevant not only to cognitive psychology but also with respect to pathophysiological states that we will discuss in more detail in chapter 5. The next section will therefore give a short background to visuospatial processing for further understanding of the study design used in the thesis.

3.2.1 Visual system pathways

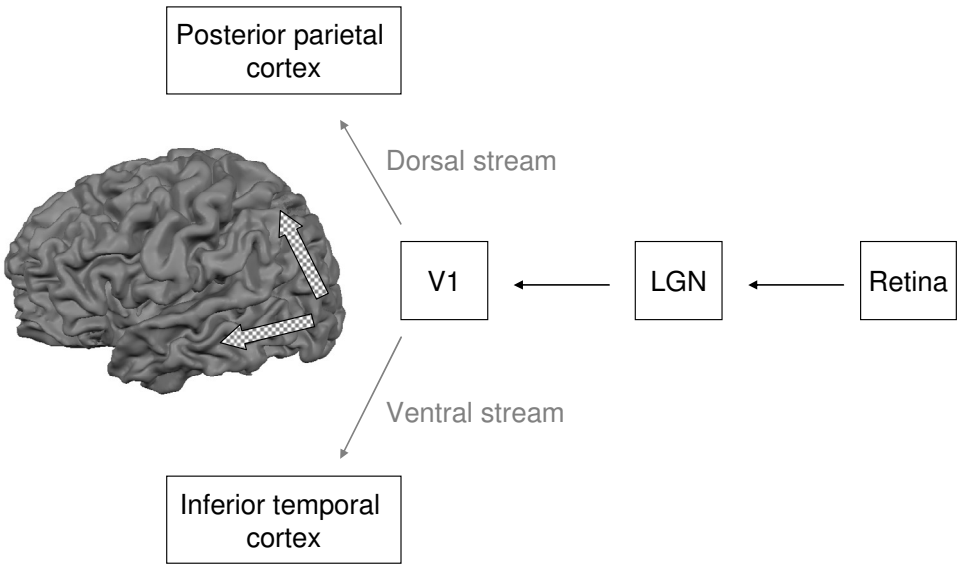
The human visual pathway begins with the eyes and extends through a complex patchwork consisting of several interior brain structures ascending to the various regions of the visual cortex, occupying the posterior 50 % or so of the cerebral cortex (see Zeki, 1993 for a review). But despite the complexity of the interconnections between these different areas, the visual system has traditionally been thought to be made up of at least two parallel pathways or broad streams of projections. These pathways process various unrelated attributes which are all coordinated in a visual image, making us experience the world as a whole. Moreover, the two pathways are quite different in anatomy as well as in function.

3.2.1.1 Anatomy of visual pathways

The division begins in the *retina* (the sensory part of the eye), where vision is generated by photoreceptors (rods and cones). The information then leaves the eye by way of the optic nerve, formed by the two major types of retinal ganglion cells (output cells of the retina); parvocellular (or type P) and magnocellular (or type M) ganglia[11]. There is a partial crossing of axons in the optic nerve at the optic chiasm. After they pass the optic chiasm, the axons of the retinal ganglion cells are now called the optic tract. The optic tract wraps around the midbrain to connect to the *lateral geniculate nucleus* (LGN) (the visual part of thalamus). In this region most of the fibers terminate in a precise retinotopic pattern (M cells terminate in two ventral magnocellular layers and P cells project to four dorsal parvocellular layers) (see e.g. Livingstone and Hubel, 1987). Other fibers terminate in the superior colliculus (SC), a paired structure on the roof of the midbrain, whereas other retinal ganglion cells project to other brain areas, such as the midbrain nuclei and suprachiasmatic nuclei. LGN serve as the primary relay nucleus for visual processing in cerebral cortex (Rosenzweig et al., 2004). From the LGN, axons fan out through the deep white matter of the brain, giving rise to the optic radiation (or geniculocalcarine tract). This highway of visual information then proceeds through the retro- and sublenticular parts of the internal capsule. The optic radiation

[10] I.e. it is involved in processing spatial information such as motion, depth, space, and position.

[11] There is also a third visual pathway, the koniocellular (K) pathway.



Adapted from Goodale and Westwood, (2004).

Figure 3.1 Schematic representation of the two streams of visual processing in the brain.. The retina sends projections to the dorsal part of the lateral geniculate nucleus (LGN) in thalamus, which projects in turn to primary visual cortex (V1) through the optic radiation. Next, from V1, two broad streams arises which are involved in complex visual perception. The ventral stream which ultimately projects to regions in the inferior-temporal (IT) cortex and the dorsal stream which projects to posterior parietal (PP) cortex (see dotted arrows overlaid on a 3-D reconstruction of the pial surface of the brain made from an anatomical MRI. The routes indicated by the arrows involve a series of complex interconnections (not shown).

ultimately projects to the *primary visual cortex* (also known as visual area 1 (V1) or striate cortex, corresponding to Brodmann area (BA) 17) at the back of the brain, in the region of the calcarine sulcus in the occipital lobe (Heimer, 1995; Rosenzweig et al., 2004). Here, inputs from the two eyes converge at the cortical level, making binocular effects possible.

3.2.1.2 Higher-order visual processing

The striate visual cortex projects next to other areas of the cerebral cortex (extrastriate visual cortical areas such as V2, V3, V4 and V5) that are involved in complex visual perception (Rosenzweig et al., 2004). It has been proposed that the cortico-cortical projections for visual processing that originate from the primary visual cortex are organized into two functionally and anatomically separate pathways, a ventral stream which runs from the occipital to the inferior temporal (IT) cortex, and a dorsal stream which runs from the occipital to the posterior parietal (PP) cortex (Ungerleider and Mishkin, 1982) (see figure 3.1). Furthermore, connections from the prefrontal cortex to both the dorsal and ventral pathways, as well as reciprocal connections within the pathways, provide a basis for top-down attentional control of perceptual processing (Madden et al., 2005).

The conclusion of two separate pathways was actually reached from the pioneering studies of temporal and parietal cortical lesions in monkeys by (Pohl, 1973; Ungerleider and Mishkin, 1982; Ungerleider et al., 1983). The results from these

studies demonstrated that lesions of IT cortex produced deficits in the animal's ability to discriminate between objects on the basis of their visual features but did not affect their performance on a spatially demanding “landmark task”. Conversely, lesions of the PP cortex produced deficits in performance on the landmark task but did not affect object discrimination learning.

Since then further support for the two visual processing streams in humans comes from lesion studies in patients (e.g. De Renzi, 1982; Newcombe et al., 1987; Farah, 1990). More recently, neuroimaging studies using PET (Haxby et al., 1991; Alivisatos and Petrides, 1997; Nobre et al., 1997), fMRI (Cohen et al., 1996; Dierks et al., 1998; Goebel et al., 1998) and fMRI in combination with transcranial magnetic stimulation (TMS) (Sack et al., 2002 a; 2002 b) have largely confirmed these basic facts while providing greater anatomical and functional specificity about the network of regions involved in object and spatial processing.

3.2.1.3 Anatomical definition of posterior parietal cortex

The human PP cortex comprises both the superior and inferior parietal lobules. Of these, the superior parietal lobule (SPL) consists generally of both the superior parietal gyrus and the intraparietal sulcus (IPS). It is defined as the area posterior to the postcentral sulcus and rostral to the IPS. The appearance of the parieto-occipital sulcus in the medial surface of the hemisphere defines the inferior limit of this area (see black drawings in figure 3.2). The inferior parietal lobule (IPL) on the other hand, can be divided into the supramarginal and angular gyri. This area is defined as the area caudal to intraparietal sulcus and anterior to the occipital area defined above. The lower limit of this area is defined by the appearance of the posterior part of the Sylvian fissure (see white drawings in figure 3.2).

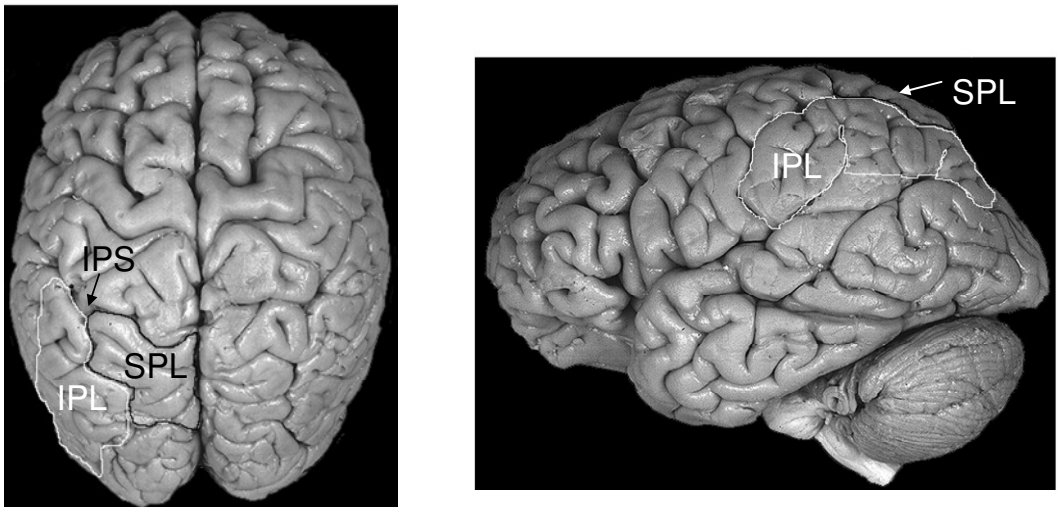


Figure 3.2 Brain surface anatomy showing the major structures (in dorsal view and lateral view of the left hemisphere) constituting the posterior parietal cortex; IPL= inferior parietal lobule; IPS= intraparietal sulcus; SPL = superior parietal lobule. Drawings by P. Vannini based on the Interactive digital atlas of brain structures (http://da.biostr.washington.edu).

3.2.2 Functions of the two visual systems

The most distinction between these two visual processing streams is the different type of information that each pathway extract from the visual scene. It has been hypothesized that the ventral stream, also called (the *What* system/pathway) is primarily concerned with object recognition information such as size, color, and texture (Mishkin et al., 1983). This system is also responsible for face recognition, and our ability to identify objects (Mishkin et al., 1983). In contrast, the dorsal stream (also called the *Where* system/pathway) is primarily concerned with the perception of spatial information, and the computation of extrapersonal and personal spatial localization (Mishkin et al., 1983). In 1992, Goodale and Milner extended the idea of distinct What and Where systems/pathways. They proposed that the Where pathway also serves as the interface between the visual system and the motor system (Goodale and Milner, 1992; Goodale et al., 1992; 1994; Goodale, 1993; Milner and Goodale, 1993; 1995; Milner, 1995; Goodale and Westwood, 2004). Because of that, they suggest that the two pathways should be renamed What and How pathways, reflecting the suggestion that visual perception occurs in the ventral pathway whereas visual processing for action occurs in the dorsal pathway. Their main source of evidence came from a stroke victim (D.F.), who had damage on her ventral pathway, leaving her dorsal pathway intact. When she was shown an oriented slot and asked to name its orientation, her performance was random. However, when asked to insert a block of wood into the slot, she performed almost flawlessly (Milner and Goodale, 1995). Today, most researchers believe that the dorsal pathway may include both these functions (as well as other not mentioned here) which have resulted in that this pathway has been termed the where/how pathway.

3.2.2.1 Increasingly complex analysis

The general principle underlying the vision pathways is that the complexity of analyses increases the further up the pathways the information travels (Ungerleider and Haxby, 1994) i.e. *bottom-up* hierarchial processing pathways. Hence, peripheral structures such as the retina, the optic nerve and tract, and primary visual cortex are multimodal in their function, whereas the visual association cortex is more specialized (Wurtz and Kandel, 2000). Following that, the analysis of visual information is in many aspects modular in design in that the output of early processes e.g. low-level visual discrimination processes in early cortical areas such as V1 and V2 supplies input for subsequent processes e.g. high-level visual functions in additional activation of large extrastriatal cortical networks (Courtney and Ungerleider, 1997; Grill-Spector and Malach, 2004; Kollias, 2004) i.e. SPL.

Thus, intuitively, the perceptual representation of an angle includes the representation of two lines as sub-parts, each part has its own properties such as orientation and length (Chen and Levi, 1996). Following this, using parametric fMRI, Ng et al. (2001) have shown that the cerebral region most specifically associated with a line orientation task was located in the right ventral extrastriate cortex. But it is also important to realize that some global attributes of angles, i.e. conjunction and area, are not attributes of the component lines (Chen and Levi, 1996). That is, that the spatial relations between the parts of an angle are not represented in the properties of the parts (Chen and Levi, 1996). Hence, it follows that more complex visual information is processed further up in the dorsal pathway.

3.3 OUTLINE OF THE STUDY DESIGN

3.3.1 Angle discrimination

The processing of spatial judgments, in particular discrimination of angles, has been found to reliably involve the dorsal pathway and especially the SPL (e.g. Dierks et al., 1998; Prvulovic et al., 2002; Sack et al., 2002 a). In these studies, the experimental task consisted of computation of the spatial coordinates of the handles in a clock and the recognition of a target angle amongst non-target angles. By combining fMRI and repetitive transcranial magnetic stimulation (rTMS)[12], Sack et al. (2002 a) recently demonstrated an enhanced fMRI signal in the SPL using an angle discrimination task and a selective impairment of performance in the same angle discrimination paradigm both during and immediately after inducement of a transient lesion in this area. Hence, providing evidence that this region is not only sufficient but also essential for successful visuospatial processing (Sack et al., 2002 a).

In this thesis, a modified version of the angle discrimination task (see methods) has been used by adapting it to a parametric design. That is, by altering two spatial aspects of the clock (angle and length of hands) a high variance of the difficulty of the task was reached. Using an event-related approach, data (fMRI and behavioral) was collected for each clock-stimuli making it possible to examine the relationship between our behavioral parameter (RT) and regional brain activity, as indexed by the BOLD signal. This is illustrated in figure 3.3. Thus, as mentioned above, by using this relationship between BOLD signal and RT we wanted to define the network for our angle discrimination task in addition to investigate the processing efficiency in different regions involved in visuospatial processing. Furthermore, we wanted to investigate if this relationship is altered in normal aging and in different stages of AD. Hence, alterations in this relationship (due to aging or Alzheimer's disease) could be discussed in terms of processing efficiency.

In addition, not outlined specifically in this study design, was the incorporation of a standard boxcar function in the analysis (discussed more in chapter 9) which made it possible to investigate any general increases of activation, that is, BOLD signal changes irrespective of task demand.

3.4 SUMMARY

This chapter has presented a short background to the theoretical framework that tries to integrate visuospatial processing to brain activation patterns as measured with fMRI. The study design included an event-related parametric approach which made it possible to examine the relationship between a behavioral parameter (e.g. RT) and regional brain activity, as indexed by the BOLD response. The underlying hypothesis is based on a theoretical approach of higher level cognition, which implies that the computation underlying the execution of a given task will generate a certain amount of resource utilization. This resource consumption can be regarded as an index of the neural system

[12] Repetitive transcranial magnetic stimulation is a technique that transiently can block the function of a specific cortical structure and allows the definition of a causal link between the behavior and regional brain function (see Pascual-Leone, A., Walsh, V. and Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience-virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology* 10: 232-237.

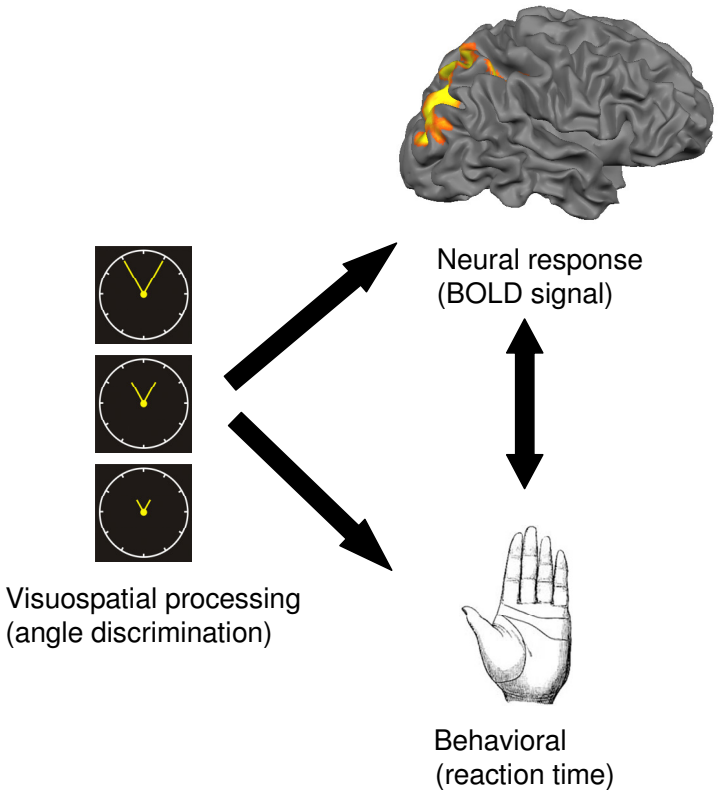


Figure 3.3 The general study design. A visuospatial (angle discrimination) task with different task demand was presented to the subjects in the fMRI experiment. Behavioral results (RT) and the corresponding neural response (BOLD signal) for each clock-stimuli were monitored and measured. Finally, these two variables were combined to look at the relationship between BOLD signal and task demand.

to process the task efficiently and could also be seen as relative to the task demand imposed in the system. Following this argumentation, when task demand increases, a physiological response would be expected including both increment of neuronal firing and number of activated neurons.

It is known that cortico-cortical projections for visual processing originate from the striate cortex and are subsequently organized into two streams in which the dorsal pathway (projecting to PP cortex) is primarily responsible for perception of spatial information including angle discrimination. Thus this approach was used in order to define (and verify) the network for the angle discrimination task used in this thesis and ultimately to examine if this relationship can be used to study age- and disease related effects (see next chapters).

4 INVESTIGATING THE AGING BRAIN

4.1 BECOMING OLD

As we grow older, we (hopefully) grow wiser, but we can also experience cognitive changes, cognitive slowing, and the like that can interfere with our daily routines. In addition to behavioral changes, both changes in brain anatomy (Raz et al., 1997) and physiology (Kety, 1956; Riddle et al., 2003) have been documented. Although it is reasonable to assume that cognitive aging is largely a consequence of cerebral aging, the relationships between these two phenomena are still largely unknown (Cabeza, 2001). The objective of this chapter is to give a short description of some of the cerebral changes of the aging brain as well as the behavioral changes that occur over the course of normal aging, focusing primarily on visuospatial processing and the proposed general mechanisms of age-related slowing. Last, an overview of the functional correlates of age-related cognitive changes as assessed by functional neuroimaging studies is presented.

4.1.1 Definition of aging

It is difficult to define aging. One way of doing this is to distinguish between the aging process from the process of aging. The *aging process* represents fundamental and universal biological processes, unaffected by disease and environmental influences, which induces changes in the living organism over time. These processes can be defined, measured, described, and manipulated (Arking, 1991), and is deeply rooted in the genetic makeup and metabolic workings of the organism in toto and its every cell (Strehler, 1986; Yu and Yang, 1996). By contrast, the *process of aging* is strongly influenced by the effects of environmental, lifestyle and disease states which exert their effect through modulating events. Hence, they are related to or change with age but are not due to aging itself. Important to notice is that many changes observed in older adults which was once perceived as concomitants of the aging process, are now more appropriately recognized as effects of disease in later life or attributed to aging-associated factors[13]. In that context, a common definition of aging rarely separates these two processes and according to these, one definition of aging would thus be:

"a progressive, generalized impairment of function resulting in a loss of adaptive response to stress and in growing risk of age associated disease" (Kirkwood, 1996).

To make things even more complicated, there is also several categorical definitions of aging of which the usual include *chronological age* (actual number of years alive), *psychological age* (how old you feel and think you are), and *social age* (how you are treated and categorized by society). By these definitions, the aging process would then be categorized as *biological age* and the process of aging as *pathological age*.

[13] For example, in the early 19th century, characterizations of senility and old age were relatively neutral, signifying the condition of being old. But by the end of the 19th century, the term senility had been appropriated by the medical profession transformed into age-associated deterioration, especially of cognitive functions (Ballenger, 2006.).

To conclude, one important implication of these definitions is that none of them are straightforward or universally applicable and as described above these definitions also have a tendency to change with history (see footnote 13). Thus, by applying these definition, for the purpose of investigating the functional neurobiology in the aging brain (biological age) we have used a chronological age of around 60 years old as inclusion criteria, and tried to exclude as much as possible of pathological aging by applying several exclusion criterias (see chapter 7).

4.2 CEREBRAL CHANGES IN THE AGING BRAIN

The biological processes that occur with aging profoundly alter anatomy, neurochemistry, and physiology of all organisms. The objective of the next two sections is to provide a (very) brief overview of some of these changes that encompasses brain aging. For more detailed description the reader is referred to the many reviews on this subject (e.g. see Kemper, 1994; Raz, 2000; 2005).

4.2.1 Anatomical characteristics

Global changes in the aging brain can be found at almost any level of observation (Raz, 2000). Postmortem investigations of the aging brain indicate that there is a persistent linear (albeit modest) age-related decline in brain weight and volume that amount to about 2% per decade (Raz, 2000). Moreover, aging is associated with expansion of the cerebral ventricles (ventriculomegaly) and generalized enlargement of cerebral sulci (e.g. Stafford et al., 1988).

However, the most common and significant structural alterations in the aging brain are in the neurons. Although, there is still some uncertainties concerning whether there exists an age-related reduction in the total population of neurons, it has been proposed that shrinkage of neurons may be a more decisive age-related change rather than their attrition (Haug, 1985). There are also age-related changes in neuronal connectivity, representing the most plastic aspect in the adult brain. These include *debranching* of the dendritic arborisation (Anderson and Rutledge, 1996) and decline in *synaptogenesis*[14] (Bertoni-Freddari et al., 1996), which are likely to be selective and regional when present (see section 4.2.1.1).

In addition, aging is also associated with the accumulation of chemicals, e.g. iron and histological features such as neuritic plaques, pathological cellular changes of amyloid origin (Raz, 2000), although these latter findings are relatively infrequent in the brains of older adults who died without signs of dementia (Troncoso et al., 1996) (c.f. chapter 5). Studies of the effect of aging on the number of glial cells have also revealed conflicting results (Kemper, 1994). With increasing age, the number of glial cells has been reported to decrease in a variety of cortical areas (Henderson et al., 1980). But these results are controversial and in contrast, Terry et al. (1987) have reported significant age-related increase in glial cells.

Apart from the above presented structural changes in the *grey matter* there are also several age-related *white matter* changes that have been reported. Although the vast majority of investigations using in vivo MRI reveal no significant age-related difference in the volume of cerebral white matter (e.g. Raz et al., 1997), post mortem studies have suggested that the observed reductions in the white matter volume

[14] Synaptogenesis is the formation of synapses.

probably reflect (in part) myelin loss (Raz, 2000). But the most striking feature of the changes is the spotty appearance of the white matter known as white matter hyperintensities (WMHs)[15] which can be observed on MR images.

4.2.1.1 Regional cortical changes

Regional differences in the magnitude of age effects on the brain may be subtle in comparison with the global deterioration, yet they are noticeable in white and grey matter alike (Raz, 2000). Age effects on the neostriatum are less substantial, whereas the hippocampus, the cerebellum, and the temporal, parietal, and occipital cortices show somewhat greater resilience (Raz, 2000). Some regions, such as the pons and the tectum, appear insensitive to the impact of aging (Raz, 2000).

Overall, it seems that the negative impact of aging is greater on the prefrontal cortex than on any other brain areas e.g. it has been found that when synaptic density and dendritic arborization of the cortical neurons is reduced with aging, it is especially significant for this region (e.g. Liu et al., 1996).

4.2.2 Physiological characteristics

Physiological indices of brain function also change with age (Raz, 2000) including age-related alterations in neurochemical systems, blood flow and in the metabolism of oxygen and glucose. Of these, neurochemical changes include decrease in the number of receptors, concentration of enzymes and neurotransmitters e.g. serotonin, acetylcholine and dopamine (Strong, 1998). Age–related reductions in rCBF as well as $rCMRO_2$ have been observed to be moderate, and in a study by (Madden and Hoffman, 1997) significant reductions were only observed in 65% and 80% of the examined samples. However, the findings concerning total brain metabolism of glucose (CMRglu) are less clear in that some studies have found significant reductions whereas others have not. Because aging is associated with reduction in brain volume, and probably, in the number of active neurons, the age-related drop in metabolic activity may perhaps be related to loss of working tissue (Raz, 2000).

Additionally, alterations of the vascular dynamics have been observed in the aging brain. Example of these include ultrastructural changes in cerebral vessels due to artherosclerosis (Furuta et al., 1991), necrosis of smooth muscle cells (Masawa et al., 1994), and thickening of the basement membrane (Nagasawa et al., 1979). Furthermore, there is an increased tortuosity of cerebral vessels with aging (Fang, 1976), changes in the density of capillaries and arterioles (Abernethy et al., 1993). Artherosclerosis is also observed in the aging brain which eventually result in collateral circulation after recanalisation of occluded cerebral vessels and changes in vascular reactivity (Olsen et al., 1991).

4.3 COGNITIVE CHANGES IN THE AGING BRAIN

Aging in cognitive skills mirrors the complex picture of brain aging by displaying a pattern of selective preservations and declines against the background of generalized changes (Raz, 2000). Thus, on the one hand steady decline in many cognitive processes is seen across the lifespan. For example, functions associated with encoding new

[15] Called leukoaraiosis when observed on CT scans.

memories of episodes and facts (episodic memory) as well as executive control[16] are more sensitive to aging than semantic memory or general knowledge such as vocabulary definitions as well as autobiographical memory and short-term memory, which typically increases or remains steady. Similarly, there is also evidence that with age comes growth and experience, which can be useful in solving complex moral and social problems (Baltes and Staudinger, 1993).

On the other hand, cumulative record of research on cognitive aging shows that a large proportion of age-related variance in cognitive performance can be explained by one or several fundamental factors[17] (see Park, 2000 for an overview) of which generalized *age-related slowing* (Meyerson et al., 1990; Salthouse, 1996; Verhaeghen and Cerella, 2002) is the focus in this thesis.

4.3.1 Visuospatial abilities in aging

Concerning visuospatial processing, research findings indicate that normal aging leads to impairments in this function (Wechsler, 1981; Salthouse, 1991) and it has been suggested that this ability is more affected by age or affected at an earlier age than other abilities (Salthouse, 1987; Koss et al., 1991). For example, it has been shown that there is a differential decline of scores on tests involving verbal and visuospatial information processing, indicating that visuospatial measures (e.g. Block Design) decline to a much greater extent than verbal measures (e.g. Vocabulary; Wechsler, 1981). However, others have argued against this fact stating that other mental abilities are affected first.

Nonetheless, it has been shown that three dimensional construction such as measured with the Block Design test, the visuospatial subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981) (see description in section 7.3) may be less accurate for old than for young adults (Plude et al., 1986; Koss et al., 1991), and may furthermore become less accurate with age within an elderly sample (Wahlin et al., 1993; Libon et al., 1994). Research has also demonstrated that healthy elderly subjects experience difficulties in clock tests (Fleming Farver and Farver, 1982; Tuokko et al., 1992), such as clock reading and clock setting, which traditionally have been used to examine abstract conceptualization and to detect constructional apraxia[18] (Luria, 1973; Mendez et al., 1992). However, another more common finding is that older adults tend to be slower than younger adults on tests of visuospatial ability (Mazaux et al., 1995), such as for example mental rotation (Dollinger, 1995). It is important to notice that the age groups may be equally accurate if tests are untimed (Cerella et al., 1981; Sharps and Gollin, 1987; Grady et al., 1994). Also important is the fact that the decline in visuospatial processing in elderly subjects is significantly less than in demented elderly individuals (c.f. chapter 5).

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[16] Executive control or processes can be defined as general purpose cognitive mechanisms for goal-oriented organization and manipulation of information stored in working memory and for switching among several tasks and sources of information.

[17] These include: the speed at which information is processed, working memory function; inhibitory function, and sensory function.

[18] Apraxia is a neurological disorder characterized by loss of the ability to execute or carry out learned (familiar) movements, despite having the desire and the physical ability to perform the movements.

4.3.2 Slowing with age

A common finding in studies examining age-related differences, as noted in the previous section, is that older adults are slower at performing (see Park, 2000; Salthouse, 2000 for a detailed discussion). Furthermore, this decrease has been demonstrated to be accentuated when the complexity of the task increases (Cerella, 1985; Bashore, 1994; Rubichi et al., 1999). Perhaps a useful analogy is to conceptualize the aging cognitive system as done by Denise Park (2000) in the book Aging and Cognition:

"…[it is] as a computer with a large hard drive that has an enormous amount of information stored on it, but the hard drive is part of a computer with limited random access memory. In this situation, we all know that the computer will behave in a slow and somewhat labored manner, despite its vast informational resources, because the processing capacity of the computer is not sufficient to use all of the information stored on it in an efficient manner. The computer works, but perhaps a little less efficiently than one would like".

The phenomenon of age-related slowing has been interpreted as a decrease in speed of information processing *(processing speed)* or a decline of processing efficiency (Salthouse, 1996). Subsequently, age-related impairments in processing efficiency have been defined as the immediate behavioral consequences of the brain changes (Salthouse, 2000) c.f. previous chapter. Although this phenomena has been observed in a variety of different cognitive measurements there are still debates with respect to the degree to which age-related slowing is specific to particular processes or also reflects broader and more general influence (Salthouse, 2000) i.e. a fundamental cognitive mechanism that may control all of the age-related declines that are observed on numerous tasks (Park, 2000).

4.3.2.1 Theories of age-related slowing

Thus, one of the major challenges in cognitive aging research today is to understand the relationship between speed of processing (or processing efficiency) and cognition and several hypotheses have been proposed. In 1996, Salthouse suggested that there are two important mechanisms that can influence this. In the first *"limited time mechanism"* he states that:

"the time to perform later operations is greatly restricted when a large proportion of the available time is occupied by the execution of earlier operations".

He further explains that this effect is most pronounced in complicated cognitive tasks, in which complex operations are dependent on the products of simpler operations. Thus, if fewer of those products from the simpler operations are available due to slower execution speed, the effects of slow processing can be expected to be most pronounced on the speed and accuracy of complex operations (Salthouse, 1996). However, because of gradual reduction in the speed of basic processes with increased age is likely to be accompanied by numerous adaptation, the consequences of slower processing are not always easy to predict. This point can be illustrated by a computer analogy similar as above. From Salthouse's, (1996) article:

"...[this point]…may be an analogous situation in reverse, in the form of the evolutions of computer programs that have occurred as successive generations of computers have become progressively faster and more powerful. The enormous increases in performance have not simply been attributable to increases in the speed of executing the same programs, because major modifications in the nature of the programs have also occurred to capitalize on the faster speed (and larger memories) of newer computers. Similar types of adaptations in the form of alterations in strategy, reliance on prestored solutions, and so forth could also occur in the human processing system as it becomes progressively slower and less efficient with increasing age"

In the second hypothesis termed the *"simultaneity mechanism"* Salthouse suggests that:

"products of earlier processing may be lost by the time the later processing is completed".

Thus the speed of processing declines with age, such that the information available from earlier stages of information processing is incompletely analyzed when it is needed by higher stages of processing (Salthouse, 1996). Hence, slowing has a cascading effect, such that at each stage the information is more degraded and sometimes arrives too late to be useful for higher stages of processing (Anderson and Grady, 2001).

In a similar way, Cerella (1990) proposed a *"disconnection hypothesis"* based on the idea that cognitive task performance requires transmission across a vast array of interconnected nodes (McClelland and Rumelhart, 1986). In this way nodes may represent individual neurons which are connectes by pathways that correspond to axonal processes. Information processing may be quick, in a more direct processing path, where the information is transmitted across a small number of nodes. However, reductions in the integrity of direct processing links between nodes require traversal of more indirect links for successful task performance. Traversal of more links may therefore lead to either greater neural activity or a reorganization of the pathways that are needed to execute the task, but slower processing.

4.4 COGNITIVE NEUROSCIENCE OF AGING

4.4.1 Insights into the aging mind

Until recently, the cognitive and neural mechanisms of age-related changes in cognition were usually studied independently of each other (Cabeza et al., 2005). One of the major challenges of *cognitive neuroscience of aging* is therefore to directly link these behavioral measures (e.g. as presented above) of cognitive aging to neurobiological function within the individual. Thus, much of the recent research on aging has focused on investigating the relationship between age-related changes in brain structure/function and concomitant changes in cognitive/behavioral abilities using brain imaging techniques such as fMRI.

4.4.2 Functional activation studies in aging

There are a number of fMRI studies that have compared functional activation patterns during sensory, motor and different cognitive processing between young and healthy elderly individuals (for reviews see Cabeza, 2001). Although, these studies

have used different paradigms and the results seem rather heterogenous at first, they seem to converge on several points.

4.4.2.1 Visual perception / visuospatial tasks

The first activation study of cognitive aging was actually a PET study performed by Grady et al. (1994) which investigated the age-related differences in visual perception by using a face and a location matching tasks. In both experiments, young and elderly subjects demonstrated similar activation patterns, that is, occipito-temporal activation during face matching and occipitoparietal activation during location matching. However, for both conditions, elderly subjects showed less activity than young subjects in occipital regions (primarily in extrastriate BA 18) but increased activation in additional brain regions including prefrontal (PFC) (BA 8, 10, and 46) and lateral temporal cortices (BA 37) (Grady et al., 1994). The authors suggested that in elderly subjects reduced processing efficiency in visual areas before ventral-dorsal bifurcation of elderly subjects may have led to the recruitment of these other cortical regions, including the prefrontal cortex. They also suggested that by recruiting anterior brain regions allowed elderly subjects to maintain a good accuracy level at the expense of slower reaction time (Grady et al., 1994), these additional brain regions could be regarded as a compensatory mechanism, c.f. the limited time mechanism by Salthouse (1996) and the disconnection hypothesis by Cerella (1990).

In a subsequent PET study, these findings were replicated using a visual search task in which selective and divided attention were studied (Madden et al., 1997). Elderly subjects showed weaker activity than young subjects in occipital regions but stronger activity in prefrontal cortex (BA 6, 9, and 32) in the divided attention task (Madden et al., 1997). The authors suggested that elderly subjects were not able to perform the search task on the basis of letter identification mediated by the ventral pathway, but rather had to rely on higher-order control processes (e.g. rehearsal, monitoring) that are mediated by the frontal lobes (Madden et al., 1997).

In a more recent study, investigating face matching for degraded and nondegraded faces (Grady et al., 2000) demonstrated that young subjects showed stronger bilateral activity occipital as well as parietal cortex and in right prefrontal cortex, whereas elderly subjects showed stronger activity in left prefrontal cortex as well as left temporal, hippocampal, insular, and thalamic region.

4.4.2.2 Working memory

A substantial amount of studies have been published that investigates age-related functional changes in working memory. The most consistent finding in these studies was that elderly subjects tend to show weaker PFC activations in the hemisphere primarily engaged by the young subjects, but stronger PFC activations in the contralateral hemisphere (e.g. Nagahama et al., 1997; Grady et al., 1998; Rypma et al., 2002)). In addition, age effects of PFC were found for dorsolateral rather than ventrolateral regions and during retrieval phase rather than during encoding and maintenance phase in the working memory task (Rypma et al., 2002).

Several studies have also examined the relationship between brain activity and RT using different working memory tasks (Reuter-Lorenz et al., 2000; Rypma and D'Esposito, 2000; Rypma et al., 2002; 2005). The results from these studies suggest that activation differences are correlated with performance differences in the older

group. Especially, the most consistent finding was that increased information processing speed is related to increases in PFC activation for younger subjects but to decreases in PFC activation for older subjects. However, the opposite pattern was demonstrated for decreased information processing speed in the two groups. This was interpreted to be an effect of age-related differences in neural correlates of processing efficiency. That is, reductions in neural efficacy may have led to slowing of cognitive processes, specifically, the speed with which information can be activated in working memory (Rypma and D'Esposito, 2000). Thus, slower activation of memory retrieval may lead to degradation in the quality of information available for later response stage processing (Rypma and D'Esposito, 2000). One correlate of low quality information available could be reductions in the neural activation levels that permit discrimination between potential responses (Rypma and D'Esposito, 2000), c.f. the simultaneity mechanism proposed by Salthouse (1996). These findings have resulted in a model (originally proposed by Rapoport and Grady (1993)) which suggests that there is a sigmoidal relation between rCBF or $rCMR_{glu}$ (y-axis) and a function of task difficulty and subject task performance (x-axis). This model will be discussed in detail in the discussion (see section 11.9.3).

4.4.2.3 Memory tasks

In functional neuroimaging studies examining episodic encoding (across a variety of tasks), the most consistent finding is an age-related decrease in activation in left PFC (e.g. Grady et al., 1995; Cabeza et al., 1997; Madden et al., 1997; Anderson et al., 2000; Stebbins et al., 2002). This decrease of activation has been suggested to reflect the poor episodic memory performance in elderly subjects due to impaired encoding operations performed by the left PFC. In addition to this decreased activation in left PFC, several studies have also found increased activation in right PFC in elderly subjects which was as strong, or even stronger than, in younger subjects (e.g. Anderson et al., 2000; Stebbins et al., 2002). This latter result suggests that PFC activity is less assymetrical in elderly subjects than in young subjects.

In functional neuroimaging studies examining episodic retrieval, age-related decreases in activation have typically been found in right PFC and right parietal regions, whereas age-related increases in activation were typically found in left PFC (e.g. Bäckman et al., 1997; Cabeza et al., 1997). Given that PFC activation in young subjects usually was found to be right lateralized, the found age-related increase in left PFC led to a more symmetric pattern of PFC activity in elderly subjects, a phenomenon called HAROLD (hemispheric asymmetry reduction in old adults) (Cabeza, 2002).

In addition, by combining the results obtained during encoding and retrieval some studies have demonstrated that while young subjects show a hemispheric encoding /retrieval asymmetry (HERA) (Tulving et al., 1994), characterised by higher PFC activation during encoding and higher right PFC during retrieval, this asymmetry is decreased in elderly subjects (e.g. Bäckman et al., 1997; Cabeza et al., 1997; Madden et al., 1999).

4.4.3 Summary

This chapter has given a short description of some of the behavioral changes of the aging brain as well as an overview of the functional correlates of these cognitive changes. In addition to behavioral changes, aging is associated with decline in several

global properties of the brain, both structural and functional occurring both in the white and grey matter. Much remains unknown about the origins how normal aging affects the neural basis of cognition although several theoretical hypotheses have been proposed.

The cognitive neuroscience of aging, which relies for the most part on neuroimaging techniques, tries to relate these cognitive changes to their neural substrates in order to understand the nature and mechanism of the relationship between behavior and neurobiology. In visual perceptual studies including visuospatial processing, all results converge on the finding of an age-related decreased activation in visual cortex coupled with an increased activation in prefrontal regions. In working memory studies, elderly subjects tend to show weaker PFC activations in the hemisphere primarily engaged by the younger subjects, but stronger PFC activations in the contralateral hemisphere. Regarding the relationship between brain activity and RT the findings in these studies suggests that there is an effect of age-related differences in neural correlates of processing efficiency. Finally, in functional neuroimaging studies investigating age-related changes in episodic memory encoding tasks the most consistent finding has been an age-related decrease of activation in left PFC, although, in contrast, right PFC activity in elderly subjects has been demonstrated to be as strong, or stronger than, in young subjects. In episodic memory retrieval tasks the so called HAROLD phenomenon has been shown i.e. hemispheric asymmetry reduction in old adults in the PFC.

To conclude, in general, lower activity in older adults has been attributed to deficits in neurocognitive processing whereas greater activity in older adults has been attributed to a compensation mechanism.

5 INVESTIGATING CLINICAL AND PRECLINICAL ALZHEIMER'S DISEASE

5.1 WITHOUT MIND

Dementia (from *lat.* de – mens without mind), is a progressive brain dysfunction which includes deterioration of intellectual function and other cognitive skills leading to gradually increasing restriction of daily activities. The term dementia includes a number of different subtypes, where the most common form is Alzheimer's disease. A consequence of the subtlety of these changes is that the diagnostic criteria (and hence further treatment and clinical management) is delayed until there is significant functional disability, a decision which is a matter of clinical judgment (Rosen et al., 2002). However, evidence indicates that before cognitive decline becomes severe enough to confirm a diagnosis of AD, a period during which pathological changes in both structure and function occur (often called *mild cognitive impairment* or preclinical phase of AD[19]). This chapter begins with a brief description of the current understanding of the neurobiology including the neuropathological hallmarks of AD. Second, the cognitive changes occurring over the course of the disease will be described followed by a short overview of fMRI studies that have investigated AD and the current status of using fMRI for the early detection of AD.

5.1.1 Short history

Alzheimer's disease, an eponym first introduced by Emil Kraepelin in 1910, was named after Alois Alzheimer (1864-1915) who published two papers on the disease. In his original report, the pathological findings and clinical history of a 51-year-old woman, Auguste D were presented (Alzheimer, 1907). The patient had shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. When Auguste D. died in 1906, her brain underwent a post mortem examination. In Alzheimer's histological preparations he described the findings of two abnormal histological lesions that became the hallmark of the disease. He reported peculiar changes in the neurofibrils (Maurer et al., 1997):

"In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability"

which was later named *neurofibrillary tangles* (NFT). He further described what is now known as senile plaques or *neuritic plaques* (NP) (Maurer et al., 1997):

"Numerous small miliary foci are found in the superior layers".

The historical importance of the case of Auguste D. lies in the fact that it marks the beginning of research into AD (Graeber et al., 1998). However, 100 years later we still

[19] The term preclinical as used here refers to the period before the clinical diagnosis of dementia is made but after the first clinical manifestation of cognitive impairment.

do not understand the aetiological, clinical, and pathological mechanisms for the disease and except for in rare cases of identifiable mutations of presymptomatic individuals, there are no biological markers[20] to allow preclinical detection of the factors and pathological hallmarks of AD have been revealed.

5.2 PATHOLOGY IN AD

5.2.1 Anatomical characteristics

5.2.1.1 Pathologic progression

The major neuropathological hallmarks of AD include damage occurring both extracellular as senile (amyloid) or NP containing β-amyloid (Aβ) and intracellular as τ-rich NFT (Glenner and Wong, 1984), as already described by Alzheimer. It has been demonstrated that the degenerative process begins in specific limbic areas of the cortex and then spreads, in a predictable pattern, across the hippocampus to the neocortex and a number of subcortical nuclei (Braak et al., 1999). The alteration in the pattern and severity of the pathology permit the distinction of stages in amyloid-deposits (stage A-C) and neurofibrillary changes (stage I-VI) (Braak and Braak, 1991). Both NPs and NFTs are regionally specific, occurring predominantely in the hippocampus, enthorinal cortex, and association areas of the neocortex

5.2.1.2 Other anatomical findings

Other findings, light microscopically, that are always present are neuronal loss, microvacuolar degeneration, Hirano bodies (eosinophilic cellular inclusions) in the hippocampal pyramidal layer, and loss of synapses. The decrease in neuronal counts in the AD brain compared to controls has been found to be significant in the inferior, middle and superior frontal gyri, superior and middle temporal gyri, and cingulate gyrus but not in the superior parietal lobule or primary visual cortex (Mountjoy et al., 1983). This reduction is more pronounced in the larger neurons compared to the small ones, and there is a close correlation of this neuronal cell loss with NFTs (see Kemper, 1994 for a review). It has further been suggested that there is a more marked effect on synaptic loss than on cell loss in the AD brain (Masliah et al., 1991). Macroscopically the brain appears atrophic, with enlarged ventricles and widened sulci. These latter changes are much more accentuated in AD then in the normal aging brain, although there exists a wide range of individual variability and frequent overlap with age-matched controls (Kemper, 1994).

Significant changes also occur in the white matter in the AD brain, including variable loss of myelin, axons, and oligodendroglial cells in association with glial response and hyaline changes in the penetrating blood vessel (Brun and England, 1986; England and Brun, 1988; 1990). However, this process is believed to be independent of

[20] Several markers have been suggested, but until now no single marker of AD exists, which makes it necessary to rely on data from multiple sources in order to arrive at the best possible diagnosis of AD. See Almkvist et al. (1999) for a discussion about early diagnosis of AD based on clinical and biological factors.

the AD pathology and is suggested to represent ischemic changes secondary to hypertension (Brun and England, 1986; England and Brun, 1988; 1990).

5.2.2 Physiological characteristics

5.2.2.1 Vascular changes

Amyloid β (Aβ) peptide has also been shown to accumulate in the blood vessels (*amyloid angiopathy*) and is observed in normal elderly individuals although it is found more frequently in AD patients (e.g. Bergeron et al., 1987). There is also evidence of altered vascularity in AD including decreased capillary density in the cerebral cortex compared to nondemented individuals, a finding which have been attributed to neuronal loss (Mann et al., 1986). In addition, twisted, coiled, and string vessels and glomerular loops have been reported in AD (see Giannakopoulos et al., 2001). Ultrastructurally, a conspicuous lack of endothelial cells in microvessels, as well as a significant increase in the number of normally occurring gaps in endothelial continuity has been demonstrated (for review see Gold et al., 1998). Moreover, vascular endothelial cells show a decreased number of mitochondria and an increased number of pinocytotic vesicles, suggesting that a metabolic deficiency leading to an accumulation of transport carriers may be present in these cells in AD (Giannakopoulos et al., 2001). There is also some evidence that these pathologic changes may be associated with an altered permeability of the blood-brain barrier causing disturbance (e.g. Hardy et al., 1986), and deposition of Aβ protein.

5.2.2.2 Changes in the brain metabolism

Imaging studies have reported reductions in CBF and glucose utilization in patients with AD. The primary markers include hypoperfusion in the temporal and parietal lobes on SPECT imaging, and hypoperfusion and hypometabolism in temporoparietal cortex and posterior cingulated cortex in PET imaging (Duara et al., 1986; Pietrini et al., 1997). Furthermore, it has been shown that the glucose metabolism in the parietal neocortical areas correlate with dementia severity both at rest and during audiovisual stimulation (Pietrini et al., 1999; 2000) (see also description in section 5.4.2.2). The reductions in AD are much greater in brain association than in primary cortical areas, consistent with the greater density in association areas of pyramidal neurons containing NFTs with paired helical filaments (Lewis et al., 1987). Finally, the metabolic and flow reductions likely reflect dysfunction and loss of synapses, which are sites of maximum energy consumption during rest and activation (Pietrini et al., 2000).

5.3 COGNITIVE CHANGES IN AD

As presented above, AD refers to the pathological process in the brain. However, these pathological changes in AD are followed by the evolution of cognitive changes or changes in brain function. Figure 5.1 shows a hypothesized course of development of both pathological changes and changes in brain function. Thus, as can be seen in this figure, these changes exist in a continuum with normal aging process in which the

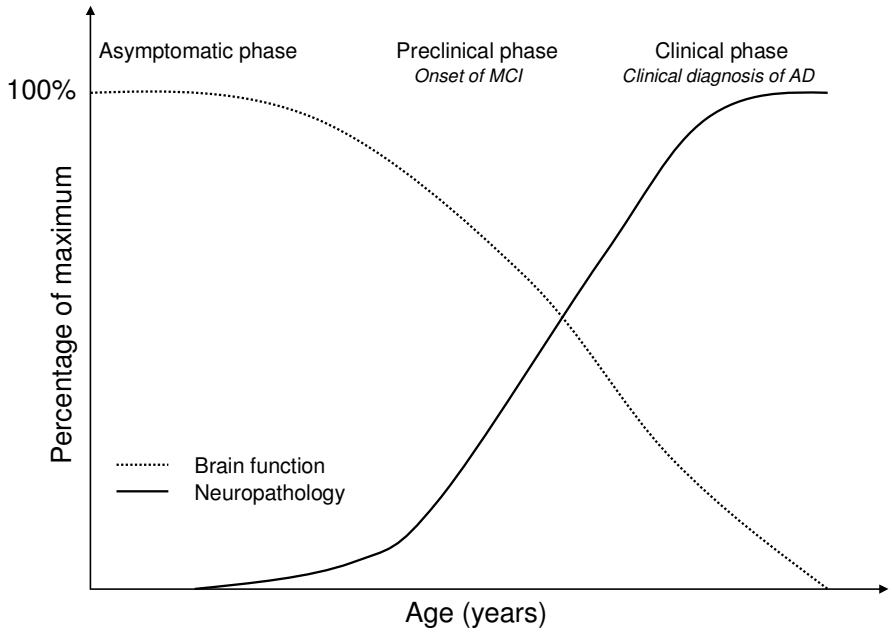

Figure 5.1 Overview of the evolution of cognitive impairment and neuropathology in AD.

person is free of objective or subjective symptoms of cognition and functional decline *(asymptomatic phase).* However, as the pathological processes continue the individual will experience cognitive and/or functional difficulties. These often begin with subjective memory complaints (which can also be benign and part of normal aged forgetfulness (Flicker et al., 1993)), but in individuals with AD pathology these deficits will gradually become more manifest. At this stage *(preclinical phas /onset of MCI)* the cognitive and/or functional difficulties are also noted objectively by persons who are closely associated with the individual. In the early *clinical phase* of AD, the symptoms of impairments become more evident and the patients typically exhibits deficits in an array of cognitive domains including memory, verbal ability visuospatial skills, problem solving, attention, and abstract reasoning. It is often at this stage that the clinicians make a clinical diagnosis of AD. With time the deficits have become of such sufficient magnitude that the individual often can no longer manage on their own in the community.

5.3.1 The preclinical phase of AD (mild cognitive impairment)

An important challenge for the clinicians is to identify subjects with developing AD in the preclinical phase of the disease. There are several reasons why this is of great interest, the most important one is perhaps to facilitate the intervention of therapeutic agents to slow down or prevent the disease progression. However, the affected individual and their caregivers may also benefit from counseling on how to handle the cognitive impairment. It is also important for subjects experiencing mild cognitive impairment to receive a prognosis with regard to their outcome. This may bring relief, may end uncertainty about their cognitive impairment, and may give opportunities to anticipate the future (Robinson et al., 1998).

However, the major clinical problem is that although the preclinical phase is characterized by mild cognitive impairment, the individuals with MCI represent a heterogeneous group with respect to both clinical presentation and outcome after follow

up. The majority of MCI patients will however progress to AD (so called *progressive MCI*, PMCI) at a rate of 10% to 15% annually (Tierney et al., 1996; Petersen et al., 1999). In these individuals, overt decline will become manifest over intervals of approximately 2 to 4 years (Flicker et al., 1991). In contrast, some patients remain relatively stable for a long preclinical phase and perhaps never progress to fulfill the dementia criteria, so called nonprogressive or *stable MCI* (SMCI). The MCI group also include individuals with functional cognitive impairment (perhaps induced by psychological disorders like depression), which improve to normal after follow-up.

5.3.1.1 Problems in recognizing the preclinical phase

Based on the above mentioned clinical problems in correctly predicting dementia in subjects with MCI, it can be difficult to conduct studies with the aim to correctly describe the clinical characteristics of preclinical AD and possible predictors of AD in subjects with MCI. In this thesis, the term preclinical AD is used to describe subjects who have MCI at the baseline assessment (see diagnostic criteria in section 7.2) of a prospective study and who become demented and have AD during the follow up period. Thus, as a consequence the diagnosis of AD can only be made in retrospect. This means that the distinction between subjects with MCI with and without preclinical AD is based on the outcome at follow up.

5.3.2 Visuospatial abilities in AD and MCI

Although the memory deficits in AD are usually predominant, the disease is also characterized by impairments in multiple additional domains, including visual cognition (Cronin-Golomb, 2001). In his original case study, Alois Alzheimer (1907) described abnormalities in object discrimination and recognition and in spatial localization:

> *"(S)he could not find her way about her home*
> *…She was disoriented as to time and place…*
> *She suffered from serious perceptual disorders*
> *…While reading she would omit sentences…*
> *She did not remember the use of particular objects "*

Similarly, clinical observations and research findings have indicate that AD lead to severe impairments in numerous aspects of spatial localization (Mendez et al., 1990 a; 1990 b; Ogden, 1990; Cronin-Golomb et al., 1993), including conctructional abilities, personal (egocentric) localization, extrapersonal (allocentric) localization, and visuospatial cognition or processing. The latter, which comprises of such abilities as form matching, mental rotation, judgement of line orientation, object localisation, and angle discrimination, has been shown to have a high prevalence in AD patients. For example, in a mental rotation test (Mendola et al., 1995) reported prevalence rates of 39% (14/36 AD patients) and 29% for a test of map reading (10/35 AD patients) (Mendola et al., 1995).

The deficits in visuospatial process has also been recognized in the early clinical stages of AD (Tierney et al., 1996; Arnaiz et al., 2000) and in MCI patients. For example, in a comparison between healthy elderly subjects and those with MCI (Flicker et al., 1991) found that objective psychological measurements, such as those testing

visuospatial ability, exhibited high sensitivity and specificity in distinguishing between subjects with and without a decline in cognitive functioning. Similarly, a recent publication from the Swedish Council on Technology Assessment in Health Care (SBU) demonstrated that the clock test had a high positive likelihood ratio (LR) [21] of 12.4 and a low negative LR of 0.14 indicating that this test is good in increasing the diagnostic certainty considerably (Edhag, 2006).

5.3.2.1 Brain basis of the impairment in visuospatial proessing

The main source of dyfunction in spatial localization and visuospatial processing in AD is believed to be the disruption of the dorsal pathway (see chapter 3) (Grady et al., 1993). Evidence in support for this is coming from studies using SPECT and PET which (see also above) consistently demonstrate reduced blood flow (Perani et al., 1988) and reductions in resting glucose metabolism (Duara et al., 1986) in the temporoparietal cortices in AD patients (but see also functional neuroimaging studies below). These metabolic functional deficits can be observed early in the course of the disease (e.g. Jelic and Nordberg, 2000) and recently it has been discovered that they are also apparent in at-risk individuals such as MCI patients (e.g. Arnaiz et al., 2001), and genetically predisposed individuals (e.g. Kennedy et al., 1995). These results are also consistent with the extensive neuropathology in the parietal lobes itself (Terry et al., 1981; Lewis et al., 1987; Braak and Braak, 1999).

5.4 COGNITIVE NEUROSCIENCE OF ALZHEIMER'S DISEASE

5.4.1 Insights into pathological brain aging

Cognitive, motor and sensory performances are closely related to the integrity and function of the neuron or perhaps more specifically the synapse (as discussed in chapter 2). Neuronal function is furthermore the basis of measures in brain activation as assessed with the BOLD signal changes (Rees et al., 2000; Logothesis et al., 2001) (see chapter 2). When conducting fMRI studies in patients with neurodegenerative disease like AD and MCI, many factors may at the end modulate the BOLD effect that we see. That is, in AD several progressive pathological alterations occur (as presented above), and these pathological changes interact cumulatively to impair neural function and interneural communication, which in turn reduce the synaptic processing that drives the CBF increase, resulting in a reduced hemodynamic response to activation (Iadecola, 2004). Thus, in that sense, the extent of activation in clinical and preclinical phases of AD is considered to reflect the integrity of neuronal or synaptic function, or inherent viability.

5.4.2 Functional activation studies in patients with AD

To date there is an abundant amount of functional activation studies devoted to study patients with manifest AD. The majority of these studies have focused on memory tasks, since this is one of the first cognitive systems to be affected and

[21] Likelihood ratio is the likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without the target disorder. It is used to assess how good a diagnostic test is and to help in selecting an appropriate diagnostic method.

considering that the medial temporal lobe is the first brain area to be affected by neurodegeneration. However, the overview will start on the findings from visuospatial tasks.

5.4.2.1 Visuospatial processing / attention

Until now, three studies have studied visuospatial processing in AD (Thulborn et al., 2000; Prvulovic et al., 2002; Gould et al., 2005). Of these, Thulborn et al. (2000) and Prvulovic et al. (2002) demonstrated less activity in the SPL in AD patients compared to controls using a visuospatial guided saccade paradigm respectively an angle discrimination task. In addition, Thulborn et al. (2000) reported that AD patients compensate the decreased right hemispheric activity in this region by recruiting the left SPL. Similarly, Prvulovic et al. (2002) demonstrated that the decreased activation in SPL was coupled to an increased activation in occipito-temporal cortex in AD patients compared to controls. Both these studies are therefore supporting a compensatory recruitment hypothesis, in that parietal dysfunction in AD patients is accompanied by the recruitment or reallocation of remote brain areas (Thulborn et al., 2000; Prvulovic et al., 2002).

However, using a parametric fMRI study, Gould et al. (2005) found almost identical brain activations in a visuospatial paired associate learning test in AD patients and control subjects if task performance (accuracy) was matched across groups. Nontheless, although adjustments for task difficulty were made on an individual basis, small differential activations were nonetheless detected between the groups i.e. greater signal changes in the lateral and medial parietal regions in the AD patients relative the controls (Gould et al., 2005).

5.4.2.2 Passive visual and auditory perception

In a series of PET studies, Mentis et al. (1996; 1998) used a passive parametric visual (flash frequency increase) stimulus to examine AD patients in different stages of severity (i.e. mild, moderate and severe). In these studies they were able to demonstrate that the level of stimulus activation exposed brain dysfunction in striate and extra striate visual as well as frontal cortex in mildly demented AD patients when large neural responses were required and in patients with moderate/severe AD when large and intermediate responses were required (Mentis et al., 1996; 1998). Similar results were recently replicated in a PET study using a passive *audiovisual* stimulation paradigm (Pietrini et al., 2000). The findings of these studies suggested to reflect the progressive loss of synaptic integrity in the AD patient.

5.4.2.3 Working memory

In visual *working memory* tasks Grady et al. (2001) used a face recognition task and demonstrated that the activation in left medial temporal regions was higher in AD patients compared to controls, although the activation in prefrontal cortex was not different between the groups. One study by Rombouts et al. (2003) aimed at finding differences in activation patterns in AD patients and patients with frontotemporal dementia (FTD) during a working memory task. The authors could distinguish the two groups on the basis of larger activations in the frontal lobes of AD patients relative to FTD patients (Rombouts et al., 2003).

5.4.2.4 Memory encoding and retrieval

In fMRI studies of memory tasks that engage verbal and visual *encoding*, several studies have demonstrated medial temporal dysfunction in AD patients compared to controls when examining whole-brain activations (Saykin et al., 1999; Sperling et al., 2003; Golby et al., 2005), although the expected differences between control subjects and AD patients did not reach the threshold in all studies (Rombouts et al., 2000; Kato et al., 2001). The results from region of interest (ROI) analysis are more consistent. For example, studies focusing on the medial temporal lobe (Rombouts et al., 2000; Machulda et al., 2003; Golby et al., 2005) have reported decreased activation in AD patients compared to healthy controls. Similarly, one study focusing on the hippocampus (Small et al., 1999) demonstrated AD related dysfunction in all hippocampal subregions including enthorinal cortex, hippocampal proper and subiculum during face encoding. In functional studies during memory *retrieval*, Bäckman et al. (1999) were able to demonstrate a reduced activation in hippocampus and parietal during cued recall of words (word stem cues) compared to baseline (word stem completion) using PET. However, they also found an increased activation in left prefrontal cortex (Bäckman et al., 1999). In a recent study by Grady et al. (2003) an extended activation in bilateral prefrontal and temporoparietal areas in AD patients was demonstrated as opposed to only left prefrontal and temporal activations in controls subjects. The results from all these studies are likely to reflect the disruption of interneural communication in these regions due to AD pathology.

5.4.3 Functional activation studies in subjects with MCI

The use of functional neuroimaging techniques in the quest for an early marker of AD is based on the hypothesis that changes in brain function precede structural changes. Similar as the studies in AD patients the majority of fMRI studies in MCI have focused on memory tasks.

5.4.3.1 Visuospatial attention

In a recent fMRI study by Rosano et al. (2005) the authors studied the effect of attentional load on activations in three ROIs (dorsolateral prefrontal cortex (DLPC), posterior parietal cortex (PPC) and anterior cingulate cortex (ACC), during a *spatial cuing paradigm*. (Rosano et al., 2005) found that with increasing attentional load, MCI patients increased their activation in PPC bilaterally. In contrast, controls showed increased activation in the DLPC bilaterally when attentional load was increased. No difference in activation was observed between the groups in the ACC. The increased recruitment of PPC in MCI was hypothesized to reflect the underlying decrease in the brain's ability to implement attentional control early in the course of the disease

5.4.3.2 Memory encoding

In a visual *memory encoding* task Small et al. (1999) found two distinct activation patterns in subjects with isolated memory decline. That is, one group showed reductions in the subiculum and one group showed, in addition to subiculum, decreased activity in the enthorinal cortex (Small et al., 1999). Unfortunately, neither post scanning memory performance data nor longitundinal information is available for this study. Similarly, Machulda et al. (2003) were able to distinguish MCI patients from

healthy controls during memory encoding. In this study, reduced activation was found in a ROI including hippocampal information, parahippocampal gyrus and fusiform gyrus, in MCI patients compared to controls (Machulda et al., 2003). However, both the imaging data and performance on the post scanning recall and recognition test could not distinguish between MCI and AD patients. In a face-repetition task Johnson et al. (2004) were able to discriminate healthy controls from MCI patients on the basis of the activation pattern in the hippocampus. Whereas control subjects showed face-repetition associated decrease in hippocampal activation, no such effect was observed in the MCI patients (Johnson et al., 2004). In a study with only MCI patients Dickerson et al. (2004) aimed at tracking down correlations between activations in three ROIs, including the hippocampal formation, parahippocampal gyrus and striate cortex (control), and degree of clinical impairment, memory performance and volume of either hippocampus or parahippocampus during scene *encoding*. Although accuracy was not associated with clinical impairment, it did correlate with greater extent of activation in the left hippocampal formation and parahippocampal gyrus bilaterally, even after correction for ROI volume (Dickerson et al., 2004). Furthermore, a regression analysis revealed an association of clinical impairment with older age, greater extent of activation in the right parahippocampal gyrus and smaller left hippocampal volume. In addition, a 2.5 year follow up showed that patients who declined (44%) had lower right parahippocampal activation during encoding and a lower baseline MMSE-score than the subjects that remained stable (Dickerson et al., 2004). Paradoxially, greater clinical impairment correlated with greater activation in the parahippocampal gyrus and greater hippocampal atrophy, even after follow up.

5.5 SUMMARY

AD is a progressive neurodegenerative disorder with characteristic clinical (Almkvist and Winblad, 1999) and neuropathological (Braak and Braak, 1991) features. The evidence suggests that there is activation of similar cascade of events by different processes, eventually leading to cell dysfunction, loss of synapses, and neuronal death (Cummings and Khachaturian, 1999). These pathological changes in AD are followed by the evolution of cognitive changes which exists in a continuum with normal aging process *(asymptomatic phase),* and slowly progresses into a *preclinical phase* in which the individual experience mild cognitive impairments that gradually become more manifest until the symptoms become more evident and the patients typically exhibit deficits in an array of cognitive domains *(clinical phase)*.

As the cognitive performances are closely related to the integrity and function of the neuron, fMRI can be used to monitor the processing efficiency of the neuron in the preclinical and clinical phase of the disease. Functional neuroimaging studies (using both PET and fMRI) have demonstrated that AD patients almost consistently show decrements of activation compared to healthy controls in several brain regions during the performance of a variety of tasks (e.g. episodic memory, working memory and visuospatial processing). However, compensatory activation has also been demonstrated, i.e. a significant increase in occipotemporal cortex was found in AD patients in an angle discrimination task. Functional neuroimaging studies in MCI patients and controls have shown that these groups can be distinguished by fMRI on the basis of activation patterns within hippocampal (sub) regions during memory encoding. Similarly, on a visual attention task patients showed different activation patterns in the posterior and DLPC.

6 AIMS OF THE THESIS

6.1 GENERAL AIM

This thesis uses fMRI to investigate visuospatial processing in early adulthood, old age and during different stages in the course of AD (including MCI), with the aim to relate the functional activation changes in aging and dementia to the task demand (assessed by RT), and task performance (% correct responses).

6.2 SPECIFIC AIMS

The specific aims of the different papers were:

I. To investigate and validate that the visuospatial paradigm evokes brain activation according to an a priori hypothesis in healthy young individuals **(study I)**. Specifically, to investigate which brain areas are activated by this task and if it is possible to see an effect of task demand in the brain?

II. To optimize the statistical method in order to detect task demand dependent brain activation evoked by the visuospatial task in a more sensitive way **(study II)**.

III. To investigate whether the visuospatial paradigm can provide further insight in the understanding of the phenomenon of age-related slowing **(study III)**. Specifically, to study if it is possible to detect age-related differences in the brain-behavioral relationship (task demand dependent changes) and general changes in BOLD signal (task demand independent changes) in elderly subjects compared to young subjects.

IV. To investigate whether the visuospatial paradigm can provide further insight in the understanding of the neural mechanism underlying the impairment of visuospatial function in mild AD **(study IV)**. Specifically, to study if it is possible to detect disease-related changes in task demand dependent and task demand independent signal changes in patients with mild AD compared to age- matched healthy controls.

V. To investigate whether the visuospatial paradigm can identify the subjects at risk for future development of dementia **(study V)**. Specifically, to study if it is possible to detect preclinical disease-related changes in task demand dependent and task demand independent signal changes in PMCI patients compared to SMCI patients respectively age- and education- matched healthy controls.

7 SUBJECTS AND METHODS

An overview of the demographic characteristics and global cognitive status of the study samples, as well as some additional methodological aspects which were not addressed in the original studies (I-V) is given below. Comprehensive descriptions of the study samples used as well as methods and statistics employed can also be found in the specific papers (I-V).

7.1 STUDY SAMPLES

7.1.1.1 Control groups

Healthy young subjects in study I-III mainly consisted of students at the Karolinska Institutet, Södertörns Högskola as well as Stockholms University or recruited relatives and friends to these students. Healthy elderly subjects included in the control group (study III-V) were mainly recruited from ongoing projects at the Geriatric Clinic, Karolinska University Hospital Huddinge, Stockholm, Sweden or were relatives to the young subjects. The young subjects in study I, II and III are overlapping as well as elderly subjects in study III and IV and III and V. Descriptive demographics are given in table 7.1. By history they had no known neurological and psychiatric disease and no evidence of cognitive decline or impairment in activities of daily living (ADL).

7.1.1.2 Patients

AD and MCI patients were recruited and examined at the Memory Clinic, Karolinska University Hospital Huddinge, Stockholm, Sweden. Sources of referral included general practitioners, neurologist, or individuals seeking help directly because of self-experienced memory problems. See table 7.1 for descriptive demographics.

7.2 MEDICAL EXAMINATIONS

All patients underwent a comprehensive investigation procedure including a detailed history from the patient and/or an informant, a general physical and mental status examination, neurological assessment, blood tests (blood hemoglobin, sedimentation rate, complete blood cell count), serum tests (glucose, sodium, potassium, calcium, chloride, phosphate, iron, creatinine, albumin, ASAT, ALAT, cholesterol, triglyceride, thyroid hormones, vitamin B_{12}, folic acid, HIV, Borrelia, syphilis), urine analysis (glucose, protein, pH, microscopic examination), cerebrospinal fluid analysis (Tau concentrations), APOE genotyping, routine EEG, MRI, SPECT, and assessment of cognitive functions (see below and appendix A).

7.2.1.1 Diagnosis of AD

The clinical diagnosis of AD was consistent with the criteria of the International Classification of Diseases (ICD-10) (World Health Organization, 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 1994) for AD[22]. These two commonly used definitions of AD

[22] There is also the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria (McKhann et al. 1984).

Table 7.1 Descriptive statistics of the study samples

Subjects	N	M/F (ratio)	Age (years)	Education (years)	FSIQ
Study I					
Young C	10	3/7	25.9 ± 3.3	15.8 ± 0.7*	126.1 ± 17.5 #
Study II					
Young C	14	4/10	26.1 ± 3.8	15.6 ± 1.2	121.3 ± 17.3
Study III					
Young C	14	4/10	26.1 ± 3.8	15.6 ± 1.2	121.3 ± 17.3
Elderly C	32	11/21	65.6 ± 85.2	13.8 ± 3.4*	113.5 ± 15.4*
Study IV					
Elderly C	13	8/5	68.7 ± 7.8	13.2 ± 3.9*	106.6 ± 11.4
Mild AD	13	4/9	68.9 ± 6.9	12.5 ± 3.6	85.5 ± 17.1
Study V					
Elderly C	13	4/9	58.5 ± 6.4	15.9 ± 3.1	115.8 ± 15.2
SMCI	8	3/5	56.8 ± 4.7	14.0 ± 4.2	105.8 ± 15.8
PMCI	5	1/4	61.4 ± 6.1	15.8 ± 1.9	100.8 ± 7.9

Mean ± SD for AD = Alzheimer's Disease; C = Control subjects; PMCI = progressive Mild Cognitive Impairment; SMCI = Stable Mild Cognitive Impairment. M = male; F = female; FSIQ = Full Scale Intelligent Quotient. Data missing for 2 subjects= *; 1 subject = #.

have similar features in that they both require that the patient exhibit a dementia syndrome and that memory loss is a major feature of the clinical presentation; they require that the patient show impairment in at least one non-memory cognitive domain; and they require that other potential causes of dementia be excluded. Both require that the absence of delirium in dementia is identified as the sole cause of the intellectual decline, although they note that delirium and dementia can occur together. In addition, both address the gradually progressive course expected in AD.

Also, the patients had a Clinical Dementia Rating (CDR) (Morris, 1993) score of 0.5 to 1.0 and Mini Mental State Examination (MMSE) (Folstein et al., 1975) score of ≥23 (mean ± SD MMSE score: 25.5 ± 2.33, range = 23-29) as compatible with mild dementia.

7.2.1.2 Diagnosis of MCI

The diagnosis of MCI was consistent with the criterias that have been defined and are employed at the Memory clinic, at the Karolinska University Hospital Huddinge, Stockholm, Sweden (Wahlund et al., 2003). These include a subjective memory complaint as well as objective signs (below 1.5 SD below age matched controls) of decline in any cognitive domain (although not severe enough to meet the criteria of dementia). No change in ADL. Also, the cognitive impairment should not be related to other medical, neurological, or psychiatric illness. The patients with MCI (at first medical examination) did not fulfill the diagnosis for dementia or probable AD.

7.2.1.3 Follow-up Examinations

MCI patients were reevaluated every 6 to 12 months and received the same comprehensive clinical routine and neuropsychological assessment as well as an informant interview regarding behavioral and functional status. In case of clinical deterioration, a neurological examination was administered again. In these cases, a multidisciplinary team including physicians, neurologist, geriatricians, neuropsychologist and nurses met again to set a consensus diagnosis. Based on the clinical follow-up (which was approximately 3 years), patients were classified as PMCI, SMCI or NMCI. PMCI referred to the MCI patients that converted to AD during follow-up. SMCI was defined as the subjects who still did not fulfill the criteria for AD during the follow up time. NMCI was patients that improved to normal after follow-up.

7.3 COGNITION AND NEUROPSYCHOLOGICAL ASSESSMENT

Subjects were tested by experienced psychologists and completed an approximately two-hour battery of neuropsychological tests. These tests were chosen to span over attention, short and long term memory, executive and visuospatial functions and are described in detail in appendix A. All patients did not complete all tests due to restrictions in time for assessment or unwillingness to complete the examination. Comprehensive descriptions and statistics of the different tests employed can be found in the specific papers (III-V).

7.4 FMRI EXPERIMENTAL SETUP

To be able to run the fMRI experiment, three essential subsystems are required: an MRI scanner with echo planar imaging (EPI) capabilities, a device to present visual stimuli and a data analysis environment. In the next section a brief presentation of the experimental design and paradigm will be given, as well as a description of the different software programs, equipment and parameters used.

7.4.1 Presentation of stimuli

When presenting stimuli to the subject in the scanner, the transmission of signal between control room and scanner room is often practically difficult, because of the risk that MR images can be degraded by interaction with the stimulus apparatus. In our fMRI experiment the visual stimuli were projected by means of MR-compatible LCD-goggles (see details below), which was connected to a laptop (PC) computer located in the control room. A schematic drawing of the setup used is shown in figure 7.1. To be able to monitor behavioral responses (RT and accuracy) to each stimuli, a MRI compatible optical keypress (with two buttons) device interfaced to the PC was used. Also, to minimize movement artefacts in the fMRI data, a head stabilization system included a vacuum-pack system that was molded to fit each subject. This and the encouragement to remain still during the examination procedure were sufficient to generate fMRI data without to extensive movement artefacts. During scanning the light in scanner room was dampened and communications with the subjects were made through speakers in the camera room. Also, to dampen scanner noise the subjects were wearing headphones.

7.4.1.1 General information and inclusion criteria

Information was given concerning the specific benefits to the individual or patient e.g. that they would receive information about some of the imaging results (T2-weighted images were collected for all individuals and screened by a neuroradiologist (M. K-W) for cortical infarction, excessive subcortical vascular disease, and clinically silent white matter lesions), potential risks e.g. they were informed about the risks of entering the MR-machine (standard MRI exclusion criteria (pacemaker, claustrophobia etc) were used). In patients, non-AD dementing disorders or concurrent illnesses, (e.g. depression or drog abuse) that might interfere with the subjects performing the fMRI activation task were used as exclusion criteria. Patients were included only if they were able to provide informed consent and to understand and execute the different tasks to be performed.

In healthy subjects, none had a history of neurological or psychiatric disease. In addition, patients with memory problems were monitored continually (before the experiment started) whether they remembered the instructions and a brief test was used to see if they were willing and able to comply with the instructions.

In all subjects handedness was assessed by The Handedness Inventory (Briggs and Nebes, 1975) modified from Annett (1967). Also, subjects were asked to refrain from caffeine as well as nicotine for at least four hours before their fMRI session. Before entering the scanner the subjects had to change into hospital gowns (only wearing underclothes beneath unless they did not contain any metal parts e.g. bra) in order to minimize the risk of disturbing the magnetic field. Finally, all subjects were informed about their right to withdraw from participation at any time during the experiment and time was set to have their questions answered.

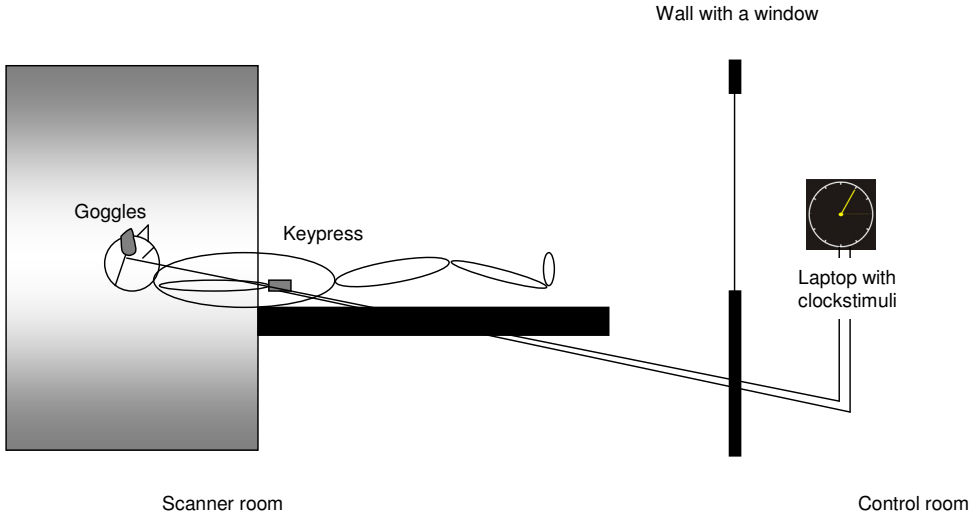

Figure 7.1 Schematic drawing of the setup used for presentation of visual stimuli in the MR unit at the Karolinska University Hospital, Huddinge. In the control room, opposite the MRI scanner, a laptop computer with the experiment paradigm is located. Subject lay supine in the MRI scanner. A MR compatible goggle system and response buttons are connected to the laptop, which enables the subjects to see and react to the stimuli. Stimulus presentation is synchronized with the fMRI sequence at the beginning of the experiment.

7.4.2 Visuospatial paradigm

The visuospatial paradigm presented to the subjects consisted of an angle discrimination task. Schematized clock images (yellow hands and black clock-face) with five angular disparities; 30°, 45°, 60°, 75°, and 90°, and three different lengths of the hands (long/middle/short) were created, see figure 7.2. Fifteen different clock images, each shown for 12 times with a different position of the hands, resulted in 180 different clock images. A control condition consisting of a clock image without hands and periods of rest (blank screen) alternated with the other experimental conditions.

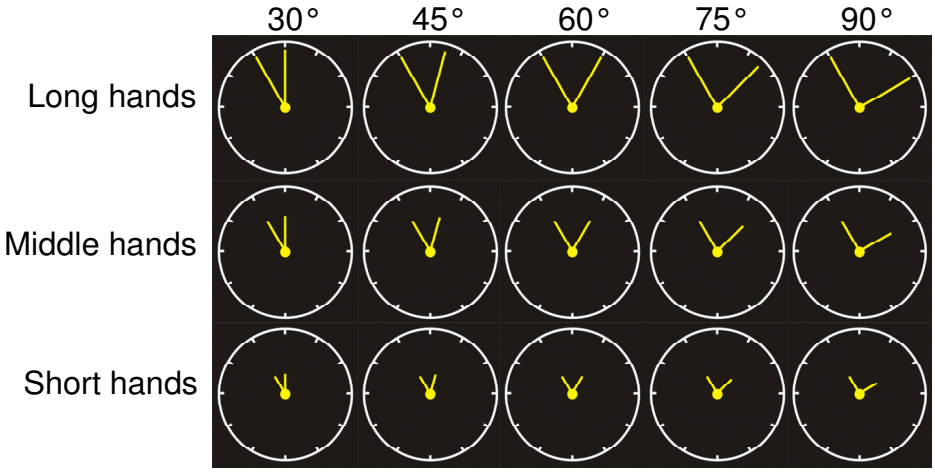

Figure 7.2 Example of stimulus material. Vertically is an example of clocks with different angles and longitudinally is an example of the same clock with different lengths of the hands.

7.4.2.1 Instructions and practice sessions

Before the experiment started, a short explanation and presentation of the procedure outside of the MR scanner were made in order to familiarize the subjects with the task. This included a short description of the MR environment and the different equipments used, such as the head coil, headphones, alarm clock, googles, response box etc. Thereafter a description of the experiment and a short training session with response buttons were performed.

The subjects were instructed to hold the response buttons in their right hand, gently placing their right index finger on the left button and their right middle finger on the right button. They were informed to look at the screen in the goggles. The subjects were told to press the key under the index finger if the angle between the hands were 60º (target) and to press the key under the middle finger if the angle was smaller or larger than 60º (non-target). In the control condition the subjects were told to press the right button (using their right middle finger) as soon as they recognized the control clock. The subjects were instructed to press one of the buttons as soon as they had made a decision. RT was measured as the time of onset of the stimulus (i.e. presentation of clock image) to the time that the subject made a response.

They were informed that they had a time limit of 6 seconds and that a new image would appear every 6 second. After pressing one button, a central fixation point (which they were told to focus on) would appear for the remaining time until a new clock

image would be presented. They were also informed that if they were not able to make a decision, they should not press any button, but wait until a new clock image appeared. Also, if a black screen was shown they were instructed to relax with their eyes open and try not to think of anything (at least not clocks) and not to press any buttons. Subjects were also instructed not to talk during the experiment.

Since one inclusion criteria was that all subjects included in the study were able to follow the instructions and complete the training session, considerable time and effort were spent in order for the subjects (especially the patients) to feel reassured and comfortable with the procedure. Inside the MR scanner, all subjects received the same instructions in written form as they had received outside the scanner. Before scanning, a second practice session was given to each subject.

7.4.3 Event-related experimental design

An event-related fMRI design was used in the current experiment which refers to a technique for detecting the brain's response to brief stimuli or cognitive events. More precisely, event-related fMRI allows detection of the BOLD hemodynamic response (see chapter 3) to neural activity over the time course of an individual event. There are several advantages using this method, the most important one being the opportunity for convergence between behavioral data and neuroimaging data drawn from the subject (see below). Furthermore, event-related designs allows different trials or stimuli to be presented in arbitrary sequences, thus eliminating the potential confounds, such as habituation, anticipation, set, or other strategy effects (Rosen et al., 1998).

Also, the occurrence of events was partially defined by the subject. That is, each trial (except for the periods of rest, i.e. blank screen) was self-paced by the participant in that, although the experiment had a Stimulus Onset Asynchrony[23] (SOA) of 6 seconds, the image disappeared with the subject's button press response. Thus, immediately after the button press response a fixation cross (in the middle of the screen) was shown for the remaining time of the SOA (figure 7.3). In addition, an incorrect response was recorded when no button was pressed during the response window. Also, when no button was pressed a new stimulus would appear after 6 seconds.

We used a sampling rate of 2 seconds per brain volume (recording three volumes per clock image), yielding a fairly powerful means to estimate the hemodynamic response during the angle discrimination task presented. All stimuli were presented in a pseudo-randomised order (so that the different clock-stimuli (angular disparity and length of hands) were presented with similar frequency across the experiment duration), starting and ending with a period of rest. In order to pseudorandomized the stimuli, 12 blocks were created. Each contained 15 different clock stimuli, one control condition and 3 blank screens (except the first and last block which contained 4). The blocks were then presented without any intermissions.

In total, 230 conditions were presented to the subject consisting of 180 clock images, 12 control conditions (clock without hands), and 38 blank screens (rest), giving an experimental duration of 23 minutes and the acquisition of 690 volumes.

[23] Or the time between the events.

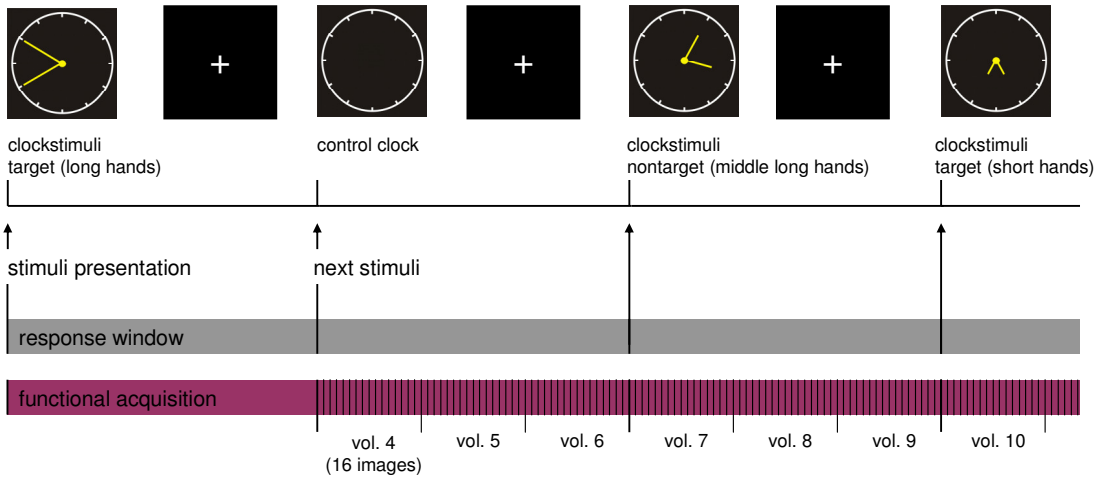

Figure 7.3 Experimental setup of the visuospatial task. SOA was 6 sec during which 3 MR-volumes (16 slices per volume) were acquired. The response window was 6 s, and the subjects were instructed to answer as soon as he/she could by pressing one of two response buttons. When the subject made a response, a fixation point was shown for the remaining time until next stimuli was presented.

7.4.3.1 Ethical issues

The protocols were approved by the local Ethics Committee and informed consent was obtained from all subjects and patients according to the Declaration of Helsinki.

Study	Ethical permission (dnr and date)
I	6-03, 2003-02-11
II	6-03, 2003-02-11
III	6-03, 2003-02-11; 180-02, 2003-02-03 (KEK)
IV	157-03, 2003-04-07
V	424-01, 2001-12-03

7.5 SUMMARY

Below is a short description of the different software programs, equipment and parameters for the data aquisiton that were used in the experiments.

Software

E-prime	The experiment was designed using E-prime software (Psychology Software Tools, Inc, Pittsburgh, USA). Stimulus presentation was synchronized with the fMRI sequence at the beginning of the experiment.
BrainVoyager	Preprocessing and analysis of the fMRI data were performed using BrainVoyager (BV) 4.9 for study I and BVQX for subsequent studies. (Brain Innovation, Maastricht, Netherlands, www.BrainVoyager.com).
STATISTICA	The software system STATISTICA version 6 for study I and 7 for subsequent studies (StatSoft Inc, 2001) was used for calculations.

Equipment

MRI scanner	All measurements were acquired with Siemens Magnetom Vision 1.5 T whole body MRI systems, with a standard headcoil, (Siemens, Erlangen, Germany).
Gogglesystem	The computer display was projected by means of MR-compatible LCD-goggles (VisuaStim XGA, Resonance Technology Inc., Los Angeles, USA). The parameters of this system were: field of view = 30°, refresh rate = 60Hz, resolution = 1024 x 768. Subjects used corrective lenses when necessary.
Key press	A MRI compatible optical keypress device (Current Designs, Inc, Philadelphia, USA, www.curdes.com), interfaced to the personal computer running E-prime software, was used to record accuracy and RT to each condition.

Data acquisition

Structural data	Each scanning session included the acquisition of a high resolution, (voxel size 1 x 1 x 1 mm and FOV 256 x 256 mm) T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE), scan covering the whole brain, lasting for 10 minutes and 52 seconds. A T2-weighted proton density scan was acquired for clinical evaluation.
Functional data	A T2*-weighted gradient echo EPI mosaic sequence (TE = 60 ms, TR = 2000 ms, FA = 90º, 16 slices covering the parietal and the occipital lobe, slice thickness = 4 mm, interslice distance = 1 mm, FOV = 240 mm, matrix size = 64 x 64, pixel size = 3.75 x 3.75 mm) was used. In total, 690 volumes were collected in the functional experiment. Vitamin E capsules were used to mark the right side of the head on each subject.

8 DATA ANALYSIS

After an fMRI experiment has been designed and carried out, the resulting data must be passed through various analysis steps before one can get answers to the questions about experimentally-related activations at the individual or multi-subject level. This chapter gives a brief overview of the various steps that were employed in the studies.

8.1 PRE-PROCESSING FMRI DATA

Before the effects of the experimental conditions can be investigated there are several transformations applied to the data, which are collectively referred to as pre-processing. Pre-processing the data acquired in an fMRI experiment is a necessary and important step in order to improve the power of the statistical analysis[24] that will be performed later. These preprocessing steps take the raw MR data, convert it to images resembling a brain, reduce unwanted noise of various types and finally precondition the data in order to aid the statistics.

First, in order to remove magnetic saturation effects the first three volumes of each run were discarded. Since the functional experiment contained 690 volumes, this left us with pre-processing of 687 volumes. The pre-processing steps used in the studies are presented below[25].

8.1.1.1 Slice scan timing correction

The slices comprising one functional volume are normally scanned sequentially, i.e. at different moments in time. A problem with this is that the later functional analysis, i.e. in event-related designs, assumes that all slices were measured at the same time and consequently a whole functional volume is treated as one data point. Because different points in the volume were scanned at slightly different times, the model fitting is not optimal. To be able to make this treatment of the data valid (i.e. for interpreting time the same way across a functional volume), the sequentially scanned slices have to be interpolated in time, that is, each voxel's time series was adjusted so that is really does appear as if all voxels were scanned at the same time. Hence, slice scan time correction was performed using sinc interpolation based on information about the TR (2000 ms) and the order of slice scanning (ascending, interleaved).

8.1.1.2 Motion correction

Movement is unavoidable in subjects and also a major concern in fMRI experiments since the high spatial resolution in fMRI sequences is sensitive to motion artefacts. That is, if the subject moves their head during the experiment, the position of the brain within the functional images will vary over time and would result in that any particular voxel's time series does not (over time) refer to the same point in the brain. One simple precaution to minimize head motion is by using a head support system. In our experiment we used a deflatable vacuum pillow which surrounds the head giving it support. However, other factors like respiration or heart pulsation will always occur and

[24] I.e. estimating where significant activation occurred.

[25] There are different approaches to pre-processing steps. However, I will only present those used by the BrainVoyager software (version 4.9 and QX) and which were applied in the studies.

create noise in the fMRI data. To improve the quality of the data a 3D motion correction was performed to detect and correct for small head movements by spatial alignment of all volumes of a subject to the first volume by rigid body transformations. Estimated translation and rotation parameters were inspected and never exceeded 4 mm.

8.1.1.3 Spatial filtering

There are two reasons for spatial smoothing of the data i.e. blurring each volume. First, blurring can increase the signal-to-noise ratio[26] in the data. Noise, as the word is suggesting, is not good. That is, we want to reduce the noise level but still keep the underlying signal. The blurring function acts as a local averaging, in that the noise values in the local neighbourhood tend to cancel out each other. To avoid that the signal is reduced as well, it is necessary that the extent of the blurring is not larger than the size of the activated area[27]. Second, certain statistical analysis (e.g. multi-subject analysis) requires the data to be spatially smoothed in order for the assumptions underlying the statistical theory to be valid (Friston et al., 1994).

The most common method for spatial smoothing is to convolve each volume with a Gaussian profile filter, where the width of the kernel (often expressed in millimeter, (mm)) determines the extent of the blurring that should be applied. A modest spatial smoothing using a Gaussian filter with full-width-half maximum (FWHM) of 4 mm was used in study I and II and a Gaussian filter FWHM of 8 mm was used in study III-V.

8.1.1.4 Temporal filtering

The aim of temporal filtering is to remove unwanted components of a time series without damaging the signal of interest. Since this step is working on each voxel's time series separately (instead of each volume as in spatial filtering), it is usually the last pre-processing stage. Temporal filtering consists of two main functions: removal of drifts and temporal gaussian smoothing. Since the drifts observed in the voxel time series often are linear, a linear trend removal was applied on all data. Next, a high pass filter of 3 cycles in time course in study I and 4 cycles in time course in study II-V were used to remove low frequency nonlinear drifts[28].

8.1.2 Summary of pre-processing steps

Slice scan time correction	Sinc interpolation, and the order ascending, interleaved.
Motion correction	Head support system. Rigid body transformation. A limit of 4 mm was set (although no subject exceeded this level).
Spatial filtering	Gaussian kernel where FWHM was 4mm in study I-II and 8 mm in study III-V.
Temporal filtering	Linear trend removal and high pass filter = 3 (cycles in time course) in study I and 4 in study II-V.

[26] Signal-to-noise is a measure of how big the signal of interest is compared to the noise level. Of course one would like to have as high a ratio as possible.

[27] So, if one expect very small activated areas, spatial smoothing should be avoided.

[28] Usually consists of physiological effects like heart beats or breathing or scanner related drifts.

8.2 SPATIAL TRANSFORMATION

Before moving on to statistical analysis of the images there are two important prerequisites for advanced data processing and visualization features; co-registration of functional and anatomical data and Talairach transformation of 3D data sets. These two procedures will be briefly described next.

8.2.1.1 Co-registration

In order to localize and visualize functional data in (normalized) 3D space, the original 2D functional (T2*) scans have to be aligned with the 3-D anatomical (T1) scan for each subject. Since most of the MRI scanners can provide the slice position parameters of the T2*-weighted measurements (number of slices, slice thickness, distance factor, Tra-Cor angle, FOV, shift mean, off-center read, off-center phase, and in-plane resolution) and the T1-weighted 3-D MP RAGE measurements (number of sagittal partitions, shift mean, off-center read, off-center phase, and resolution), co-registration of 2-D functional and 3-D structural measurements can be performed fairly easy. A successfully performed 2D-3D co-registration offers the possibility to visualize statistical results on top of anatomical 3D data sets including resliced sagittal, coronal and transversal slices. It is also the first step for superimposing statistical data in normalized (Talairach-based) 3D space.

8.2.1.2 Talairach transformation

Just as road maps are useful for navigating around the country side, brain atlases are useful for navigating around brain images (Jenkinson, 2003). Basically, there are two tasks the atlas can provide information to. First, to specify the location of a place in a common reference framework, much like using the grid references on a road map (Jenkinson, 2003). Second, to find other information, like histological or functional data, about some location of interest, which is similar to looking for tourist attractions, hotels etc. on a road map) (Jenkinson, 2003). Also, in order to compare activated brain regions across subjects it can also be helpful to first have transformed the anatomical and functional 3-D data sets into a brain atlas.

The atlas used here (and the most commonly used) is the one developed by Talairach and Tournoux (1988), which was originally based from a detailed examination of one single post-mortem brain. The 3D coordinates were assigned relative to a system based on eight landmark points in the brain; Anterior Commissure (AC); Posterior Commissure (PC), and related to the AC-PC line: the most superior (S), inferior (I), anterior (A) and posterior (P) points on the brain surface and the most extreme right (R) and left (L) points on the brain surface. Consequently, individual brain images can be manually registered, by identifying these landmark points, with a piece-wise affine transformation to the standard Talairach space (Talairach and Tournoux, 1988).

8.2.1.3 Visualization of activation maps

In order to be able to visualize the results of multisubject analysis, group activation maps were overlaid on averaged anatomical maps produced by averaging the individual Talairach 3D maps across subjects.

9 STATISTICAL ANALYSIS

After the pre-processing and the spatial transformation steps, statistical analysis is carried out to determine which voxels are activated by the stimulation. Various possible statistical approaches are available to obtain activation maps, the most popular and frequently used being the General Linear Model (GLM). This chapter first describes an overview of the GLM and then discusses some specific terms that are important to know in order to grasp the specific analysis used. Finally, a short description of the different statistical analyses used in the studies is presented.

9.1 GENERAL LINEAR MODEL

General Linear Modelling sets up a model (i.e., what you expect to see in the data) and fits it to the data. That is, the statistical model[29], derived from the timing of the different stimulation that was applied to the subject in the scanner is compared with the measured time course at each voxel. As a result of that, a good fit between the model and the data means that the data was probably caused by the stimulation. The comparison of the model and the data is expressed as a T, R or F value for each voxel which tells us how good the overall model fits or explains the data and if the T, R or F value of a voxel passes a statistical threshold, the respective voxel will be highlighted by appropriate color-coding[30].

The basic equation of the general linear model for a *response* (i.e. observed fMRI data) variable y_{ij} at voxel $j = 1,\ldots J$ is:

$$y_{ij} = \beta_0 + x_{i1}\,\beta_{1j} + \cdots + x_{ik}\,\beta_{kj} + e_{ij}, \qquad (1)$$

Where β_0 is a constant and correspond to the baseline (rest) intensity value in the data, β_{kj} are k unknown parameters (parameter estimates) for each voxel j. The coefficients x are explanatory or modeled variables under which the observation (i.e. fMRI volume) i was made. Finally, e is the error in the model fitting, which accounts for the residual error between the fitted model and the data (Friston et al., 1995).

9.1.1.1 Matrix formulation

The GLM can be succinctly expressed using matrix notation. Consider re-formulation the equation (1) above in terms of matrices it becomes:

$$\mathbf{Y} = \boldsymbol{X\beta} + \boldsymbol{e} \qquad (2)$$

where $\mathbf{Y}$ is a data matrix containing all the observed data x_{ij}; with one column for each voxel j and a row for each fMRI volume. $\boldsymbol{X}$ is a matrix containing the coefficients x_{ik} (often known as the so-called design matrix) with one column for every modeled (i.e. "designed") effect and one row for every fMRI volume. If you would to visualize the design matrix it would consist of 1 and 0 values in the different columns, corresponding to a sharp on/off waveform of the different stimuli or in the case of our reaction time dependent response predictor each stimulus in the design matrix would consist of their

[29] The model is specified in a design matrix which consists of a set of predictors or explanatory variables.

[30] Thus, hopefully giving us colorful activation maps in the regions that we are expecting to be activated!

corresponding RT, (see response time as a linear regressor, section 9.2.3). $\boldsymbol{\beta}$ is the parameter matrix which has one row for each column of $\boldsymbol{X}$ and one column for every voxel in the volume (see more below). Finally, $\boldsymbol{e}$ is a matrix of error terms (Friston et al., 1995).

9.1.1.2 Hemodynamic response function

In order to get the best possible fit of the model to the data, the stimulus values were convolved with the HRF. This process mimics the effect that the brain's neuro-physiology (a delayed and blurred version of the input time series) has on the input function or stimulation (Smith, 2003). In short, the HRF is a mathematical operation that transforms the square wave function into a blurred and somewhat delayed version which is a better fit with the data. In this thesis, all the design matrixes have been convolved with a HRF function.

9.1.1.3 Beta-weights estimate

Our main task in the analysis is to identify the voxels that fit the estimated model and to obtain an estimate for beta (β). This is achieved by least squares and the least square estimates are the maximum likelihood estimates and the best linear unbiased estimates. Assuming normally distributed noise, this can be accomplished by computing the correlation between the model and the data for each voxel. As a consequence, given that the model is individually fit to every voxel in the data set, this will give a unique set of weights (β coefficients) for each voxel. The calculated beta-weights then tell us the relative heights, or amplitudes, of the different postulated predictor functions. Hence, if a particular voxel responds strongly to one of the models (i.e. stimuli) the model fitting would have a large value for that β value (see also parameter estimates sections 9.2.3.2 and 9.2.5.2). We can also use these beta-weights to estimate the time courses in a specific region (see estimation of time courses, section 9.2.6 below).

9.2 MULTI-SUBJECT ANALYSIS

The combination of statistics across subjects could also allow the generalization of one conclusion to a population. This approach was used in order to pinpoint the region of interest for study I-V, as well as look for between-group differences in study III-V. A short outline of the different analyses is given below.

9.2.1 Fixed and random effects analysis

When conducting a multi-subject GLM, it is important to distinguish between effects that are fixed and effects that are random. Fixed effects analyses determine the regions "typically" activated in the general population (Friston et al., 1999). In study I the subjects were treated as a fixed effect and as a consequence the resulting significant results are only valid for this group of young individuals included in the analysis.
In study II-V random effects analyses were used to create the statistical parametric maps. This analysis should provide the most robust conclusions about the ability to generalize the results from a group of subjects to the population at large (Friston et al., 1999). In addition, this approach tends to be a little more conservative then the fixed effect analysis. Random effects analyses also take into account intersubject variability

and use one “summary” scan per subject (the contrast image, containing the estimable parameters of the individual subject’s analysis) in a simple one-sample Student’s t-test.

9.2.2 Cognitive subtraction

In study I the classical approach of cognitive subtraction was applied in order to identify regions activated from the visuospatial task. This approach is a straightforward and under certain conditions very effective method for mapping cognitive processes. The tenent of this approach is that the difference between two tasks can be formulated as separable cognitive components and that the regionally specific differences in brain activity identify the corresponding functionally specialised area (Frackowiak et al., 1997). In the angle discrimination task used in this thesis, this means that to be able to identify the areas involved in visuospatial processing, we have to subtract the brain activity evoked by the control task (clock image without hands) from the brain activity due to the process of clock images. To correct for multiple comparisons, the Bonferroni correction method was used, adjusting the single-voxel threshold in such a way that an error probability of 0.05 was retained at the global level.

9.2.3 Parametric modulation

9.2.3.1 Response time as a linear regressor

As the type of the relationship between the stimulus parameters and the hemodynamic response may vary among different brain regions and is unknown in advance, the a priori definition of a fit function for a regression analysis (e.g. linear) might result in a partial or insufficient characterization of the data (Buchel et al., 1996; 1998). For this reason, in study II-V we were using a slightly different framework that allowed us to characterize brain responses as a linear combination of (basis) functions of our experimental parameter. Especially, based on the premise that hemodynamic responses vary with the amount of cortical processing engaged by the the experimental task (Buchel et al., 1998), this model can provide information about the relationship between a stimulus parameter or behavioral response and the neurophysiological response elicited.

More in detail, this means that the stimulus functions which usually are described as vectors consisting of ones and zeroes are now assigned numbers other than 1 and more importantly, one can assign different values to different individual trials (Kiebel and Holmes, 2003). In our case the trial-wise acquired RT was used to weight the stimulus function, which means that after convolution of the stimulus functions with the basis function, different weights in the stimulus function essentially control the relative height of the expected response of all trials (Kiebel and Holmes, 2003). Hence, this gives the opportunity to characterize and differentiate brain regions using their response profile in response to the stimulus parameters (Buchel et al., 1998).

A framework was used that allows characterizing BOLD signal responses in terms of a hierarchical set of orthogonal basis functions (polynomials). Using this approach voxel-specific model selection is straightforward using the extra sum of squares principle in the context of the GLM (Draper and Smith, 1981). In total, three covariates were designed and entered into the GLM model. Origin was a standard fixed boxcar (see above) predictor coding the onset of each clock-stimulus (FixedClock). A second fixed boxcar predictor whose values coded the onset of each control stimulus

(FixedControl), and a third boxcar predictor whose values coded the RT (in seconds) for each single trial (RT predictor) (as presented above).

The fixed boxcar predictor coding the clocks (FixedClock) and the RT predictor were then orthogonalized since orthogonal basis functions span the parameter space in an efficient way and have the advantage that the parameter estimates are independent of each other under the null hypothesis (as stated in study II):

$$RT^0 = FixedClock - FixedClock\,(FixedClock^T FixedClock)^{-1} \times FixedClock^T RT \qquad (3)$$

where RT^0 is the orthogonalized linear term RT. In our case of a linear RT predictor, the orthogonalization equals the centering of the RT predictor to have a mean value of zero. Also, prior to model fitting, these covariates were convolved with a double gamma function in order to model the typical hemodynamic reponse characteristic.

Hence, we can use these to test for specific effects using t-statistics, assessing the significance of the explanatory effects designated interesting (covariate of interest) with all uninteresting effects designated confounds (covariates of no interest). This means that the individual created modulated regressor allows one to test for a linear dependence between reaction times and height of response (calculating mean change in BOLD signal for 1s increase in RT) while taking into account all other modelled effects (Kiebel and Holmes, 2003) i.e. task demand dependent changes of brain function. Furthermore, using the function based on the simple boxcar (FixedClock), we can model the average BOLD signal increase from baseline irrespective of RT i.e. task demand independent or general changes of brain function.

9.2.3.2 Parameter estimates

In order to visualize the RT-BOLD relationship in study II, the mean change in BOLD signal for 1 s increase in RT was computed for each individual and each ROI (mean ± standard error (S.E) over all subjects).

9.2.4 Conjunction analysis

In studies II-V, to identify the regional activation associated with visuospatial processing and to reveal focal maxima of activation, multiple subjects contrast images (t-test) using the GLM framework (random effects analysis) were computed for each subject group using conjunction analysis of the linear RT predictor and FixedClock predictor described above. This was done based on the following steps: (i) random effects group analysis based on the individual subject results from the FixedClock predictor, and (ii) random effects analysis using the results from the RT predictor, and (iii) conjunction of the previous 2 random effects analysis.

A conjunction is defined as the intersection of the two statistical maps for the two predictors, thresholded at the specific alpha rate (Nichols et al., 2005). This approach can be simply defined in logic. That is, if we have two truth statements A and B, then the conjunction of A and B is true, if and only if, both A and B are true. In neuroimaging terms, it would mean that we are looking for brain regions that respond to two sets of different conditions, i.e. A and B are statements about the presence of an effect for a particular comparison. Thus, the activated areas are those which are active in both predictors. Following this, the conjunction map of RT predictor AND Fixed predictor is obtained at each voxel by computing a new statistical value as the minimum of the statistical values obtained from the defined contrasts.

In our study, a conjunction was chosen, since for a region being visuospatial task demand dependent, it needs to fulfill two conditions: first, the region must show task induced response with the typical hemodynamic response characteristics (modeled with the FixedClock predictor), and second the amplitude of this response needs to be correlated with RT (our RT predictor). Both are necessary but not sufficient conditions.

To conclude, the resulting conjunction maps made it possible to outline the visuospatial network in each subject group. Furthermore, in these areas we could expect a general pattern of a linear relationship between cortical activation and behavioral performance, hence reflecting increased cortical processing (i.e. increment in intensity of neuronal activity), due to the linear RT regressor.

9.2.5 Between-group analysis

In studies III-V we also performed a between-group comparison of the linear RT predictor respectively the simple FixedClock predictor to reveal possible changes in the functional contribution in the areas demonstrated to be activated in the angle discrimination task i.e. regions activated in the conjunction analyses. First, a multi-subject GLM with predictors separated for each included subject was performed. Second, the two groups were compared by computing the mean of the summary statistics (contrast) for each group followed by a t-test (random effects) to compare the group means. Subsequently, looking at between-group differences in task demand modulated BOLD changes the only covariate of interest was the linear term (i.e. RT predictor) (see also description above), and the remaining two predictors are designated as confound or covariates of no interest. Hence, the significant areas that are activated are those for which the RT predictor can explain a significant amount of variance (on top of the other predictors). Similarly, when looking at between-group differences of general or categorical differences in BOLD signal, irrespective of RT, the FixedClock predictor was chosen as the covariate of interest.

9.2.5.1 Correction for multiple comparisons

To correct for multiple comparisons, a spatial extent method was applied in studies II-V. This method relies on the observation that neighboring voxels often activate in clusters based on the Monte Carlo stimulations calculating the likelihood to obtain different cluster sizes (Forman et al., 1995). Thus, a cluster extent threshold of 135 mm^3 (5 adjacent voxels) was applied in order to reduce the probability of false positive results, (minimal cluster size extrapolated from Table 2 in Forman et al., 1995).

9.2.5.2 Parameter estimates

In order to visualize the differences found in the between-group analyses in studies III-V for the RT respectively the FixedClock predictor, the mean change ± S.E. in BOLD signal for 1 s increase in RT was obtained for the RT predictor as well as the mean change ± S.E. in BOLD signal was obtained for the FixedClock predictor.

9.2.6 Region of interest analysis

9.2.6.1 Estimation of time courses

In study I-V a ROI analysis was performed to access the statistical parameters for the time course of subsequent voxels. This was done using the GLM to estimate the finite impulse response (FIR) (Ollinger et al., 2001) associated with each clock-stimuli (i.e.

15 clocks). This procedure is equivalent to the method of selective averaging (Dale, 1999). With the FIR model, there were no a priori assumptions about the shape of the hemodynamic response and no requirement of a uniform transition matrix, since this set of basis functions is able to capture any shape of response up to a given frequency limit (Henson et al., 2001). Hence, for all clock types, a stimulus convolution matrix (SCM) was defined, that is, a matrix operator representation of the time-discretized convolution with the event sequence (Dale, 1999; Ollinger et al., 2001). This is accomplished by placing a "1" in the row corresponding to the time at which each image was acquired and in the column corresponding to the appropriate point of the hemodynamic response. By inverting the model it yields estimates of the time course at each point. The final design matrix was a horizontal concatenation of the SCM. In study I we used a single subject GLM approach and computed a ROI analysis in four regions (bilateral SPL, right striate visual cortex and left sensorimotor cortex) for each subject. For this study a model with 13 FIR time bins was used. In study II the same procedure was used although computed from the multisubject GLM. In this study a model with 10 FIR time bins was used, extracting the event-related data for the 0 – 18 s after stimulus onset. This latter FIR model was used also in studies III-V, where ROI analyses were performed in all brain regions that were detected in the between-group analysis of the RT and FixedClock predictors.

Finally, for all studies, in order to show the event-related time course of the HRF, the BOLD signal time courses were averaged (± S.E.) across subjects from select ROIs. In study I this was done in the four ROIs mentioned above, which were averaged across subjects and across the different stimulus categories over 4 volumes before and 10 volumes after stimulus onset. In studies II, averaged time courses were shown for all clocks and the control clock in selected ROIs. Finally, in studies III-V averaged time courses were shown from the between-group analyses in selected ROIs.

9.3 ANALYSIS OF BEHAVIORAL DATA

Reaction times and accuracy measures (% correct button presses) were analyzed using a three-way repeated measures analysis of variance (ANOVA) with age-group as independent factor and clock-stimuli as the repeated measure. Post hoc tests (t-tests for independent samples and Sheffé´s test) were computed in case of significant main effects respectively significant interaction effects. F values were Greenhouse–Geisser corrected, to decrease the risk of type I errors.

9.4 OVERVIEW OF ANALYSING STEPS

An overview of the different pre-processing and statistical analysing steps is given in figure 9.1.For more detail about the pre-processing steps see chapter 8 and for details concerning the different statistical analysis see this chapter.

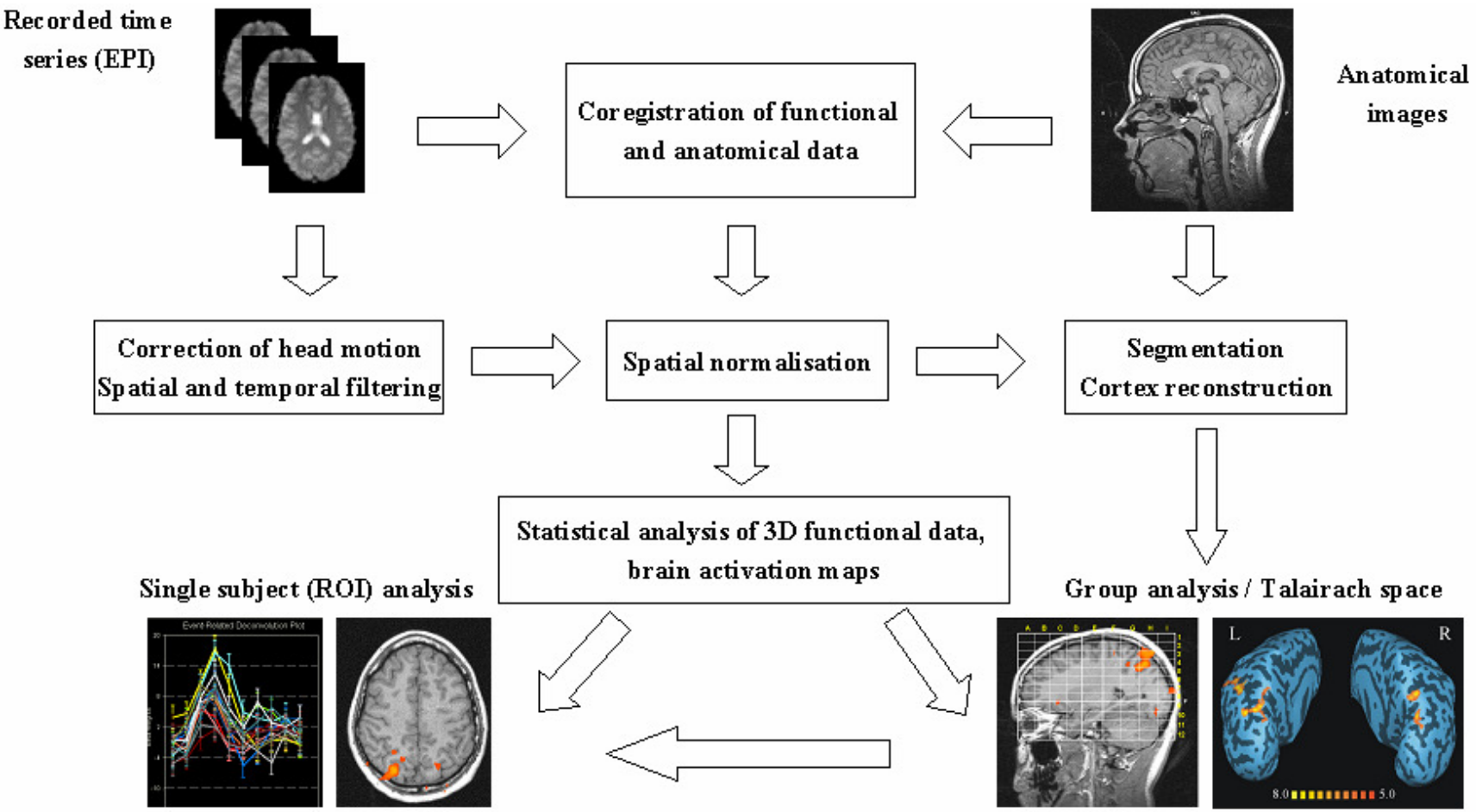

Figure 9.1 Overview of the different analysing steps (pre-processing and statistical) that were made in the studies.

The transformations begin with the imaging timeseries and end with the statistical parametric map. These statistical procedures can vary in different studies (e.g. only study I have single subject ROI analysis). For details concerning the different steps see text.

10 SUMMARY OF RESULTS

10.1 STUDY I: VALIDATING OUR PARADIGM

Complex mental operations like visuospatial processing are often subserved by large-scale, spatially distributed neurocognitive networks. Although the anatomical substrates for visuospatial function have been extensively studied (see chapter 3), the functional contribution of these brain regions is not well known. We hypothesized that by examining the quantitative relationship between the functional activation and the behavioral performance of the task, it would allow a more specific statement concerning the relevance of a certain area within the processing visuospatial network. Our approach was to investigated in 10 healthy young subjects (mean age 25.9 years) how the amount of task demand (as measured with RT) in our angle discrimination task was related to neural activity as measured with event-related fMRI.

Multisubject group analysis revealed significant activation in the parieto-occipital network subserving visuospatial processing. Peak values were extracted from four different cortical regions, comprising of bilateral SPL (BA 7), left sensorimotor cortex (BA 4), and left striate visual cortex (BA 18). Linear regression analysis was used to investigate the relation between the amount of neuronal activity and task demand in these ROIs. A highly statistically significant correlation between RT and BOLD signal in both right and left SPL (r= .58, $p < .0001$ and r= .47, $p < .0001$, respectively) was found after inclusion of a subject factor into the model. Also, a weaker significant correlation, according to the correlation coefficient, was detected in the motor cortex (r=.28, $p < .001$), whereas no statistically significant correlation was found in the visual cortex (r=.16). Similarly, a statistically significant linear relationship was found between task demand and mean number of activated voxels per clock-category for all subjects in right and left SPL (r=.83, $p <.001$ and r=.93, $p <.001$ respectively), whereas no statistically significant correlation was found in the sensorimotor and striate visual cortex.

These results were in agreement with our hypothesis and indicate that the imposed task demand, and thus computational demand to execute the task, is associated with increases in neuronal activation (amplitude of the BOLD signal and spatial extent of activation) in certain regions relevant to the angle discrimination task. Thus, providing further evidence that these regions are critically involved in a large-scale cortical network subserving visuospatial processing.

10.2 STUDY II: IMPROVING THE METHOD

The classical cognitive subtraction approach usually used in fMRI studies[31] is a straightforward and under certain conditions very effective method of mapping cognitive processes, such as visuospatial processing. However, with the aim to identify brain regions most specifically associated with performance on a given task, this approach suffers from several methodological caveats (see section 9.2.3). For this reason, an extended general linear model including a single-trial reaction time dependent hemodynamic response predictor was implemented in study II. This model

[31] Used also in study I.

made it possible to take into account the variability of the BOLD signal response due to variable task demand and behavioral performance (RT) on the level of each single trial.

Thus, study II was designed to further examine angle discrimination with respect to the whole visuospatial network and the aim was to compare these two models in fourteen healthy young subjects (mean age = 26.1 years). Comparison between the statistical parametric maps (random effects) revealed that the use of the reaction time dependent hemodynamic response predictor made it possible for detection of a more specific visuospatial network including task demand dependent regions not being detected using the cognitive subtraction method. In addition to the already known regions in the SPLs (BAs 7) as well as inferior parietal lobules (IPLs) (BAs 40), known to be implicated in visuospatial processing and also detected in study I, we also found activation in bilateral caudate nucleus and insula (BAs 13), right inferior frontal gyrus (IFG, BA 44) as well as left precentral gyrus (GPrC, BA 6).

Hence, the use of the reaction time dependent hemodynamic response predictor increased the sensitivity of the model and allowed us to better identify and characterize brain regions that are responsible for execution of our angle discrimination task.

10.3 STUDY III: INVESTIGATING ELDERLY SUBJECTS

Much remains unknown about the origins how normal aging affects the neural basis of cognition. Common age-related findings suggest that older adults are slower at performing many tasks and sometimes are less accurate than when they were younger. This phenomenon of age-related slowing has been interpreted as a decrease in speed of information processing or decline of processing effiency (Salthouse, 1996) (see section 4.3.2).

To further explore this we examined 32 two healthy elderly (mean age 65.6 years) and 14 healthy young (mean age 26.1 years) subjects using our fMRI visuospatial paradigm. As expected, elderly showed a general significant slowing of RTs across clock-stimuli compared to young subjects, although accuracy was similar between the groups. Extending our earlier findings in young subjects (study I and II), we found that both groups revealed similarly activated networks for the execution of the angle discrimination task. These included bilateral core regions in the parieto-occipital cortex (centered in the SPLs and IPLs and visual cortex). By adapting the technique to model the dependency of the BOLD signal on the subject's RT, it allowed us to investigate differences in task demand dependent and independent signal changes between the age-groups. We found that the use of a linear basis function in conjunction with the GLM revealed that almost all regions of the reported visuospatial network had a weaker BOLD signal increase with increased task demand for elderly compared to young subjects. This result suggests that age modulates the utilization of cerebral networks, which has bearing on the behavioral task performance i.e. leading to increased processing speed in the elderly subjects.

In addition, we also found a task demand independent age-related reduction in occipital activity coupled with an age-related increased activation of additional brain regions in bilateral frontal areas in the elderly subjects. This latter finding is consistent with the view that age-related cognitive deficits are partly due to a decline in sensory processing and that the recruitment of additional brain regions in the prefrontal cortex might reflect a strategic shift in elderly subjects to help process the visual information and hence the execution of the visuospatial task.

Taken together, this study is providing new results concerning the effects of aging on the visuospatial processing system and provides further insight in the understanding of the mechanisms behind the phenomenon of age-related slowing.

10.4 STUDY IV: INVESTIGATING MILD AD PATIENTS

Alzheimer's disease is associated with disturbances of visual cognition, such as spatial processing. Disturbances in e.g. visuospatial processing (Ska et al., 1990; Tetewsky and Duffy, 1999; Fujimori et al., 2000) and visual attention (Parasuman et al., 1992; Rizzo et al., 2000) are greatly affecting the patients' activities of daily living. However, the neural mechanism underlying this impairment is largely unknown.

In study IV, disease-related alterations in the cerebral networks subserving visuospatial processing were examined in 13 mild AD patients (mean age 68.9 years, mean MMSE score = 25.5, range = 23-29) and 13 healthy age- and education- matched controls (mean age 68.7 years).

The AD patients performed the task with similar response latencies as the control subjects, although the accuracy was lower in the AD patients compared to the controls. By investigating the brain-behavioral relationship for each group, we could here demonstrate that although both groups demonstrated overlapping activation in the visuospatial networks, the AD patients showed a significant weaker and sometimes absent increase in BOLD signal due to increased task demand compared to controls in several regions in the dorsal visual pathway (e.g. bilateral precuneus (BA 7), IPL (BA 40), and cuneus (BAs 17 and 19). This result suggests failure to modulate the neural response to increased task demand. In addition, we found a significant general decreased activation in several areas, mainly located in occipital cortex (e.g. BAs 18 and 19) and more importantly an increased activation in the middle temporal gyrus (MTG) (BA 22) in AD patients compared to controls. These latter findings could reflect a plausible plasticity mechanism in AD that tries to compensate for these dysfunctional brain areas in the visuospatial network.

Hence, the present results confirm the deficit in visuospatial processing in mild AD patients and provide additional knowledge of the neural mechanisms underlying this impairment.

10.5 STUDY V: INVESTIGATING MCI PATIENTS

Detection of good markers in people with high risk of developing AD still remains a challenge. Especially, there is a lack of data investigating individuals during different stages in the course of the disease. Such data is necessary in order to establish the functioning of neural networks responsible for preclinical symptoms in AD that could possibly provide sensitive markers for pathological changes occurring early in the disease. Mild cognitive impairment refers to the transitional state between the cognition of normal aging and mild dementia (American Psychiatric Association, 1994; Petersen et al., 2001), in which individuals experience minor impairment in cognitive function, but do not meet the accepted clinical criteria for dementia (e.g. Almkvist et al., 1998) (see section 7.2). This period has also been called the preclinical phase of AD (e.g. Almkvist et al., 1998).

To further explore this, in study V, 18 patients with MCI were evaluated and clinically followed for approximately 3 years. Five progressed to dementia (PMCI) and 8 remained stable (SMCI). Thirteen age- gender- and education- matched controls also participated in the study.

The MCI patients performed the task with similar behavioral (RT and accuracy) responses as the control subjects. Extending our earlier findings (study I-IV), we found that both MCI patients and controls revealed similarly activated networks for the execution of the angle discrimination task. The most striking findings were that compared to SMCI and controls, PMCI showed stronger relation between task demand and brain activity in left SPL (also detected in right SPL compared to SMCI), with remarkably similar peak foci. That is, as the task became more difficult to solve, the PMCI patients had bigger changes in BOLD signal than did the other two groups. Also, looking at the average BOLD signal increase from baseline irrespective of RT, revealed that compared to SMCI and controls, PMCI demonstrated a higher BOLD signal in left precuneus (similar peak foci), and also areas in frontal cortex (superior frontal gyrus, SFG) as well as thalamus compared to SMCI.

The increase in signal intensity among the PMCI group suggests that in order to accomplish the task more brain resources have to be recruited. That is, in PMCI patients the brain's processing capacity is dynamically augmented to meet the cognitive demand of the task. This can be done by increasing the number of neurons firing and/or by increasing the rate at which the neurons are firing.

Thus, the detected additional brain activity may serve as a compensatory role for PMCI patients to achieve the same level of performance as subjects without in situ AD pathology. Hence, the current findings indicate that the clinical heterogeneity of MCI can be distinguished using event-related fMRI.

11 DISCUSSION

11.1 THE VISUOSPATIAL NETWORK

11.1.1 Activation of the SPL in different visuospatial tasks

All studies in this thesis consistently activated a parieto-occipital network of areas including the SPL, IPL, precuneus, striate and extrastriate visual areas. Additionally, areas in the frontal cortex (e.g. IFG, middle frontal gyrus, MFG, and medial frontal gyrus, MeFG) and the basal ganglia (e.g. caudate nucleus, insula, and thalamus) were found to be activated in all subject groups (study II-V). The original evidence that the parietal lobes are involved in spatial vision comes from the contrasting effects of IT and PP lesions in monkeys (Mishkin et al., 1983), where only PP lesions caused a severe deficit in visuospatial performance while having no effect on visual discrimination performance (see also section 3.2). Further evidence that the parietal region is particularly implicated in visuospatial processing is supported by several subsequent neuroimaging studies that have showed significant increases in rCBF (using PET or fMRI) during the performance of different visuospatial tasks.

An overview of recent results of some relevant neuroimaging studies examining different visuospatial tasks including our studies is given in table 11.1, which summarizes for both hemispheres the location of the local maxima (in Talaraich's coordinates) within the parietal cortex. As can be observed in table 11.1 these parietal activations do not correspond just to a single point in the Talairach's stereotactic space. In each of the studies mentioned, the superior parietal activations extend between +30 mm and + 55 mm above the bicommisural plane. This area corresponds to the SPL in Talairach's atlas of the human brain, comprising both the superior parietal gyrus and the intraparietal sulcus (see anatomical definition, section 3.2 .1.3).

Figure 11.1 also shows four different Talairach's axial slices where these parietal local maxima are located. This figure, together with table 11.1, clearly demonstrates that all tasks depend on similar large-scale neurocognitive networks, including SPL, although performance on these tasks may depend on somewhat different visuospatial processes. Subsequently, this also gives support to the fact that the type of visuospatial processing has a major role in which brain regions are recruited, which can help explain some of the inconsistency in the literature.

11.1.1.1 Lateralization of visuospatial processing

Although not a topic in our studies, the question whether there exists lateralization in the parietal cortex still remains controversial. Some functional studies and the majority of clinical observations have argued in favour of a right hemispheric specialization (e.g. Ditunno and Mann, 1990; Harris et al., 2000), whereas there are others demonstrating left hemispheric specialization (e.g. Mehta and Newcombe, 1991; Alivisatos and Petrides, 1997) or symmetrical bilateral involvement (e.g. Haxby et al., 1991; Tagaris et al., 1996; 1997; Kosslyn et al., 1998). In our angle discrimination task the results were bilateral, a result which is also in accordance with the proposition that bilaterality may increase with increasing task demand and which has been observed in several functional studies that have employed a parametric mental rotation task using

Table 11.1 Anatomical regions (Talairch coordinates; x, y, z of local maxima) detected in the parietal lobe related to the performance of various visuospatial tasks.

	Spatial task / reference	Subjects	Left			Right			Technique
			x	y	z	x	y	z	
Angle discrimination									
1	Dierks et al., 1999	Yc	-25	-63	+39	+28	-67	+33	fMRI
		HD	-29	-66	+31	+25	-65	+32	
2	Sack et al., 2002 a	Yc	-19	-74	+47	+26	-69	+48	fMRI
			-26	-75	+46	+29	-67	+53	
3	Sack et al., 2002 b	Yc	-13	-67	+52	+21	-69	+49	fMRI
			-1	-72	+49	+16	-72	+48	
4	Prvulovic et al., 2002	Ec	-4	-48	+55	+13	-67	+47	fMRI
			-10	-66	+51	+29	-52	+45	
		AD	-27	-56	+49	+12	-71	+41	
			-22	-69	+36	+23	-59	+54	
5	Vannini et al., 2004*	Yc	-21	-69	+44	+24	-64	+46	fMRI
6	Lehmann et al., 2006*	Yc	-27	-57	+46	+20	-67	+51	fMRI
7	Vannini et al., study III*	Yc	-27	57	+45	+20	-67	+50	fMRI
		Ec	-20	-66	+45	+25	-60	+38	
8	Vannini et al., study IV*	AD	-24	-78	+40	+25	-64	+29	fMRI
			-23	-56	+42				
		Ec	-23	-63	+40	+23	-71	+41	
9	Vannini et al., In press*	MCI	-23	-63	+46	+26	-59	+46	fMRI
		Ec	-24	-54	+45	+23	-56	+45	
			-18	-65	+47				
Fragment puzzle task									
10	Deutsch et al., 1988	Yc	Parietal lobe activated. Talairach coordinates not reported						PET
Line orientation									
11	Deutsch et al., 1988	Yc	Parietal lobe activated. Talairach coordinates not reported						PET
12	Ng et al., 2000	Yc	-9	-72	+42	+20	-61	+48	fMRI
13	Ng et al., 2001*	Yc	-17	-61	+48				fMRI
Mental rotation (spatial imaginary)									
14	Deutsch et al., 1988	Yc	Parietal lobe activated. Talairach coordinates not reported.						PET
15	Parsons et al., 1995		-20	-64	+46	+34	-54	+48	PET
			-30	-58	+52	+26	-56	+46	
16	Wendt and Risberg, 1994*	Yc	Parietal lobe activated. Talairach coordinates not reported.						PET

Table 11.1 continued

	Spatial task / reference	Subjects	Left			Right			Technique
			x	y	z	x	y	z	
17	Cohen et al., 1996	Yc	Parietal lobe activated. Talairach coordinates not reported.						fMRI
18	Tagaris et al., 1996*		ROI analysis including SPL. Talairach coordinates not reported.						fMRI
19	Alivisatos and Petrides, 1997	Yc	-13	-68	+48	+12	-69	+51	PET
20	Tagaris et al., 1997	Yc	ROI analysis including SPL. Talairach coordinates not reported.						fMRI
21	Kosslyn et al., 1998	Yc	-15	-68	+44	+12	-65	+48	PET
			-20	-68	+44				
22	Carpenter et al., 1999*	Yc	ROI analysis including SPL. Talairach coordinates not reported.						fMRI
23	Ng et al., 2001*	Yc	-6	-64	+48	+14	-64	+42	fMRI
			-6	-58	+37	+17	-69	+37	
24	Podzebenko et al., 2002*	Yc	-42	-54	+46	+22	-78	+54	fMRI
						+34	-56	+50	
Mirror reading									
25	Goebel et al., 1998	#	-23	-68	+47				fMRI
			-33	-48	+51				
26	Dong et al., 2000*	Yc				+26	-54	+56	fMRI
Perceptual maze test									
27	Ghatan et al., 1995	Yc	-25	-58	+50	+45	-55	+52	PET
Surface orientation									
28	Shikata et al., 2001*	Yc	-16	+68	+57	+20	-67	+58	fMRI
Spatial location matching									
29	Haxby et al., 1991	Yc	-16	-62	+44	+26	-58	+44	PET
30	Haxby et al., 1994	Yc	-16	-64	+48	+10	-58	+44	PET
31	Grady et al., 1994	Yc	Parietal lobe activated. Talairach coordinates not reported.						PET
		Ec							

Distances are in millimetres to the right (+) and left (-) of the midline for the x coordinates, anterior (+) and posterior (-) to the VAC line for y coordinates and above (+) and below (-) the AC-PC line for the z coordinates. Abbreviations: VAC = vertical plane passing through the anterior commissure; AC = anterior commissure; PC = posterior commissure. AD = Alzheimer's disease; C = controls; fMRI = functional magnetic resonance imaging; HD = Huntington's disease; MCI = mild cognitive impairment; rTMS = repetitive transcranial magnetic stimulation; YC= young controls; * = Parametric design looking at correlation between activation signal and behavioral parameter; # = not reported.

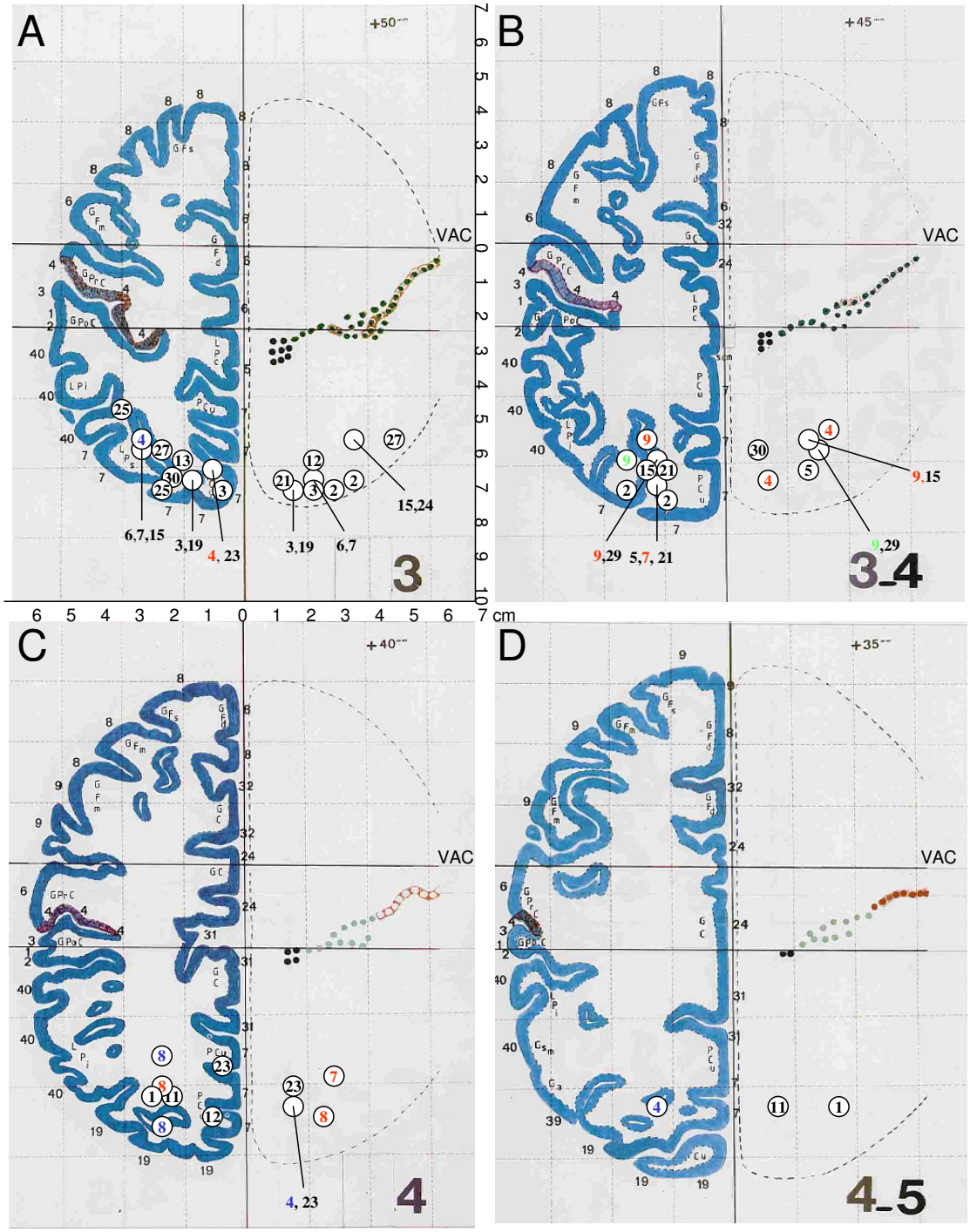

Figure 11.1 Parietal activations observed during performance of various visuospatial tasks, as demonstrated by increased rCBF measured with fMRI and PET. Numbers in symbols indicate the study reporting each activated focus listed in Table 11.1. Numbers in black = young subjects; red = elderly subjects; blue = AD patients; green = MCI patients.These results are displayed on four axial stereotaxtic grids of Talairach and Tornoux atlas (1988), +50, +45, +40, and +35 mm above the anterior commissure-posterior commissure line. Distances are in millimetres anterior (+) and posterior (-) to the vertical plane passing through the anterior commissure line, and to the right (+) and left (-) of the midline.

the Shepard and Metzler figures (Cohen et al., 1996; Tagaris et al., 1996; 1997; Kosslyn et al., 1998). Also, regarding angle discrimination a series of studies were conducted by Sack and collegues (2002a; 2002b) but see also Sack et al. (2005), where the functional relevance of brain activity in the parietal cortex was investigated by combining fMRI with repetitive TMS (rTMS). By inducing temporary regional deactivations, rTMS can block the function of a specific cortical structure thereby allowing the definition of a causal link between behavior and regional brain function (Pascual-Leone et al., 2000). Sack and collegues (2002a) could demonstrate an impairment of performance both during and immediately after inducement of a transient lesion in the SPL. In a subsequent study they also found that only the group that had received rTMS to the right parietal lobe showed an impairment of performance during and immediately after rTMS, indicating a capacity of the right parietal lobe to compensate for a temporary suppression of the left hemisphere but not vice versa (Sack et al., 2002 b).

11.1.2 Other areas in the network

It seems plausible that visuospatial task processing is not the function of a single brain area, but instead involved the cooperative interaction of a number of brain areas. With regard to angle discrimination, this task presumably involves several operations, including encoding of the visual images (clocks), judging whether the angle between the hands are 60 degrees or not, making a discriminatory motor response, etc. It is also obvious that some general processes are involved as well, such as attention and working memory. It is therefore not surprising that a number of brain areas are engaged in this task, although the mere fact that a certain brain area is activated during the task does not mean that this area is specifically involved in angle discrimination per se.

11.1.2.1 Early visual areas

It is not surprising that areas in the early visual areas should be activated considering that both the ventral and the dorsal pathway originate in primary visual cortex (V1) or striate visual cortex (Courtney and Ungerleider, 1997). The areas along both the pathways are furthermore organized hierarchically, such that low-level inputs are transformed into more useful representations through successive stages of processing (Ungerleider and Haxby, 1994) thus representing a *"bottom-up"* process subserved by feedforward projections between successive pairs of areas within a pathway (see also section 3.2). Several previous studies have consistently found striate (V1) activity in for example mental rotation (Podzebenko et al., 2002), angle discrimination (Dierks et al., 1998; Sack et al., 2002 a; 2002 b) and in the perceptual maze test (Ghatan et al., 1995). However, others including our studies have reported a weak or nonexistent effect of this area (e.g. Cohen et al., 1996; Alivisatos and Petrides, 1997; Prvulovic et al., 2002). In our studies only study I demonstrates activation in primary visual cortex. This divergence in the findings could perhaps reflect different stimuli used and perhaps also the type of statistical analysis employed i.e. if a control task is used which include visual information a traditional cognitive subtraction analysis could easily remove this activation. However, visual inspection of the activation maps produced in our studies (III-V) reveals that the activation in some maps actually extends into striate visual areas, although a peak foci is not found in these areas.

Extrastriate visual activations are more commonly observed in studies examining different visuospatial tasks. Several groups, including our studies, have reported activation in V2 (corresponding to BA 18 and V3 (corresponding to BA 19) during visuospatial processing (e.g. Haxby et al., 1991; 1994; Ghatan et al., 1995; Dong et al., 2000; Ng et al., 2001; Podzebenko et al., 2002; Sack et al., 2002 a; 2005). Of these, V2 is the second major area in the visual cortex and receives strong feedforward connections from V1 and it also sends strong connections to V3, V4, and V5 and strong feedback connections to V1. Functionally this region has been found to process simple properties such as orientation, spatial frequency, and color but this region also process more complex properties of the visual scene such as perception of illusory contours (Von der Heydt et al., 1984). The V3 on the other hand has been suggested to consist of two subdivision, one which is part of the dorsal stream (also called dorsomedial area (DM) and projects to the PP cortex. This region has been proposed to contain a represention of the entire visual field and respond to coherent motion (Liu et al., 2006) but also in perceptual "filling in" (DeWeerd et al., 1995).

11.1.2.2 Frontal regions

Activation in IFG (BA 9/44) was observed bilaterally in all subject-groups and is consistent with previous fMRI studies of visuospatial processing e.g. mental rotation (Podzebenko et al., 2002), mirror reading (Dong et al., 2000), perceptual maze test (Ghatan et al., 1995), and spatial location matching (Haxby et al., 1994). This region is believed to play a role in visuospatial working memory (Goldman-Rakic, 1988; Jonides et al., 1993). Furthermore, it has been suggested that both processing pathways have projections to the frontal lobe, which in turn send reciprocal projections back to the visual processing areas (Courtney and Ungerleider, 1997). These reciprocal, or feedback, projections are thought to play a "*top down*" role in vision, such as in the allocation of attention to selected visual stimuli (Courtney and Ungerleider, 1997). Thus, this activation found in our studies indicates that spatial working memory is part of the frontal cognitive processing during angle discrimination. In detail, it may represent processes that help maintain and process visuospatial information as for example comparing the clock-stimuli with an internal template of the target stimuli or perhaps by holding the clock-stimuli in memory while extrapolating the length of the hands towards the edge of the clockface.

11.1.2.3 Frontal motor regions

Our findings of bilateral frontal motor area involvement in angle discrimination are consistent with other fMRI studies (e.g. Ghatan et al., 1995; Dierks et al., 1998; Podzebenko et al., 2002; Prvulovic et al., 2002; Sack et al., 2002 a; 2002 b), although Haxby et al. (1994) have reported activation (in BA 6) only in the right hemisphere. Regions of activation were found within the premotor area (BAs 4, 6, 8, 9) including MFG and MeFG. These areas, especially BA 6, have furthermore been suggested to play a role in the planning of complex, coordinated movements. The angle discrimination includes a minor motor response which is preceded by a choice between the left and the right button (choice of finger). Thus, the area of activation in these regions could represent motor performance. However, prior studies in mental rotation have suggested that these areas are also recruited due to the dynamic motor imaginary components of visual imaginary, especially when there is a personal/internal factor in

performing the task (i.e. the subjects imagine themselves manually rotating the stimulus) (Richter et al., 2000). Thus, it could be conceivable that involvement of some of these frontal motor areas in angle discrimination could be interpreted similarly as an attempt of the subjects to imagine an internal template of the target stimuli or be a result of the process to extrapolate the length of the hands towards the edge of the clockface (c.f. 11.1.2.2). Similarly, an area in the frontal motor regions has also reported to be activated in a visual attention task (Buchel et al., 1998).

Taken together, this activation could therefore also reflect the fact that the subjects are coordinating their eye movements during the task or perhaps be due to the substantial attention that is required for angle discrimination.

11.1.2.4 Deep grey matter structures

In our studies we consistently found activation in the deep grey matter structures; basal ganglia (i.e. caudate nucleus and insula) and thalamus. These areas have been suggested to be part of an attentional network including the anterior cingulate gyrus as well as dorsal prefrontal regions (see Madden et al., 2005). The specific role of the basal ganglia is however less clear, although there is evidence of extensive and topographically organized projections from the basal ganglia to both prefrontal and motor cortical regions (Middleton and Strick, 2002). In one fMRI study by (Huettel et al., 2001), that separated visual search and response generation processes, a phasic activation in the basal ganglia and thalamus was associated with the execution of a manual response to a visual display. Activation in caudate nucleus has also been directly implicated in spatial processing e.g. from lesion studies (Divac and Oberg, 1992). Similarly, in a PET study examining rCBF changes related to the performance of two spatial cognitive tasks (Alivisatos and Petrides, 1997) found activation of the head of caudate nucleus in the right hemisphere in both tasks, providing the first neuroimaging evidence that this region is involved in purely cognitive motion of stimuli in space. However, apart from our studies, only one other fMRI study (Prvulovic et al., 2002) examing angle discrimination has found activation in caudate nucleus, although this region has been demonstrated to be activated in mirror reading (Dong et al., 2000).

More frequently reported is the activation in thalamus both in visuospatial processing (Podzebenko et al., 2002; Prvulovic et al., 2002) and across different types of visual task conditions related by the common factor of attentional engagement (Kinomura et al., 1996; Schulman et al., 1997). It has further been proposed that attentional states depend on the operation of a triangular circuit, in which the thalamus modulates activity in the posterior sensory cortex (e.g. extrastriate) on the basis of top-down signals from prefrontal regions (LaBerge, 2000).

11.2 SUMMARY

The results in the present studies are in accordance of several previous neuroimaging studies and support the existence of a visuospatial network, including parieto-occipital, as well as frontal, basal ganglia and thalamus activation. Of these, the dorsal stream, including SPL, has been attributed to be primarily concerned with the perception of spatial information (Mishkin et al., 1983). Nevertheless, our results underscore that angle discrimination is not a simple process and that like most cognitive processes, it appears to be carried out by a system of operations working together. Understanding

the contribution of different operations to the overall process will require a series of additional studies. However, based on the literature it seems reliable to think that each cortical region contributes with various specialities, including for example the computation of angle, object and object part identification, and information maintenance. The findings of similar areas activated in all subject-groups suggest that all individuals activated the same network for execution of our angle discrimination task.

11.3 BEHAVIORAL MEASUREMENTS OF ANGLE DISCRIMINATION

11.3.1 Reaction time in the angle discrimination task

The speed of performance (as measured with RT) is a general measure that reflects how fast subjects processes information, irrespective of success rate. Also, as discussed in section 3.1, by measuring RT an operationalization of task demand in the angle discrimination task is possible. Across the studies we consistently found that angle discrimination of clock categories with angles close to the target angle (45 and 90 degrees) was determined more slowly than clock categories far from the target angle (30 and 90 degrees). Furthermore, across subject groups we could also demonstrate a linear increase of the RT with decreasing lengths of the hands. In addition, an interaction effect of angle and length was found in all studies, which almost always showed that clocks with short hands and angles close to the target angle took longer time to process than clocks with long hands and angles far from the target angle.

To elucidate why some clocks were perceived as more difficult to discriminate then others we administrated a questionnaire to some of the subjects after the functional experiment, asking them how they had perceived the instructions and more importantly if they employed a certain strategy when trying to discriminate the angle between the hands. The majority of the subjects (including MCI and AD patients) answered that they first tried to discriminate the target angle by seeing if the angle between the hands corresponded to 10 minutes alternatively two hours or not, i.e. regarding the stimuli as a "real" clock with handles pointing to a specific time. They reported that they did this by exploring the areas at the end of each clock hand and subsequently looking towards the edge of the clockface. Thus, if the length of the hands was decreased this procedure was made more difficult as it required the individual to extrapolate the length of the hands towards the edge of the clockface. Based on this information it seems reasonable to assume that clocks with shorter lengths (in addition to clocks with angles close to the target angle) place more demand on the mental processes or computations that are required to discriminate the angle.

To further elucidate this question it would have been interesting to conduct visual tracking during the experiment and explore the eye movement behavior during visual exploration of the clock-stimuli. Actually, in a recent study by Mosimann et al. (2004), this was done in patients with probable AD and age-matched controls to compare if there exists any differences in visual exploration (i.e. looking at the sequence of fixations and saccades) during a clock reading task. They found that in healthy controls, exploration was focused on distinct areas at the end of each clock hands, whereas in the AD patients, visual exploration was less focused including longer fixations and smaller amplitudes of saccades (Mosimann et al., 2004). They conluded that this results might be related to the reported parietal dysfunction in AD or to an imbalance between a

degraded occipito-parietal and relatively preserved occipito-temporal visual network (Mosimann et al., 2004).

11.3.1.1 Differences in RT between the subject-groups

Regarding the difference in RT between the subject groups (see figure 11.2), we have only demonstrated a significant decrement in processing speed in the elderly subjects compared to the young subjects (study III). The elderly subjects had significant longer RT throughout all clock-categories compared to the young subjects which is in accordance with the theory of gradual slowing of performance associate with advancing age (Welford, 1981; Cerella, 1985; Salthouse, 1985; Vercruyssen, 1993) (see also section 4.3.2). However, no statistically significant difference was found when comparing the MCI patients with healthy controls (study V) or AD patients with healthy controls (study IV).

Especially this latter result was a bit surprising considering that slowed response speed has been reported to be one of the concomitants or features of AD (e.g. Muller et al., 1991). Although the basis of this slowing in AD has not been convincingly established, it has been argued that it is the results of slowing of the decisional phase rather then problems with sensory/motor output components (e.g. Benton, 1986). Similarly, it has been suggested that slowness of decision phase also seems to account for the slowing seen with aging (Cerella, 1985). In contrast, there is also some evidence that changes in both of these variables are responsible for this slowing (Gordon and Carson, 1990). Furthermore, by comparing AD patients with controls in a choice reaction time task Gordon and Carson, (1990) also found that these changes can be observed in older controls, by demonstrating an overlap between the mean RT in AD patients and controls. The authors argued that this result could speak for the fact that the behavioral changes responsible for differences in RT among controls can be put on a plausible continuum with that of the AD patients. With increasing RT regardless of whether it is found in a normal but still slower control subject or in an AD patient, there is a smooth change in both the decisional and the sensory/motor components. Therefore, it seems that the processes giving rise to the RT distributions have a relatively nonspecific response to the malfunction(s) caused by AD in the patients or by, perhaps, aging in the normal controls (Gordon and Carson, 1990).

The findings in our studies of no differences in RT between the patient group and healthy controls could therefore speak for the fact that either we have recruited a group of controls that are slower than the general population of elderly individuals. Another explanation is the fact that our AD patients were in the mild, intitial state of the disease. Thus, the slowing of operational (motor) functions is perhaps not as pronounced as the decline in cognitive functions. The findings of similar response latencies in the Trail making test A (see appendix A) (mean RT ± SD for AD patients = 58.1 ± 21.2 s and controls = 47.1 ± 20.2 s) further support this conclusion.

11.3.2 Accuracy in the angle discrimination task

Without the adequate behavioral measurements in cognitive tasks such as ours, it is difficult to know whether an activation difference between different subject-groups is caused by worse performance or non-compliance (for example in patients) (Prvulovic et al., 2005). Thus, it is important to record task performance measurements in order to attribute functional activation differences to the disease, to differences in performance,

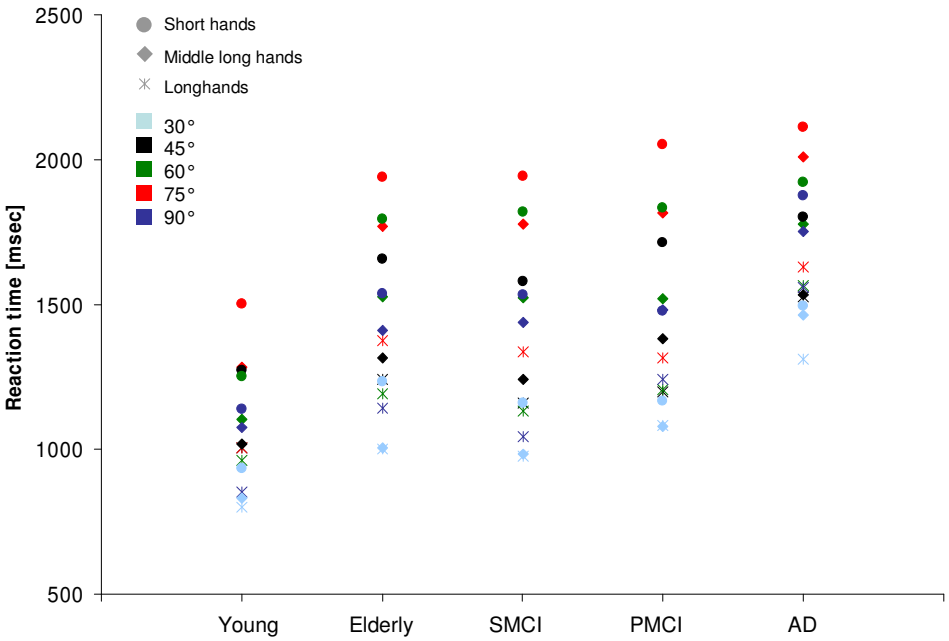

Figure 11.2 Scatterplot of mean RT in msec for each clock-stimulus (see symbols) in each subject-group. In the young (n=14) and the elderly (n=32) group all the subjects are included.

or to lack of cooperation (Prvulovic et al., 2005). Therefore, in all studies in the thesis the percentage of correct answers was also registered for each subject and clock-stimulus. Similarly as the RT, we almost consistently found that subjects perceived that clocks with angles close to the target angle were more difficult to discriminate than clocks with angles far from the target angle. In addition, all subjects also found it more difficult if the length of the hands was decreased. Also, an interaction effect of angle and length was found in all studies, which almost always showed that clocks with short hands and angles close to the target angle were more difficult to interpret than clocks with long hands and angles far from the target angle.

The percentage of correct responses provides an overall assessment of performance without being specific for any particular process. That is, error in the angle discrimination task can be the result of a multitude of factors, from encoding the visual image, wrong judgement in angle discrimination, to making the motor response. However, together with the RT measurements it can help to distinguish between functional activation differences that are due to physiological dysfunction, performance deficits, or both. The findings of a negative correlation between mean RT and mean accuracy per clock-stimuli (i.e. with decreased accuracy, the RT was longer) in all subject-groups support that RT can be used as a measurement of the imposed task demand that each individual is experiencing on the different clock-stimuli and also tells us that in overall the subjects complied with the test.

11.3.2.1 Differences in accuracy between the groups

We found an overall high percentage of correct reponses in all subject-groups (see figure 11.3). No statistical difference in accuracy was found between young and elderly subjects (study III) or between controls and MCI (study V). In addition, the age difference in error rates was less than 5 % (mean error rate for young = 4.1 % and

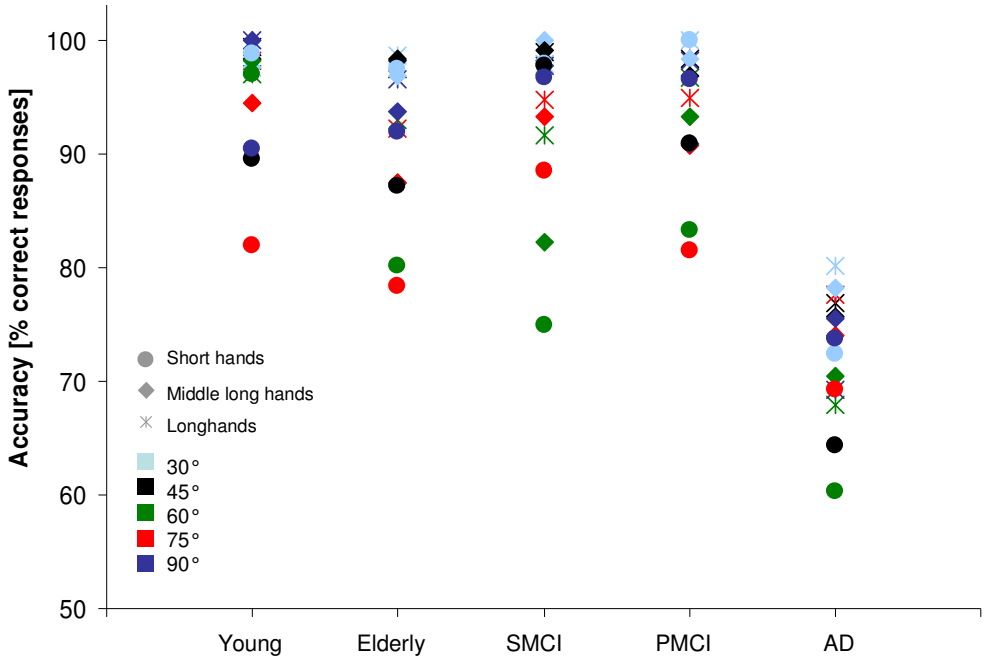

Figure 11.3 Scatterplot of mean accuracy in % correct responses for each clock-stimulus (see symbols) in each subject-group. In the young (n=14) and the elderly (n=32) group all the subjects are included.

elderly = 8.2 %), indicating that although elderly subjects were on average slower than young subjects in every clock-stimulus, it is unlikely that such slowing was due to an age difference in speed-accuracy trade-off[32]. Similar results were obtained for the MCI patients compared to the controls (mean error rate for PMCI = 5.9 %; SMCI = 6.1 %, and matched controls = 4.7 %) where the difference was even smaller between the groups. However, in study IV we found a statistical significant difference between the AD patients and the controls (study IV) demonstrating that the AD patients almost consistently performed less accurately than the controls. In addition, the group difference in error rates was almost 20 % (mean error rate for AD patients = 27.6 % and control subjects = 7.9 %) indicating that although the AD patients had the same response pattern, they had more errors than the controls. However, one also has to take into account that in AD patients the mean correct response ranged between 60-80 % for all clock-stimuli, which would indicate that the patients were attending to and understood the task to be performed (i.e. compliance was good). Taken together the effect of less accuracy in the AD patients could perhaps be attributed the physiological dysfunction due to the disease, i.e. there is a decline in correctly discriminating clock angles.

11.4 SUMMARY

The behavioral results across all studies show that some clocks were more difficult to solve then others (took longer time and had more errors). However, except for the comparison between young and elderly subjects, the RT was similar between the groups. In addition, accuracy was similar between the groups except for the AD patients which showed decrements in performance (i.e. they made more errors).

[32] The speed accuracy trade off states that longer RT in elderly subjects could be partly due to increased caution in responding, with a propensity to emphasize accuracy to the detriment of speed.

11.5 TASK DEMAND CHANGES IN BOLD SIGNAL

11.5.1 Seeing an effect of task demand in the brain

Most of the presented functional neuroimaging studies treat behavioral tasks as qualitative variables in that different tasks lead to different functional activation maps, and inferences about behavior are usually made by assessing the qualitative differences in these maps, for example, whether a new area is activated when a specific task manipulation is introduced. Although this approach is useful, it is also important to relate qualitatively levels of activation to specific performance measures (see chapter 3 for a discussion about this). Attempts in this direction have been made in recent fMRI studies, most focusing on mental rotation (e.g. Tagaris et al., 1996; 1997; Carpenter et al., 1999; Ng et al., 2001), but also in mirror reading (Dong et al., 2000), which have used both RT as well as accuracy and rate of mental rotation to assess the difficulty levels in the task (see studies marked with * in table 11.1).

For example, using a mental rotation task, Tagaris et al. (1996) found that superior parietal activation increased with a higher proportion of errors in performance. They hypothesized that the increase in error-rate and concomitant increase in activation could be due to an increased difficulty in, and therefore increased demands for, information processing at several stages during performance of the task. In a subsequent study by Tagaris et al. (1997) clustering techniques were used to analyze the pattern of activation change in several frontal and parietal neural areas, along with behavioral measures, including error rate and rotation rate. In general, the activation changes in most of the parietal areas clustered more in with the behavioral measures, particularly error rates (Tagaris et al., 1997). A similar result was found by Carpenter et al. (1999) and Ng et al. (2001) who used increasing angular disparity to manipulate task difficulty, and found that activation in parietal cortex increased linearly with angular disparity. The results from our studies (I-V) are in accordance with these results and consistent with the assumption that visuospatial processes such as angle discrimination make more demand on resources as the angle becomes more difficult to discriminate (see figure 11.4.).

These results also fit neatly with the theoretical assumption that processing efficiency is reflected in the consumption of neural resources. That is, just as physical energy systems require resources, so do neural energy systems (Carpenter et al., 1999). Furthermore, these results demonstrated that the consumption of different types of resources can be measured with a metabolically based neuroimaging technique such as fMRI. Specifically, that greater task demand translates into greater resource demand (Carpenter et al., 1999), as indicated by a higher BOLD signal. However, in contrast to previous studies, our studies (II-V) have employed a method of using a reaction time dependent hemodynamic response predictor in order to compare the subject-groups. This method is both easily incorporated and interpreted in a random effects model and to our knowledge these are the first studies that have reported using this approach in order to study age- or disease-related changes.

11.5.2 Age-related changes

In our quest to investigate the functional neurobiology in our healthy elderly individuals we came across the common observed phenomenon of age-related slowing in our visuospatial task. Furthermore, when we compared the young and elderly

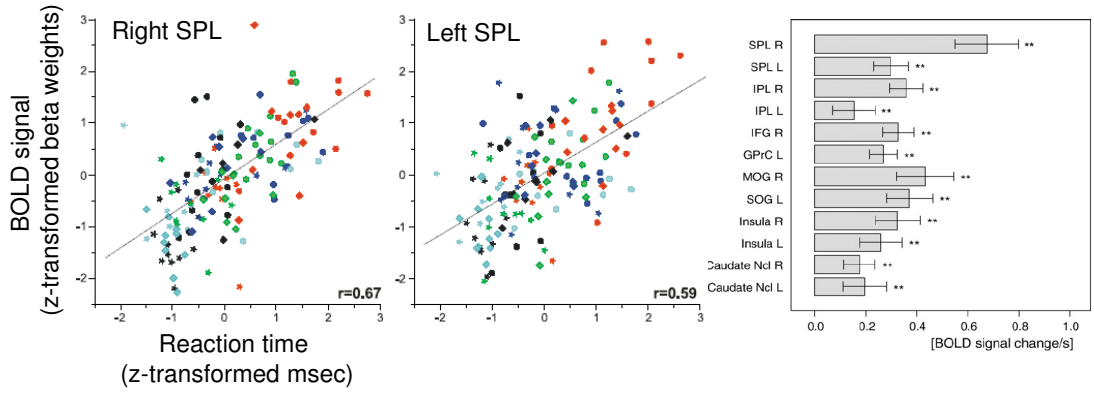

Figure 11.4 A positive correlation between reaction time (milliseconds) and BOLD signal changes (in beta weights) in young subjects shown in the two pictures on the left side. The picture on the right side is showing the mean change in BOLD signal for 1 s increase in RT (i.e. the slope value).

subjects using the reaction time dependent response predictor, we found that several areas in the network subserving visuospatial processing demonstrated a task demand dependent change of activation. In these areas there was a stronger increase in BOLD signal due to increasing task demand in young subjects compared to elderly subjects (see table 11.2). These results are consistent with previous neuroimaging studies that have examined the relationship between brain activity and RT (e.g. using different working memory task (Reuter-Lorenz et al., 2000; Rypma and D'Esposito, 2000; Rypma et al., 2002; 2005), (but see table 8.2 in Reuter-Lorenz and Sylvester, (2005) for a summary) which have suggested that activation differences are correlated with performance differences in the older group. That is, increased information processing speed was related to increases in PFC activation for younger subjects but to decreases in PFC activation for older subjects (see also section 4.4.2.2). Although our study is at variance with these previous studies in that we are using a different task, it nonetheless provides additional support for the hypothesis that elderly individuals are working with a diminishing pool of resources relative to that of younger individuals.

This theory, originally proposed by Salthouse (2000) states that reductions in processing efficiency could result from decreases in the number of functional neurons, in the extent of dendritic branching or myelin sheating for surviving neurons, in the quantity of particular types of neurotransmitters, etc. In that sense, processing efficiency could be regarded as the immediate behavioral consequences of brain changes. According to this perspective, the amount of resources invested determines the rate of processing output produced (as measured with RT) (Navon, 1984).

Following this, as the task demand increases, more resources are needed to accomplish the task (Just et al., 1999). So, if elderly subjects have smaller supplies of the relevant cognitive processing resources (e.g. neural resources as measured indirectly with the BOLD signal) than do young subjects, they would be expected to suffer greater impairments in behavioral performance as the demands on their more limited resources increase (Salthouse et al., 1989). As a consequent, although a significant correlation could be found between RT and BOLD signal in all areas, the elderly subjects were not able to modulate their neuronal response as efficiently as the young subjects which have bearing on the behavioral response in the elderly subjects,

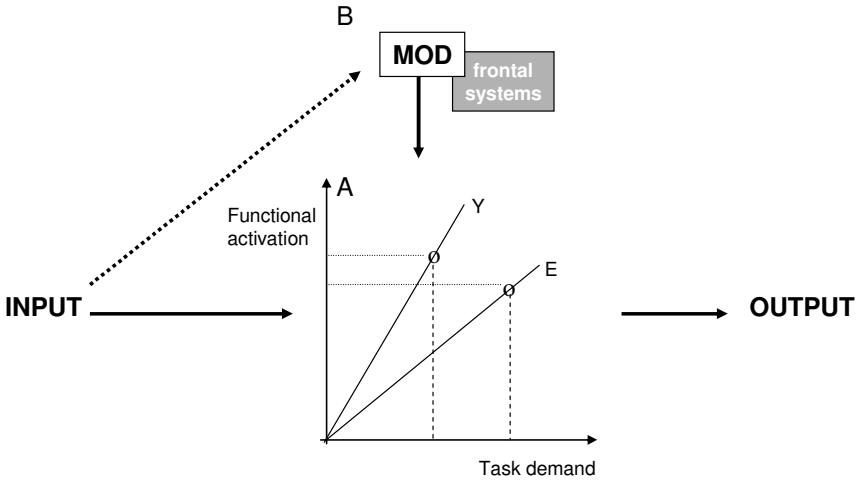

Figure 11.5 An integrative model to depict the task demand dependent (A) and task demand independent (B) task demand independent changes occurring with age. Abbreviations: Y = young subjects and E = elderly subjects. The dotted lines in the figure is showing the difference between the age-groups for one imaginary clock-stimulus, i.e. RT is longer and BOLD signal is lower for the elderly compared to the young subjects. For a description of the INPUT, MOD and OUTPUT see section 11.9.4.

(i.e. generating longer RT whilst keeping the same accuracy across clock-stimuli compared to young subjects). This is illustrated in figure 11.5 A.

11.5.3 AD related changes

The comparison between AD patients and controls revealed task demand BOLD signal changes in several areas in the dorsal pathway, including bilateral regions in the precuneus (BA 7) and occipital lobe (BA 19) (see table 11.2). In these areas, AD patients showed either a significantly weaker or absent increase in BOLD signal with increasing task demand compared to controls. Noteworthy is the finding that several of these areas are the same as the ones reported in the age-related comparison of the task demand dependent activation (see above). These results are providing further evidence on the function of these areas in the visuospatial network and giving additional knowledge of the neural mechanism that underlies the impairment of visuospatial abilities in AD. In addition, these results are also in accordance with previous PET studies that have used a parametric approach to investigate the disease-related changes in AD (Mentis et al., 1996; 1998). Using a passive visual (flash frequence increase) stimuli Mentis et al. (1996; 1998) were able to demonstrate that the level of stimulus activation exposed brain dysfunction in mildly demented AD patients when large neural responses were required and in patients with moderate/severe AD when large and intermediate responses were required (see also section 5.4.2.2). Similar results were recently replicated in a PET study using a passive audiovisual stimulation paradigm (Pietrini et al., 1999; 2000). The authors found that glucose metabolism in parietal regions including SPL and occipital regions correlated with dementia severity (as assessed with the Mattis Dementia Rating Scale Score) during stimulation, although this correlation could not be found at rest (Pietrini et al., 1999).

Taken together the findings of Mentis et al. (1996; 1998) and Pietrini et al. (1999; 2000) demonstrate that, given that regional cerebral glucose metabolic rate is an index

of synaptic activity and increases with increasing neuronal firing and rate stimulation, the capability of neurons to respond to stimulation is progressively compromised by AD. Similarly as in our study, these findings illustrate that that neuronal failure can be induced by increasing the functional (task) demand on the brain.

11.5.4 Preclinical AD changes

The comparison between preclinical AD patients (PMCI) to SMCI and controls revealed task demand BOLD signal changes in only two regions in the dorsal pathway (see table 11.2). Again, similar as our previous studies, the findings of task demand changes were observed in SPL (BA 7), speaking for the fact that the function of this region is important when solving our angle discrimination task. Compared to SMCI and controls, we found that the PMCI patients had a stronger relation between task demand and brain activity in left SPL (also detected in right SPL compared to SMCI), with similar peak foci. That is, as the task became more difficult to solve, the PMCI patients had bigger changes in BOLD signal than did the other two groups.

Considering that the behavioral performance (RT and accuracy) was similar as the other two groups, it is likely that the PMCI group's normal performance is linked to the preserved modulation of brain activity in this area during the task. Thus, the increase in signal intensity among the PMCI group suggests that a higher neuronal effort was necessary to reach a similar degree of accuracy as subjects without in situ AD pathaology. This can be done by increasing the number of neurons firing and/or by increasing the rate at which the neurons are firing.

The findings of increased activation in our PMCI patients are in line with previous fMRI studies comparing asymptomatic subjects genetically at risk for late-onset AD, which have found that APOE ε4-carriers showed increased brain activation across cerebral cortex as compared to APOE ε3-carriers, even though cognitive performance was equal among the groups (Bondi et al., 1995; Bookheimer et al., 2000; Burggren et al., 2002; Smith et al., 2002). Although, these studies have not reported follow-up data whether these individuals eventually progress to AD or not, one study reported a correlation of the level of brain activation at base-line with memory decline as assessed after two years (Bookheimer et al., 2000). Somewhat similar is also the study by Dierks et al. (1998) who investigated angle discrimination with fMRI and compared the functional activation differences in one patient with Huntington's disease (HD) to that of a group of healthy controls. They were able to demonstrate that the signal amplitude in the HD patient was higher than that in the control group, and argued that this increase of activation could have accounted for the fact that the HD-patients had the same accuracy as the control subjects. However, at variance with our results was the finding that RT was increased in the HD patient compared to the control subjects. The reason for this disparity of the results could perhaps be explained by the fact that different diseases were examined in the study. Also, whereas the HD patient had suffered from movement disturbances for 8 years and from memory impairment for 3 years our PMCI patients were not exhibiting any clinical signs of AD and could not be clinically separable from the SMCI patients without follow-up data several years later. Thus, the studies were conducted at different stages of the disease. However, similar as our study, these findings suggest that higher neuronal effort was necessary to reach the same behavioral results as the control subjects. Thus, a reduced neuronal efficacy can be observed in the MCI patients that progressed to AD due to in situ AD pathology.

11.6 SUMMARY

The hypothesis that angle discrimination per se is a property of the dorsal stream including SPL is further supported by a strong positive modulation of the signal in these areas by performance compared with other areas of activation (including frontal, occipital and basal ganglia). This correlation between behavior and BOLD signal changes suggests a major involvement of this area in the task. However, the processing efficiency or relative contribution of the components in this network, especially in the parietal cortex, differed depending on age and disease.

In short, a decreased processing efficiency was found in the elderly subjects compared to the young subjects, in which the utilization of cerebral resources was coupled to the behavioral response, i.e. generating longer RT whilst keeping the same accuracy as the young subjects. Similarly, a decreased neuronal efficacy was detected in individuals with preclinical AD, revealing that increased neuronal effort was needed to reach the same behavioral results (RT and accuracy) as the elderly controls. As the pathological changes progresses, the ability to compensate for the reduced ability to process the angle discrimination task is diminished, leading to a failure to modulate the neuronal response to increased task demand.

11.7 TASK DEMAND INDEPENDENT CHANGES IN BOLD SIGNAL

11.7.1 General changes in BOLD signal

Using the function based on the simple boxcar, modelling the average BOLD signal increase from baseline irrespective of RT, we could analyse any general differences between the age-groups using t-statistics (random effects). This suggests that the role of these areas may be of a more general nature (rather then modulated by the task demand) on which we can only speculate which influence it may have on the behavior in the subjects. Since, this analysis is more or less equivalent to previous functional imaging studies which have not related quantitatively levels of activation to specific performance measures the interpretation of between-group differences can be made more easily based on already existing hypotheses.

11.7.2 Age-related changes

The main finding in the difference in general BOLD signal was the observation of an age-related decreased activation in the occipital cortex (BAs 18 and 30) coupled with an increased activation in prefrontal regions (BAs 6, 9, 46) (see table 11.2). These results are in accordance with several other neuroimaging studies investigating age-related changes during tasks examining visual perception (Grady et al., 1994; 2000; Madden et al., 1997) (see description of these results in section 4.4.2.1) visual attention (Cabeza et al., 2004), temporal-order memory (Cabeza et al., 2000), and working memory (Rypma et al., 2001). Of these, the findings of and age-related decreased activation in the occipital cortex has been attributed to inefficient sensory processing, suggesting a general effect of aging on visual processing. The function of the observed additional prefrontal activation seen in our study and also in other studies is however still uncertain. Behaviorally the prefrontal cortex have been implicated in a variety of cognitive operations including working memory, inhibition monitoring, episodic memory, strategic organization and planning (Stuss and Knight, 2002). Although our task did not explicitly invoke working memory, the age-related changes in BOLD

signal of the prefrontal regions (especially BA 46) that were found may indicate that this visual task places more demand on some aspects in working memory in elderly subjects than in young subjects. For example, elderly subjects may need to organize the various elements of task performance and hence place greater demand on the central executive, thus reflecting the fact that more elaborate processing is required by elderly subjects in order to resolve the visuospatial task. In that sense, the involvement of the frontal brain areas may reflect a strategic shift in elderly subjects in order to solve the task with the same accuracy as the younger subjects. This is illustrated in figure 11.5 B, but see also a discussion about modulatory effects below.

11.7.3 AD related changes

There were several regions found in occipital cortex (BA 18 and 19) bilateral in which the AD patients demonstrated a lower BOLD signal increase compared to the control subjects (see table 11.2). Activation deficits in occipital cortex have also been demonstrated in AD patients during passive visual stimulation (Mentis et al., 1996), and similar as the findings in study III, these results could reflect an even more reduced processing efficiency in the visual areas in the AD patients. However, in contrast to the elderly subjects (study III) AD patients failed to recruit the frontal cortices to compensate for this deficiency. As a note, the controls are demonstrating a higher BOLD signal compared to AD patients in several bilateral frontal areas (BA 6 and 9/44) of which these regions in the right hemisphere were also reported to be activated in the elderly compared to the young subjects in study III), see table 11.2.

Instead, an additional activation was found in an area in the right ventral pathway, MTG (BA 22). These results are in accord with previous findings by Prvulovic et al. (2002) who used a similar angle discrimination task[33] as the one used in this study to investigate main effects of between-group differences between AD patients and controls. Prvulovic et al. (2002) demonstrated that although the network for visuospatial processing was similar in AD patients and controls, parietal dysfunction in mild to moderate AD is compensated by the recruitment of brain areas in the occipito-temporal cortex. Although our activation foci was located more superior to the medial temporal area reported by Prvulovic et al. (2002), it encompassed the same BA (22) and hemisphere. It has previously been demonstrated that this foci is associated with the color and object information processing of visual stimuli (e.g. Haxby et al., 1991).

The findings that areas in the ventral pathway are activated during spatial processing have also been demonstrated in young individuals e.g. Haxby et al. (1994) found activation in the left superior temporal gyrus (BA 22) during location matching and in the left inferior temporal gyrus (BA 37) during mirror reading. These activations were suggested to reflect inadvertent processing of irrelevant object information, such as identification of the objects to be localized (Haxby et al., 1994). One could therefore speculate that the AD patients used a different strategy in recognizing the presented clock-stimuli, by processing them as unique objects and not as two lines with a specific orientation (Prvulovic et al., 2002).

In addition, a reduced activation was found in the thalamus (both hemispheres). As discussed earlier (see section 11.1.2.4), this region has been implicated to have a role in the attentional state of the individual. Thus, the findings of activation deficits found in

[33] However, the angle discrimination task used by Prvulovic et al. did not have different task demands.

bilateral thalamus in the AD patients could represent a reduced attention in the patients. Important to notice is, that based on the neuropsychological test scores, AD patients performed significantly worse than controls in only one subtest. Namely the Trail making test B (TMT:B). Taken together, this suggests that attention is not severely affected in these patients.

11.7.4 Preclinical AD changes

The results of a task induced increase in BOLD signal in precuneus in the left hemisphere in our PMCI patients compared to SMCI and controls are in line with previous findings in at risk individuals (Bookheimer et al., 2000; Smith et al., 2002) using paired associates recall task respectively a letter fluency task. Although the processing demands for the increased activation in left parietal lobe are probably different than the studies presented above, the findings of Bookheimer et al. (2000) and Smith et al. (2002) nonetheless suggest reflecting the disruption of the functional circuits involving the left parietal lobe in asymptomatic individuals at increased risk for AD. That is, the increased activation in the left hemisphere could be due to an increased cognitive work needed because of the occurrence of a compromised visuospatial network due to in situ AD pathology. Plastic compensatory mechanisms, including changes in dendritic length and arborization (Arendt et al., 1998) and synaptic remodeling (DeKosky and Scheff, 1990), have been shown to occur early in the disease progress in AD and may help maintain relative stable functional responsiveness in the brain. Supporting this idea is the finding that mildly demented AD patients show almost normal brain functional responsiveness during a passive audiovisual stimulation paradigm assessed with PET, but fail with worsening dementia severity, reflecting the progressive loss of synaptic integrity (Pietrini et al., 2000).

11.8 SUMMARY

Our parametric task allowed us to characterize different forms of rate-dependent responses. Several task demand independent BOLD signal responses to the angle discrimination task irrespective of rate were found when comparing the subject-groups.

For example, the findings of a decreased activation in the occipital cortex in the elderly compared to young subjects as well as in the AD patients compared to the elderly subjects could reflect a decline in sensory processing due to age which is worsening further by the neurodegenerative disease. We also found an age-related increase in several prefrontal regions, which was interpreted to reflect a compensatory pathway in which older brains may apply a different strategy in order to solve the task with similar task performance as the younger subjects. A similar compensatory effect could be demonstrate in the PMCI patients, reflected as an increase of activation in left precuneus (as compared to SMCI and controls). However, AD patients demonstrated a weaker general increase in BOLD signal in these areas (e.g. left precuneus, and prefrontal cortex) suggesting that the above reported compensatory pathways are limited in AD patients. Instead, we found an increased activation in the right ventral pathway, which might reflect a potential secondary compensatory mechanism for the reduced functional capacity of the parietal regions in AD patients.

Tabell 11.2. Summary of results of task demand dependent and task demand independent changes observed between subject-groups in studies III-V.

Study	LEFT HEMISPHERE																RIGHT HEMISPHERE													
	Parietal		Occipital				Temporal			Frontal					Subcortical			Parietal		Occipital				Temporal			Frontal					Subcortical		
	7	40	17	18	19	30	22	37	39	2	6	8	9/44	46	cn	in	th	7	40	17	18	19	30	22	37	39	2	6	8	9/44	46	cn	in	th
Task demand dependent																																		
III	●				●					●			●		●	●		●	●			●								●			●	
IV	■		■		■			■									■	■	■			■												■
V	◙																	◙			◙													
																					■													
Task demand independent																																		
III		○		○							□		□	□									○									○		
IV	□			□	□		◊				□		□				□				□	□				□			□		□			□
V	◘				☼							◘					◘										◘							
																											☼							

Regions with larger increase in BOLD signal with increasing task demand in:
● = young subjects
■ = elderly/control subjects
◙ = PMCI
Regions with task induced BOLD signal increase irrespective of task demand in:
○ = young subjects
□ = elderly/control subjects
☼ = SMCI
◘ = PMCI
◊ = AD patients

11.9 MODELS AND HYPOTHESIS FOR INTERPRETATION

Several models and hypotheses have been proposed for the interpretation of functional activation effects seen in aging and dementia (for an overview see Prvulovic et al. 2002). Based on these models it is possible to interpret our findings in slightly different ways.

11.9.1 Under-recruitment and nonselective recruitment

In a recent fMRI study, Logan et al. (2002) proposed that there are two dissociable neural mechanism associated with aging: *under-recruitment*[34] and *nonselective recruitment*[35], that may play a role in the observed changes of activation patterns presented above. This model states that in order for the aging brain to compensate for the inability to sufficiently engage specific cortical regions during cognitive performance, additional areas that had originally not been designated for the specific task are recruited and become activated. Although this model was originally presented by using an episodic encoding task focusing on frontal areas, it can nonetheless be applicable to other functional activation studies.

The findings of additional increased activation in the prefrontal areas in our elderly subjects (study III) would thus represent nonselective recruited areas perhaps due to the insufficiently activated visual areas. Thus, this increase of activation could be regarded as a form of compensation for the evolving perceptual difficulties (Baltes and Lindenberger, 1997). Applied to the findings in the demented patients (study IV), the failure to activate areas in the parieto-occipital cortex to the same extent as the control subjects could have led to recruitment of areas less specific for visuospatial computations (ventral pathway).

11.9.2 Degenerate systems

The theory of *degenerate systems* is based on the ability of different structures to subserve the same function (Price and Friston, 2002). This model, which is often discussed with reference to biological networks (Tononi et al., 1999) makes a distinction of neuronal systems that are sufficient and those that are necessary for a specific cognitive task. When different neuronal systems are sufficient to perform a cognitive task each on their own, the damage to only one or a subset of those systems will have no adverse effect on task performance but lead to important differences in brain-activation patterns. However, if a necessary neuronal system has been damaged that cannot be compensated for by any other system or when a complete set of degenerate systems are affected an effect on task performance (accuracy) will been seen. Thus, in contrast to the model proposed by Logan et al. (2002), degenerate systems also take into account performance benefits.

In relation to our findings, one can speculate that the elderly subjects and the MCI patients still have the necessary systems and subsystems intact to be able to execute the task with normal task performance. However, when degenerate sets of neuronal systems are available, damage to one system might affect the RT (Price and Friston, 2002), an effect seen in our elderly subjects compared to young subjects (study III). In

[34] Under-recruitment is defined as less activity in elderly subjects compared to young subjects.

[35] Nonselective recruitment is defined as relative increase in activity in regions not typically activated in young subjects in a given task.

the AD patients, it is likely that the neural damage is more global, affecting all neuronal systems and leading to global activation deficits or non-specific (aberrant) activation patterns across the brain. However, the recruitment of these areas is not sufficient which lead to a decrement in task performance.

11.9.3 Sigmoid activation model

While these previously presented models above can be applied both to age- and disease -related changes in brain function, a third model has been developed to explain why in studies with AD patients the same brain areas are sometimes overactivated and sometimes underactivated (Rapoport and Grady, 1993). It is also the first model that explicitly looks at the response behavior of a cortical region. In detail, Rapoprt and Grady (1993) hypothesised that parametric cognitive or passive stimulation during in vivo imaging could be used to elucidate the pathological basis of reduced flow and metabolic abnormalities seen in patients with AD. They proposed a model of a *sigmoidal relation*[36] *between rCBF or rCMRglu (y-axis) and a function of task difficulty and subject task performance (x-axis).* By implementing several degrees of neuronal damage into the model, an alteration of the shape of the brain-response curve could be investigated. In early stages of AD, neuronal damage is not so extensive and results in shifts only in the rising phase of the sigmoidal response curve to the right. Thus, this shift would reflect the findings of reduced rCBF in control tasks with very low processing demand or during rest. As a consequence, the task-related increase of rCBF during highly demanding tasks would often be higher in early AD than in controls. Ultimately, early AD patients will reach the same absolute amount of task-related rCBF as controls in the model. Also, with increasing neuronal damage, the maximum activation capacity of the brain decreases, and AD patients reach a lower maximum rCBF in activated states than controls.

In sum, these three models suggest separate neural mechanisms that can be applicable to explain most age- and disease related functional changes found in previous neuroimaging studies[37]. They explicitly consider the unspecific coactivation or nonselective recruitment of regions in a manner atypical of young subjects (Logan et al., 2002) or distributed specific coactivation in subsystems which can perform similar functions (Price and Friston, 2002), but only the last model takes into account the multiple response patterns observed in different subject-groups (Rapoport and Grady, 1993). However, this latter approach only considers one specific affected cortical region without further consideration of its embedding in the network.

11.9.4 Putting it all together in one model

Recently, Prvulovic et al. (2005) presented a theoretical model that combines these previously presented approaches into an integrated model. It addresses the different response patterns of cortical regions to increasing task demand. Additionally, it considers various possible ways of interaction between brain regions in relation to brain damage and compensatory mechanisms (Prvulovic et al., 2005). In the next section a modified version of this model will be presented that attempts to integrate the findings from our studies and explain the underlying mechanisms of functional activation

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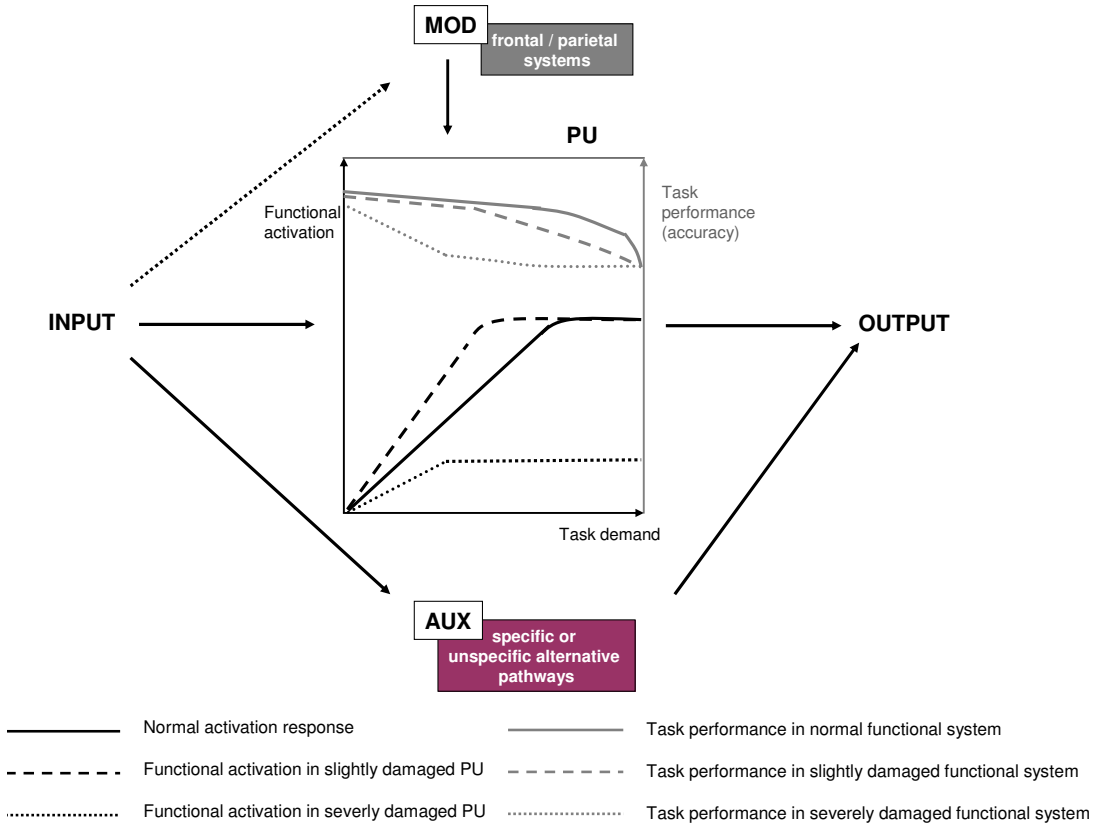
[36] A nonlinear monotonically increasing relation reaching a horizontal asymptote.

[37] There are additional models and hypotheses published although these are not presented here.

changes in aging and during different stages of dementia. However, in presenting this model, we make no claims that this model could explain the general mechanisms of functional changes in aging and dementia. It should only be considered as a stepping stone to provide deeper insight into human visuospatial processing and how this it is affected by aging and neurodegeneration.

The definitions and explanations concerning the different aspects of the functional activation and behavior are based from the original model presented by Prvulovic et al. (2005). Also, for purpose of simplification, possible feedback loops are not considered.



Modified from Prvulovic et al., (2005).

Figure 11.6 An integrative model of possible relations between damage to a processing unit, the dynamics of its activation response in relation to task demand, and the integrated network engaged during the processing of a visuospatial task. Possible feedback loops are not considered. PU = processing unit; MOD = modulatory unit; AUX = auxiliary unit. The relation between task performance and task demand is also integrated (grey lines).

11.9.4.1 The processing unit

The central element of the model is a cortical region(s) called processing unit (PU) that is part of a cortical circuitry required for succesful processing of the task at hand (Prvulovic et al., 2005). In case of our angle discrimination task, this area would most likely correspond to the dorsal pathway, especially the SPLs. In this/these area(s), functional activation at any given time point is determined by the number of subunits (e.g. single neurons or populations) recruited within this region. Subsequently, if the task demand to execute the task is increasing, this will lead to an increased total activation (i.e. increment in intensity of neuronal activity) in the PU. Thus, based on the premise that hemodynamic responses vary with the amount of cortical processing

engaged by the task (e.g. Buchel et al. 1996), fMRI can measure this increment quantitatively in the BOLD signal, demonstrating a positive linear relationship between task demand and BOLD signal (see also section 3.1). In our studies, this relationship was repeatedly found in all subjects in the dorsal pathway, suggesting a major involvement of this area in the angle discrimination task. In the original model, this linear relationship continues until task demand exceeds the maximal processing capacity, i.e. exceeding the threshold for total number of functioning subunits in the PU. This threshold was never reached in our studies but is nonetheless incorporated in the model as a theoretical end point. Consequently, assuming that the subjects are still complying and try to execute the task, the amount of available functional subunits at a certain level of task demand is termed *"functional reserve capacity"*. This reserve capacity, or buffer, partly determines how much additional task demand can be mastered without loss of task performance or, in cases of neurodegeneration, how much damage to the subunits and their connections can be sustained (Prvulovic et al., 2005).

11.9.4.2 INPUT region

The model further comprises an INPUT module, which can be considered a cortical region that provides information that is essential for the PU to process the task (Prvulovic et al., 2005). Considering the known network for visuospatial processing, also reported with our angle discrimination task, it would be conceivable that the early visual areas could play an important role, especially considering that the activation in e.g. extrastriate visual areas (BA 19), has been noted to be the differentiating/separating point of the two visual streams (see section 11.1.2.1).

11.9.4.3 Modulatory unit

The model further comprises a MOD unit, that can modulate the activity of the PU (Prvulovic et al., 2005). Regions in the network that have a modulatory effect are proposed to provide a direct enhancement of processing efficiency in the PU or in the amount or quality of the input signal into the PU[38] (Prvulovic et al., 2005). For instance, several neuroimaging studies have reported age-related additional increased prefrontal activation and its functional connectivity with posterior cortical regions in several cognitive tasks (Grady et al., 1994; 1999; Madden et al., 1997; McIntosh et al., 1999; Cabeza et al., 2000; 2004). Prefrontal activation is related to both attentional load and to working memory and it has therefore been suggested that this increased activation can enhance the performance in the elderly subjects during different cognitive tasks. In accordance with these studies, the additional activation of the prefrontal regions in elderly subjects compared to young subjects (study III), could also fit with the theory that elderly subjects place greater demand on some aspects of working memory and that this increased elaborate processing made it possible for the elderly subjects to process the task with similar task performance as the young subjects. This is also illustrated in figure 11.5.

Additionally, the findings of a task induced increased activation in the parietal cortex (mainly left sided) in the PMCI patients compared to SMCI and controls (study

[38] This region/s could be regarded much the same as a battery booster in a car. That is, as the battery begins to lose its charge, adding a battery with similiar capacity and current-capability *in series* with the main battery, brings the rig's operating voltage back up to nominal (or close to it).

V) could in a similar way represent a modulatory effect to enhance processing of the visuospatial task leading to preserved task performance in the PMCI compared to elderly controls and SMCI patients.

11.9.4.4 Auxiliary unit

If the PU for some reason cannot conduct task processing sufficiently, other brain areas that initially are not directly related to the PU may become involved (i.e. auxiliary pathways: AUX) (Prvulovic et al., 2005). These regions or pathways, could be more or less specific for the processing of the task and the role of their involvement would be to partly or completely compensate for the insufficient output from the PU (Prvulovic et al., 2005). The findings by Prvulovic et al. (2002) that parietal dysfunction in AD patients was compensated for by recruitment of ventral pathway during angle discrimination are an example that has shown this effect. The use of auxiliary pathways may reflect a different processing strategy (Prvulovic et al., 2005). Thus, considering that ventral visual areas have been shown to be essential for color, object, and face processing, the increased activation found in the study by Prvulovic et al. (2002) was interpreted to represent a different strategy in AD patients in recognizing the presented angles by processing them as unique objects and not as two lines with a specific orientation. In a similar way the findings of activation in parts of ventral pathway (BA 22) in AD patients (study IV) may indicate an attempt to compensate for dysfunctional areas in the dorsal pathway.

11.9.5 What we see and what to expect

The amount of activation in the PU itself is determined by the relation between its processing efficiency (the integrity of processing within single subunits of the PU and the integrity of communication between subunits within the PU), its processing capacity (the number of subunits), the task demand, the task performance of the subject, and the quality of the input signals (Prvulovic et al., 2005). In that sense, processing efficiency impacts the slope of functional activation, while processing capacity limits the maximum of functional activation that can be reached in the PU (Prvulovic et al., 2005). Consequently, in our angle discrimination task, the workload of the PU is determined by these five factors and depending on the combination of these factors, two scenarios are possible:

11.9.5.1 Slightly damaged PU

With a decreased processing efficiency in combination with almost preserved processing capacity and input, this will lead to a compensatory recruitment of an increased number of subunits within the PU (dashed black functional activation curve in the PU, figure 11.6). This can be done by increasing the number of neurons firing and/or by increasing the rate at which the neurons are firing. Thus, the brain's processing capacity is dynamically augmented to meet the cognitive demand of the task, resulting in a higher workload than normal. This effect can be observed in our PMCI patients in which the detected additional brain activity may have served as a compensatory role for the PMCI patients to achieve the same level of performance as subjects without in situ AD pathology. Althought not shown in our experiment, it is conceivable that due to the impairment of processing capacity and the consequent higher work load in this group, it will automatically lead to a reduced functional reserve in the PU. Subsequently, the limits of the processing capacity of the PU will be reached

earlier with increasing task demand and thus lead to earlier decompensation of task performance than normal (dashed grey line in figure 11.6).

The findings of a shallower slope in elderly subjects compared to young subjects seem, at first glance, not to conform to the proposed model. That is, according to the model slight impairments in processing efficiency should lead to compensatory overactivation rather than underactivation of the PU (Prvulovic et al., 2005). However, assuming that even slight damage to grey and particularly white matter leads to impaired coordination of the visuospatial network, functional activation will not be disturbed in the most efficient way, and the most specialized areas for execution of the angle discrimination task might not be fully engaged (Prvulovic et al., 2005). Instead, this would result in underactivation of the PU and overactivation of less specific areas (see figure 11.5).

11.9.5.2 Damaged PU

A greater amount of damage in the PU with a significant decreased processing efficiency or disruptions of the input channel(s) to PU will lead to diminished activation in the PU (dotted black functional curve, figure 11.6) (Prvulovic et al., 2005). Thus, due to the progressive pathological alterations in AD including accumulation of amyloid plaques and neurofibrillary tangles, loss of neurotransmitters and reduction of synaptic binding sites (Terry et al., 1981; Lewis et al., 1987; Braak and Braak, 1999), only a small part of the PU can be recruited for task processing. In this sense, very simple tasks performance might be preserved although slightly increases of task demand will lead to a fast decrease of task performance (dotted grey line in figure 11.6). Thus, even in areas with less neuropathological involvement, neuronal failure can be demonstrated by increasing the functional demand on the brain (e.g. Pietrini et al., 1999). Our findings of a significant weaker and sometimes absent increase in BOLD signal due to increased task demand in mild AD patients compared to controls are demonstrating this failure to modulate the neuronal response to increased task demand (study IV).

11.10 SUMMARY

Our findings suggests that the differences of functional activation patterns between young and elderly subjects and patients in different stages of AD can be explained by a model, similar to the one originally presented by Prvulovic et al. (2005) and which contain a combination of mechanisms within single functional units and large-scale mechanisms within networks of multiple units.

In this model, there are two separate mechanisms involved to aid or to compensate for reduced processing capacity in the network. These include the activation of alternative or reallocation of (AUX) pathways and that of compensatory or supportive modulatory (MOD) systems. In functionally normal brains, these mechanisms can aid successful adaptation to task demands. However, in functionally impaired brains (i.e. due to in situ AD pathology) these same processes are engaged to maintain task performance as well, but can only compensate for the reduced processing capacity up to a certain level (as can be observed in the AD patients). The different activation patterns that can be observe can therefore be explained as a result from a complex interplay between task demand, effort, amount of damage to functional processing units, their necessity for the processing of a particular task, and the integrity of connections within large-scale networks (Prvulovic et al., 2005).

11.11 METHODOLOGICAL CONSIDERATIONS

There are several methodological problems in the studies presented in this thesis. In the last section, a discussion how we dealt with some of these problems and how they may have influenced the results of the studies is presented.

11.11.1 Subject selection

11.11.1.1 Inclusion criteria for elderly subjects

Strict inclusion criteria are often applied in most cognitive aging studies, especially in neuroimaging studies, to rule out extracognitive influences on behavioral performance. The most typical criterias include that the subjects must live independently (i.e., not in a nursing home), be relatively well educated, and have normal or corrected-to-normal vision and audition (Anderson and Grady, 2001). In addition, subjects are screened for cardiovascular disease, history of stroke or neurological disorders, as well as use of medications that might affect brain function (Anderson and Grady, 2001). These inclusion criterias was also applied in our studies (see section 7.4.1.1), as well as some additional standard MRI exclusion criterias.

11.11.1.2 Diagnosis and heterogeneity of AD

Because of the insidious onset of AD, the time of diagnosis is often defined as the time when the diagnostic criteria for dementia and AD are fulfilled. Thus, over the years several sets of diagnostic criteria have been developed, both for aid in the clinical diagnosis and for research purposes (see section 7.2 for the diagnostic criterias used in study IV). However, although the initial clinical diagnosis of AD can be made with high accuracy, (the sensitivity after medical examination is around 90 %), a pathological confirmation post-mortem by the accumulation of NP and NFT is often necessary, (the specificity has been calculated to be around 70 %). Thus, one limitation of study IV is that the diagnosis of AD is only based on the clinical diagnosis and the use of more definitive standard, such as autopsy or biopsy proof, was not possible at the time of the report and the writing of this thesis. However, the high sensitivity (compared to the specificity) of the clinical diagnosis implies a low false-negative rate. Thus, the risk that some of the AD patients might have had other causes of dementia could be regarded as very small.

In addition, there could also be heterogeneity of our AD patients' general clinical presentation. That is, AD is also a heterogeneous disease in terms of several factors, including family history, rate of progression, and presenting or predominant behavioral symptomatology, and age at disease onset (Cronin-Golomb, 2004). Also the age at testing, education level, disease duration, and medication usage could also attribute to the small differences found in our patient-group. In order to reduced some of these effects, when conducting the between-group analysis we have tried to matched the AD patients as closely as possible to elderly controls regarding some of these factors (e.g. age and education).

11.11.1.3 Diagnosis and outcome of MCI patients

There is a large MCI heterogeneity including international differences regarding diagnostic criterias, institutional practice, and different recruitment approaches as well as cultural differences. Apart from these, individuals with MCI also represent a

heterogenous group with respect to both clinical presentation and outcome after follow up. To circumvent some of these difficulties and considering that our aim was to investigate the preclinical phase of the disease, we decided to perform a prospective study. Thus, we evaluated and clinically followed our MCI patients for approximately 3 years and defined our PMCI patients as individuals that fulfilled the criteria for dementia. Regarding this group, similar argument as presented above could also be applied to this group.

In addition, some MCI patients also improved to normal after follow up. These were excluded from the study since there was a risk that this group included individuals with non-dementia etiology and also due to the reason that we were mainly interested to study individuals at high risk for impending clinical decline.

11.11.2 Technical considerations

11.11.2.1 Neurovascular coupling

There are several potential confounds to consider when using fMRI as a method of studying age-and disease related changes. Perhaps most importantly, as stated before the neuronal activity is measured indirectly, by influencing the hemodynamic properties of the microvasculature (Malonek and Grinvald, 1996). Thus, comparisons across subject populations rely on a neurovascular response that does not change with age or disease. Although still uncertain, there is some evidence that suggests that the integrity of the coupling between vascular response to regional brain activity may be altered by age, neurodegenerative diseases, cerebrovascular processes and drug intake and that this factors might account for the activation deficits seen in elderly and dementia patients (for review and discussion see D´Esposito et al., 2003).

During the years, several measures have been proposed to control for the influence of possible different hemodynamic response functions between groups in functional activation studies, including a group-by-task interaction analysis instead of main group differences and the control for vascular risk factors (diabetes and hypertension) and already present cerebrovascular changes (e.g. arteriosclerosis, cortical infarction, white matter lesions). All the studies included in the thesis have employed these measures to avoid confound of neurovascular decoupling in our elderly subjects and MCI and AD patients.

11.11.2.2 Control of eye movements

Eye movements were not controlled in any of the experiments. Considering that the task inherently was designed to involve eye movements (i.e. they were not told to fixate their eyes to a specific point in the clock-image), the possibility of differential eye movements in the different subject-groups cannot be ruled out. However, although the consideration of eye movements could have been benefical for the interpretation of the between-group differences in activation patterns, the eye-tracking procedure requires a system that is not only expensive but also makes the functional experiment more complex and time-consuming.

11.11.2.3 Effect of atrophy

When the brain atrophies such as with age or AD, a given voxel in the image is more likely to include both brain and non-brain areas. This phenomenon has been called *partial volume effect*, and is usually seen in in functional imaging techniques with

lower spatial resolution such as PET and SPECT, although they are present also in fMRI (Johnson et al., 2000). Although not applied in our studies, one way to avoid this effect is to use local cerebral atrophy as a covariate when looking at brain activation differences between groups.

Previous neuroimaging studies investigating the effect of atrophy on the BOLD signal have reported mixed results. In AD patients, atrophy-associated hyperactivations in the left IFG (Johnson et al., 2000) as well as hypoactivations in the superior temporal lobe (Prvulovic et al., 2002) and hippocampus (Sperling et al., 2003) have been found, possibly reflecting that the effect of neurodegeneration is region-specific. Previous studies in MCI patients also give mixed results. In a study by Johnson et al. (2004) no differences in atrophy was found between MCI patients and healthy elderly controls. In contrast, Dickerson et al. (2004) have demonstrated an effect of atrophy on the BOLD signal. In MCI patients, those patients with greater clinical impairment, were on average older, had more activation in the right parahippocampal gyrus, and a smaller left hippocampus (Dickerson et al., 2004). Similarly, Saykin et al. (2004) were able to demonstrate that patients with less hippocampal atrophy recruited more frontal areas during a working memory task after stabilization on a cholinesterase inhibitor. Finally, in subjects genetically at risk for late-onset AD, it is unlikely that atrophy explains between-group differences in BOLD signal (Bookheimer et al., 2000; Bondi et al., 2005). Taken together, regional atrophy may affect the BOLD signal, but the impact differs across brain regions and disease status. As a note, it is believed that by using a parametric approach, examining relative changes of BOLD signal, the partial volume effect can be reduced (Rosen et al., 2002), as for example was one by (Mentis et al., 1996; 1998). Presumably, the artefact would still degrade sensistivity in a constant manner, but relative changes would be unaffected (Rosen et al., 2002).

11.11.2.4 Treatment effects in AD patients

At the time of the study (IV), ten AD patients were receiving acetylcholinesterase inhibitor treatment for cognitive impairment. Until now, few pharmacological fMRI studies have been conducted to investigate the effect of such treatment effects on the BOLD signal in AD patients. Rombouts et al. (2002) demonstrated that a single dose of rivastigmine increased the activation in the fusiform gyrus bilaterally during a face encoding task, in the left superior frontal gyrus during a 1-back working memory task, and in the right inferior and superior frontal gyri during a 2-back working memory task in AD patients. Decreases in activation were found in the right middle and superior frontal gyri in the 2-back working memory task alone (Rombouts et al., 2002).

Similarly, there are empirical findings on treatment effects in AD patients as demonstrated by glucose metabolism using PET as well as indices of cognitive function (Kadir et al., 2007 a; 2007 b). Results show short-term effects, i.e. when baseline values are compared to values after 3-6 months of treatment in several brain regions and on tests of cognition. However, at 12 months, no such effects was demonstrated when treated and untreated AD patients where compared. These data support the conclusion that there are no long-lasting effects on brain activity in AD patients following treatment with acetylcholinesterase inhibitors. Considering that the AD patients in our study (IV) had had medical treatment for a longer time period than 6 months it is conceivable that the treatment effects are small in the reported between-groups differences found.

12 CONCLUSIONS

Understanding how the brain functions is perhaps the most challenging problem in modern biology, with major implications for improving human health. The findings of the work presented in this thesis have provided deeper insights into the normal brain function of the cortico-subcortical networks underlying visuospatial processing and how it is affected by aging and dementia. The integration of our functional studies of both healthy aging and patients with AD and its precursors in an adapted model similar to the one originally proposed by Prvulovic et al. (2005), reveals that alterations in the visuospatial network, independently of its cause, lead to changes in functional activation which seems to follow similar rules in aging and dementia. Thus, the findings presented in this thesis are providing one step in the unraveling of the physiological and pathophysiological mechanisms behind age- and disease -related cognitive decline. The results and the general conclusions of these experiments can be summerized as follows:

- There seems to be general principles that govern the relation of active thinking to the cortical systems that subserve those mental processes. Just as physical energy systems require resources, the computational work underlying thinking and the execution of a given task must be accompanied by some resource utilization. Specifically, greater task demand translates into greater resource demand. We have shown that fMRI has the possibility to measure a facet of this resource utilization, albeit indirectly in the BOLD response.

- Furthermore, we have demonstrated that using a parametric approach, looking at the the task dependent modulation of the hemodynamic signal (either by using correlation analysis or by incorporating the reaction time dependent hemodynamic response predictor in the GLM model) is a fruitful strategy for differentiating the specific function that a particular area fullfils in a coactivated network.

- We have also shown the feasibility of using this approach when investigating age- and disease -related changes. Specifically, that the use of a RT-dependent hemodynamic response predictor is easily incorporated and interpreted in a random effect model using two or more groups.

- We further have demonstrated that the integration of task demand and task performance, amount of damage to the functional processing units, their necessity for processing of the angle discrimination task, and the integration of connections within large-scale networks, in a theoretical model similar to that of Prvulovic et al. (2005), all seem to interplay and result in differences in the brain activation patterns between healthy young and elderly subjects and patients with AD and its precursors.

- The finding that reduction of the processing effiency in regions considered to have a major involvement in angle discrimination (especially the SPL) induces different compensatory mechanisms within and/or outside the concerned regions. These mechanisms include the recruitment of higher number of neurons (or neuronal population) assessed by an increasing peak activation (study V) and the coactivation of specific or less specific remote areas, which can either directly take over a part of the processing burden (auxiliary pathway) (study IV) or facilitate the task processing in the affected regions (study III and V).

13 PERSPECTIVES

The results of this work have raised additional questions and opened possibilities for new projects. This last chapter of the thesis now concludes with recommendations for future research in the field of cognitive neuroscience of aging and disease and the clinical consideration of the findings.

13.1 USING FMRI TO PROBE BRAIN FUNCTION

Although fMRI has been criticized as a million dollar relative to phrenology (see section 1.1.1), the last decade has seen several advances in imaging techniques and protocols, which yield more useful information than was initially thought possible Nair, 2005). This is evident in the unprecedented increase during the last decade in the use of fMRI to understand not only the neurobiological correlates of behavior and cognition but also as a tool to improve diagnosis and therapy of AD. However, as with each neuroscience tool (including the microscope, the microelectrode, and behaviour) it has its limitations; each tool informs us about some, but not all, components of neural computation (Logothesis and Wandell, 2004). Hence, fMRI will be integrated effectively when we can identify which aspects of the neural signals fMRI measure and how these measurements relate to those made with other instruments (Logothesis and Wandell, 2004). Especially, one of the great methodological challenges for the coming years will be to resolve the pathophysiology of neurovascular coupling and its impact of the results of functional activation studies in aging and dementia.

13.1.1 Recommendations for future research in dementia

On the basis of the results described in this thesis, the following recommendations for future research in dementia can be made. Studies that investigate elderly patient with dementia represent a challenge for fMR imaging because of the high level of cooperation required and the need for paradigms to be appropriate to cognitive performance of this population. It is therefore important that the instructions are simple and easy to follow. Also, a short training session should be conducted before the real experiment starts and time should be set for the individual to ask questions about the experiment or the fMRI environment. Perhaps unnecessary to mention is of course that the environment before and during the experiment is calm and relaxing for the patient. Comfortable positioning and reduced duration of the experimental paradigm are two things that can help provide this. Also, one measure to decrease the stress and anticipation in the patient is to perform the fMRI experiment immediately after instructions rather than after the conventional anatomical MR examination.

Considering that there are several behavioral factors that can influence and complicate the interpretation of the data obtained with fMRI, it is important to ensure that adequate task performance is ensured and measured. These behavioral measurements can with advantage be used for correlation with activation.

13.2 CLINICAL CONSIDERATIONS

The fMRI method has several strengths that are encouraging its increased use in the study of preclinical and clinical AD. First, fMRI can be performed in any clinical MRI scanner and is entirely non-invasive, allowing the patients to be studied repeatedly over the course of their disease. Second, technical improvement also allows for robust and

reproducible evaluation of physiological as well as morphological functions. However, to use fMRI for early detection of AD, there is a need to determine whether there is a pathognomonic pattern of functional activation which can be used to distinguish people with AD from healthy controls (Rosen et al., 2002). We propose that an integrative account, which allows for different neural response patterns depending on the amount of neuronal damage and the recruitment of compensatory pathways, should be used in trying to predict outcome in subjects with preclinical AD. Useful variables to take into consideration are task demand and task performance, amount of damage to the functional processing unit, their necessity for processing of the specific task, and the integration of connections within large-scale networks. The functional paradigm used in the study specifically targeted visuospatial function. Although these studies yield a good picture of visuospatial functioning in healthy individuals as well as in early and preclinical AD, other areas of theoretical interest were missed and should be thoroughly investigated in future research. Thus, paradigms adopting a similar parametric approach but investigating other domains such as for example episodic memory, semantic memory, and working memory could be of interest to investigate if the findings of changes in functional activation follow similar rules in aging and dementia as the ones presented in this thesis.

13.2.1 Clinical relevance

In AD, deficits in spatial localization which may manifest itself in wandering in some patients, and may render an individual unable to orient effectively to the environment, arebelieved to arise from the pathological change in parietal cortices and their inputs (Cronin-Golomb, 2001). Our findings of a failure to modulate the neuronal response to increased task demand in this area support this deficit in the AD patients. Similarly, the findings that this area is affected even in preclinical AD demonstrate that fMRI has the possibility to monitor the changes in neuronal integrity during the course of the disease. However, it is still debatable whether imaging markers like the once provided with fMRI can provide precise sensitivity, specificity and diagnostic utility. The robust and reproducable results in many studies have prompted researchers to explore the possibility to use imaging techniques with the aim to identify individuals who are in high risk of developing AD or even more important, individuals who are in the preclinical phase, i.e. affected by AD but are not expressing the disease (Rosen et al., 2002). Although, the findings in this thesis are promising in that we can find difference in functional brain activation that support preclinical detection of AD, the clinical relevance of these findings have to await further investigations. Especially, there is a need for translation of the paradigm used in this thesis to the clinic. That is, to be applied as a clinical tool, it would be important to develop approaches to characterize psychometric parameters such as predictive validity and reliability, which have not been conducted at present time. Future research using the same approach as presented in this thesis should also address high risk individuals, individuals with susceptibility genes (e.g. APOE ε4) or individuals carrying genes responsible for early-onset autosomal dominant AD (amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2)) as the results from these studies could help reveal the pathognomonic pattern of functional activation even more and perhaps yield further insights into the etiology of AD.

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APPENDIX A

Detailed description of the different neuropsychological tests, administred to all subjects in the study.

Global Cognitive Function

To assess cognitive functioning or general intelligence the full-scale intelligence quotient (FSIQ) from the WAIS-R (Wechsler, 1981) was used. The FSIQ was estimated from five WAIS-R tests. See table 7.1 for FSIQ in all groups. In patients, mini mental state examination (MMSE) (Folstein et al., 1975) was also administered (although not reported in all studies).

Attention

Two measures of attention were used in this thesis. Both are believed to assess focus and executive components of attention, and are evaluated by task drawing in psychomotor speed.

Trail Making Test (Rey, 1959) which consists of two parts. Trail Making Test A in which the subjects must draw lines to connect consecutively numbered circles randomly distributed on a sheet of paper. Trail making B which requires subjects to draw a line alternately connecting an ascending series of letters and numbers in circles randomly distributed on a sheet of paper. The number of accurate items for the total number of items completed and the performance time in seconds is registered.

Digit Symbol Test from the WAIS-R (Wechsler, 1981), which consists of four rows containing 100 black squares (25 on each row). Each square is paired with a randomly assigned number from one to nine. A printed key that pairs each number with a different nonsense symbol is displayed above these rows. The subjects are instructed to first study the printed key and then to fill in the black squares as fast as possible. The number of squares completed during 90 seconds as well as the time to complete all squares is registered.

Short term memory

Only one measure of short term memory was used in the thesis, in which the capacity of rapid access of information as well as the amount of number of active information chunks is tested.

Digit Span Forward and *Backward* from the WAIS-R (Wechsler, 1981), which was administred according to an up-and down technique. Both tests consist of in total seven pairs of random number sequences (with increasing amount of numbers in each pair) which are read aloud by the examiner (one number per second). The subjects are instructed to try to repeat the number sequence after he/she has heard it (either forward as heard or backwards). The two tests are combined to obtain the total score.

Long term memory

Long term memory was assessed by investigating two types of long term memories; episodic memory and semantic memory. In the first, declarative knowledge as for example personal time-associated single events acquired in a particular temporal-spatial context is tested. In the latter the declarative knowledge that consists of facts related to

the person or genetic knowledge is tested. Three measures of episodic memory were used in the study:

Rey Osterrieth Copy and Retention Test (Rey, 1941) copy delayed recall, which consists of a complex figure that the subjects are instructed to first copy immediately and then to try to recall and reproduced the figure again after 30 minutes. The first part of the test is assessing mainly the perceptual organization and visuospatial function of the subjects (see executive functions below), whereas the retention test is assessing visual (episodic) memory.

Rey Auditory Verbal Learning Test (Rey, 1959), consists of a 15 word list which is read aloud by the examiner (one word per second). The subjects are instructed to repeat as many words as possible, which is assessing the immediate memory span. This procedure is repeated for 5 times which is assessing the learning curve and learning strategies. After 30 minutes the subjects are instructed to try to recall the words again, in that way assessing long-term memory.

Two measures of semantic memory were used in the study:

Similarities from the WAIS-R test (Wechsler, 1981), in which several word pairs are presented. The subjects are instructed to explain what each pair of words has in common. The word pairs range in difficulty from most easiest to most difficult and are assessing verbal concept information.

Information from the WAIS-R test (Wechsler, 1981), is assessing the general knowledge of the subject and consists of different questions concerning for example geography or culture. The questions are arranged in order of difficulty from most easiest to most difficult.

Visuospatial function

Two measures of visuospatial function were used in the study, in order to assess both perceptual organization and also the ability of the subject to perform a task which requires executive functions (i.e. the ability to plan, organize and execute actions step by step in order to solve the task).

Block Design test from the WAIS-R test (Wechsler, 1981) is a construction test in which the red and white blocks (four or nine) are used to create different patterns by the examiner. The subjects are instructed to copy the block pattern and the time and ability to copy are registered.

Rey Osterrieth Copy Test (Rey, 1941) is also used (see description above).