Pathological cognitive decline in the elderly participants of the Vogel Study

Pathologische kognitive Verschlechterung in den älteren Studienteilnehmern der Vogel Studie

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The author Sophia Haberstumpf declares no conflict of interest.

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Abbreviations

α	statistical significance level (alpha level)
AAN	American Academy of Neurology
Aβ-Plaques	β-Amyloid Plaques
AD	Alzheimer's Dementia/Disease
ADRDA	Alzheimer's Disease and Related Disorders Association (=Alzheimer's Association)
ADT	Angle Discrimination Task
AIC	Akaike Information Criterion
AT	Attention
ANOVA	Analysis of Variances
ApoE/APOE	Apolipoprotein-ε (genetic phenotypes)
ASI-3	Anxiety Sensitivity Index – 3/Anxiety Status Inventory
AWMF	*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*
b/β	statistical beta coefficient (regression coefficients, values/factors)
B-ADL	Bayer - Activities of Daily Living
BDI-II	Beck Depression Inventory - 2
BDNF	Brain-Derived Neurotrophic Factor
BIC	Bayesian Information Criterion
BMI	Body-Mass-Index
BOLD	blood-oxygenation level dependent
BSA	Bovine Serum Albumin
CA	Calcium
CBF	Cerebral Blood Flow

CBV	Cerebral Blood Volume
cCT	cranial Computed Tomography
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CFT	Rey-Osterrieth Complex Figure Test
CI	Confidence Interval
cMRI	cranial Magnetic Resonance Imaging
CNS	Central Nervous System
COVID-19	Corona Virus Disease 2019
CRP	c-reactive protein
CRUNCH Model	Compensation-Related Utilization of Neural Circuits Hypothesis
cm	centimeter(s)
CSF	Liquor Cerebrospinalis/Cerebrospinal fluid Analysis
CST	Cognitive Stimulation Therapy
CW	Continuous Wave
DemTect	Dementia Detection test/Test for Dementia Detection
d/d_z	Cohen's *d* (statistical effect size), d_z for standardized difference scores
df	degree(s) of freedom
DGPPN	*Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e.V.*
DGN	*Deutsche Gesellschaft für Neurologie e.V.*
dl	deciliter(s)
DM	Declarative Memory

DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th version
DNA	Deoxyribonucleic Acid
EEG	Electroencephalography
EDTA	Ethylenediaminetetraacetate
EFA	Exploratory Factor Analysis
ELISA	Enzyme-Linked Immunsorbent Assay
ELSA Model	Early-to-Late-Shift in Aging-Model
FCSRT	Free and Cued Selective Reminding Test
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
F	statistical *F*-test test size
f	statistical effect size
fMRI	functional Magnetic Resonance Imaging
fNIRS	functional Near Infrared Spectroscopy
g	acceleration force (centrifuge)
GABA	Gamma Amino Butyric Acid
Gamma-GT	Gamma-Glutamyl Transferase
GDS	Geriatric Depression Scale
GG-ε	Greenhouse-Geisser correction
GLM	General Linear Model
GOT	Glutamate-Oxaloacetate-Transaminase
HAROLD Model	Hemispheric Asymmetry Reduction in Older Adults Model
[HHb]/[deoxy-Hb]	Deoxygenated Hemoglobin
Hb	Hemoglobin
HDL	High-Density-Lipoprotein (cholesterol)

HDS	Hamilton Depression Scale
HRF	Hemodynamic Response Function
HRP	Horseradish Peroxidase
HVDS	Hachinski Vascular Dementia Scale
Hz	Hertz [frequency unit]
ICD-10	International Statistical Classification of Diseases and Related Health Problems – 10th version
IMD	Intima Media Thickness
IPC	Inferior Parietal Cortex
ISI	Inter-Stimulus-Interval
K	Kalium
KMO	Kaiser-Meyer-Olkin criterium
l	liter(s)
LATE	Limbic Predominant Age-Related TDP-43 Encephalopathy
LDL	Low-Density-Lipoprotein (cholesterol)
ln(RT)	logarithmized Reaction Time
LogLik	Log-Likelihood
LVEF	Left Ventricular Ejection Fraction
M	Mean
mAb	monoclonal antibody
major NCD	Major Neurocognitive Disorder
MANCOVA	Multivariate Analysis of Covariance
MCI	Mild Cognitive Impairment
MD	Mean Difference
MI	Measurement Invariance

mild NCD	Mild Neurocognitive Disorder
µg	microgram(s)
µl	microliter(s)
µmol	micromol(s)
mg	milligram(s)
ml	milliliter(s)
MLR	maximum likelihood estimation
mm	millimeter(s)
MMSE	Mini Mental Status Examination
MoCA	Montreal Cognitive Assessment Test
MRI	Magnetic Resonance Imaging
ms	millisecond(s)
NA	Natrium
Na_2CO_3	Sodium Carbonate
$NaHCO_3$	Sodium Hydrogen Carbonate
NAKOS	*Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen*
NE	Number of Errors
NFT	Neurofibrillary Tangle
ng	nanogram(s)
NIA	National Institute on Aging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NIRS	Near Infrared Spectroscopy
N/n	population size (total/partial sample)

n_p^2	partial n^2 (statistical effect size)
nm	nanometer(s)
NMDA	N-Methyl-D-Aspartate
Npar	Non-Parametric tests
[O_2Hb]/[oxy-Hb]	Oxygenated Hemoglobin
OR	Odds Ratio
p	significance level (*latin* probabilitas)
PASA Model	Posterior-Anterior Shift in Aging Model
PASTOR Model	Positive Appraisal Style Theory of Resilience Model
PBS(-T)	Phosphate-Buffered Saline (with Tween 20)
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
pg	picogram(s)
pH	hydrogen potential (*latin* pondus hydrogenii, potentia hydrogenii)
p-tau	phospho-tau
PMCI	MCI patients who progressed to AD 3 years later
pointer	pointer length
PSA	Process Spezific Alliances
r	statistical regression coefficient
R^2	statistical coefficient of determination
RCT	Randomized Controlled Trial
RDoC	Research Domain Criteria
RMSEA	Root Mean Square Error of Approximation
ROI	Region of Interest
ROT	*Realitätsorientierungstraining* (Reality Orientation Training)

RT	Reaction Time
RWT	*Ravensburger Wortflüssigkeitstest*
s	second(s)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - type 2
SCAAREED	Screen for Adult Anxiety Related Disorders scale
SD	Standard Deviation
SE	Standard Error
SeKo	*Verein Selbsthilfekontaktstellen Bayern e.V.*
SEM	Structural Equation Modeling
SPC	Superior Parietal Cortex
SPECT	Single Photon Emission Computed Tomography
STAC-(r) Model	Scaffolding Theory of Aging and Cognition (-revised)
SMCI	MCI patients who remained stable 3 years later
SNAP	Suspected Non-Alzheimer's Disease Pathophysiology
t	statistical *t*-test test size
TAP	*Testbatterie zur Aufmerksamkeitsprüfung* (Battery of Tests for Attentional Performance)
TDP-43	Transactive response Deoxyribonucleic Acid (DNA) binding Protein 43 kDa
TFDD	Test zur Früherkennung von Demenzen mit Depressionsabgrenzung
[tHb]	total Hemoglobin
THC	Temporal Hypothesis for Compensation
TMT	Trail Making Test
TSH	Thyrotropin
t-tau	total-tau

U/l	Unit(s) per liter
V	Pillai's trace statistic
V1	visit 1, baseline investigation
V2	visit 2, first follow-up
V3	visit 3, second follow-up
VFT	Verbal Fluency Test
VLMT	*Verbaler Lern- und Merkfähigkeitstest* (Verbal Learning and Memory Test)
VSEP	Vagus Somatosensory Evoked Potentials
VSP	Visual-Spatial Processing
Waldχ^2	statistical test size of the Wald-test
WHO	World Health Organization
WM	Working Memory
WMS-R	Wechsler Memory Scale – Revised
χ^2	Chi-squared distribution
z	statistical standardization

Abstract

Due to the global aging society and the enormous global incidence and prevalence rates that will result in the coming years, Alzheimer's Dementia (AD) represents a growing challenge for the health care system. The pathogenesis, which is unclear in parts, the chronic progression of AD, which often lasts for years, as well as insufficient diagnostic and therapeutic options complicate an adequate psychotherapeutic and medical approach to the disease. To date, AD is also considered an incurable disease. Therefore, it is essential to gain deeper insights into the early detection or even prevention of AD. Consideration of prodromal syndromes such as Mild Cognitive Impairment (MCI) can provide significant evidence about high-risk groups for AD progression and differentiate cognitively "normal" aging individuals from those with pathological cognitive decline. Thus, for example, functional Near-Infrared Spectroscopy (fNIRS) imaging helps identify early neurodegenerative processes. In contrast, potential risk factors and predictors of later-onset clinical symptoms of MCI and AD can most often be revealed and quantified via the use of neuropsychiatric test batteries.

The present thesis consists of four studies and aimed to assess and describe the pathological cognitive decline in a sample of elderly study participants (age: ≥ 70 years; N = 604 at baseline) of the longitudinal, observational, and prospective "Vogel Study" from Würzburg, Germany, who were primarily healthy at baseline, over two measurement time points approximately 3 years apart, to differentiate between healthy and diseased study participants and to define predictors of MCI/AD and longitudinal study dropout.

Studies 1 and 2 differentiated healthy study participants from MCI patients based on the baseline hemodynamic response of the parietal cortex recorded by fNIRS during the processing of a paradigm (here: Angle Discrimination Task [ADT]) for visual-spatial processing performance. Neuronal hypoactivity was found in the MCI patients, with both healthy study participants and MCI patients showing higher superior and right hemispheric activation. MCI patients had more difficulty resolving the paradigm. Thus, no evidence of possible compensatory mechanisms was uncovered in the MCI patients.

Study 3 first defined the four latent factors declarative memory, working memory, attention, and visual-spatial processing based on structural equation model (SEM)

calculations of the sample using adequate measurement (in-)variant confirmatory factor models from the baseline assessment to the first of a total of two follow-up assessments after approximately 3 years. This allowed a dimensional assessment of pathological cognitive decline versus classificatory-categorical assignment (healthy/diseased) of the sample. In addition, the superiority of the latent factor approach over a composite approach was demonstrated. Next, using a mixed-model approach, predictive analyses were calculated for the prediction of latent factors at first follow-up by baseline risk factors. The sex of study participants proved to be the best predictor of cognitive change in all the cognitive domains, with females performing better than men in the memory domains. Specifically, for declarative memory, older age predicted lower performance regardless of sex. Additional predictive evidence emerged for low serum levels of Brain-Derived Neurotrophic Factor (BDNF) on lower attention performance and higher depression symptoms on lower visual-spatial processing performance.

Study 4 further reported baseline predictors of study dropout at first follow-up. Cognitive performance, as defined in Study 3 using the four latent cognitive factors, was a predictor of study dropout for cognitive decline in the domains of declarative memory, attention, and visual-spatial processing. Conspicuous dementia screening on the Mini-Mental Status Examination (MMSE) also predicted dropout.

Overall, both the use of fNIRS imaging to detect visual-spatial processing performance in the parietal cortex during applying ADT and the dimensional perspective of the neuropsychiatric test battery in the context of prediction and dropout analyses were found to be suitable for early detection research of MCI and AD. Finally, the results will be interpreted in the overall context and implications, limitations, and perspectives will be discussed.

Zusammenfassung

Aufgrund der global alternden Gesellschaft und der damit auch in den nächsten Jahren einhergehenden enormen globalen Inzidenz- und Prävalenzraten stellt die Alzheimer-Demenz (AD) eine wachsende Herausforderung für das Gesundheitswesen dar. Die in Teilen unklare Pathogenese, die oft über Jahre bestehende, chronische Progression der AD sowie bislang unzureichende Diagnose- und Therapiemöglichkeiten erschweren einen adäquaten psychotherapeutischen und medizinischen Umgang mit der Erkrankung. Bis heute gilt die AD außerdem als unheilbare Erkrankung.

Umso wichtiger ist es, tiefergehende Erkenntnisse zur Früherkennung oder gar Prävention der AD zu gewinnen. Insbesondere die Berücksichtigung von Prodromalsyndromen wie das *Mild Cognitive Impairment* (MCI) können wichtige Hinweise über Risikopersonengruppen für eine AD-Progression liefern und kognitiv „normal“ alternde Menschen von Menschen mit pathologischer kognitiver Verschlechterung differenzieren. Zur Identifikation früher neurodegenerativer Prozesse eignet sich z.B. die funktionelle Nahinfrarotspektroskopie (fNIRS), während potenzielle Risikofaktoren und Prädiktoren für später auftretende, klinische Symptome der MCI und AD am häufigsten über die Anwendung neuropsychiatrischer Testbatterien aufgedeckt und quantifiziert werden können.

Die vorliegende Dissertation besteht aus vier Studien und verfolgte das Ziel, die pathologische kognitive Verschlechterung in einer zur Baseline-Erhebung größtenteils gesunden, älteren Stichprobe (Alter: ≥ 70 Jahre; $N = 604$ zur Baseline-Erhebung) der longitudinalen, beobachtenden und prospektiven „Vogel Studie“ aus Würzburg über zwei Messzeitpunkte im Abstand von ca. 3 Jahren zu erfassen und zu beschreiben, zwischen gesunden und erkrankten StudienteilnehmerInnen zu differenzieren und Prädiktoren der MCI/AD sowie des longitudinalen Studien-Dropouts zu definieren.

Studien 1 und 2 differenzierten gesunde StudienteilnehmerInnen von MCI-PatientInnen anhand der über die fNIRS zur Baseline-Erhebung erfassten hämodynamischen Antwort des Parietalkortex während der Bearbeitung eines Paradigmas (hier: Winkeldiskriminationsaufgabe [ADT]) zur visuell-räumlichen Verarbeitungsleistung im Rahmen der Baseline-Erhebung. Es konnte eine neuronale Hypoaktivität bei den MCI-PatientInnen festgestellt werden, wobei sowohl gesunde StudienteilnehmerInnen als auch MCI-PatientInnen eine höhere superiore und rechts-hemisphärische Aktivierung zeigten. MCI-PatientInnen hatten mehr Schwierigkeiten,

das Paradigma zu lösen. Dennoch konnten keine Hinweise auf Kompensationsmechanismen bei den MCI-PatientInnen aufgedeckt werden.

Studie 3 definierte zunächst die vier latenten Faktoren deklaratives Gedächtnis, Arbeitsgedächtnis, Aufmerksamkeit und visuell-räumliche Verarbeitung basierend auf Strukturgleichungsmodell-Berechnungen (SEM) der Stichprobe anhand von adäquat mess(in-)varianten konfirmatorischen Faktormodellen von der Baseline-Erhebung zum ersten von insgesamt zwei Follow-up-Erhebungen nach rund 3 Jahren. Dadurch wurde eine dimensionale Einschätzung pathologischer kognitiver Verschlechterung gegenüber klassifikatorisch-kategorialer Zuweisung (gesund/krank) der Stichprobe ermöglicht. Zusätzlich konnte die Überlegenheit des latenten Faktor-Ansatzes gegenüber eines Composite-Ansatzes gezeigt werden. Anschließend wurden anhand eines Mixed-Model-Ansatzes Prädiktionsanalysen zur Vorhersage der latenten Faktoren zum ersten Follow-up durch Risikofaktoren der Baseline-Erhebung berechnet. Das Geschlecht der StudienteilnehmerInnen erwies sich als bester Prädiktor für die kognitive Veränderung in allen kognitiven Domänen, wobei Frauen in Gedächtnis-Domänen eine bessere Leistung als Männer erzielten. Vor allem für das deklarative Gedächtnis sagte geschlechterunabhängig ein höheres Alter eine geringere Leistung vorher. Zusätzlich zeigten sich prädiktive Effekte eines geringeren *Brain-Derived Neurotrophic Factor* (BDNF) Serum-Levels auf geringere Aufmerksamkeitsleistung und der erhöhten Depressivität auf geringere visuell-räumliche Verarbeitungskapazitäten.

Studie 4 berichtet darüber hinaus von Baseline-Prädiktoren des Studien-Dropouts zum ersten Follow-up. Die kognitive Leistung, wie in Studie 3 anhand der vier latenten kognitiven Faktoren definiert, stellte für eine kognitive Verschlechterung in den Domänen deklaratives Gedächtnis, Aufmerksamkeit und visuell-räumliche Verarbeitung einen Prädiktor für Studien-Dropout dar. Auch ein auffälliges Demenz-Screening im *Mini-Mental Status Examination* (MMSE) sagte Dropout vorher.

Insgesamt erwiesen sich sowohl die Anwendung des fNIRS-Bildgebungsverfahrens zur Erfassung visuell-räumlicher Verarbeitungsleistung im Parietalkortex während Bearbeitung der ADT als auch die dimensionale Betrachtung der neuropsychiatrischen Testbatterie im Rahmen prädiktiver und Dropout-Analysen als für die Früherkennungs-Forschung der MCI und AD geeignet. Die Ergebnisse werden abschließend im Gesamtkontext interpretiert und Implikationen, Limitation und Perspektiven diskutiert.

1. Introduction

"What is your name?"
"Auguste."
"Last name?"
"Auguste."
"What is your husband's name?"
"Auguste, I think."

- Alzheimer's Cardboard file describing the symptoms of Auguste D. (Alzheimer, 1901, as cited in Maurer et al., 1997, p. 1547).

The beginnings of the oldest, scientific, psychiatric anamnestic protocol of an initial interview with a German patient suffering from Alzheimer's Disease (AD) dates from Alois Alzheimer, the discoverer of the disease, more than a century ago in 1901. A short time later, in 1906, Alzheimer first published his findings as a "peculiar disease of the cerebral cortex". He described, for example, memory problems, a varying mood, perplexity, and orientation deficits as characteristic of the disease. The very advanced investigations of the German psychiatrist and neuropathologist, also known as the "psychiatrist with the microscope", went so far that the first post-mortem brain examinations of deceased patients with the novel disease were carried out. For example, the characteristic "Alzheimer's plaques" described by him, i.e., pathological amyloid deposits on the brain's nerve cells, are still an internationally popular term today. Alzheimer himself described three anatomical characteristics for the "peculiar disease process". A "pathological metabolic product not yet studied in detail" had formed in the nerve cells, of the "upper cell layers" of the cortex "1/4 to 1/3 had completely disappeared", and there were "neurofibrils" that would survive "the demise of the cell." Thus it came that the term "Alzheimer's dementia", based on Alois Alzheimer's case descriptions, was first named by Emil Kraepelin in 1910 (Alzheimer, 1906; Kraepelin, 1910; Perusini, 1909).

Initially forgotten again until the second half of the 20th century, AD is still considered a much researched and so far, not fully curable disease that can affect anyone.

For example, Hans Förstl, a German physician and researcher of AD, retrospectively reported evidence from autopsy findings of frontal brain degeneration and thus a dementing disease in King Ludwig II of Bavaria, who died in the 19th century (Förstl et al., 2008). At that time, dementia diagnoses according to today's medical standards were not available. Nevertheless, these investigations emphasize the relevance of dementia- and AD-research that still exists today.

Thus, to this day, numerous prominent people worldwide are also known to suffer or have suffered from AD. For example, former U.S. President Ronald Reagan (1911-2004) who described the onset of the disease in himself as follows:

> "I now begin the journey that will lead me into the sunset of my life."
>
> - Personal communication of U.S. President Ronald Reagan, November 05, 1994.

Another tragic example is provided by the ex-professional soccer player Gerd Müller, "the nation's bomber," who died only recently on August 15, 2021, and is known beyond Germany's borders. He succumbed to his long-preceding AD at the age of 75 (Focus Online, 2021).

The high relevance of AD research is also evident in the judicial context due to existing ambiguities about the clinical picture of AD and, thus, controversial case law. For example, as recently as July 2021, relatives of a 51-year-old AD patient who died of starvation in 2017 were acquitted in Würzburg. A refusal of food or malnutrition is often a concomitant of AD patients and is considered a frequent cause of death in the advanced stages. In this case, the court refrained from accusing the relatives of negligent homicide (Hasenauer, 2021).

Alois Alzheimer was born in Marktbreit near Würzburg in 1864 and studied medicine, including at the Julius Maximilian University in Würzburg. Later, he worked for various hospitals in Frankfurt am Main, Heidelberg, Munich, and Breslau, where he last died in 1915 (Shampo et al., 2013). To this day, 7 years after the 100th anniversary of his death, Alzheimer's birthplace near Würzburg houses a small museum, conference rooms, and a memorial plaque dedicated to him on the wall of the house.

In addition to the current research interest in the disease, the proximity of the Julius-Maximilians-University of Würzburg to the work of Alois Alzheimer is understandable.

Thus, the present doctoral thesis aims to extend the scientific knowledge regarding AD by focusing mainly on the early detection and prevention of the disease. The potential of the so-called *Mild Cognitive Impairment* (MCI), a neurodegenerative syndrome in the prodromal phase of AD, should be considered in the early detection of neurodegeneration. In the "Vogel Study", an observational, follow-up, 10-year longitudinal study with a total observation period of the participants of 6 years, predictions will be made as to which participants will decline cognitively over time in a pathological manner. For this purpose, both a modern brain imaging technique and neuropsychiatric test battery will be used to identify differences between participants by examining potential predictors and risk factors.

1.1 Theoretical background

1.1.1 Epidemiology

AD is often equated with other dementia syndromes in everyday life, probably because it is the most common form with up to 60-70% within all dementia syndromes and is the most popular subtype (World Health Organization, 2021).

Current estimates by the World Health Organization (WHO) indicate 50 million people worldwide with dementia, with approximately 10 million new cases annually (World Health Organization, 2019; World Health Organization, 2021). Overall, around 5-8% of people over the age of 60 are affected. Due to the steadily aging population as a result of improving healthcare systems and the doubling of cases of the disease every 20 years, 152 million patients with dementia are expected by the year 2050 (Bickel, 2020; Alzheimer's Disease International, 2021; World Health Organization, 2019; World Health Organization, 2021; Vieira et al., 2013). This means that every 3 seconds on earth a person develops dementia (Federal Ministry for Family Affairs, Senior Citizens, Women and Youth & Federal Ministry of Health, 2020; Alzheimer's Disease International, 2021; Patterson, 2018). Although dementia usually occurs at older ages, dementia with early-onset before age 65 gets increasingly common (Alzheimer's Disease International, 2021; see also „early-onset" according to the International Classification of Diseases, 10th Revision [ICD-10], Dilling & Freyberger, 2016, or chapter 1.1.4.1). To date, the detection and diagnosis of AD occurs in many cases at a very late stage (Alzheimer's Disease International, 2021).

In the USA, 6 million people currently have dementia. The high cost of the disease to their healthcare system is estimated to be $355 billion in 2021 and $1.1 trillion in 2050. Since the onset of the Severe Acute Respiratory Syndrome Coronavirus - type 2 (SARS-CoV-2/COVID-19) pandemic in 2020, up to 16% higher death rates have been recorded among patients with dementia ("2021 Alzheimer's disease facts and figures", 2021; Alzheimer's Association, 2021).

In Germany, as well, up to 1.7 million patients with dementia are currently registered, with 2/3 more women suffering from dementia (Alzheimer Europe, 2019; Bickel, 2020; Deuschl & Maier, 2016; Kurz, 2019). Every year, the number of dementia patients in Germany increases by 40,000 (Bickel, 2020). Of these, about 50-70% are AD patients, and about 15-25% have some form of vascular dementia. The current annual incidence rate of developing dementia in Germany is estimated to be 244,000 (Deuschl & Maier, 2016; Ziegler & Doblhammer, 2009). Estimates predict 2.8-3 million dementia patients in Germany by 2050 (Alzheimer Europe, 2019; Federal Ministry for Family Affairs, Senior Citizens, Women and Youth & Federal Ministry of Health, 2020; Kurz, 2019). Today, dementia affects one in every 100 people in Germany in people over 60 years, while it affects one in every six people over 80 years and as many as one in every two people over 90 years (Kurz, 2019). The enormous age-dependency of the disease is evident in that there is a higher probability of developing the disease with increasing age. In Germany, too, negative effects of the COVID-19 pandemic on the lives of dementia patients are expected since the social distance and contact restrictions have led to much poorer (family) support for the patients (Federal Ministry for Family Affairs, Senior Citizens, Women and Youth & Federal Ministry of Health, 2020).

A much more difficult estimate of prevalence rates can be made for patients with MCI. This is due to the use of inconsistently defined criteria for the syndrome. Roughly, it can be assumed that around 10-20% of all people over 60 years of age are affected by the disease (Anderson, 2019; Cooper et al., 2015; Förstl, 2011; Petersen, 2016). MCI is often described as a transitional stage between "normal aging" and AD. Approximately 30-50% of all MCI patients meet diagnostic criteria for AD within 3-10 years of follow-up. About 8-17% in clinical samples and 5-12% in representative samples of MCI patients convert to AD within a year (Bickel, 2020; Cooper et al., 2015; M. Davis et al., 2018; Liss et al., 2021; Mitchell & Shiri-Feshki, 2009; Petersen, 2016; Ward et al., 2013). In comparison, only about 1-2% of healthy older people develop

AD within a year (Anderson, 2019; Farias et al., 2009; Petersen et al., 1999). The American Academy of Neurology (AAN) practice guidelines report the prevalence of MCI by age: 60-64 years 6.7%, 65-69 years 8.4%, 70-74 years 10.1%, 75-79 years 14.8%, and 80-84 years 25.2%. In addition, these estimates assume that among MCI patients older than 65 years, a cumulative incidence of dementia is approximately 14.9% (Petersen et al., 2018). AD development is often dependent on whether risk or resilience factors are present in those affected (see chapters 1.2.1 and 1.2.3). This emphasizes the importance of studying MCI in more detail to identify preclinical AD at an early stage and to be able to take preventive action. In addition, insights into the neuropathogenic development of MCI/AD will first be provided.

1.1.2 Pathogenesis

To date, the cause of AD has not been fully investigated. However, the loss of neurons in the brain is observable in that the death of brain cells and thus lesions of the gray and white matter, lacunes, and micro-bleedings cause a reduction of brain tissue (=brain atrophy; Raskin et al., 2015; Tariq & Barber, 2018; Traini et al., 2020). Thereby, especially in temporal, parietal, and frontal brain regions as well as the cingulate cortex, the sulci of the cerebral cortex deepen and increase the enlargement of the cerebral ventricles, gyri become more superficial (Traini et al., 2020). Because of this neuronal, neuropile, and synaptic loss, the brain atrophy is also described as a "negative" lesion (Pini et al., 2016; Serrano-Pozo et al., 2011). In addition, two characteristic "positive" neuropathological alterations are apparent (“mixed proteinopathy“; Bloom, 2014; DeTure & Dickson, 2019).

On one side, there is an accumulation of neurofibrillary tangles (NFTs), which are abnormal, thread-like filaments made of the up to 3-fold hyperphosphorylated tau protein within brain cells (Gao et al., 2018; J. Z. Wang et al., 2013). Under normal conditions, the brain-specific tau protein provides structure and stabilization for a subset of brain cells, the microtubules, whereby e.g., nutrients are transported (Bakota & Brandt, 2016). Neurochemical changes in the tau protein during the AD development result in an accumulation within the neuron in the form of fibers called tau fibrils. As a result, the cells lose their shape and stability as well as their function, they die off (Wang & Mandelkow, 2016). The formation of NFTs can be divided into 6 phases according

to Braak and Braak (1991), Braak et al. (1993), and Braak and Braak (1995), respectively: Transentorhinal Phases 1-2, Limbic Phases 3-4, and Neocortical Phases 5-6. Phases 1-2 are considered clinically inconspicuous phases. Initial neurofibrillary modifications occur in the temporal lobe. In part, amyloid deposits develop in mostly weakly myelinated areas of the basal neocortex (Braak & Braak, 1991, 1997). Especially in stage 1, only a few lesions of projection cells are present. In the later stage 2 entorhinal regions are more involved, the first Ammon's horn (Hippocampus) sector is moderately involved (Braak et al., 1999; Braak & Braak, 1991). This results in the first information transmission impairments between neocortical brain areas via entorhinal areas to the hippocampus and the full limbic system, respectively (Braak et al., 1999). Although advanced age is considered the most potent risk factor for developing AD, these initial abnormalities are not age-dependent and can be detected early and in symptom-free individuals (Braak & Braak, 1997). They are the first sign of neurodegenerative processes in the brain, which cannot be cured and progressively progress towards death by destruction of the cytoskeleton (Braak & Braak, 1998). Phases 3 and especially 4 are considered the phases of incipient or mild AD due to the manifestation of clinical symptoms such as mental deficits and personality changes (Braak et al., 1999; Braak & Braak, 1991, 1995, 1997, 1998). Characteristic is the increasing impairment in the (trans-)entorhinal cortex and structures of the limbic system such as the hippocampus and temporal and insular proneocortical brain areas as well as in phase 4 also the first neocortical regions. Dysfunction in these phases results from the impairment of both cerebral hemispheres, which increasingly affect the transmission of information between sensory association fields, the limbic system, and the prefrontal cortex, depending on the individual cognitive reserve (Braak et al., 1999). Phases 5 and 6 are finally supposed to be the phases of a pronounced moderate to severe AD, and this is usually when the AD diagnosis is first made (Braak et al., 1999). The number of symptoms increases with age (Braak et al., 1999; Braak & Braak, 1991, 1995, 1997, 1998). Stage 5 is characterized by extensive destruction of the neocortex and other association areas, lesions in inferior temporal as well as superolateral areas. The transition to stage 6 ultimately begins with the destruction of primary motor areas, sensory areas, and unimodal secondary areas (Braak et al., 1999). Cortical atrophy as described above, widened ventricles, and brain weight loss become demonstrable (Braak et al., 1999).

On the other side, extracellular or intercellular amyloid plaques develop, i.e., characteristic proteolytic protein deposits (also known as „Amyloid-Cascade-Hypothesis“; Barage & Sonawane, 2015; Breijyeh & Karaman, 2020; Edwards, 2019). Under healthy conditions, the transmembrane amyloid precursor protein is usually degraded. However, neuropathological changes give rise to β-amyloid proteins, which also gradually accumulate, clump, and deposit as toxic and soluble β-amyloid oligomers (also known as the "modified amyloid hypothesis" or "oligomer hypothesis"; Fessel, 2018; Klein, 2013; Koss et al., 2016; Lesné et al., 2013). This process leads to the irreversible, senile β-amyloid plaques (Aβ-plaques) - or the typical AD plaques already mentioned in the introduction. To date, Aβ, total-tau (t-tau), and phospho-tau (p-tau) can be used as biomarkers for early AD detection (Blennow & Zetterberg, 2018). Parallel to the developmental stages of the above-described pathological neurofibrils, it can be assumed that the accumulation of Aβ-plaques occurs in 3 stages (A/B/C; Braak & Braak, 1991, 1997). Whereas in stage A, a low density of Aβ-plaques develops in weakly myelinated areas of the frontal, temporal, and occipital lobes of the neocortex, by stage B, an intermediate Aβ density is present throughout the neocortex, usually except sensory and motor areas, and hippocampal structures. In addition, the parietal lobe is also affected. Finally, in stage C, numerous subcortical structures (e.g., thalamus, hypothalamus, striatum) are involved in addition to all neocortical areas, which are also densely myelinated. Table 1 opposes both described “positive” pathogenetic brain alterations due to AD progression for a concise review.

In further disease progression, additional deposits and, for example, dystrophic neurites and neuropil fibers develop, astrocytes and microglia emerge, axons and dendrites are damaged, synapses perish (see again synaptic loss; Bloom, 2014; Cai et al., 2017; De Strooper & Karran, 2016; Iqbal & Grundke-Iqbal, 2008; Narayanan et al., 2020). Brain regions affected first are mostly basal, temporal, and orbitofrontal regions of the neocortex and later the hippocampus and amygdala (limbic system), diencephalon, and basal ganglia (Tiwari et al., 2019). Thereupon, the tau-tangle formation in the locus coeruleus and (trans-)entorhinal brain regions can be observed (Goedert, 2015; Tiwari et al., 2019). These neurochemical changes ultimately cause functional deficits in memory, thinking, language, and orientation due to their neurotoxic effects (Bloom, 2014). In addition to the typical pathogenetic changes, other neurodegenerative factors, such as inflammation or stress-related changes, are often

added to promote pathological processes (Forloni & Balducci, 2018; Holmes, 2013; Narayanan et al., 2020; Sotiropoulos et al., 2019).

In recent etiologic research, a neurovascular hypothesis is increasingly emerging as a causal trigger for NFTs and Aβ-plaques. Studies suggest that amyloid plaques are not only detectable between neurons but possibly also in smaller blood vessels of the brain (Solis et al., 2020). This, in turn, could explain the high comorbidity with vascular dementia and represents an indicator of the increased risk of, for example, stroke and other cerebrovascular diseases (Kivipelto et al., 2001; Skoog, 1997; Skoog & Gustafson, 2006; Solis et al., 2020). Vascular abnormalities can be detected in more than half of all AD cases (Toledo et al., 2013). Blood-brain barrier dysfunction is discussed as the causative factor underlying vascular damage. It is assumed that Aβ elimination is impaired, cerebral blood flow (CBF) is reduced, and dysfunctional neuronal coupling occurs ("hit 1"), resulting in vasculotoxic and neurotoxic Aβ accumulation in the brain ("hit 2"; = two-hit vascular hypothesis of AD; Solis et al., 2020; Zlokovic, 2005, 2011; Zlokovic et al., 2010). Consequently, neurodegenerative cognitive decline up to full AD may develop. Thus, the consideration of vascular risk factors and especially the potential of brain imaging techniques seem to be of enormous importance for the early detection of MCI/AD (J. de la Torre, 2018).

Further established and relevant for pharmacological therapy is the so-called acetylcholine hypothesis. Evidence shows that changes in the cholinergic transmitter system occur during the development of AD. Early cell death in the Meynert basal nucleus (basal forebrain), which causes a deficiency of acetylcholine, is often referred to as the initiator. This impairs information processing and consequently leads to memory deficits. Cholinesterase inhibitors are still used today in the pharmacological treatment of AD, but they only influence the progression of the disease (Barage & Sonawane, 2015; Claassen & Jansen, 2006; Hampel et al., 2018; see also chapter 1.1.4).

In addition to primary AD, rarer causes may form the basis for the development of secondary AD in the sequelae of other neurodegenerative diseases (e.g., Parkinson's disease), metabolic diseases (e.g., diabetes), craniocerebral injuries, infections, medications (e.g., neuroleptics, antidepressants), tumors, hemorrhage, or vitamin and hormone deficiencies.

Nevertheless, it is still not completely understood why one in five people with the described formations also age healthily (Oedekoven & Dodel, 2019). In particular, the inflammatory foci that develop around the deposits generate further research questions, such as whether the body defends itself in healthy people, or whether inflammations are causative for the development of AD, or to what extent etiologic pathogenesis depends on risk and resilience factors (Holmes, 2013).

Therefore, also findings regarding neuropathological changes in MCI patients remain ambiguous in the sense that MCI patients often cannot be differentiated from healthy or AD patients. Possible changes that could be indicative of later AD development in MCI patients include atrophy of the medial temporal lobe (mainly hippocampus, entorhinal brain areas, cingulate cortex), hypometabolism in the tempo-parietal and posterior areas of the cingulate cortex, and hypoperfusion in the parietal cortex and hippocampus (Anderson, 2019; Fennema-Notestine et al., 2009; Habert et al., 2011; S. H. Kim et al., 2010; Stephan et al., 2012). Due to the pathogenetic proximity to AD, the amyloid plaques and neurofibrils typical of AD may already be present in this condition. Both MCI and AD have their pathogenetic origin in the transentorhinal and medial perirhinal cortex, respectively, which is why the loss of integrity of the rhinal and hippocampal brain areas in the sense of atrophy can be observed (Anderson, 2019; Braak & Braak, 1995; Leal & Yassa, 2013; Taylor & Probst, 2008; Zhou et al., 2016). Today's studies describe a "paradox" overactivation for these brain areas for MCI patients, which is all the higher with more severe lesions and represents an attempt by the brain to maintain the original level of function despite neuropathological degeneration (Anderson, 2019; Dickerson et al., 2005; Putcha et al., 2011). Nevertheless, in 50-60% of MCI patients, no neuropathogenetic abnormalities can be found (J. A. Schneider et al., 2009; Wagner et al., 2012).

Subsequently, the characteristic course of MCI/AD will be outlined.

Table 1

Encountering "positive" neuropathological brain changes in terms of AD development.

Formation of neurofibrillary tangles in orientation to Braak and Braak (1991, 1995) and Braak et al. (1993)		**Development of Aβ-plaques in orientation to Braak and Braak (1991, 1997)**	
Transentorhinal Phase 1	▪ Involvement of the temporal lobe ▪ Involvement of the basal neocortex	Stage A	▪ Involvement of frontal, temporal, and occipital regions of the neocortex
Transentorhinal Phase 2	▪ Involvement of the entorhinal cortex ▪ Involvement of the Ammon's horn sector (Hippocampus)		
Limbic Phase 3	▪ Increased involvement of the entorhinal cortex ▪ Increased involvement of the limbic system	Stage B	▪ Increased involvement of neocortical regions with no involvement of sensory and motor regions ▪ Involvement of the Hippocampus
Limbic Phase 4	▪ Involvement of the neocortex		
Neocortical Phase 5	▪ Increased involvement of the neocortex and association areas ▪ Lesions in temporal and lateral regions	Stage C	▪ Increased involvement of the neocortex ▪ Involvement of subcortical regions
Neocortical Phase 6	▪ Lesions of primary motor, sensory, and unimodal secondary regions		

Note. AD = Alzheimer's Dementia/Disease.

1.1.3 Characteristic Progression

AD development is a chronic progressive process. Characteristic neuropathological changes described in chapter 1.1.2 usually occur 10-20 years before a behavioral assessment can diagnose AD. Therefore, it is often a challenge to recognize early or preclinical stages of AD (Braak & Braak, 1998; Butterfield & Halliwell, 2019; Markesbery, 2010; R. N. Martins et al., 2018). In addition, MCI should not be ignored for early detection of neurodegenerative processes as it is a prodromal syndrome of AD. However, inconsistent diagnostic criteria of MCI (see chapter 1.1.4.2) and divergent attempts to classify the AD course may complicate the diagnosis.

The WHO, for example, divides the course of dementia into three stages: First, the “early stage”, characterized by conspicuous forgetfulness, orientation deficits, or the loss of the sense of time. At this stage, dementia can be easily overlooked. Second, the “middle stage”, in which clearer symptoms are recognizable and patients appear increasingly impaired. Characteristics include increased forgetfulness (e.g., experiences, names), orientation and communication problems, behavioral changes (e.g., repeating questions), and even the need for nursing care. The third and final stage, the “advanced stage”, is characterized by patient dependency, inactivity, severe memory problems, physical problems (e.g., loss of sense of time and space), greater need for assistance and care, gait difficulties, and problematic behavioral changes such as aggressiveness. At this stage, family and acquaintances are often no longer recognized either (World Health Organization, 2021).

Förstl (2011) expands these three stages to four stages: "pre-stage", "mild", "moderate" and "severe" dementia. In the pre-stage, neuropsychological deficits are rarely recognized in those affected but impairments are hardly reliable in terms of prognosis. In particular, the storage of new information, action planning, and semantic memory is impaired, although those affected can still benefit well from supportive intervention techniques. Affected individuals rarely need help at this stage. MCI could be suspected at this stage. MCI patients usually show an increasing decline in the areas of orientation, short- and long-term memory, verbal, motor, constructive, and arithmetic deficits, with aphasia, apraxia, and orientation deficits, in particular, making AD progression likely. Förstl (2011) recommends regular examination of those affected with MCI (every 6-12 months). In the mild dementia stage (mild AD), cognitive deficits in everyday tasks, planned action, organization, and judgment become noticeable.

Deficits in language, drawing, and spatial orientation are prominent. Around 3 years after diagnosis, the moderate dementia stage begins. In addition to disturbances of the memory, deficits in logical thinking, planning, and acting and increasing linguistic problems become apparent. Affected persons are often more easily distracted, less aware of their illness, and no longer carrying out complex actions (e.g., eating, personal hygiene). Surrounding stimuli are recognized less often. Sometimes optical hallucinations develop. In addition to this disorientation, emotionality/aggressiveness, restlessness, and incontinence are increasing problems, and patients depend on social help. In the severe dementia stage, about 6 years after diagnosis, all cognitive functions are affected. Memories, language, and personal needs are lost. Stereotyped motor activity and disturbed circadian rhythms may occur. Patients are in total need of care at this point. In addition to AD symptomatology, neurological symptoms and other concomitant disorders may occur. Förstl (2011) suggests a life expectancy of 5-8 years after diagnosis, with patients frequently dying from pneumonia, myocardial infarction, or sepsis.

Furthermore, according to the Alzheimer's Association *Deutschland*, a seven-step classification of stages can be cited (Alzheimer's Association Deutschland, 2021). Stage 1 describes an “adequate functional level” without the presence of memory deficits and everyday restrictions. Level 2 represents only a "very slight reduced perceptual capacity", e.g., in the sense of subjective memory problems. Clinical differentiation between normal aging or pathological degenerative processes, indicative of AD development, is hardly possible at this stage. In stage 3, there would be a "slight diminished perceptual capacity", which is also recognized by the environment and sometimes already by doctors due to occurring memory and concentration difficulties. This stage is considered an early stage of AD, which sometimes remains undetected. Stage 4 describes a "moderate diminished perceptual capacity", i.e., apparent AD symptoms that can be diagnosed in a doctor's consultation, such as forgetfulness, affect lability, or deficits in performing complex tasks. This stage is also considered mild or early AD. Stages 5, 6, and 7 finally differentiate "medium diminished," "severe diminished," and "very severe diminished perceptual capacity" from each other in terms of moderate, moderately severe, and advanced AD. The characteristic of stage 5 AD is the need for support in everyday life with more pronounced memory deficits. In stage 6, known difficulties get more intense, and

usually, there are additional personality changes. In the last stage 7, daily care of the affected person is indispensable (e.g., help with food intake due to swallowing disorders), communication and movement are severely restricted.

A short comparison of the stepwise classification attempts of the characteristic AD progression described above can be found in Table 2.

At this point, additional reference should be made to the systematic review and meta-analysis by Parnetti et al. (2019) on AD progression across different stages for a more in-depth insight, but it will not be further elaborated within the scope of this thesis.

In the following, an overview of current diagnostic standards and treatment options for MCI/AD will be provided.

Table 2

Characteristic progressive stages of the AD.

World Health Organization (2021)	**Förstl (2011)**	**Alzheimer's Association Deutschland (2021)**
		adequate functional level
	pre-stage	very slight reduced perceptual capacity
early stage	mild dementia	slight diminished perceptual capacity
		moderate diminished perceptual capacity
middle stage	moderate dementia	medium diminished perceptual capacity
		severe diminished perceptual capacity
advanced stage	severe dementia	very severe diminished perceptual capacity

Note. AD = Alzheimer's Dementia/Disease; WHO = World Health Organization.

1.1.4 Diagnostics and therapy

1.1.4.1 Alzheimer’s Dementia/Disease (AD)

Since the beginning of AD research more than 100 years ago, diagnosis of AD has been difficult to this day, despite state-of-the-art research and brain imaging techniques, due to often ambiguous symptoms and the gradual progression of the disease as described previously (Hane et al., 2017).

Nevertheless, the internationally used differential diagnostic criteria of AD are mainly defined by the ICD-10 published by the WHO in chapter F00. To fulfill the diagnostic criteria of AD, the general presence of dementia must first be confirmed. It is described in the ICD-10 as "a consequence of a usually chronic or progressive disease of the brain with impairment of many higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning, language, and judgment" (Dilling & Freyberger, 2016, p. 24). Until late stages, awareness remains clear in dementia, e.g., in contrast to delirium. However, in addition to the decline in memory and other cognitive abilities such as judgment, dementia is often accompanied by altered affectivity, motivation, abnormalities in social contact, and impaired everyday life. In principle, the syndrome must be present for at least 6 months. Apart from AD, vascular dementias such as multi-infarct dementias or Binswanger's disease and dementias associated with other diseases such as Pick's disease or Lewy body dementia or frontotemporal dementias are among the most common subtypes (Dilling & Freyberger, 2016). Thus, it is evident that dementia is not a normal aging process, but a disease by itself (World Health Organization, 2021).

Because of the characteristic gradual progression of primary AD over many years, classification into subgroups is possible using the fourth position of the F code: F00.0 Dementia in AD with early-onset (corresponds to type 2 presence dementia with onset before age 65) and F00.1 Dementia in AD with late-onset (corresponds to type 1 senile dementia with onset after age 65). While type 2 AD usually progresses more rapidly and higher cortical dysfunction is imprinted, type 1 AD develops more slowly, and memory impairment is primarily evident. Additional F codes can be used to diagnose atypical, mixed, or unspecified forms of AD. In particular, the differential diagnosis should include consideration of other causes of dementia, e.g., neurologic focal signs to exclude vascular dementia or other conditions leading to secondary AD (e.g.,

Parkinson's disease). The ICD-10 also states that the etiology of AD is largely unknown, but typical neuropathological changes occur (see chapter 1.1.2). Thus, a definite diagnosis is still possible only post-mortem based on the findings of neurofibrillary tangles and neuritic plaques in addition to the ante-mortem symptomatic course (Dilling & Freyberger, 2016; Hane et al., 2017; Hyman et al., 2012).

Furthermore, in the context of dementia diagnostics, it is particularly important to take into account the S3 guideline of the *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (*AWMF), published by the *Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e.V. (*DGPPN) and the German Society for Neurology e.V. (DGN; Deuschl & Maier, 2016). The authors argue that the etiological differentiation of dementia via diagnostic criteria alone is insufficient.

A more comprehensive diagnostic care of patients must be ensured for the early detection of the disease. Therefore, a self/stranger/family and social anamnesis, including a vegetative and drug anamnesis, should be performed first to provide initial assessments of the development, course, and differential diagnosis.

In addition, physical, internal, neurological, and psychopathological examinations with a focus on cardiovascular, metabolic, and endocrinological diseases should be performed (Deuschl & Maier, 2016). For more specific measurability, as well as severity and progression of cognitive deficits, brief cognitive tests such as the Mini-Mental Status Examination (MMSE; Folstein et al., 1975), the Dementia Detection test (DemTect; Kalbe et al., 2004), the *Test zur Früherkennung von Demenzen mit Depressionsabgrenzung* (TFDD; Ihl et al., 2000) or the Montreal Cognitive Assessment Test (MoCA; Nasreddine et al., 2005) should be used. Diagnostic screenings are not recommended in the absence of symptoms but may be used, particularly in a medical care context and in persons at increased risk (Deuschl & Maier, 2016). For a more precise finding in the sense of differential diagnostic clarification, the short cognitive tests should be supplemented by neuropsychological diagnostics (Cullen et al., 2007; Deuschl & Maier, 2016). For example, the most significant procedures regarding AD include the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Moms et al., 1989), the *Regensburger Wortflüssigkeitstest* (RWT; Aschenbrenner et al., 2000), or the Free and Cued Selective Reminding Test (FCSRT; Grober et al., 1988). In addition, both the daily life impairment and psychological and behavioral

symptoms of the potential patients should be considered (Deuschl & Maier, 2016). For example, depressive symptoms can be assessed via questionnaires and self-ratings such as the Beck Depression Inventory (most recent version: BDI-II; Beck et al., 1996) or the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986).

For further differentiation of the dementia disease, extensive laboratory diagnostics should be carried out within the framework of serological and biochemical blood diagnostics, which record the following values, for example: electrolytes (natrium [Na], kalium [K], calcium [Ca]), fasting blood sugar, thyrotropin (TSH), blood sedimentation or c-reactive protein (CRP), glutamate-oxaloacetate-transaminase (GOT), gamma-glutamyltransferase (Gamma-GT), creatinine, urea, vitamin B12, folic acid. By this means, causes of dementia syndromes such as endocrinopathies, vitamin deficiency diseases, metabolic encephalopathies, intoxications, electrolyte disorders, hematological disorders, chronic infectious diseases, or late forms of leukodystrophies such as ceroid lipofuscinosis can be detected. For primary AD, however, no diagnostic blood markers are known so far (Deuschl & Maier, 2016). To detect AD and exclude inflammatory Central Nervous System (CNS) diseases as a cause of symptoms, Cerebrospinal Fluid Analysis (CSF) of neurodegeneration markers beta-amyloid-1-42, total-tau/tTau, and phospho-tau/pTau may also be performed.

Cerebral imaging techniques such as conventional cranial Computed Tomography (cCT) or cranial Magnetic Resonance Imaging (cMRI) and nuclear medicine techniques such as (amyloid) Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) may also help clarify the cause of dementia and etiologic differentiation of primary dementias (Deuschl & Maier, 2016). In about 5% of dementia patients, imaging studies can identify a treatable underlying cause such as a tumor (Deuschl & Maier, 2016; Gifford et al., 2000; Hejl et al., 2002). In the case of AD, for example, cMRI could provide an early indication of the characteristic progressive brain atrophy in the medial temporal lobe (Deuschl & Maier, 2016; Zakzanis et al., 2003). In addition, Electroencephalography (EEG) can detect, for example, a slowed baseline rhythm in AD patients and thus be an asset in differentiating neurodegenerative and non-neurodegenerative dementias (Andersson et al., 2008; Deuschl & Maier, 2016). Especially in the field of vascular dementias, doppler and duplex examinations in the context of sonography of the vessels supplying

the brain may be indicated for the identification of stenoses (Ackermann et al., 2012; Deuschl & Maier, 2016).

Finally, molecular genetic diagnostics can be performed if patients are suspected of being genetically vulnerable. However, according to the guideline, no causal therapy or prevention options result from this. Also, the determination of the apolipoprotein-ε genotype is not suggested due to low discriminatory power and low predictive value (Deuschl & Maier, 2016; Mayeux et al., 1998; Thies et al., 1999).

Pharmacological interventions still represent the primary therapy for AD. According to the expert consensus of the AWMF, pharmacological treatment should be considered after unsuccessful or insufficient, or unavailable psychosocial interventions, as well as in cases of danger to self or others (Deuschl & Maier, 2016). Today, approved antidementives are considered effective for the treatment of AD symptoms and influence the progression of the disease but do not cure or even have a preventive effect (Breijyeh & Karaman, 2020; Cummings et al., 2019; Deuschl & Maier, 2016). To date, acetylcholinesterase inhibitors such as donezepil (Aricept®, Aricept Evess®, generics), galantamine (Reminyl®, generics), and rivastigamine (Exelon®, Exelon transdermales plaster®, generics) have been approved for the pharmacological treatment of mild to moderate AD symptoms. The mode of action of these drugs is based on the acetylcholine hypothesis of AD (see chapter 1.1.2), which assumes underactivity of cholinergic neurons and a reduction of the synthesizing enzyme choline acetyltransferase. This can lead to cognitive deficits in the course of the disease, e.g., in memory, attention, sensory information processing, and learning processes. Therapy with acetylcholinesterase inhibitors increases synaptic availability (Breijyeh & Karaman, 2020; Deuschl & Maier, 2016; Köhler, 2008). On the other side, antagonists of the N-methyl-D-aspartate (NMDA) for glutamate such as memantine (Axura®, Ebixa®, generics) are approved not only for the treatment of moderate but also for the treatment of severe AD symptoms in, e.g., neuronal disorders. In addition, the blockade of NMDA receptors, which release glutamate during the cell death typical for AD, can slow down AD pathogenesis (Breijyeh & Karaman, 2020; Deuschl & Maier, 2016; Köhler, 2008). Often, therapy with memantine is given as an add-on treatment in AD patients with severe symptoms after treatment with donezepil (Deuschl & Maier, 2016).

Less effective may be the use of nootropics without an explicit effect on acetylcholinesterase inhibition, such as Ginkgo biloba (Tebonin®, Kaveri®, Rökan®, generics), nimodipine (Nimotop®, Nimotop S®, generics), piracetam (Nootrop®, generics), and pyritinol (Encephabol®). These preparations have, for example, a circulatory effect, possibly an antioxidant effect, block calcium channels, possibly act on the gamma-amino-butyric acid (GABA)-ergic system, or improve glucose utilization (Deuschl & Maier, 2016; Köhler, 2008). Considering the recommendations of the AWMF, only Ginkgo biloba should be considered as a pharmacological therapy (Deuschl & Maier, 2016).

Ultimately, however, the pharmacological treatment of AD is always a symptom-specific treatment, which is why, for example, antidepressants, anxiolytics, anticonvulsants, or antipsychotics are often used (caution: interactions with acetylcholinesterase inhibitors!). Remarkable is the failure rate of clinical drug trials in the last years, with about 99.6% (Anderson, 2019; Cummings et al., 2014; L. S. Schneider et al., 2014). An overview of drugs already tested in the past in terms of dementia and AD prevention, such as statins, antihypertensives, non-steroidal anti-inflammatory drugs, hormone replacement therapies, and other nutraceuticals, is also provided by, e.g., Mangialasche et al. (2012). However, significant protective effects of these drugs were absent in Randomized Controlled Trials (RCTs). More recently, aducanumab (Aduhelm®), a human antibody that selectively targets pathological Aβ-plaques typical of AD, was also considered promising (Sevigny et al., 2016). However, controversial findings on efficacy, as well as side effects such as brain bleeding and swelling in up to 40% of high-dose patients, put these hopes into perspective despite recent approval (Fleck, 2021).

In addition to pharmacological therapy, psychosocial interventions such as cognitive procedures, ergotherapy, physical activities, artistic therapies, sensory procedures, specific interventions (e.g., for characteristic swallowing disorders), and family work can play a role in AD therapy. In particular, the cognitive techniques (e.g., cognitive training, stimulation, rehabilitation, reminiscence) are of great importance for the psychotherapeutic treatment of AD patients (Deuschl & Maier, 2016). A successful example of cognitive reality orientation trainings (ROTs) is the one according to Taulbee and Folsom (1966), which aims to train patients' temporal, spatial, and social orientation and memory skills. The effectiveness of the training has been proven by

numerous RCTs (Spector et al., 2000). Cognitive Stimulation Therapy (CST), which additionally includes reminiscence and multisensory stimulation, is considered a newer form of ROT training (Aguirre et al., 2013; Camargo et al., 2015; Rai et al., 2018; Spector et al., 2008). Recent minimally invasive approaches also report positive effects for the method of deep brain stimulation, e.g., of the nucleus basalis Meynert (see again: acetylcholine hypothesis, or chapter 1.1.2) and the Papez circuit with pathways between fornix and hippocampus (=limbic system) in the therapy of neurodegenerative diseases, thereby also early AD disease phases (Daniels et al., 2020; Hardenacke et al., 2016; Lozano et al., 2016; Lozano et al., 2019).

1.1.4.2 Mild Cognitive Impairment (MCI)

MCI patients are considered as a high-risk group for AD progression (Portet et al., 2006), because in addition to benign age-related forgetfulness, numerous patients develop AD as they progress (Förstl, 2011). Nevertheless, to this day MCI criteria are defined inconsistently (Deuschl & Maier, 2016; Matthews et al., 2008). Therefore, the assessment of whether MCI is present is based on clinical impression, progression, etiologic factors, degenerative lesions, vascular factors, psychiatric disorders, and non-neurologic comorbid conditions (Portet et al., 2006; Ritchie et al., 2001). Generally characteristic is a memory loss in the areas of short-term memory, comprehension, and attention, which cannot be explained by age alone and does not yet meet dementia criteria (Förstl, 2011; Portet et al., 2006). Phenomenologically, reduced quality of life, increased depressive symptoms, and often a social withdrawal are possible, whereby psychosocial deficits are often experienced subjectively but not objectively (Anderson, 2019; Förstl, 2011).

The development of current MCI criteria proceeded in several steps and is heterogeneous to date (Cooper et al., 2015; Petersen, 2016).

A reference to MCI as such was first made in 1979 via the "global deterioration scale", and the term was first used in 1988 (Petersen, 2016; Reisberg et al., 1988). Petersen et al. (1999) were the first to define the criteria of MCI, the "Mayo Criteria", more than two decades ago. They included: 1. subjective memory complaints, at best reported by the affected person and an informant, 2. objective impairment of memory (not explainable by age and education), 3. normal general level of functioning, 4. normal

daily activity level, and 5. no evidence of dementia. The later "Key Symposium criteria" differentiated four subtypes of MCI of different etiologies for the first time (Petersen, 2004; Petersen, 2016). To date, MCI patients can thus be classified into an amnestic or non-amnestic subtype and, depending on the number of impaired cognitive domains, into single- or multiple-domain subtype respectively (Anderson, 2019; Petersen, 2016). In particular, the subtype of amnesic MCI that involves impaired episodic memory is considered predictive of AD progression (Cooper et al., 2015).

In parallel, the concept of prodromal AD developed in 2007, describing amnestic MCI with adequately detectable biomarkers as a precursor to AD (Dubois et al., 2014; Petersen, 2016).

In addition, the research group around Portet et al. (2006) also described feasible diagnostic criteria of MCI in collaboration with the MCI working group of the European Consortium on Alzheimer's disease, which largely overlap with the criteria of Petersen et al. (1999), but are understood as their modification or further development: 1. Subjective cognitive impairment reported by the patient or their families, 2. decline in cognitive functioning level over 1 year reported by the patient or their families 3. objective cognitive impairment as determined by a clinician (memory or other cognitive domains), 4. no massive impairment in daily functioning level, and 5. no evidence of dementia. In addition, the authors extended the concept of MCI subtypes first to include classification at syndrome level and subsequently at etiopathogenetic level, which predicts AD progression.

Later, in 2011, these criteria were also further specified for research by the National Institute on Aging (NIA) and the Alzheimer's Association, for example, by pathophysiological biomarkers, etiological, and predictive additions, but without distinguishing by subtype (Albert et al., 2013; Petersen, 2016; Sperling et al., 2011). Clinical criteria included 1. subjective memory problems (reported by the patient, an informant, or a clinician), 2. objective impairments in at least one cognitive domain that could not be explained by age or education, 3. independent functional abilities, and 4. no evidence of dementia (Albert et al., 2013). Thus, for the first time, preclinical AD, MCI, and AD were differentiated (Hickman et al., 2016; Petersen, 2016). In particular, the preclinical phase has been considered a leading finding for research in MCI since the early days of MCI research (Braak & Braak, 1997). Following the entry of MCI into lexicons or further research by the International Working Group on MCI (Dubois et al.,

2010; Winblad et al., 2004), the MCI criteria ultimately found their way into the international diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders – 5th version (DSM-5) as part of the “Neurocognitive Disorders” (NCD) chapter as "Mild Neurocognitive Disorder" in 2013 (=mild NCD; American Psychiatric Association, 2014; Sachs-Ericsson & Blazer, 2015). These criteria included: 1. cognitive decline in at least one cognitive domain (reported by the patient, an informant, a clinician, or elicited by objective testing), 2. subjective functional independence, 3. the abnormalities exist outside delirious episodes, 4. the cognitive impairments cannot be better explained by other conditions (e.g., depression), and 4. no evidence of dementia. Thus, the DSM-5 did not make a direct AD reference in the criteria but titled AD as a "Major Neurocognitive Disorder" (=major NCD) and differentiates from delirium (Petersen, 2016). To date, MCI can also be found in the ICD-10 in F06.7 as “Mild Cognitive Disorder”. To justify a diagnosis, the ICD-10 requires the presence of a subjective cognitive impairment for at least two weeks, reported by the individual or an informant, and related to at least one of the cognitive domains of memory (relearning or new learning), attention and concentration, thinking (deficits in problem solving or abstraction), language (word comprehension and finding), or visual-spatial functions.

Diagnostics should comprise neuropsychological assessment of, for example, memory, attention, or visual-spatial abilities, as well as paraclinical investigations, laboratory tests, imaging procedures to assess hypoperfusion and metabolism (Anderson, 2019; Burns & Zaudig, 2002). In addition to the medical and psychosocial anamnesis, diagnostics are therefore of great importance. A cognitive screening method alone should not be used to make a diagnosis, although there is no standardized test battery for MCI diagnostics to date (Anderson, 2019). In general, a combination of the tests recommended for AD diagnostics should be performed (Deuschl & Maier, 2016).

Therapeutically, like AD therapy, the focus is often on modifiable risk factors and cognitive functioning levels to maintain mental health or promote cognitive reserve (Anderson, 2019; Petersen et al., 2018). Again, there is much overlap with the therapeutic options for AD. Medication is often given as off-label use of acetylcholinesterase inhibitors or memantine (Roberts et al., 2010).

Recent biomarker research provides evidence that may contribute to improved individual prediction of the risk of developing dementia as a sequel to MCI diagnosis

(Rostamzadeh & Jessen, 2020; see also chapter 1.1.2). Relevant biomarkers relate to amyloid pathology (“A markers”; β-amyloid1-42 and β-amyloid42/40 ratio), tau pathology (“T markers”; pTau and tTau), and neurodegeneration (“N markers”; atrophy of the medial temporal lobe and hippocampus, reduction in cortical thickness, glucose hypometabolism in the medial parietal lobe and tempoparietal and frontal brain regions; C. R. Jack et al., 2016; C. R. Jack Jr. et al., 2013; C. R. Jr. Jack Jr. et al., 2018). While amyloid deposits can already be detected preclinically via CSF or PET diagnostics and later also pathological tau deposits beyond the temporal lobe, clinical symptoms become measurable in the stage of neurodegeneration on the basis of Magentic Resonance Imaging (MRI; atrophy) or FDG-PET diagnostics (functional abnormalities; Braak & Braak, 1991; Rostamzadeh & Jessen, 2020). By means of detection or exclusion of corresponding AD pathology in MCI patients, statements can thus be made not only about the probability of developing dementia, but also about the disease course. Thus, the aim is to divide the MCI risk group into groups with low, middle, and high risk of developing dementia (Handels et al., 2017; Herukka et al., 2017; Rostamzadeh & Jessen, 2020; Shaw et al., 2018; Vos et al., 2015). Approximately 10% of MCI patients with inconspicuous CSF biomarkers develop AD within 5 years, whereas 45-50% develop AD in the presence of only one pathologic CSF biomarker (amyloid or tau deposits) and up to 90% develop AD in the presence of both pathologic biomarkers (amyloid and tau deposits; Vos et al., 2015).

Currently, the described diagnostic approach is applied and evaluated solely in research, and methodological standards or normative values do not yet exist (Vos et al., 2015). Likewise, the validity of various predictive models is still being researched, which is also a reason why CSF should not be applied as a stand-alone diagnostic method for individual diagnoses (Martínez et al., 2017; van Maurik et al., 2019; van Maurik et al., 2017; Zhang et al., 2014). The S3 guidelines of the AWMF described in chapter 1.1.4.1 so far recommend CSF diagnostics in dementia, but not with regard to biomarker-based early AD detection and dementia prediction in case of already existing MCI diagnosis (Deuschl & Maier, 2016).

Despite all existing diagnostic and therapeutic possibilities presented up to this point, it should be emphasized once again that AD is still a disease that cannot be cured. Only symptom improvement or slowing down of the progressive course is possible (Sun et al., 2018). Approximately one in three seniors still dies from the complications

of dementia today ("2021 Alzheimer's disease facts and figures", 2021). This high mortality rate results, for example, from malnutrition or bedriddenness and the resulting infections, lung problems, or cardiovascular diseases (Stiftung Gesundheitswissen, 2018).
This knowledge and the high prevalence of MCI and AD, in turn, highlight the absolute need for early detection of AD or possible prodromal syndromes such as MCI.

1.2 The need for early detection

1.2.1 Neurodegenerative decline and healthy aging

The differentiation between normal and pathological aging processes is essential for adequate early detection of neurodegenerative brain degradation. Even healthy seniors show age-related altered but robust performance levels in various cognitive-neuropsychological domains such as working memory, executive functions, and processing speed (Sperling et al., 2011; Toepper, 2017). But also various neuroanatomical and -chemical modifications, e.g., of the gray and white brain matter, brain structures, cerebral activation patterns and brain functions, are common in healthy seniors (Toepper, 2017).
However, in contrast to a normal healthy aging process, some pathogenetic features detectable post-mortem for AD development (chapter 1.1.2) may develop without any clinical symptoms identifiable ante-mortem via neuropsychological diagnostics in affected individuals (Arenaza-Urquijo & Vemuri, 2018; Hane et al., 2017; Hyman et al., 2012; Mormino & Papp, 2018). On the one side, this explains the characteristic, long preclinical phases of AD, which are crucial for early detection. Still, it equally highlights those individual differences in seniors have a seminal influence on their aging process (Sperling et al., 2011). Aging should not be viewed as some stable, permanent condition, but rather as a condition that can be influenced and treated and that can be both slowed and reversed (Isaev et al., 2019; Katsimpardi & Lledo, 2018). Healthy aging, for example, can be defined as a lifelong maturation process within which there are ongoing adjustments in mental abilities (R. Martins et al., 2015). In this context, in addition to looking at risk factors and predictors of AD (chapter 1.2.3) it is particularly rewarding to differentiate between protective and resilience factors in older people.

Commonly defined as a person's hardiness, “resilience” describes coping with an existing pathological change (Arenaza-Urquijo & Vemuri, 2018; James & Bennett, 2019). Thus, the resilience concept goes beyond the simple idea of failing disease processes by describing adaptive mechanisms on a biological basis (Russo et al., 2012). To illustrate this concept, the so-called „Positive Appraisal Style Theory of Resilience“ Model (PASTOR Model), according to Kalisch et al. (2015), can be cited as an example: The authors describe a connection between the positive appraisal of stressors, successful stress coping, and thus an increase in resilience.

“Resistance”, in contrast, can be used as a concept of healthy aging in the absence of underlying pathology (Arenaza-Urquijo & Vemuri, 2018). However, the idea of “cognitive reserve”, first defined by Stern (2002), is particularly relevant for differentiating healthy and pathological aging models. It describes functional and interindividual differences between pathological neurodegeneration and clinical expression of symptoms. Individual but passive physical processes and characteristics (=”brain reserve”) or active coping attempts to compensate for deficits can be distinguished (=”cognitive reserve”). While the cognitive reserve is further characterized by the use of neuronal networks to perform typically or improved, neuronal compensatory mechanisms are distinguished from it, i.e., the use of neuronal networks that would not have been actively used in the absence of neurodegeneration (R. Martins et al., 2015; Stern, 2002, 2009, 2012; Stern et al., 2020; Stern et al., 2019; Stern & Barulli, 2019). Thus, the concept of the cognitive reserve should be considered primarily in the field of epidemiological investigations and in the application of imaging techniques and should be embedded in the context of aging and dementia development (Stern, 2002; Stern & Barulli, 2019).

In recent research, "brain maintenance" is also increasingly used (Cabeza, Albert, et al., 2018; Nyberg, 2017; Nyberg et al., 2012; Stern et al., 2019). It describes the influence of life experience and genetics on brain reserve maintenance, explaining why some people are better than others at maintaining brain function as they age. Thus, this is an evolving process over the lifespan, but one to which great importance is attached, particularly in old age (Cabeza, Albert, et al., 2018; Nyberg et al., 2012; Stern et al., 2019).

Based on the neural compensation hypothesis, many models and assumptions about aging processes have emerged over time, of which some central models will be briefly presented below.

The so-called "Hemispheric Asymmetry Reduction in Older Adults" Model (HAROLD Model) describes an under comparable conditions decreasing lateralization of Prefrontal Cortex (PFC) activity during the performance of cognitive tasks in older compared to younger people. Furthermore, the model assumes that the increasingly symmetrical hemispheric PFC activity represents a compensatory mechanism that maps age-related cognitive deficits and/or describes problems of de-differentiation of neuronal mechanisms (Cabeza, 2002; Cabeza et al., 2002). In doing so, the authors integrated psychological and neuroscientific findings of aging from the fields of functional imaging and the cognitive domains of episodic, semantic, and working memory, perception, and inhibitory control into the HAROLD model. Therefore, compensatory mechanisms are thought to have both a cognitive and neuronal origin. Recent studies also confirm, for example, an age-related reduction in asymmetric PFC activity in terms of lower activity in the left PFC during verbal working memory tasks and lower activity in the right PFC during spatial working memory tasks toward bilateral activation (Kirova et al., 2015).

An expansion of the HAROLD model is the “Posterior-Anterior Shift in Aging” Model (PASA), according to N. A. Dennis and Cabeza (2008), which is due to Grady et al. (1994). The key message of the model is that an age-related decrease in brain activity in the occipital lobe is observable with a concomitant increase in PFC activity, particularly in visual perception (S. W. Davis et al., 2008; R. Martins et al., 2015). Thus, the PASA also implies the presence of age-related compensatory mechanisms. Recently, moreover, the "load-shift" or “Early-to-Late Shift in Aging” Model (ELSA) has also found application in the aging research, which describes the spatiotemporal partitioning of brain activity in different brain areas, but especially the PFC, as a strategy shift in older people. Here, it is hypothesized that due to deficient top-down retrieval processes (e.g., executive functions) in the PFC, older individuals resort to other brain areas, such as the medial-temporal temporal lobe, as a compensatory mechanism at a later time (Dew et al., 2012; Grandi & Tirapu Ustárroz, 2017; Velanova et al., 2007).

Another compensation model that considers not only the elderly but also the young when exploring compensation mechanisms is called the “Compensation-Related Utilization of Neural Circuits Hypothesis” (CRUNCH) and dates back to Reuter-Lorenz and Lustig (2005), Reuter-Lorenz and Cappell (2008), and Cappell et al. (2010), respectively. It describes higher cortical brain activation with increasing task difficulty in, for example, visual-spatial paradigms. In older people, according to this model, a reverse effect in terms of compensatory overactivation is also observable. Moreover, older people would need to recruit a higher number of neuronal resources than younger people, even at less demanding levels, to achieve the same cognitive performance (Jamadar, 2020; R. Martins et al., 2015). Accordingly, resources available earlier in life are limited in older people, leading to the "CRUNCH point" at which brain activity and performance decline or stagnate unchanged (R. Martins et al., 2015). However, especially in samples of healthy people, the CRUNCH model is considered controversial and relatively under-researched (Jamadar, 2020).

Also known as a compensation hypothesis is the “Temporal Hypothesis for Compensation” (THC), which attributes an age-related temporal delay in brain activity as the causal factor for deficits in cognitive processing. Although this theory also focuses on the PFC and frontostriatal circuits, it emphasizes the relevance of the temporal aspect of when instead of where brain activation occurs. The resulting shift of proactive to reactive control strategies, in addition to functional modifications in cerebral activation patterns, also cause the maintenance of cognitive performance at slower processing speeds (R. Martins et al., 2015).

The "Compensatory Recruitment Hypothesis" can be described similarly, which assumes, especially in AD patients, that neuronal deficits in one brain area can be compensated for by recruiting other brain areas to the extent that, given sufficient neuronal resources, even a task performance comparable to that of healthy people can continue to be performed (Prvulovic et al., 2002; Thulborn et al., 2000).

Finally, the "Scaffolding Theory of Aging and Cognition" (STAC Model), according to Park and Reuter-Lorenz (2009), will be described as an integrative model of the aging brain that summarizes the hypothesis, theories, and models presented above: Characteristic of aging processes, they argue, is increased frontal brain activation as an indication of adaptive processes in the brain to cope with increasingly deficient neuronal structures and functions. This is an indication of the presence of

compensatory mechanisms (="cognitive scaffolding"). "Scaffolding" thereby represents a "normal" way of dealing with challenges and a lifelong process to achieve cognitive goals via the dynamic and adaptive use of complementary neuronal resources. The origin of "scaffolding" is localized in the PFC. The authors suggest that "scaffolding" is likely to be promoted by cognitive flexibility and practice. The authors' extension of the STAC model, the revised STAC-r, published 5 years after initial publication, includes life course factors in addition to lifespan factors that may enhance neuronal resources or functional and structural cognitive "scaffolding" on the one hand (e.g., intellectual engagement) and contribute to resource depletion on the other (Reuter-Lorenz & Park, 2014).

In summary, the exploration of different brain areas is highly relevant for studying healthy and pathological aging. Ultimately, however, research on the cognitive abilities of the aging brain is also always worthwhile from a holistic perspective, e.g., by observing functional connectivity between the different brain areas (see also "Process-Specific Alliances" [PSAs]; Cabeza, Stanley, et al., 2018). Presumably, plasticity, density, and connectivity of neurons are decisive for performance and functionality in individuals, not only the mere number of neurons (Stern & Barulli, 2019). Research in this regard is made possible, for example, using brain imaging techniques or neuropsychological/-psychiatric test diagnostics. Therefore, an overview of the brain imaging technique functional Near-Infrared Spectroscopy (fNIRS) follows.

1.2.2 Functional near infrared spectroscopy (fNIRS)

As discussed in chapter 1.1.3, early neurodegenerative processes and prodromal altered brain activity often emerge many years before diagnostically measurable symptoms during the preclinical phase, making early detection of MCI and AD even more important. In this context, the identification of objective biomarkers can help uncover indicators of neurodegeneration with high prognostic and diagnostic value (Nestor et al., 2004). Biomarkers are physiological, biochemical, or anatomical variables that can be measured in humans in vivo and can precisely characterize pathological changes, for example, through analysis of CSF, Aβ concentrations, amyloid tracer methods, a genetic mutation analysis, or the use of imaging techniques

(DeKosky & Marek, 2003; Hickman et al., 2016; Lloret et al., 2019; Parnetti et al., 2019).

In addition to the potential of imaging techniques, it is also essential to consider the practical applicability in previously inconspicuous study participants, especially in early detection. As an economical and practicable as well as non-invasive and thus also low-risk technique, fNIRS offers itself as an examination method for the measurement of cerebral blood flow based on optical properties of hemoglobin, which will be presented below.

1.2.2.1 Development

In 1977, Frans Jöbsis first reported the possibility of detecting changes in hemoglobin (Hb) oxygenation in the cortex via noninvasive real-time measurements using near-infrared light (="transillumination spectroscopy"; Jöbsis, 1977). In subsequent years, this resulted in numerous animal, infant, and adult (collaborative) studies aimed at determining hemodynamic changes in oxygenated ([O2Hb]), deoxygenated ([HHb]), and total hemoglobin ([tHb]), cerebral blood volume (CBV), and CBF (Ferrari, De Marchis, et al., 1986; Ferrari et al., 1982; Ferrari et al., 1980; Ferrari et al., 1985; Ferrari & Quaresima, 2012; Ferrari, Zanette, et al., 1986; Giannini et al., 1982; Reynolds et al., 1988; Wyatt et al., 1990). Thus, in 1989, a commercial imaging system, the single-channel, and multi-trial Continuous Wave (CW) system NIRO-100 of Hamamatsu Photonics K.K. was marketed for the first time (Hamamatsu City, Japan). This system emitted near-infrared light constantly and used optodes to detect light absorption and thus hemoglobin changes from [O2Hb] to [HHb] (Agbangla et al., 2017; Ekkekakis, 2009; Ferrari & Quaresima, 2012; Villringer & Chance, 1997). Subsequently, in 1993, almost 30 years ago, the first six fNIRS studies involving adult subjects with measurements at a single site were published, marking the beginning of fNIRS research (Chance et al., 1993; Ferrari & Quaresima, 2012; Hoshi & Tamura, 1993a, 1993b; Kato et al., 1993; Okada et al., 1993; Villringer et al., 1993). By developing multi-channel systems, numerous high-density systems and single-trial stimulations have emerged to date suitable for multimodal imaging, complex data analysis, and the establishment of cortical activation patterns (Ferrari & Quaresima, 2012). An example of a modern fNIRS system that measures hemodynamic response using two different

wavelength ranges (695 ± 20nm, 830 ± 20nm) is the Hitachi ETG-4000 (Hitachi Medical Corporation, Japan). Higher wavelength spectra are well suited for differentiation of [O_2Hb], lower ones for differentiation of [HHb]. The depth of light irradiation is thereby dependent on the optode positioning on the elastic hood, divided into emitters and detectors. The coverage of the cortical region is thus variable (Bunce et al., 2006). Multi-channel systems with numerous optodes are considered to have higher resolution (Obrig & Villringer, 2003). The method provides a temporal resolution of approximately 10 Hertz (Hz; Hamaoka & McCully, 2019).

1.2.2.2 Mode of operation

Optical methods can measure physiological brain activity. An increase in neuronal activity is characterized by increased glucose and oxygen depletion from the local capillary bed. Consequently, the so-called neurovascular coupling occurs: If the local glucose and oxygen stores are reduced for a short time (="initial dip" after approximately 1-2 seconds; Bunce et al., 2006; A. J. Fallgatter et al., 2004; Huppert et al., 2006), the brain reacts with local arteriolar vasodilation, which increases the local CBF and the CBV for approximately 5-6 seconds (Cui et al., 2010). Also within seconds, the increased CBF provides transport of glucose and oxygen to activated areas of the brain. The resulting increased oxygenated hemoglobin in the blood leads to an excess of cerebral blood oxygenation in activated brain areas (Bunce et al., 2006; Fox et al., 1988). A few seconds later, the hemodynamic response is again comparable to baseline levels (Villringer & Chance, 1997). This progression is similar to the hemodynamic "blood-oxygenation level dependent" (BOLD) response known from functional magnetic ressonance imaging (fMRI).

Near-infrared light in the range of 650-950nm is suitable for measuring physiological changes (Bunce et al., 2006; Obrig & Villringer, 2003). Water, as the main component of blood and tissue, absorbs little energy under these wavelengths, but the chromophores oxy-Hb and deoxy-Hb absorb much energy (="optical window"; Ferrari & Quaresima, 2012; Jöbsis, 1977; Scholkmann et al., 2014). Photons entering via the scalp and cranial dome are both elliptically scattered and absorbed on their way back to the scalp, and the number of backscattered photons can be measured in a readily predictable manner using photodetectors on the scalp. Wavelengths that maximize

chromophore absorption result in changes in the number of photons absorbed and backscattered, and therefore in altered light intensity at the surface of the scalp. Using empirical quantification of the optical attenuation of radiation in strongly scattering matter, the modified Beer-Lambert law (Cope, 1991; Cope & Delpy, 1988; Delpy et al., 1988), the hemodynamic response or brain activity of humans is measurable through the intact skull (Bunce et al., 2006; Hamaoka & McCully, 2019; Scholkmann et al., 2014). The selection of the wavelengths is additionally relevant because of the different optical absorption spectra of the chromophores [O_2Hb] and [HHb] to minimize the so-called "cross-talk" and to ensure a more reliable measurement (Hoshi, 2007).

1.2.2.3 Strengths and weaknesses

The application of the fNIRS technique is particularly interesting because of its numerous advantages to the comparatively few disadvantages. For example, the use of fNIRS allows study participants to make noninvasive measurements that are repeatable and can provide real-time (<1 second) resolutions (Ferrari et al., 2004; Gratton & Fabiani, 2001; Hoshi, 2007; Hoshi, 2011). Measurements can take place in the natural environment of the study participants and, accordingly, involve fewer movement restrictions than, for example, an fMRI or PET measurement. This is also facilitated by available portable and wireless fNIRS devices (Agbangla et al., 2017; Ekkekakis, 2009; Hoshi, 2007; Hoshi, 2011; Lloyd-Fox et al., 2010). In this context, measurements are usually motion resistant due to the multi-channel wireless fNIRS systems (Agbangla et al., 2017; Grassi & Quaresima, 2016; Perrey & Ferrari, 2018), allowing, for example, even muscle oximetry measurements during exercise (Piper et al., 2014). The fNIRS is a fast, quiet method with an acceptable signal-to-noise ratio (Agbangla et al., 2017; Ekkekakis, 2009; Lloyd-Fox et al., 2010). All these advantages promote the tolerance of the measurement method among study participants (Chen et al., 2020).

Similarly, the fNIRS application is beneficial for researchers because an measurement can be easily combined with other imaging techniques to measure different types of brain activation (metabolic, electrical) and check functional connectivity (=multimodality; Agbangla et al., 2017; Anwar et al., 2016; Giacometti & Diamond, 2013; Hoshi, 2007; Hoshi, 2011; Peng et al., 2014). This advantage is supported by

numerous comparative and correlation studies with other imaging modalities in the past (Anwar et al., 2013; Cui et al., 2011; Obrig & Villringer, 2003; Okamoto et al., 2004; Strangman, Boas, et al., 2002; Strangman, Culver, et al., 2002) and studies on the reliability of fNIRS data (Hoshi, 2003; Plichta et al., 2007; Plichta et al., 2006). In addition, fNIRS is considered cost-effective and easier to apply than other imaging techniques due to its non-ionizing technique (Chen et al., 2020; Ferrari et al., 2004; Perrey, 2008).

Finally, to date, fNIRS is the only imaging technique that measures [O_2Hb] and [HHb] changes (Leff et al., 2011). The precise fit to the thesis research question is additionally provided by the consistent findings supporting the suitability of fNIRS for the study of aging and ecological measurement of cognitive paradigms (Agbangla et al., 2017; Ferreri et al., 2014).

The disadvantages of the method include the characteristic selective and quantitative data collection (Hoshi, 2007). Thus, [HHb] changes cannot be quantified, leading to limitations in clinical and research settings (Hoshi, 2011). Deficits in anatomical specificity should also be considered. Despite the described real-time resolutions in fNIRS, a comparatively lower temporal resolution is achieved than, for example, in EEG (e.g., up to 100Hz in fNIRS, up to 1000Hz in EEG). Nevertheless, temporal resolution in fNIRS is higher than in fMRI, which is particularly advantageous for identifying neurovascular coupling. In contrast, the spatial resolution of fNIRS is lower than in fMRI or PET, for example, depending on the number of detection optodes and light scattering from emitter to detector (about 1-3cm), but again higher than in EEG. Similarly, as is common in other imaging modalities, anatomical images cannot be obtained from fNIRS measurements (Lloyd-Fox et al., 2010; Strangman, Boas, et al., 2002; Strangman, Culver, et al., 2002). Further, measurements of deeper brain structures such as the diencephalon are not possible using fNIRS techniques (except neonates; Agbangla et al., 2017; Bunce et al., 2006; Chen et al., 2020; Hoshi, 2007; Perrey, 2008; Strangman, Boas, et al., 2002; Strangman, Culver, et al., 2002). Due to the characteristics of fNIRS, limitations in intraindividual reproducibility due to environmental factors must be expected in some cases (e.g., ambient light, hair density, and color altered light transmission, skull thickness, head movement; (Agbangla et al., 2017; Chen et al., 2020; Ferrari et al., 2004; Lloyd-Fox et al., 2010; Perrey, 2008). At this point, again, a potential cross-talk as described above should be

mentioned (Hoshi, 2007). In the next step, it is important to note that no standard data analysis procedures exist for the fNIRS method as for fMRI and PET (Hoshi, 2007; Hoshi, 2011). This poses the risk of overestimating signals due to, for example, blood flow changes in the skin (Agbangla et al., 2017; Kirilina et al., 2012; Takahashi et al., 2011).

It can be summarized that within the last 30 years, significant progress has been made in developing fNIRS systems, which further strengthened the advantages of the application of the fNIRS. To date, despite some disadvantages, the application of fNIRS holds numerous advantages over other imaging techniques. Thus, it can be assumed that fNIRS will continue to have great potential in the future, both in brain function research and in the clinical field, e.g., for diagnostic purposes (Hoshi, 2007; Hoshi, 2011; Scholkmann et al., 2014). Thus, promising research findings can be expected, especially in the early detection of MCI and AD.

1.2.2.4 Application and current research

Even in the healthy aging process, impairments of the CBF occur due to impaired cardiovascular functions and concomitant homeostatic disruption of the neuronal microenvironment. However, in the development of MCI or AD, an excessive decrease in cerebral and cardiovascular functions is observable in that cerebral hypoperfusion, increased CBF pulsatility, and impaired blood pressure control are apparent (Tarumi & Zhang, 2018; Yeung & Chan, 2020). Due to oxidative enzyme damage that develops, there is subsequently an equally reduced glucose metabolism (Butterfield & Halliwell, 2019). These processes accelerate and chronify neurodegenerative processes such as Aβ accumulation, tau hyperphosphorylation, synaptic dysfunction, neuronal loss, white matter lesions, or neuroinflammation (J. C. de la Torre, 2012; Zhao & Gong, 2015). In addition to the reduced hemodynamic response, there is altered neurovascular (un-)coupling (Kisler et al., 2017; Yeung & Chan, 2021).

Thus, current research mostly reports a reduced hemodynamic response in MCI/AD patients (Arai et al., 2006; M. J. Herrmann et al., 2008; Hock et al., 1997; Yeung & Chan, 2020; J. B. Zeller et al., 2010). Strikingly, reduced lateralization (A. Fallgatter et al., 1997) and increased superior (parietal) brain activity (Vannini et al., 2007; Vannini et al., 2008) were often described.

To date, fNIRS has been used in numerous studies using various tests and paradigms to examine neuronal activation patterns in elderly participants or MCI and AD patients. For example, the successful use of this imaging technique has been reported using the Stroop and Trail Making test (Blum et al., 2021; Ehlis et al., 2005; Hagen et al., 2014; Müller et al., 2014; Shibuya-Tayoshi et al., 2007). However, in addition to neuroscience research, the practical application of fNIRS in clinical settings is becoming increasingly popular (Scholkmann et al., 2014). For example, cognitive deficits have been revealed in depressed patients (Rosenbaum et al., 2016) or patients with neurodegenerative diseases such as Parkinson's disease (Hofmann et al., 2021) and, increasingly, AD. Thereby, in the field of AD research, the focus has mostly been on fNIRS application during word fluency tasks (Arai et al., 2006; A. Fallgatter et al., 1997; M. J. Herrmann et al., 2008; Hock et al., 1997; Katzorke et al., 2017; Katzorke et al., 2018; Richter et al., 2007). For example, Metzger et al. (2016) reported significant frontoparietal and dorsolateral prefrontal hypoactivity in 8 AD patients compared with 8 healthy controls. According to the authors, this was indicative of pathophysiological mechanisms during neurodegenerative progression.

However, visual-spatial processing also represents a rather under-researched but potential biomarker for MCI or AD early detection due to the early measurable deficits in neurodegenerative disease progression (Bublak et al., 2011; Chou & Lan, 2013). Visual-spatial processing is located at the central nervous level in the (superior) parietal cortex. In this context, it is assumed that the ventrodorsal pathway often first shows deficits in spatial perception and orientation in the context of an AD. In particular, the dorsal pathway, which is located between the visual and parietal cortex and projects to frontal, premotor, and medial-temporal brain areas, is considered to significantly influence visual-spatial processing (Goodale & Milner, 1992; Jacobs et al., 2012; Ungerleider, 1982). Compared with the ventral pathway, the earlier metabolic and neurodegenerative impairment of the dorsal pathway may be considered causative. For example, the parietal regions of the dorsal pathway often show increased amyloid plaques and differences in neuronal activation patterns in AD patients compared to healthy individuals (Bokde et al., 2010; G. Frisoni et al., 2009).

Thus, especially for research on early AD detection, the consideration of visual-spatial processing in the parietal cortex is of great importance for imaging studies (Mandal et al., 2012; Metzger et al., 2016; Yeung & Chan, 2020). In the context of fNIRS

application, paradigms of mental rotation (M. Herrmann et al., 2005; Shimoda et al., 2008) or line orientation are common (M. Herrmann et al., 2005; J. B. Zeller et al., 2010). Using the Benton Line Orientation Test, for example, J B. Zeller et al. (2010), referring back to M. Herrmann et al. (2005), found abnormal oxygenation patterns in the parietal cortex of AD patients compared to a healthy control group. Thereby, a decreased brain activity, especially in superior parietal brain areas, became apparent. At present, no studies are known to assess visual-spatial processing in the parietal cortex in MCI patients. Nevertheless, Katzorke et al. (2017), Katzorke et al. (2018), and J. B. Zeller et al. (2010) reported lower frequency oscillations and reduced brain activation in frontal brain areas during performance of a word fluency task (VFT) in MCI patients.

The angle discrimination task (ADT) also represents an enriching paradigm to study visual-spatial processing in the parietal cortex (Mandal et al., 2012). For example, this paradigm was used by Vannini et al. (2004) for 10 young and healthy study participants (age: 21-31 years), based on preliminary studies by A. T. Sack, D. Hubl, et al. (2002) and A. T. Sack, J. M. Sperling, et al. (2002) with AD patients, which is again illustrated in the following studies (see chapters 3.1 and 3.2). Based on fMRI examinations, study participants were presented with clocks with different angular positions of the hands (40°, 60° as target angle, 80°). In addition to the preliminary studies according to A. T. Sack, D. Hubl, et al. (2002) and A. T. Sack, J. M. Sperling, et al. (2002), the task was modified in that varying hand lengths were presented to capture different levels of difficulty (e.g., short, middle, long pointer length, greater task difficulty with shorter pointer length). Increased (superior) parietal brain activity was revealed in the healthy sample, which led the authors to suggest that more neuronal resources are required as task difficulty increases. A study conducted later by the authors using a different analysis method also replicated these findings (Lehmann et al., 2006). The authors extended their fMRI analyses to MCI and AD patients using ADT (Vannini et al., 2007; Vannini et al., 2008). In the MCI sample (18 study participants), the authors were unable to uncover any differences from the healthy control group (13 participants). Still, parietal cortex activity increased demonstrably during the performance of ADT compared to a control task. Both samples managed to perform the same task performance. 5 MCI patients who received an AD diagnosis 3 years later showed more significant associations between ADT difficulty and superior parietal brain activation

and, independent of ADT, activations in the left precuneus compared with the healthy control group and the 8 remaining MCI patients (Vannini et al., 2007). In contrast to the MCI sample, Vannini et al. (2008) demonstrated significantly decreasing hypoactivation of the parietal cortex with increasing task difficulty as well as performance deficits for 13 AD patients (Mean [*M*] = 69 years), again compared to a healthy control group (13 participants). Especially the inferior parietal cortex and bilateral precuneus showed significant deficits. Interestingly, both AD patients and the healthy control group utilized overlapping neuronal networks to process ADT. Thus, in addition to parietal brain regions, occipital and frontal areas also played a significant role. In addition, task-independently, the middle temporal gyrus was significantly hyperactivated only in the sample of AD patients. This finding argued for Vannini et al. (2008) or compensatory mechanisms within and outside the dorsal pathway. Similar results were previously reported, for example, by Prvulovic et al. (2002). The authors applied the ADT (not modified for task difficulty; angular positions: 60° as target angle, 90°) during an fMRI measurement in an elderly sample (*M* = 69 years) of 14 AD patients: During visual-spatial processing, overlapping neuronal networks were activated both in the AD patients and within the control group (14 participants). However, in addition to parietal hypoactivation in AD patients, parallel hyperactivation was evident in the occipitotemporal cortex. Task performance remained comparable in both groups. The findings of Vannini et al. (2008) and Prvulovic et al. (2002) are reminiscent of the “Compensatory Recruitment Hypothesis” (see chapter 1.2.1).

In addition to these findings, attention should be drawn to the recent review by Yeung and Chan (2020), in which the authors summarize 36 studies reporting differences in oxygenation levels in MCI and AD patients on fNIRS measures using different paradigms. This revealed frontal and long-range connectivity deficits and reduced CBF changes in several cognitive domains for MCI and especially AD patients compared to healthy study participants.

Thus, in exploring visual-spatial processing in the parietal cortex using ADT while performing imaging procedures, promising findings emerge overall for AD samples. Equally encouraging, but much less studied to date, is the high-risk group of MCI patients (H. J. Li et al., 2015). Although partially comparable findings with AD patients concerning parietal hypoactivation, an equally common trend is that MCI patients can often maintain similar activation patterns in the parietal cortex for long periods during

visual-spatial processing, with marked hypoactivation having long since emerged in AD patients (H. J. Li et al., 2015). Heterogeneous findings may be due to, among other things, methodological differences such as divergent sample age, the use of different paradigms, measurements of varying brain regions, or inconsistently defined MCI criteria. However, it is often unclear to what extent compensatory mechanisms play a role. Thus, the application of fNIRS, which has rarely been used so far, and the concomitant deeper exploration of neuronal activation patterns, especially in the high-risk group of MCI patients, during the implementation of paradigms for visual-spatial processing in the parietal cortex seems required. However, in addition to the use of brain imaging techniques, the consideration of potential predictors and risk factors, as well as the assessment of an aging individual's cognitive performance, appear to be relevant to the early detection of MCI/AD, which is why these topics will be addressed in the following chapter.

1.2.3 Predictors and risk factors and early pathological cognitive decline

In addition to the consideration of imaging methods in early detection research of MCI and AD, it is also worthwhile to take possible predictors and risk factors that can significantly influence the development, course, and treatment of neurodegenerative diseases into account. Numerous research papers, systematic reviews, and meta-analyses have been published to date, a brief selection of which is presented below.
Among the most critical fixed risk factors for developing cognitive decline or AD to date is predominantly age (Armstrong, 2019; Hickman et al., 2016; World Health Organization, 2021). In this regard, an approximately 19% increased likelihood of developing AD between 75-84 years of age and approximately 30-50% above 85 years of age can be assumed (Ferri et al., 2005; Knopman, 2001). However, biological sex is also one of the significant risk factors. In this context, an increased risk applies to women, but this is also due to their higher life expectancy of around 4.5 years (Riedel et al., 2016). With an initially comparable incidence with increased prevalence for females, the higher incidence is found in females at older ages (Barnes et al., 2003; Ruitenberg et al., 2001). In addition, there are hormonal factors of the female sex. For example, recent studies are exploring the effects of menopause on neurodegenerative processes caused by reduced metabolic activity and increased amyloid-β deposition

(Scheyer et al., 2018). In addition, the apolipoprotein-ε (ApoE/APOE) gene, among other genetic factors, is considered a significant risk factor for the development of MCI/AD. The ApoE gene consists of three alleles ε2, ε3, and ε4 and produces isoforms from them. Especially allele ε4 is considered as a risk factor (Hickman et al., 2016; Liu et al., 2013; Mayeux et al., 1998; Mayeux et al., 1993; Oyama et al., 1995; Sharma et al., 2020; Silva et al., 2019). For example, the research literature reports that lesions or neurofibrillary changes are found as early as stage I in samples of young, non-demented individuals with Apo-ε4 gene variants, but not in an age-matched, nondemented control sample (Braak et al., 1999; Ghebremedhin et al., 1998). Based in part on the increased Aβ deposition in ε4 allele carriers, it is reasonable to speculate that the interaction between inflammation, ApoE gene, and Aβ deposition influences cognitive decline (Berr et al., 1994; Marottoli et al., 2017; Polvikoski et al., 1995).

Ultimately, because of the evident interplay, age, Apo-ε4 gene variant, and biological sex can be seen as a risk triad for AD development (Riedel et al., 2016). About 60% of AD patients are female carriers of at least one ApoE-ε4 allele (Riedel et al., 2016).

Other relevant risk factors reported include a person's level of education, socioeconomic status, or even origin (Armstrong, 2019; Jessen, 2019). For example, lower education is thought to lead to lower cognitive reserve (Livingston et al., 2017; Valenzuela & Sachdev, 2006).

In addition, one of the most effective prevention approaches in AD research today focuses on risk-modifying lifestyle factors. Estimates suggest that approximately 20-50% of dementia risk is driven by these same factors (Jessen, 2019; Livingston et al., 2017; Xu et al., 2015). In this regard, approximately 50% of all AD cases can be attributed to seven modifiable risk factors. Therefore a 10-25% reduction in these risk factors could translate into the prevention of 1.1-3.0 million fewer AD cases worldwide (Barnes & Yaffe, 2011). According to Barnes and Yaffe (2011), these seven risk factors are diabetes mellitus, hypertension and middle-age obesity (45-65 years), smoking, depression, low educational attainment, and physical inactivity. Other authors, with high overlap based on their meta-analysis of 24 cohort studies and a total of 159,594 included study participants in middle age, recommend, for example, the five risk factors of obesity, diabetes mellitus, smoking, hypercholesterolemia, and hypertension, the presence of which can increase the risk of developing dementia between 41-78% (X.-Y. Li et al., 2019). Any risk factors can also be classified into early, midlife, and late-

life risk factors (Litke et al., 2021). Following this classification, Livingston et al. (2017), for example, report nine risk factors, the combination of which can explain 35% of the risk of dementia: A low level of education in early life (< 45 years), hypertension, obesity, and hearing loss in midlife (45-65 years), and smoking, depression, physical inactivity, low social contact, and diabetes mellitus in late life (> 65 years). In particular, X.-J. Wang et al. (2019) extend the importance of early life factors to include risk factors such as urban residence, number of siblings, traumatic brain injury, premature death of a parent, or new spouses of a parent. If recommendations from the AWMF are considered, risk factors for the development of MCI/AD, which are consistent with most reviews, are also identified. The use of preventive measures is recommended from middle age onwards (Deuschl & Maier, 2016). If one tries to group possible risk factors, overall studies on pre-existing cardiovascular conditions such as hypertension, diabetes mellitus, elevated cholesterol levels can be found (Cooper et al., 2015; Hersi et al., 2017; Jessen, 2019). Medical history such as tumors, stroke, traumatic brain injury, and infections are considered (Armstrong, 2019). Vascular risk factors in midlife and amyloid accumulation in late life may favor MCI/AD development (Gottesman et al., 2017; He et al., 2020; Larsson & Markus, 2018; Takeda, 2019). Factors equally include humoral and blood parameters such as vitamin B12, folic acid, and homocysteine (Ellinson et al., 2004). However, for example, studies of vitamin B12 supplementation, as well as non-intervention predictive and systematic studies, report inconsistent results that do not yet allow conclusive interpretations (Ellinson et al., 2004; McCleery et al., 2018). Pre-existing psychiatric conditions such as depression, anxiety, and stress are also often considered risk factors of MCI/AD (Armstrong, 2019; John et al., 2019; Tan et al., 2019). For example, metabolic interactions between depression and AD are possible (Banerjee et al., 2017). Depressive symptoms later in life may also indicate a prodromal phase of AD (John et al., 2019; Kuo et al., 2020). However, their psychometric extent of predictive value also remains unclear. For example, Tan et al. (2019) described community-based samples in which depression predicted the progression from MCI to dementia and clinical samples in which the evidence for these associations was quite heterogeneous. The relevance of lifestyle factors such as deficient exercise, diet, and obesity, alcohol, and nicotine use is equally emphasized by numerous research papers (Cooper et al., 2015). For example, increased exercise promotes cerebral blood flow, increases hippocampal volume, and

positively affects neurogenesis (Cass, 2017). Priority should be given to mental activity, often associated with social integration and engagement. In this context, a lack of mental activity can usually be identified as a predictor of, for example, lower MMSE sum scores (J. Q. Li et al., 2016). Meanwhile, environmental factors such as air quality, heavy metals, other metals, trace elements, occupational exposure are also increasingly discussed as risk factors (Killin et al., 2016).

Overall, it must be assumed that the interaction of several risk factors is usually relevant for the development of MCI/AD. For example, Peters et al. (2019) report a 20% higher risk of developing dementia in the presence of one risk factor. In contrast, the risk of developing the disease is 65% with two risk factors and a risk ratio of 2.2 with three risk factors. Thus, the risk factors for developing AD overlap with those for MCI, with increasing studies addressing early MCI (Cooper et al., 2015; Song et al., 2018).

In addition to considering risk factors, it is worth mentioning the high importance of protective factors for preventing these neurodegenerative diseases by, e.g., cognitive reserves (see also chapter 1.2.1). Often, modifiable risk factors can be "turned around" into protective factors. For example, a protective factor and nonspecific biomarker may be the Brain-Derived Neurotrophic Factor (BDNF), which can induce healthier brain aging under certain circumstances (Hickman et al., 2016; B. Y. Kim et al., 2017). It can be described as an unspecific biomarker indicating neurodegeneration based on altered serum or plasma levels (B. Y. Kim et al., 2017). As compared to healthy samples, at early stages of AD and in MCI, patients often show elevated BDNF serum levels, while reduced levels mark late stages of AD (B. Y. Kim et al., 2017). In conclusion, it may pose as a powerful correlate of current cognitive abilities. Interactions with other risk factors such as depression are also conceivable (Balietti et al., 2018). It is also known that age and sex could influence BDNF serum and plasma levels and thus sample homogeneity (Balietti et al., 2018). Ultimately, preventive measures increase cognitive reserve via, e.g., mental training, reduce neuroinflammation via, e.g., medication, and reduce vascular, neurotoxic, or oxidative brain damage via, e.g., nicotine abstinence (Livingston et al., 2017).

Despite the in previous chapters described findings that neurodegenerative processes often occur years before the first measurable clinical MCI/AD symptoms and that imaging techniques are thus of enormous relevance, neuropsychological or -

psychiatric test diagnostics still represent the most important approach for (early) detection and thus the prediction of MCI/AD based on potential risk factors (Braak & Braak, 1991; Mandal et al., 2012). Paradigms, e.g., to assess visual-spatial processing, are likewise found in modern AD test diagnostics, see the clock-drawing test or geometric tasks in the MMSE (Folstein et al., 1975; Mandal et al., 2012; Shulman et al., 1993). Longitudinal surveys are crucial for analyzing within-subject data (Cooper et al., 2015). However, in the context of longitudinal studies, two distinctive issues should be mentioned from a methodological perspective: To detect cognitive decline at the earliest possible time point, a dimensional rather than categorical interpretation of neurocognitive change using diagnostic criteria might be beneficial (Walhovd et al., 2014). Neuropsychiatric test batteries or even dementia screening procedures such as the MMSE may provide promising indicators of cognitive decline (J. Kim et al., 2017). To define adequate statistical indicators of dimensional and pathological cognitive change, it is also essential to find out which approach proves to be reliable, especially in long-term studies and fitting to the characteristics of a sample. For example, the definition of (weighted) composite variables or latent factors of cognitive domains that are reflected across the sample over several measurement time points could be considered.

In addition, dropouts are typically a major problem in long-term studies. Particularly in samples of high age, where study participants have some pre-existing or comorbid illness, high dropout rates can occur due to advanced disease, death, institutionalization, and more (Burke et al., 2019; Coley et al., 2008; Hill et al., 2016). The use of retention techniques appears to be essential (Robinson et al., 2007; Robinson et al., 2015).

1.3 Research summary and objectives of the current thesis

To sum up, both early detection and successful treatment of MCI and AD are of great importance, mainly due to the constantly aging world population and the resulting increase in the number of neurodegenerative diseases (see chapter 1.1.1). Pathological aging processes leading to MCI or AD often develop years before the first clinically visible symptoms and usually remain undetected (see chapter 1.1.2). The pathogenesis is still largely unclear, but the characteristic course of AD, which is often

preceded by the development of the MCI syndrome, offers promising starting points for the early detection of the disease (see chapter 1.1.3). These should be urgently exploited, primarily because of the irreversible course of the disease to date and the lack of treatability of AD (see chapter 1.1.4).

Early detection of MCI and AD holds great potential in that disease progression could be decisively influenced, delayed, and/or halted. Two starting points are of great importance:

First, various biomarkers have a crucial role in differentiating between age-related and pathological changes (see chapter 1.2.1 and 1.2.2). A potential biomarker is fNIRS imaging, which can visualize hemodynamic changes in brain regions such as the parietal cortex during cognitive tasks. The performance of this method is simple, easy to implement, economical. It has few side effects, which is why it is usually superior to other imaging methods like fMRI or PET, especially in the field of early detection. Current research reports promising findings of detecting differences in parietal cortex activity during visual-spatial performances, e.g., during ADT implementation, between MCI/AD patients and healthy individuals (see chapter 1.2.2).

Second, it is known that the development of MCI or AD depends critically on a variety of fixed and modifiable predictors and risk factors. Minor changes in cognitive performance could provide information about dimensional cognitive decline, especially in the context of long-term studies. Therefore, and because it is still the most common diagnostic method, the detection and investigation of predictive factors via neuropsychiatric test diagnostics should not be disregarded in addition to imaging techniques. Moreover, a special focus should also be placed on the specifics of long-term studies, such as predicting study dropout, including based on cognitive change (see chapter 1.2.3).

To answer the question of early detection of cognitive change concerning MCI and AD over time within a large sample that mainly was healthy at baseline (Vogel Study, see also Polak et al., 2017, and chapter 2.), a total of four studies were conducted.

In the first study, the healthy sample's behavioral parameters and neuronal activity patterns at V1 were collected using fNIRS. During the assessment, study participants completed an ADT to assess visual-spatial processing performance. The second study related the findings of the healthy sample from the first study to the behavioral parameters and neuronal activity patterns of a matched MCI sample. The subsequent

third study focused on the identification of latent factors instead of composite variables to investigate features of cognitive domains, possible compensation mechanisms, and the dimensional prediction of cognitive decline of all study participants from V1 to V2. Lastly, in the fourth Study, risk factors and predictors from V1 were examined regarding the predictability of study dropout at V2.

After a concise general methodological overview, all four studies are presented cumulatively below, with each of the four studies followed by their respective implications for the follow-up study and concluding with a joint discussion of the studies.

2. Methods

At this point, reference should be drawn to the method chapters contained in the individual publications (see chapter 3.). Therefore, only a brief overview of the underlying Vogel Study and the data analysis methods relevant and overlapping for the individual publications will be given below. The presentation of the statistical analysis methods of the fNIRS data and the neuropsychiatric diagnostics performed within the framework of the respective publications will be omitted here.

2.1 Vogel Study Sample

As mentioned at the beginning of the thesis, all subsequent publications are based on (parts of) the sample of the longitudinal, observational, and prospective Vogel Study, which has been ongoing since 2011 and has been conducted to date at the Center for Mental Health of the Department of Psychiatry, Psychosomatics, and Psychotherapy of the University Hospital Würzburg (Polak et al., 2017). The study consists of three measurement time points (visit 1 [V1], visit 2 [V2], visit 3 [V3]) and thus of a single case observation of 6 years and a total study duration of about 10 years. The study was approved by the Ethics Committee of the University of Würzburg (vote no. 23/11) and complied with the Declaration of Helsinki (World Medical Association, 2013; Williams, 2015). Additionally, the Vogel Study was registered at *https://www.clinicaltrials.gov/* and with the number *NCT02224326*. The Vogel Study is financially supported by the *Vogel Stiftung Dr. Eckernkamp* (Würzburg, Germany).

Any contact information (<7000) was obtained from the registry office, and 5124 potential study participants were then contacted by letter in two hundred random steps and invited to an information session. Interested potential study participants were registered for V1 and, after receiving all information, gave their written informed consent to participate in the study. Thus, the Vogel Study baseline survey included a total of $N = 604$ study participants who were born between April 1936 and March 1941 (age: ≥ 70 years) and resided in the city of Würzburg at the time of inclusion. Exclusion criteria against participation in the Vogel Study were severe previous internal, neurological, and psychiatric diseases (e.g., Parkinson's disease) that occurred or existed within the last year, severe and uncorrected visual and hearing impairments, and use of psychoactive medication at V1. At V2, $n = 507$ study participants were still

participating. The last measurement point V3 is currently still running, but until December 2021, the data of more than *n* = 330 study participants could already be collected. V3 is scheduled for completion during January 2022.

2.2 Data Analysis

The structure of the respective measurement time points and the neuropsychological diagnostic instruments used are presented in Tables 3 and 4. The diagnostic classification of the study participants for MCI patients was based on the diagnostic criteria explained in chapter 1.1.4.2 according to Portet et al. (2006). To meet the criteria for an AD diagnosis, participants had to score less than 24 on the MMSE or less than 9 on the DemTect. A diagnosis of depression was attributed if participants scored 20 or more on the BDI-II or 6 or more on the GDS. Subjects who met the inclusion criteria of the Vogel Study but could not be assigned to one of the other three groups were considered healthy (cf. Katzorke et al., 2018; Polak et al., 2017).

Table 3

Data collection and analyses methods in the Vogel Study.

Visit 1 (V1)	Visit 2 (V2)	Visit 3 (V3)
Blood test		
Clinical examination		
Neuropsychology		
VSEP, NIRS		CERAD-Plus battery
-	IMD, LVEF	-
-	MCI/AD patients: MRI, PET, CSF	

Note. Table modified following Polak et al. (2017). Gray shaded areas apply to the marked measurement time points. Abbreviations: VSEP = Vagus Somatosensory Evoked Potentials, NIRS = Near-Infrared Spectroscopy, IMD = Intima Media Thickness, LVEF = Left Ventricular Ejection Fraction, MCI = Mild Cognitive Impairment, AD = Alzheimer's Dementia/Disease, MRI = Magnetic Resonance Imaging, PET = Positron Emission Tomography, CSF = Cerebrospinal fluid Analysis, CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

Table 4

Neuropsychological diagnostics in the Vogel Study (V1-V2).

Cognitive and affective screening questionnaires	Neuropsychiatric diagnostics	NIRS paradigms
MMSE	VLMT	ADT
DemTect	WMS-R	VFT
B-ADL	RWT	TMT
HVDS	CFT	-
GDS	TAP	-
BDI-II	-	-
HDS	-	-
ASI-3	-	-

Note. Table modified following Polak et al. (2017). NIRS = Near-Infrared Spectroscopy, MMSE = Mini-Mental Status Examination (Folstein et al., 1975), DemTect = Dementia Detection test (Kalbe et al., 2004), B-ADL = Bayer-Activites of Daily Living (Hindmarch et al., 1998), HVDS = Hachinski Vascular Dementia Scale (Hachinski et al., 2012), GDS = Geriatric Depression Scale (Sheikh & Yesavage, 1986), BDI-II = Beck Depression Inventory – II (Beck et al., 1996), HDS = Hamilton Depression Scale (Hamilton, 1960), ASI-3 = Anxiety Sensitivity Index – 3 (Reiss et al., 1986), VLMT = Verbal Learning and Memory Test (Helmstaedter et al., 2001), WMS-R = Wechsler Memory Scale – Revised (Härting et al., 2000), RWT = *Regensburger Wortflüssigkeitstest* (Aschenbrenner et al., 2000), CFT = Rey complex figure test (Meyers & Meyers, 1996), TAP = *Testbatterie zur Aufmerksamkeitsprüfung* (Fimm & Zimmermann, 2001), ADT = Angle discrimination task, VFT = Verbal Fluency Test, TMT = Trail Making Test.

To date, the Vogel study has resulted in the following published papers: de Rojas et al. (2021); Sophia Haberstumpf et al., 2021; S. Haberstumpf, J. Leinweber, et al., 2021; Haberstumpf et al., 2020; S. Haberstumpf, A. Seidel, et al., 2021; Katzorke et al. (2018); Katzorke et al. (2017); Müller et al. (2014); Polak et al. (2017); Reimann et al. (2020); J. B. M. Zeller et al. (2019).

3. Results

In accordance with the aims of this thesis, four publications are presented below. Each of the publications focuses on the pathological cognitive change and/or decline in the elderly participants of the Vogel Study. The content of the four publications corresponds to their accepted or published versions in the respective journals. If necessary, changes other than to the formal-linguistic of the publications are indicated (e.g., numbering of captions, Tables, Figures).

The publications are presented in the sequence that follows:

1. Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia,* *148*, 107650. https://doi.org/10.1016/j.neuropsychologia.2020.107650.

2. Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy. *Journal of Psychiatric Research*, *146*, 31-42. https://doi.org/10.1016/j.jpsychires.2021.12.021.

3. Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. *Journal of Neuropsychology*, *n/a*(n/a). https://doi.org/https://doi.org/10.1111/jnp.12269.

4. Haberstumpf, S., Leinweber, J., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Factors associated with dropout in the longitudinal Vogel Study of cognitive decline. *European Journal of Neuroscience*, 1-14. https://doi.org/10.1111/ejn.15446.

After each publication, implications for the subsequent paper are discussed. A general discussion follows in the fourth chapter.

3.1 Paper 1: Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals

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Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia, 148*, 107650. https://doi.org/10.1016/j.neuropsychologia.2020.107650.

Abstract

Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) are a globally rising issue. It is necessary to detect such diseases early to find strategies for prevention. Typically, patients with MCI or AD show deviant neuronal patterns, which could be detected early through brain imaging techniques enabling assumptions about pre-existing diseases. Functional Near-Infrared Spectroscopy (fNIRS) is an appropriate imaging method because of its easy and economical nature with hardly any drawbacks. An early measurable risk factor indicating neurodegenerative processes could be a deficit in visual-spatial processing, which is localized in the parietal cortex. In this study, we aimed to measure the hemodynamic response of the visual-spatial processing in the healthy elderly participants of our long-term Vogel Study with fNIRS during the clock-hand-angle-discrimination task (ADT) to deepen our understanding of healthy brain mechanisms. Our results revealed for our healthy sample a significantly increased neuronal brain activity with increasing task difficulties, namely from the long to the middle to the short clock hand during ADT and significantly higher activation in the right hemisphere compared to the left hemisphere as well as in the superior parietal cortex compared to the inferior parietal cortex. Additionally, our behavioral data demonstrated longer reaction times and more errors with an increasing task requirement. We, therefore, assume that visual-spatial processing can successfully be operationalized with fNIRS for healthy elderly people based on ADT. Further fNIRS analyses are planned to investigate pathological neuronal correlates of visual-spatial function in MCI or AD study participants.

Bullet Points:

- Parietal cortex activation during visual-spatial tasks can be measured with fNIRS.
- Visual-spatial processing can be measured using angle discrimination tasks.
- Significant activation of the parietal cortex can be found in healthy elderly.
- Higher task requirement results in an increased (right-lateral) neuronal activity.
- Higher task requirement results in higher reaction times and more errors.

Keywords: functional near-infrared spectroscopy; angle discrimination task; visual-spatial processing; parietal cortex; healthy controls

3.1.1 Introduction[1]

Dementia disorders represent a major challenge for the health sector worldwide (Bickel, 2000; Prince et al., 2013). Especially the continuously aging society results in a drastic expansion of these disorders which validates the research on the elderly (Abbott, 2011). Up to now, the detection of frequent forms of dementia such as Alzheimer's Disease (AD), or prodromal stages such as Mild Cognitive Impairment (MCI), is largely possible through neuropsychiatric diagnostics (World Health Organization [WHO], 2016). However, the early neurodegenerative processes emerge 10-20 years before the first measurable cognitive deficits, which is the reason why intervention mostly takes place when the brain has long been irreversibly damaged (Braak & Braak, 1991; Chrem Mendez et al., 2019; Gauthier, 2005). Therefore, the identification of objective biomarkers helps to recognize biological processes with prognostic or diagnostic value and to use these as indicators for pathological neurodegenerative processes in the brain (Nestor, Scheltens, & Hodges, 2004).

Functional brain imaging has the potential to show prodromal alterations in brain activity and can be used as a biomarker (Counts, Ikonomovic, Mercado, Vega, & Mufson, 2017; Henriques, Benedet, Camargos, Rosa-Neto, & Nóbrega, 2018; Lashley et al., 2018; Sun et al., 2018). In the last years, imaging research focused largely on the investigation of risk factors and their impact on imaging methods such as functional Magnetic Resonance Imaging (fMRI) or functional Near-Infrared Spectroscopy (fNIRS) (DeKosky & Marek, 2003; Hampel et al., 2008; Katzorke, Zeller, Müller, et al., 2018; Melrose et al., 2011; Veitch et al., 2019; Wurtman, 2015).

Optical fNIRS imaging can retrace changes of the hemodynamic blood flow in frontal brain regions and is an alternative and extending imaging method to the potentially most frequent used fMRI (Chrem Mendez et al., 2019; Lashley et al., 2018; Lawrence et al., 2017; Metzger et al., 2016). Compared to fMRI, fNIRS has several advantages: Participants can remain in a natural sitting position, which makes the investigation easier for the elderly or also claustrophobic people (Plichta et al., 2006; Suzuki et al., 2004). Moreover, there are almost no exclusion criteria to pass for an fNIRS measurement. Because of its easy and feasible nature, this imaging method is cost-

[1] Please note that in order to maintain the consistent structure and to ensure readability of the thesis, all subsequent chapter numbers of the **four** publications - in deviation to their published versions - have been adapted to the structure of the general thesis. The content of the publications remains unchanged.

effective. Portable devices enable measurements in the private environment of participants which could be important for an elderly sample with possible physical constraints or restricting behavioral symptoms (Metzger et al., 2016; Prvulovic, Bokde, Faltraco, & Hampel, 2011; Prvulovic et al., 2002). Furthermore, fNIRS is relatively robust against motion artifacts (Fallgatter et al., 2004) compared to fMRI measurements. All in all, the comparability of fNIRS with imaging methods like fMRI has been shown (Fallgatter et al., 2004).

A recently published review describes both MCI and dementia-specific hypo-frontality and reduced frontal-cerebral oxygenation changes in study participants with MCI or dementia during cognitive tasks compared to healthy controls (Yeung & Chan, 2020). Tasks of word retrieval and verbal fluency, memory, motor control, and visual-spatial perception seem appropriate and are often used during fNIRS (Metzger et al., 2016; Yeung & Chan, 2020). However, most studies apply fNIRS to explore pathological neuronal activation during verbal fluency tasks (Arai et al., 2006; Fallgatter et al., 1997; Herrmann, Langer, Jacob, Ehlis, & Fallgatter, 2008). Moreover, recent reviews describe that a brain region like the (superior) parietal cortex can further be a good indicator for neurodegenerative processes and refer to here localized specific impairments in visual-spatial processing with perceivable deficits in spatial orientation (Arvanitakis, Shah, & Bennett, 2019; Colangeli et al., 2016). Visual-spatial deficits are equally one of the first symptoms of MCI/AD (Zeller, Herrmann, Ehlis, Polak, & Fallgatter, 2010). Frequently used paradigms to measure visual-spatial activity in the parietal cortex are for example mental rotation tasks (Alivisatos & Petrides, 1997), spatial allocation (Haxby et al., 1994), line orientation (Gur et al., 2000; Herrmann, Ehlis, Wagener, Jacob, & Fallgatter, 2005) and the identification of angles by clock processing exercises and angle discrimination tasks (ADTs; Lehmann, Vannini, Wahlund, Almkvist, & Dierks, 2006; Mandal, Joshi, & Saharan, 2012; Prvulovic et al., 2002; Sack et al., 2002a,b; Vannini et al., 2004; Vannini et al., 2008).

The study of Vannini et al. (2004), based on the previous ADT studies of healthy individuals by Sack et al. (2002a,b), is of particular interest for our study. Vannini et al. (2004) investigated the functional relevance of the parietal cortex for visual-spatial information processing via event-related fMRI in healthy participants. The authors presented clocks with various angular disparity and, contrary to Sack et al. (2002a,b), length of hands (short, middle, long) to ten healthy participants (years: 21-31),

challenged them to detect the 60° angles among all angles presented and, consequently, to press a key as soon as possible. The shorter the clock hands, the more challenging was it to detect the 60° angles. The authors described this effect by stronger and more spatially extended activation in the left and right (superior) parietal cortex and supported their hypothesis that more neuronal resources are required to solve the increasingly difficult tasks. Even later modified analysis approaches on the same sample yielded the identical results as the studies of Sack et al. (2002a,b) and Vannini et al. (2004): independent of the chosen data analysis, the parietal cortex showed increased activation (Lehmann et al., 2006).

In the current study, we aimed to test the results of Vannini et al. (2004) in a larger sample of older, healthy volunteers. We expected activation in the left and right parietal cortex, which increases with increasing task difficulty, while the reaction time (RT) and the number of errors (NE) increase on the behavioral level. Furthermore, due to the results of Vannini et al. (2004), we also expected a higher relevance of the superior parietal cortex as opposed to the inferior parietal cortex during the ADT.

In contrast to Vannini et al. (2004), we used the fNIRS method since our objective was to verify the predictive value of functional brain activation for the prediction of dementia in a large, longitudinal study (Polak, Herrmann, Müller, et al., 2017). As it has been shown that gender differences exist in visual-spatial processing, we included gender as an additional factor in the analysis (Gur & Gur, 2017; Irvine, Laws, Gale, & Kondel, 2012; Li & Singh, 2014). Moreover, we controlled the factor laterality, as previous studies in elderly participants have found an altered involvement of both hemispheres in cognitive tasks (Herrmann, Walter, Ehlis, & Fallgatter, 2006) described in the so-called HAROLD model (Cabeza, 2002).

3.1.2 Material and methods

3.1.2.1 Subjects

In total *N*=604 participants took part in the first data collection (out of three) of our Vogel Study. The Vogel Study is a long-term study on the early diagnosis of dementia over 10 years with 6 years of single participant monitoring (Polak, Herrmann, Müller, et al., 2017). For this purpose, inhabitants with origin or residency of the city of Würzburg

(age: 70-77 years, born between April 1936 and March 1941) were recruited. The following exclusion criteria were applied: 1) a severe psychiatric, neurologic, or internal disease in the last 12 months, 2) a severe and uncorrected visual or hearing impairment at the time of the baseline examination and 3) the intake of psychoactive medication during the first follow-up examination. The study was conducted in accordance with the Ethics Commission of the Medical Faculty of Würzburg University Hospital and the Declaration of Helsinki (vote no. 23/11). All volunteers were informed about the planned examination and gave their written consent to participate in the study.

As described in previous studies of the Vogel Study (Katzorke et al., 2017; Katzorke, Zeller, Müller, et al., 2018; Polak, Herrmann, Müller, et al., 2017; Zeller et al., 2018), *n*=484 participants were considered as healthy (not demented, MCI or depressed). Dementia (*n*=6) and MCI (*n*=74) symptoms were assessed using the Mini-Mental Status Examination (MMSE) and the dementia detection test (DemTect; Folstein, Folstein, & McHugh, 1975; Kalbe et al., 2004). The Beck Depression Inventory-II (BDI-II) and the Geriatric Depression Scale (GDS) were used to test depressive symptoms (*n*=40; Beck, Steer, & Brown, 1996; Sheikh & Yesavage, 1986). A previous disease of the central nervous system (CNS; e.g. multiple sclerosis, epilepsy, pain syndrome, restless legs syndrome, stroke, head injuries, traumatic brain injury, cerebral bleeding, transient ischaemic attack, skull base fracture) diagnosed during the examination was also considered a reason for exclusion in the fNIRS analysis (*n*=52).

Besides, participants had to be excluded for whom the following difficulties occurred during ADT execution: 1) only right-handed people were included in the data analysis to ensure the comparability of the cortical structures (*n*=28 participants were excluded), 2) difficulties with ADT execution (still more than 5 errors after the third exercise run; more errors than >2 *SD* from *M*) during the experiment (*n*=27), 3) technical difficulties (*n*=19), 4) incomplete fNIRS or genetic data (*n*=12). From the remaining *n*=346 participants we excluded further *n*=59 participants, which were defined as a matched control group for *n*=59 MCI patients (and therefore as an independent replication sample in a further analysis) which will be described elsewhere. Therefore, the final sample of this paper consisted of *n*=287 healthy participants (age: *M*=73.9 ± 1.6 years; 131 females, 156 males; see flow-chart in Figure 1 for details).

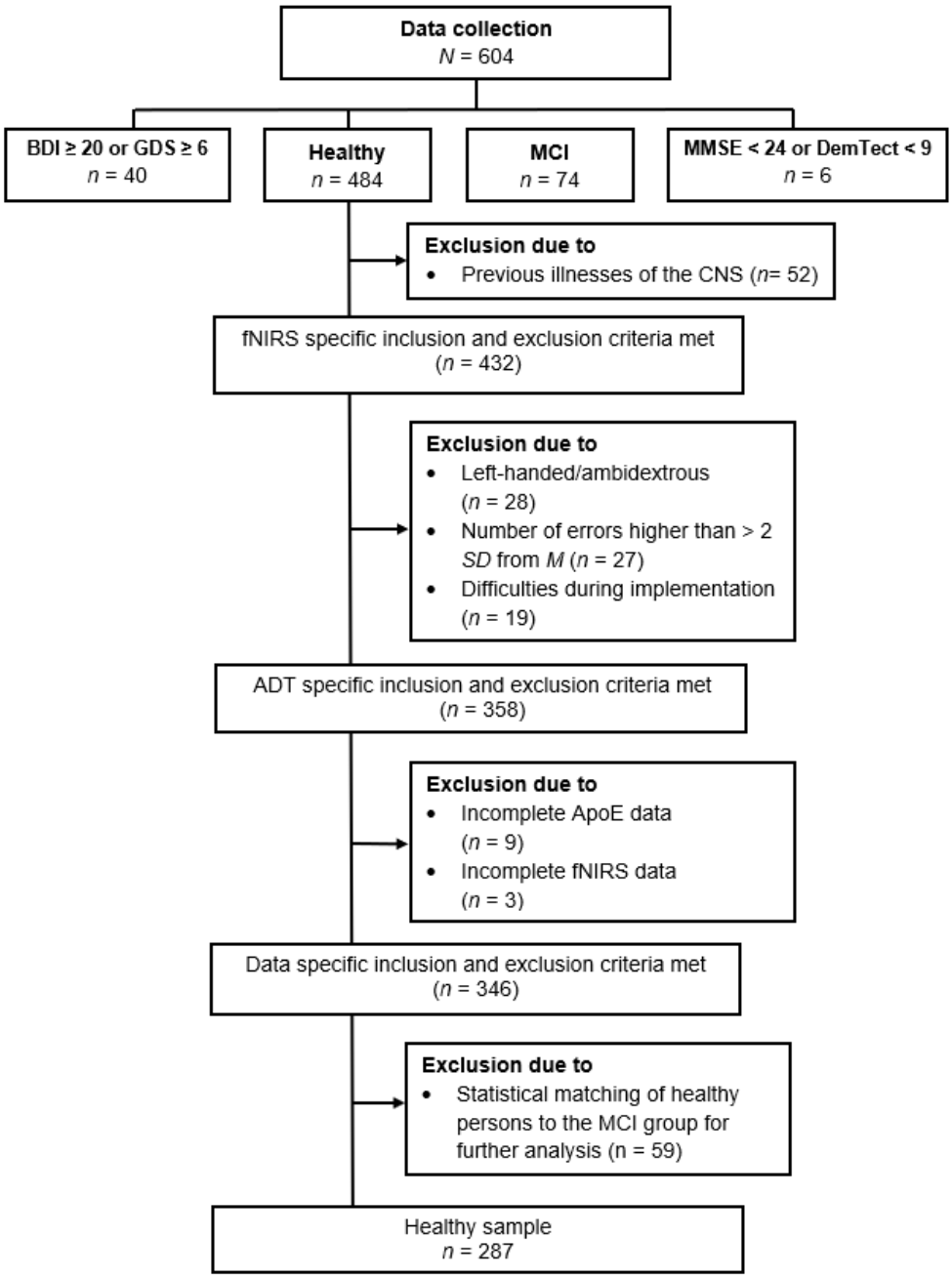

Figure 1[2]*.* Course of exclusion for data analysis. BDI=Beck Depression Inventory-II (Beck, Steer, & Brown, 1996); GDS=Geriatric Depression Screening Scale (Sheikh & Yesavage, 1986); MCI=Mild Cognitive Impairment; MMSE=Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975); DemTect=dementia detection test

[2] Please note that in order to maintain the consistent structure and to ensure readability of the thesis, all subsequent figures of the **four** publications - in deviation to their published versions - are numbered consecutively in ascending order. Captions and content of the figures remain unchanged.

(Kalbe et al., 2004); CNS=Central Nervous System; fNIRS=functional Near-Infrared Spectroscopy; ADT=angle discrimination task; ApoE=Apolipoprotein-ε.

3.1.2.2 Clock-hand-angle discrimination task

A modified version of the ADT (Lehmann et al., 2006; Vannini et al., 2004) was used to operationalize the visual-spatial processing. Analog clocks (yellow outlines/hand and black dial) were presented to the test persons on a black computer screen (18-inch diagonal display). The diameter of the stimuli was 18.5 cm. The two hands of the clock stood either at a 40°, 60°, or 80° angle to each other. The lengths of the hands varied between short, middle, and long. Thus, it should be possible to modify the task difficulty (Vannini et al., 2004). The control task consisted of a clock without hands. The resulting 10 different stimuli combinations were presented in pseudorandomized order 15 times each with varying positioning of the hands (=a total of 150 stimuli).

The experiment was developed and generated using the software *Presentation®* (Version 16.5, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). The test persons sat at a distance of about 80 cm from the computer screen. Initially, the participants were instructed to press the “Left Arrow” key when the hands were at a 60° angle to each other. The “Right Arrow” button should be pressed when the angle size was different (40° or 80°) and when the control tasks appeared. Only the right index finger (=60°) and right middle finger (≠60°) should be used. See Figure 2 to gain an impression of the different clock-stimuli with an indication of the required key to press.

Exercise runs were used to check whether the participants could implement the instructions. For this purpose, each of the ten stimuli combinations (see above) was presented once and had to be assigned correctly. Then the experiment started. After 10 seconds, the first stimulus appeared on the black screen. The duration of each stimulus presentation was 3 seconds. An Inter-Stimulus-Interval (ISI) followed immediately, which varied randomly between 2-4 seconds. During the ISI, a white fixation cross appeared in the center of the monitor. The participants were encouraged to concentrate on this. During both the stimuli presentation and the ISI, the participants were able to press the supposedly correct answer. In total, the presentation lasted about 15 minutes.

Using the *Presentation®* software (Version 16.5, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) it was possible to register the reaction times (RT) as well as the number of errors (NE) directly. If no key was pressed during the response interval, this was considered an error. A pressed key could not be corrected by pressing it again. During the execution of the ADT, the parietal activity was recorded with the help of fNIRS.

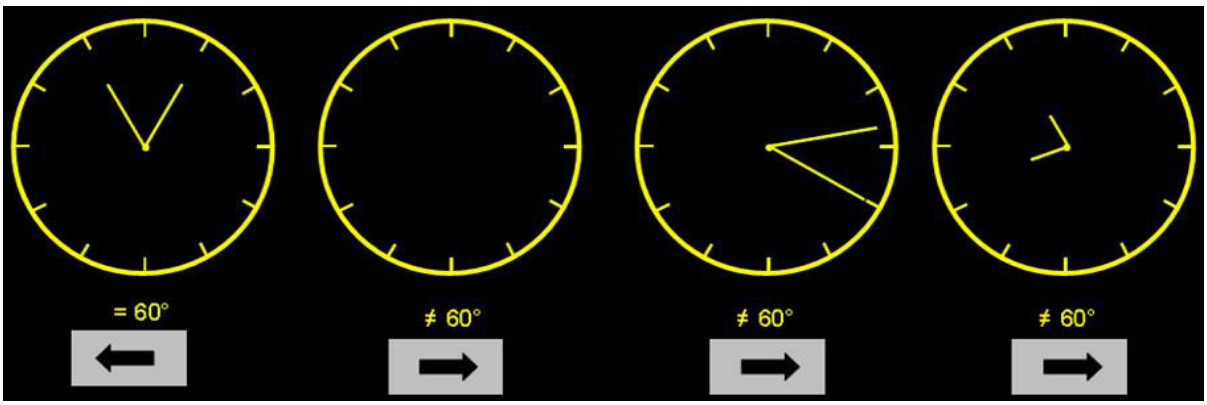

Figure 2. Overview of the various clock-stimuli with the instruction for the required key press.

3.1.2.3 Functional near-infrared spectroscopy (fNIRS)

“Brain activity” was measured using the continuous wave fNIRS system ETG-4000 (Hitachi Medical Corporation, Tokyo, Japan): Near-infrared light with two different wavelengths (1: 695 nm ± 20 nm; 2: 830 nm ± 20 nm) was transmitted through the skull calotte to the parietal cortex to subsequently determine changes in the hemoglobin level. The sampling rate was 10 Hz. Identical probe sets for both hemispheres were used to measure parietal activity. The probe sets each consisted of eight laser emitters and seven photodetectors (arrangement 3x5), resulting in 22 channels each (channel=inter-optode distance of the emitters/detectors). The mean inter-optode distance was 3 cm, so the light penetrated about 1.5-2.5 cm deep into the parietal cortex (Hoshi, 2005).

The two probe sets were fixed and connected using an elastic hood on the back of the participant’s head. The positioning followed the international 10-20 system according

to Jasper (1958). Emitters 17 and 27 were then placed to the right and left of electrodeposition Pz. The assignment to anatomical correlates was based on Okamoto et al. (2004). To minimize movement and muscle artifacts, the participants were instructed not to move or bite their teeth together during fNIRS recording.

3.1.2.4 Data analysis

The statistical data analysis of the behavioral parameters and the fNIRS data was performed with the statistical software *IBM SPSS* (Version 25, SPSS inc., USA), further correlation analyses partially with the statistical software *R* (*rmcorr* package version 0.4.0; Bakdash & Marusich, 2017).

Behavioral parameters

On the one hand, the RTs (averaged over the different conditions; in ms) and on the other hand, the NE (sum of errors and missings per condition) were recorded as behavioral parameters. We logarithmized the RT into ln(RT) to avoid skewed data as described for example by Ratcliff (1993). To replicate the results of Vannini et al. (2004) using the healthy control group, an analysis of variance (ANOVA) with repeated measurements was performed separately for both parameters. The between-subject factor was gender (2: female, male) and the inner subject factor the pointer length (3: short, middle, long).

The alpha-level (α) was set to .05. If significant, post-hoc *t*-tests were performed with Bonferroni-corrected α (Holm, 1979). The Mauchly's test was checked for sphericity and the Greenhouse-Geisser-corrected values were reported if necessary (Greenhouse & Geisser, 1959). The effect size of the ANOVA analyses was given as partial η^2 (η_p^2), for t-tests Cohen's *d* was reported.

Functional near-infrared spectroscopy (fNIRS)

Preparing the fNIRS data

To evaluate the imaging data, they were first smoothed using the moving average filter with a time interval of 5 seconds. Data were filtered with a high-pass filter of 0.08 Hz and a low-pass filter of 0.5 Hz. Additionally, to remove slow drifts, a 7-element discrete cosine transform basis set was used. Motion artifacts were minimized using a

correlation-based method for signal enhancement developed by Cui, Bray, and Reiss (2010). Within this algorithm, a joint value that is a linear combination of oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb) signals is calculated to adjust for large spikes caused by head-motion induced noise (and other white noise). This new calculated value has the characteristics of oxy-Hb and was used as a basis for further statistical analyses. The subsequent data analysis of the fNIRS data used the general linear model (GLM) approach validated by Plichta, Heinzel, Ehlis, Pauli, and Fallgatter (2007). Here estimated beta weights were calculated by using an ordinary least square regression model, where the hemodynamic response function (HRF) is defined by a Gaussian function with a preak time of 7.5s. Previous studies reported possible systemic artifacts especially over the prefrontal cortex (Kiriliana et al., 2012). To account for that, it was suggested to calculate a common average reference (Bauernfeind et al., 2013), which we have done previously for measurements of the prefrontal cortex (Herrmann et al., 2018). For the parietal cortex, in contrast, no systemic artifacts have been described. Therefore, no correction was applied.
In a first step, we aimed to determine a general, region-specific brain activity of visual-spatial processing in the parietal cortex. Therefore, we calculated the contrast between the experimental conditions (pointer length short vs. middle vs. long) and the control condition (=empty clock blade). The estimated beta weight were further analysed channel wise using ANOVA as described below. For subsequent Region of Interest (ROI) analyses the beta weights were averaged within the defined ROIs of the left and right hemisphere, separately.

Regions of Interest (ROI)

Based on the literature (Vannini et al., 2004), we expected brain activation in the bilateral superior parietal cortex. As described in the section “2.1 Subjects”[3], we divided our sample into two parts of healthy participants. The analyses of the first part of the sample aim to describe the effects of the ADT and in a second step the modulation effects of relevant factors such as gender or laterality. The second part of the sample is matched to patients with MCI and will investigate differences in brain activation (considering laterality, brain regionality) between patients and healthy volunteers (which will be reported elsewhere). To describe the effects of the ADT in this first

[3] Please note that this section now is numbered 3.1.2.1.

sample of healthy elderly, we computed ANOVAs for every single channel (#1 - #22) with the inner subject factors pointer length (3: long, middle, short) standing in 40° and 80° to each other and laterality (2: left, right). Bonferroni correction for multiple testing results with $\alpha < .0023$ (.05/22) will be applied. By this approach, we aim to define a bilateral ROI, which will be used for further analyses to evaluate the effects of laterality, brain regionality (superior and inferior parietal cortex), and gender on the neuronal activation during the ADT in the elderly. We calculated a repeated measurement ANOVA with between-subject factor gender (2: female, male) and the inner subject factors pointer length (3: short, middle, long), laterality (2: left, right), and brain regionality (2: superior, inferior) with the mean activity in the ROI as a dependent variable.

Identical to the behavioral data, a significance level of $p<.05$ was determined. Sphericity was tested using the Mauchly's test and, if necessary, the Greenhouse-Geisser correction was applied (Greenhouse & Geisser, 1959). The effect size was reported based on η_p^2. Significant results were followed by post-hoc *t*-tests with Bonferroni-corrected α (Holm, 1979).

Pearson's correlation coefficient between behavioral (ln(RT)) and neuronal activation were calculated to better understand the meaning of neuronal activation. Here we used difference scores between long and short pointer length conditions, both for the ln(RT) and brain activation in the selected ROIs.

Correlation Analysis

To further strengthen the scope of our current study, we calculated the Pearson's correlation-coefficient on a between- and within-subject brain-behavior level. Between-subject comparisons were calculated in *IBM SPSS*, a within-subject comparison was calculated as a repeated measurement correlation in *R* (see section "2.4 Data analysis"[4]). To do so, we indexed the experimental conditions as a repeated measurement variable per participant and correlated the measured brain activity level with the two behavioral parameters ln(RT) and NE. This procedure resulted in one Pearson's correlation-coefficient. As usual, significance level was set at $p<.05$ with a 95% confidence interval.

[4] Please note that this section now is numbered 3.1.2.4.

3.1.3 Results

3.1.3.1 Behavioral parameters

Regarding the behavioral data, similar results were reflected for the ln(RT) and the NE: For the main effect gender there was no significance (RT: F[1, 285]=3.74, p=.054, η_p^2=.01; NE: F[1, 285]=1.60, p=.208, η_p^2=.01), while the pointer length effect became highly significant (RT: F[1.63,465.12]=1291.89, GG-ε=.816, p<.001, η_p^2=.82; NE: F[1.53, 435.56]=137.70, GG-ε=.764, p<.001, η_p^2=.33). Post-hoc-t-tests with α-adjustment showed: The ln(RT) and the NE decreased from short (ln(RT): M=7.42 ln(RT), SD=0.13; NE: M=2.60, SD=0.82) to middle (ln(RT): M=7.24 ln(RT), SD=0.14; NE: M=1.07, SD=1.92) to long (ln(RT): M=7.12 ln(RT), SD=0.13; NE: M=0.66, SD=1.56) pointer length. Concerning the interaction "pointer x gender", there was a significant effect regarding the NE, but no significance was found concerning the ln(RT) (ln(RT): F[1.63, 465.12]=2.14, GG-ε=.816, p=.129, η_p^2=.01; NE: F[1.53, 435.56]=3.67, GG-ε=.764, p=.038, η_p^2=.01). Accordingly, post-hoc analyses were only carried out concerning the NE with only the condition of the short pointer length showing a tendency towards an increased error rate in women compared to men (t[285]=-1.92, p=.056, d=-.23). This effect only reached marginal significance. No gender differences were found in the other two conditions of pointer length (middle: t[285]=-0.83, p=.408, d=-.10; long: t[285]=0.14, p=.891, d=.02). Only in the condition of the short pointer length women (short: M=2.95, SD=3.01; middle: M=1.18, SD=2.13; long: M=.64, SD=1.40) tended to make slightly more mistakes then men (short: M=2.31, SD=2.63, middle: M=0.99, SD=1.73; long: M=0.67, SD=1.69).

3.1.3.2 Task dependent neuronal brain activity

Due to the high number of participants, and the power of statistical analysis that goes with it, 15 channels out of 22 reached a significant effect of task condition (see Table 5, and Figure 3, all main effects condition with F[2,572]≥6.98, p≤.0012). One channel (#16, η_p^2=.164) reached a η_p^2 greater than .1, which can be interpreted as a medium to strong effect (Cohen, 1988). In Figure 4, the time course of channel 16, separately for [oxy-Hb] and [deoxy-Hb] for the three conditions is displayed. The surrounding four channels (see Figure 3, channel numbers #11, #12, #20, #21) reached all significance levels and showed η_p^2 between .065 and .088. The ROI thus defined contains the five

channels with the highest effect strengths for the task condition (consisting of channels #16, #11, #12, #20, #21). All of them were highly significant. The five channels can be assigned to the inferior (#11, #12) and the superior (#16, #20, #21) parietal cortex according to Okamoto et al. (2004), which is exactly the region described in Vannini et al. (2004). The mean effect size of η_p^2=.093 of this five channels allows replication of this effect (with power=.95 and α=.05) with a sample size of n=27 (according to *G*Power; see also* Erdfelder, Faul, & Buchner, 1996), all significant channels had a mean effect size of η_p^2=.056, leading to a sample size of n=45. Due to the localization of the five channels as well as the higher effect strength, we focus on a narrow ROI for further analyses instead of defining all significant channels as ROI.

Table 5[5]

Task effects on a channel-wise level.

	Condition pointer length						Statistics		
	Long		Middle		Short		Main effect condition		
Channel	***M***	***SE***	***M***	***SE***	***M***	***SE***	***F***	***p***	η_p^2
#01	0.024	0.003	0.022	0.004	0.030	0.004	4.4	.013	.02
#02	0.010	0.005	0.014	0.012	0.014	0.010	0.2	.799	.00
#03	0.010	0.002	0.015	0.002	0.022	0.003	**12.9**	**<.001**	.04
#04	0.030	0.004	0.035	0.005	0.045	0.006	**8.5**	**<.001**	.03
#05	0.043	0.005	0.038	0.005	0.051	0.006	3.9	.032	.01
#06	0.025	0.007	0.037	0.012	0.039	0.010	2.8	.087	.01
#07	0.012	0.003	0.018	0.003	0.026	0.004	**13.7**	**<.001**	.05
#08	0.022	0.003	0.027	0.005	0.037	0.005	**9.7**	**<.001**	.03
#09	0.035	0.009	0.050	0.014	0.049	0.007	3.1	.071	.01
#10	0.030	0.005	0.032	0.006	0.040	0.006	**7.1**	**.0011**	.02
#11	0.021	0.003	0.029	0.003	0.040	0.004	**23.4**	**<.001**	**.08**
#12	0.025	0.003	0.035	0.003	0.043	0.004	**27.7**	**<.001**	**.09**
#13	0.023	0.003	0.032	0.003	0.035	0.004	**15.7**	**<.001**	.05
#14	0.023	0.009	0.026	0.011	0.033	0.006	0.5	.518	.00
#15	0.029	0.004	0.036	0.004	0.043	0.004	**13.4**	**<.001**	.04
#16	0.039	0.003	0.052	0.003	0.068	0.004	**56.0**	**<.001**	**.16**
#17	0.026	0.003	0.035	0.003	0.040	0.004	**16.0**	**<.001**	.05
#18	0.019	0.003	0.025	0.003	0.028	0.003	**8.8**	**<.002**	.03
#19	0.021	0.008	0.015	0.004	0.010	0.006	0.9	.347	.00
#20	0.028	0.003	0.036	0.003	0.043	0.003	**19.9**	**<.001**	**.07**
#21	0.027	0.003	0.036	0.004	0.043	0.004	**21.6**	**<.001**	**.07**
#22	0.019	0.003	0.025	0.003	0.026	0.003	**7.0**	**.0012**	.02

Note. *M*=mean, *SE*=standard error; df=2,572; Bold *p*-values indicate significant channels, bold η_p^2 indicates the defined ROI for this task.

[5] Please note that in order to maintain the consistent structure and to ensure readability of the thesis, all subsequent tables of the **four** publications - in deviation to their published versions - are numbered consecutively in ascending order. Captions and content of the tables of the publications remain unchanged.

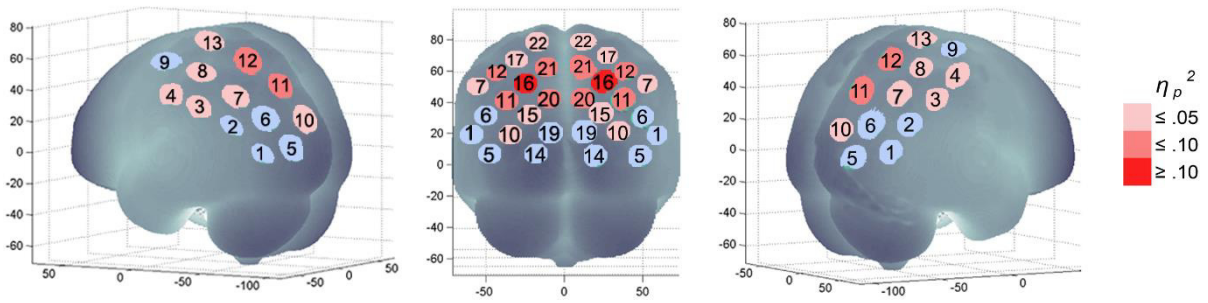

Figure 3. Graphical representation of the effect sizes of the significant (red) and non-significant (blue) channels during the calculation of the central Regions of Interest (ROI) for the main effect Pointer length; the red color shading represents the effect strength (η_p^2) of the found effect in each channel; view of the brain from 1) left-lateral, 2) posterior, 3) right-lateral.

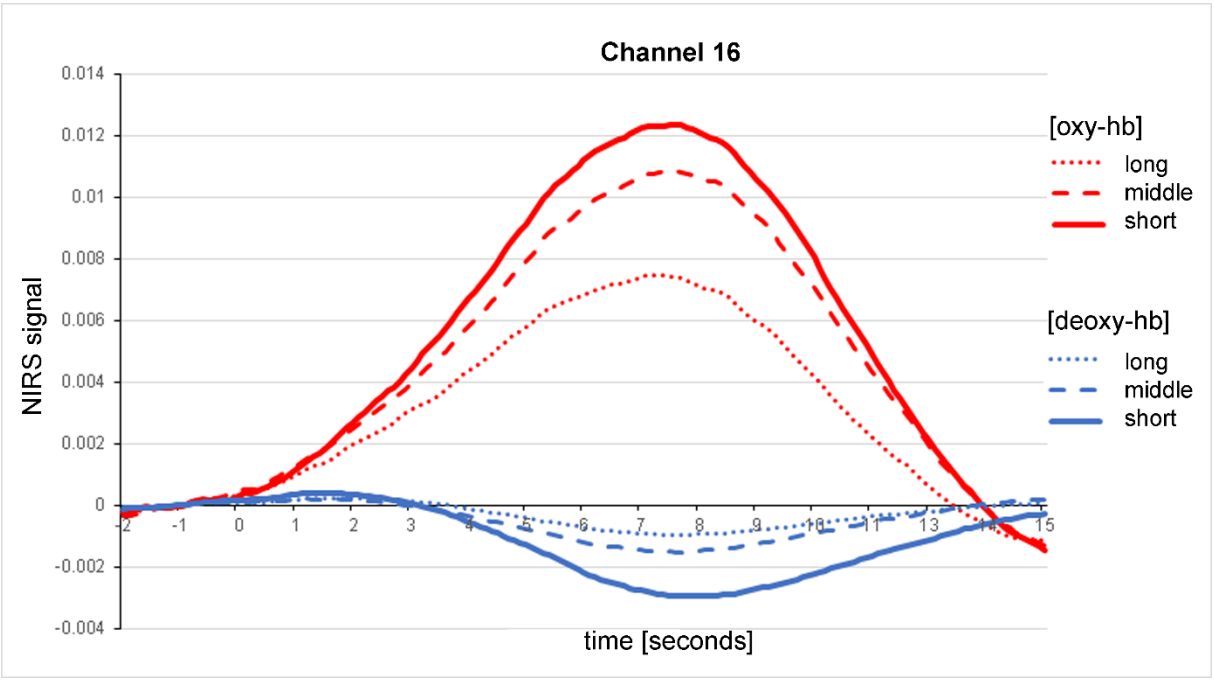

Figure 4. Mean time course for channel #16 of the left hemisphere for [oxy-Hb] in red and [deoxy-Hb] in blue color (baseline corrected, -2 to 0 s). The long, middle and short pointer length trials of the of the 40° and 80° conditions were contrasted against control condition.

3.1.3.3 Modulatory effects of neuronal brain activity

As Table 6 shows, there was a significant main effect of pointer length (short: M=0.046, SE=0.004; middle: M=0.037, SE=0.003; long: M=0.027, SE=0.003), laterality (left: M=0.032, SE=0.003; right: M=0.042, SE=0.003), and brain regionality (superior: M=0.041, SE=0.003; inferior: M=0.032, SE=0.003). Neither gender nor interaction effects were found. Subsequent t-tests (Bonferroni-corrected) showed a decrease in brain activity from the short to the middle to the long clock hand (short vs. middle: t[286]=-4.22, p<.001, d_z=-.261; short vs. long: t[286]=-7.18, p<.001, d_z=-.424; middle vs. long: t[286]=-4.42, p<.001, d_z=-.249). A significantly higher activation was found in the right hemisphere (M=0.042, SE=0.003) compared to the left (M=0.0315, SE=0.003; t[286]=-7.56, p<.001, d_z=-.446). Moreover, a significantly higher activation was also found in the superior parietal cortex (M=0.041, SE=0.003) as opposed to the inferior parietal cortex (M=0.032, SE=0.002; t[286]=6.11, p<.001, d_z=.361). More detailed, Figure 5 and 6 shows plots of these altering brain activity levels.

Table 6

F-value, degrees of freedom (df), significance (p), and effect size (η_p^2) of the repeated measurement ANOVA for neuronal parietal activity.

	F	df	*p*	η_p^2
Pointer	30.74	1.88; 534.92	**<.001**	.10
Laterality	55.31	1.00; 285.00	**<.001**	.16
Brain regionality	36.73	1.00; 285.00	**<.001**	.11
Gender	0.1	1.00; 285.00	.713	.00
Pointer x laterality	1.09	1.89; 538.99	.338	.00
Pointer x brain regionality	2.01	1.92; 547.56	.134	.01
Laterality x brain regionality	0.10	1.00; 285.00	.751	.00
Pointer x gender	3.01	1.88; 534.92	.053	.01
Laterality x gender	1.36	1.00; 285.00	.244	.01
Brain regionality x gender	0.03	1.00; 285.00	.875	.00
Pointer x laterality x gender	0.39	1.92; 546.47	.671	.00
Pointer x brain regionality x gender	0.15	1.92; 547.56	.861	.00
Laterality x brain regionality x gender	2.96	1.00; 285.00	.087	.01
Laterality x pointer x brain regionality	0.22	1.90; 540.08	.795	.00
Laterality x pointer x brain regionality x gender	1.27	1.90; 540.08	.281	.00

Note. Pointer = pointer length.

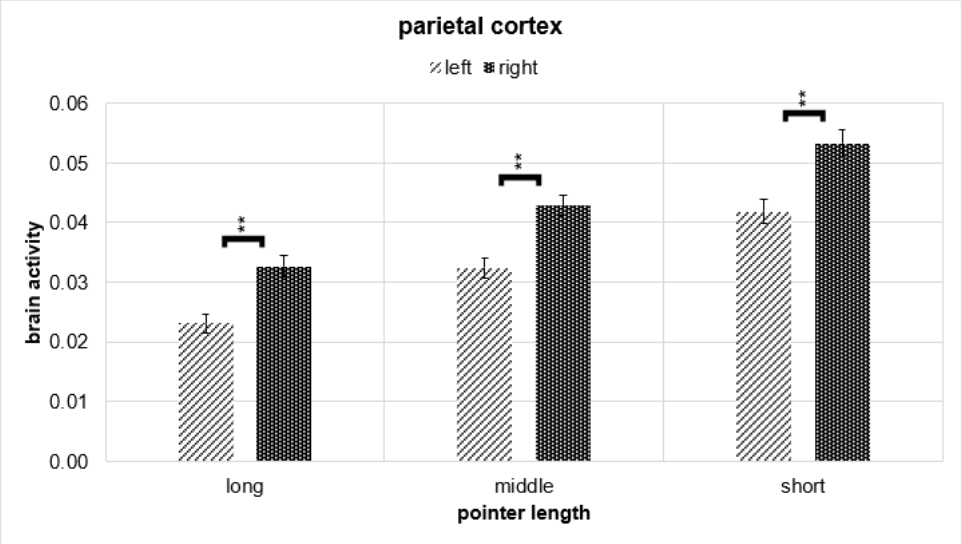

Figure 5. Brain activity levels (M ± SE) in the left and right parietal cortex during increasing ADT requirement (long, middle, short pointer length). Beta-weighted means were derived from significant ROIs. Highly significant differences were noted (** = p<.001).

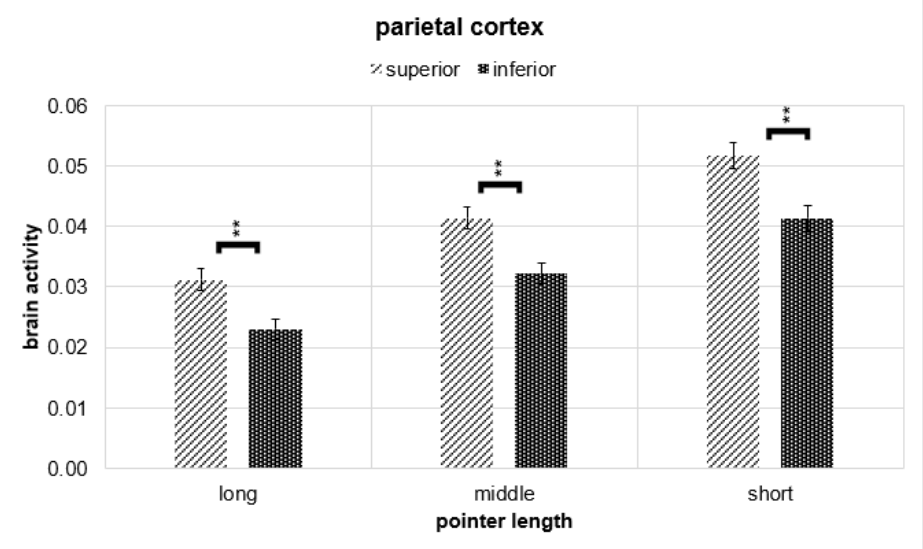

Figure 6. Brain activity levels (M ± SE) in the superior and inferior parietal cortex during increasing ADT requirement (long, middle, short pointer length). Beta-weighted means were derived from significant ROIs. Highly significant differences were noted (** = p<.001).

3.1.3.4 Between- and within-subject brain behavior correlations

To further evaluate the meaning of increased brain activity with increased ADT difficulty we calculated in a between-subject design the brain activity (differences between short and long pointer length condition) in each ROI (superior, inferior parietal cortex and left, right hemisphere) with the ln(RT) (the differences between short and long pointer length condition). Highly significant positive correlations (p<.001) could be found for the left superior parietal cortex (r=.15), the right superior parietal cortex (r=.16), the left inferior parietal cortex (r=.12), and the right inferior parietal cortex (r=.12). As mentioned previously (see "1. Introduction"[6]), age-related effects in brain activity during visual-spatial-processing tasks are described in the literature. In our analysis, we could find similar effects revealed by the correlation-coefficient for age and both the ln(RT) in the middle (r=.13, p<.05) and long (r=.15, p<.05) pointer length (40°, 80°) conditions, whereas we could not find a significant effect for correlation with the difference of the ln(RT) between short and long pointer length in the 40° and 80° conditions (r=.06, p=.32).

Moreover, also the within-subject brain-behavior correlation revealed a highly significant result (r=.36, p<.001) between the behavioral variables ln(RT) and NE with the individual brain activity level per experimental condition (short, middle, long pointer length) within our healthy sample.

3.1.4 Discussion

As described previously, the parietal cortex is attributed a central role (especially the superior parietal cortex) in visual-spatial processing in research literature. Thus, studies with tasks on mental rotation (Alivisatos & Petrides, 1997; Vingerhoets, de Lange, Vandemaele, Deblaere, & Achten, 2002), spatial displacement of stimuli (Corbetta, Shulman, Miezin, & Petersen, 1995) or spatial assignment (Haxby et al., 1994) showed increased activation in the parietal cortex. These are structures that can be assigned to the dorsal flow of visual information processing (Ungerleider & Mishkin, 1982). The fact that the parietal cortex is of decisive importance not only in general visual-spatial processing but specifically in the discrimination of angles, was already shown for example in Vannini et al. (2004). Using 10 healthy participants, they

[6] Please note that this section now is numbered 3.1.1.

investigated the relationship between neuronal activity and an ADT with, in contrast to Sack et al. (2002a,b), varying task difficulty due to changing pointer length (short, middle, long) next to angle discrimination (30°, 45°, 60°, 75°, and 90°, with the 60° angle as target angle). They also confirmed the central role of the parietal cortex in recognizing and discriminating angles.

Accordingly, in our present work we aimed to investigate the neuronal activation of the parietal cortex during the implantation of a modified version of the ADT, following Vannini et al. (2004), and extending the literature with an elderly healthy sample collecting data via successful implementation of the fNIRS.We tested the hypothesis that bilateral activation in the parietal cortex can be measured with fNIRS in our sample when performing an ADT. As expected, a clear activation of the parietal cortex could be observed during the discrimination of angles with varying task difficulty: we found that our healthy sample showed increased activity in the parietal cortex from the long to the middle to the short clock hand during ADT. There was a particularly strong activation around the electrode-position Pz, an area partly assigned to the superior parietal cortex and partly to the inferior parietal cortex (Okamoto et al., 2004).

In consequence of the results of Vannini et al. (2004), we also tested the hypothesis that as the task difficulty of the ADT increases, the ln(RT) and the NE increase at the behavioral level. As expected, our analysis revealed that, with an increasing task requirement, our healthy sample had longer RTs and a higher NE. This underscores that it was possible to modulate the task difficulty in the ADT of this study (similar to Vannini et al. 2004). A gradual increase in the difficulty of tasks could be operationalized: as the pointer length became shorter, the participants needed more time to complete the task and, at the same time, the brain activity increased in different channels around the electrode-position Pz. In the condition with a short pointer length, more neuronal effort was required to master the visual-spatial task.

Based on the results of our single-channel analyses we defined two ROIs on both hemispheres (inferior and superior parietal cortex) for further analyses to evaluate the effects of laterality, brain regionality, and gender. The ROIs were further used to calculate correlations with behavior and age. In contrast to Vannini et al. (2004), who did not find any laterality effects, we found higher activation in the ROI of the right hemisphere than in the left hemisphere in our healthy sample. We controlled the factor laterality, as previous studies in elderly participants have found an altered involvement

of both hemispheres in cognitive tasks (Herrmann, Walter, Ehlis, & Fallgatter, 2006) described in the so-called HAROLD model (Cabeza, 2002). Therefore the more right hemispheric activation pattern in our study with healthy elderly may be due to a compensation mechanism of aging. This would explain the lack of effect in Vannini et al. (2004) since the age range of their participants was between 21 and 31 years. In our study, all participants were at least 70 years old. The effect of laterality should therefore further be evaluated concerning cognitive status in our sample with MCI patients. Also due to the results of Vannini et al. (2004), we hypothesized a higher activation in the superior parietal cortex as compared with the inferior parietal cortext during ADT. Our finding was similar to the results of Vannini et al. (2004) and several articles published in the research literature, as exactly this expectation came true.

We also controlled for gender effects in visual-spatial processing as previous studies showed males performing better on spatial processing (Gur & Gur, 2017; Irvine, Laws, Gale, & Kondel, 2012; Li & Singh, 2014). Here we found a tendency for slower reaction times in females compared to males and a tendency for more errors in the short pointer length condition in females. Our results, therefore, go in the same direction as those in the literature, but also show that these gender effects are very small.

The fNIRS ROI analyses revealed a tendency for a “gender x pointer” interaction. This can be explained by a lower increase in brain activity from long to short pointer length in females.

The analyses of between-subject correlations between behavior and brain activity in our study showed a clear association between ln(RT) and the brain activity in the 4 different ROIs. With increasing task difficulty (from long to short condition) the ln(RT) and, correspondingly, the brain activity increased. Similar associations could also be found for a within-subject brain-behavior correlation (brain activity for each pointer length – ln(RT) and NE).

In our sample, only one group of persons of a very homogeneous age structure was examined. It is therefore not surprising that we did not find a correlation between age and slower ln(RT) with increasing task difficulty. However, a general slowdown was observed with increasing age, confirming the results of the literature.

Our study also had some limitations. Firstly, we mentioned the different average age in the study of Vannini et al. (2004) and our analysis. Therefore it could be for example that the higher activation in the right hemisphere compared to the left in our healthy

participants is a compensatory mechanism to balance neurodegenerative processes (Maillet & Rajah, 2013; Prvulovic et al., 2002; Thulborn, Martin, & Voyvodic, 2000). The so called «*Compensatory Recruitment Hypothesis*» says that in early AD sufficient neuronal resources are still available, so that the same cognitive performance can be achieved requiring more cognitive effort (Prvulovic et al., 2002). Applied to visual-spatial processing, this means that deficits in the dorsal pathway of the parietal cortex can be compensated by additional neuronal recruitment of the ventral pathway, for instance. In fact, some studies showed no (Prvulovic et al., 2002) or only small deficits (Vannini et al., 2008) in visual-spatial performance detecting angles for AD patients. Hence, it might be possible that some of our healthy participants already are in an unrecognized prodromal or early MCI/AD stage. In addition, several fNIRS studies show that deficits in neuronal activation during cognitive tasks occur with non-pathological, healthy aging (Herrmann et al., 2005; Hock et al., 1995; Schroeter, Zysset, Kruggel, & Von Cramon, 2003). However, there are still no studies available yet specifically comparing neuronal activation patterns during ADT in healthy younger and older people.

Secondly, further studies are necessary to compare different visual-spatial tasks other than the ADT in terms of factors such as complexity and task requirement. Likewise, task requirement is strongly associated with individual performance, hence individual findings would be helpful (Unterrainer, Wranek, Staffen, Gruber, & Ladurner, 2000). For future research, it would be conceivable to match the sample in terms of behavioral performance.

In summary, a successful operationalization of visual-spatial processing can be recorded with older people based on ADT. With fNIRS, it was possible to measure a significant activation of the parietal cortex during the visual-spatial task. An increasing task requirement increased neuronal activity, which was reflected on the behavioral level by longer RTs and a higher NE. With the data of the current analysis, a comparison will be drawn with the measured activation patterns in MCI or AD patients of the Vogel Study elsewhere. In these future analyses, we expect a significantly lower activation of the parietal cortex as well as a higher NE and ln(RT) during ADT with increasing task difficulty in the MCI/AD sample as compared to the healthy sample. As described above, it seems useful to investigate accompanying laterality effects. Doing so, risk factors and predictors for the development of MCI or AD can be investigated.

Contributors

Sophia Haberstumpf, Alexandra Seidel, and Martin J. Herrmann analyzed the data and wrote the first version of the article. Martin Lauer and Thomas Polak carried out and supervised medical investigations. Thomas Polak, Jürgen Deckert, and Martin J. Herrmann contributed significantly to conception and design. All authors critically reviewed the manuscript. All authors accepted the final version to be published.

Conflicts of interest

None.

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3.1.6 Implications for the second study

The first study assessed neuronal brain activation patterns during visual-spatial processing in the parietal cortex of *n* = 287 healthy, elderly study participants for baseline assessment using fNIRS imaging. For this purpose, an ADT paradigm modified according to three difficulty levels was applied (long, middle, short pointer length). Neuronal activation was found to increase significantly with increasing task difficulty in the healthy sample. These findings were accompanied by correspondingly increasing behavioral deficits (reaction time [RT], number of errors [NE]). In addition, significant right-hemispheric and superior parietal activation patterns were evident. Overall, the hemodynamic response was thus successfully measured using ADT and fNIRS techniques in the healthy study participants.

For the second study, the question now arose whether the healthy participants differed from the *n* = 59 MCI patients at baseline in terms of their hemodynamic response measurable by fNIRS during applying the same paradigm. For this reason, a healthy control group of also *n* = 59 study participants was matched to the MCI patients. Due to their disease presumably pre-existing neurodegenerative processes, a lower activation level as well as higher RT and more errors with increasing task difficulty were expected. It was also to be examined whether possible compensatory mechanisms in the MCI sample could explain activation or behavioral abnormalities compared to the healthy study participants.

3.2 Paper 2: Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy

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Abstract

Functional Near Infrared Spectroscopy (fNIRS) may be a suitable, simple, and cost-effective brain imaging technique for detecting divergent neuronal patterns at an early stage of neurodegeneration. In course of Mild Cognitive Impairment (MCI) or Alzheimer's disease (AD), a deficit in visual-spatial processing, located in the parietal cortex, is a reliable risk factor. Earlier, we established the application of the clock-hand-angle-discrimination task (ADT) during fNIRS to identify neuronal correlates of the visual-spatial processing in a healthy elderly sample. In this analysis, we aimed to measure and find out differences in the hemodynamic response in MCI participants compared to matched healthy controls. As expected, MCI participants showed more errors over all conditions of pointer length and a higher reaction time in the long and middle pointer length condition. Moreover, results revealed a significant reduction of cortical activation in MCI patients. There was a generally increased activity in both the right as compared to the left hemisphere and the superior parietal brain region as compared to the inferior parietal brain region in both groups. In summary, fNIRS can be implemented in the measurement of visual-spatial processing in MCI patients and healthy elderly based on ADT. MCI participants had difficulties to cope with the ADT. Since neuronal hypoactivity occurs with concomitant behavioral deficits, an additional analysis was performed on a subgroup of MCI patients who performed as well as the control group in behavior. This subgroup analysis also showed a hypoactivation of the parietal cortex, without evidence of a compensatory activation. Therefore, we assume that MCI patients are characterized by a deficit in the parietal cortex. Overall, these findings confirm our hypothesis that hemodynamic deficits in visual-spatial processing, localized in the parietal cortex, are reliable and early diagnostic markers for cognitive decline in risk groups for the development of AD.

Key words: functional near infrared spectroscopy, visual-spatial processing, parietal cortex, mild cognitive impairment, Alzheimer's disease, healthy controls.

3.2.1 Introduction

Neurodegenerative disorders such as dementia pose a problem to the health care systems worldwide (Abbott, 2011; Bickel, 2000; Prince et al., 2013). There are still no drugs available to cure the disease (Meyer, Podolski, Pickert, & Polidori, 2020). With 60-70% incidence of cases, the Alzheimer's disease (AD) is the most common type of dementia (World Health Organization [WHO], 2016). The identification of Mild Cognitive Impairment (MCI) helps to detect neurodegenerative processes at an early stage. Nevertheless, the first measurable cognitive deficits occur years after the first neurodegenerative processes that even may emerge 10-20 years before the onset of the disease (Chrem Mendez et al., 2019). Hence, neuropsychiatric diagnostics and intervention frequently are conducted after the brain has been irreversibly affected (Braak & Braak, 1991; Gauthier, 2005).

This illustrates the importance of objective biomarkers representing indicators of prognostic benefit (Nestor, Scheltens, & Hodges, 2004). Potential biomarkers could be functional brain imaging techniques such as functional Near Infrared Spectroscopy (fNIRS; Counts, Ikonomovic, Mercado, Vega, & Mufson, 2017; DeKosky & Marek, 2003; Hampel et al., 2008; Henriques, Benedet, Camargos, Rosa-Neto, & Nóbrega, 2018; Katzorke et al., 2018; Lashley et al., 2018; Melrose et al., 2011; Sun et al., 2018; Veitch et al., 2019; Wurtman, 2015). This is supported by a recent review, which reports a typical hypofrontality and reduced frontal-cerebral oxygenation modifications measured with fNIRS for MCI and dementia patients during cognitive tasks (Yeung & Chan, 2020). Deficits within visual-spatial cortical networks are typical in the early progression to MCI or AD (Belleville, Fouquet, Hudon, Zomahoun, & Croteau, 2017; Iachini, Iavarone, Senese, Ruotolo, & Ruggiero, 2009; Mandal, Joshi, & Saharan, 2012). These networks are localized in the (superior) parietal cortex which is, in consequence, also a reliable indicator for neurodegenerative processes (Arvanitakis, Shah, & Bennett, 2019; Colangeli et al., 2016). In fact, research suggests that the ventro-dorsal pathway is the first brain region to be affected and often shows the most serious deficits in the optic flow perception and spatial orientation, respectively (Arvanitakis et al., 2019; Colangeli et al., 2016; Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012; Yamasaki et al., 2012).

One of the most frequently used paradigms to measure visual-spatial activation patterns in the parietal cortex is the identification of angles by clock processing or angle

discrimination tasks (ADTs; Lehmann, Vannini, Wahlund, Almkvist, & Dierks, 2006; Mandal, Joshi, & Saharan, 2012; Sack et al., 2002a,b; Vannini et al., 2007; Vannini et al., 2004; Vannini et al., 2008). In the ADT paradigm presented by Vannini et al. (2004), clocks with changing angular disparity and varying length of clock hands (short, middle, long) were shown. In this study 10 young and healthy participants were asked to identify the 60° angles, while functional magnetic resonance imaging. Vannini et al. (2004) reported an increasing task difficulty with shorter clock hands and observed a higher and more spatially extended activation in both hemispheres of the (superior) parietal cortex with shorter clock hands. This confirmed their hypothesis that, with increasing task difficulty, a higher number of neuronal resources is needed to solve the task. We recently established the application of the ADT with fNIRS and investigated a sample of healthy elderly (Haberstumpf et al., 2020). In this study we confirmed increased parietal brain activation with increasing task dificulty in inferior and superior parietal cortex, with significant higher activation in the right compared to the left hemisphere and in the superior compared to the inferior parietal cortex.

There are also some fMRI pilot studies which use the ADT in MCI and AD samples (Vannini et al., 2007; 2008) to further investigate the relevance of parietal cortex activation deficits as an indicator for neurodegenerative processes (Arvanitakis, Shah, & Bennett, 2019; Colangeli et al., 2016). In the first study with 18 MCI patients and 13 healthy controls (Vannini et al., 2007), both samples showed significant task induced brain activation in superior and inferior parietal lobe compared to a control task, but no group differences were found. Additionally, both samples did not differ with respect to task performance in this study. The authors further divided their sample of 18 MCI patients into 5 patients who progressed to AD after 3 years (PMCI) and 8 MCI patients that remained stable (SMCI). Within these analyses they found in PMCI patients a stronger association between activity in the left superior parietal lobe and task difficulty compared to heathy controls and SMCI. In the next study, 13 patients with AD were compared with 13 matched healthy controls (Vannini et al. 2008). The patients with AD showed a lower brain activation with increasing task difficulty in contrast to the healthy controls. Additionally, patients with AD showed lower accuracy in behavioral performance in this study. Both studies showed that parietal cortex activity can be measured with ADT in MCI and AD patients, but the small number of participants in these studies limits the conclusions which can be drawn. In general, there is a limited

number of relevant studies investigating visual-spatial processing in MCI indicating that more studies are needed (Li et al., 2015).

Therefore, our objective was to examine the visual-spatial activation patterns in the parietal cortex of MCI participants. Due to a larger sample size in our study, with the consequent higher statistical power, we expected deficits at the behavioral level in MCI patients with a corresponding hypoactivation in parietal cortex during the ADT.

3.2.2 Methods

3.2.2.1 Subjects

The study involved a total of *N*=604 subjects in the first data collection (out of three) of the Vogel Study (Polak et al., 2017). With our Vogel Study we conduct a prospective and longitudinal study on the early diagnosis of dementia over a period of 10 years with 6 years of single subject observation, in which residents of the city of Würzburg were recruited whose year of birth was between April 1936 and March 1941 (age: 70-77 years). Various exclusion criteria have been established: 1) a severe psychiatric, neurologic, or internal disease in the last 12 months, 2) a severe uncorrected visual or hearing impairment and 3) the intake of psychoactive medication during the first follow-up examination. The study was conducted after verification of compliance with the Ethics Commission of the Medical Faculty of the University Hospital Würzburg and the Declaration of Helsinki (vote no. 23/11). All volunteers gave their written consent to participate in the study after having been informed about the planned procedure.

As already described in previous studies of the Vogel Study (Katzorke et al., 2017; Katzorke et al., 2018; Polak et al., 2017; Zeller et al., 2018), *n*=484 participants were regarded as healthy after application of the exclusion criteria (not demented, MCI or depressed).

By using the Mini-Mental State Examination (MMSE) and the dementia detection test (DemTect; Folstein, Folstein, & McHugh, 1975; Kalbe et al., 2004), dementia symptoms could be detected (*n*=6).

We applied a depression screening (Beck Depression Inventory-II [BDI-II]<20, Geriatric Depression Scale [GDS] – short version [15 items]<6; Beck, Steer, & Brown, 1996; Sheikh & Yesavage, 1986) and identified *n*=40 participants with elevated depressive symptoms.

MCI was diagnosed based on the classification criteria by Portet et al. (2006): A participant had to affirm a subjective cognitive impairment (e.g., forgetting names), at least one pathological objective cognitive impairment has to be examined clinically (regarding state of awareness, orientation, alertness, perception, concentration, and short and long term memory), or neuropsychologically in the MMSE (< 27), DemTect (<13), or cognitive domains (T<37.1) such as memory, attention, executive functioning, and speech from the Verbal Learning and Memory Test (VLMT; Helmstaedter et al., 2001), the Wechsler Memory Scale-revised (WMS-R; Härting et al., 2000), the Rey Complex Figure Test (CFT; Meyers and Meyers, 1996), the battery of Tests for Attentional Performance (TAP; Zimmermann and Fimm, 2009), and the Regensburger Wortflüssigkeitstest [Regensburger verbal fluency task] (RWT; Aschenbrenner et al., 2000)[7]. Moreover, the participant had to affirm that he or she had no impairment of daily activities (e.g., hygienic self-care) as well as an ordinary dementia (MMSE>23, DemTect>8), without elevated depressive symptoms. Applying these criteria, *n*=74 participants with MCI were identified.

For the analyses of the fNIRS data, additionally exclusion criteria were applied. A previous disease of the central nervous system (CNS; e.g., multiple sclerosis, epilepsy, pain syndrome, restless legs syndrome, stroke, head injuries, traumatic brain injury, cerebral bleeding, transient ischaemic attack, skull base fracture) was diagnosed in *n*=52 healthy volunteers and *n*=2 MCI participants during the examination. Also participants had to be excluded because of ADT specific exclusion criteria such as left-handedness to guarantee the comparability of the cortical structures (healthy: *n*=28; MCI: *n*=4), problems with ADT execution (still>5 errors after the third exercise run; more errors than >2 *SD* from *M*) during the trial (healthy: *n*=27; MCI: *n*=4), technical problems (healthy: *n*=19; MCI: *n*=2), as well as data specific exclusion criteria such as diverse missing data (healthy: *n*=12; MCI: *n*=3).

To compare the visual-spatial processing between MCI participants and healthy persons with as little influence of interfering variables as possible, the healthy control group was selected from the total sample (described in Haberstumpf et al., 2020) by using the statistical approach of propensity score method as described by Bacher (2002). Based on Katzorke et al. (2018), the following potentially confusing interference

[7] Subsequent author's note: The references of most of the here presented diagnostic test procedures (see also Figure 7, Tables 7 and 8) can be found in the general reference list (chapter 5.) due to the reprint of the accepted version of paper 2.

variables were checked: age, gender, educational level (in years), Apolipoprotein-ε (APOE), depression, and dementia in family history.

This resulted in an MCI sample with *n*=59 patients (26 females, 33 males) and a healthy comparison sample with *n*=59 (29 females, 30 males). The two groups did not differ in age, educational level (in years) and nonclinical depressive symptoms. There were also no significant differences in gender ($\chi^2_{(1,\ N=118)}$=0.31, *p*=.58), family history of dementia ($\chi^2_{(1,\ N=118)}$=1.35, *p*=.25) and APOE genotype ($\chi^2_{(5,\ N=118)}$=3.62, *p*=.61). The remaining healthy participants (*n*=287; 131 females, 156 males) were previously published to establish the paradigm with fNIRS (Haberstumpf et al., 2020). For a more in-depth analysis of potential compensatory mechanisms of MCI patients, the matched MCI patients (n=59) and healthy controls (n=59) were later matched into a sub-group based on their mean behavioral outcomes (reaction time [RT], number of errors [NE]) ± 1SD (each *n*=31; see also section 3). Also, the sub-group did not differ in the above mentioned covariates (more in detail: gender: $\chi^2_{(1,\ N=62)}$=1.64, *p*=.20; family history of dementia: $\chi^2_{(1,\ N=62)}$=1.35, *p*=.25; APOE genotype: $\chi^2_{(5,\ N=62)}$=2.84, *p*=.73). For details see Figure 7 and Tables 7 and 8.

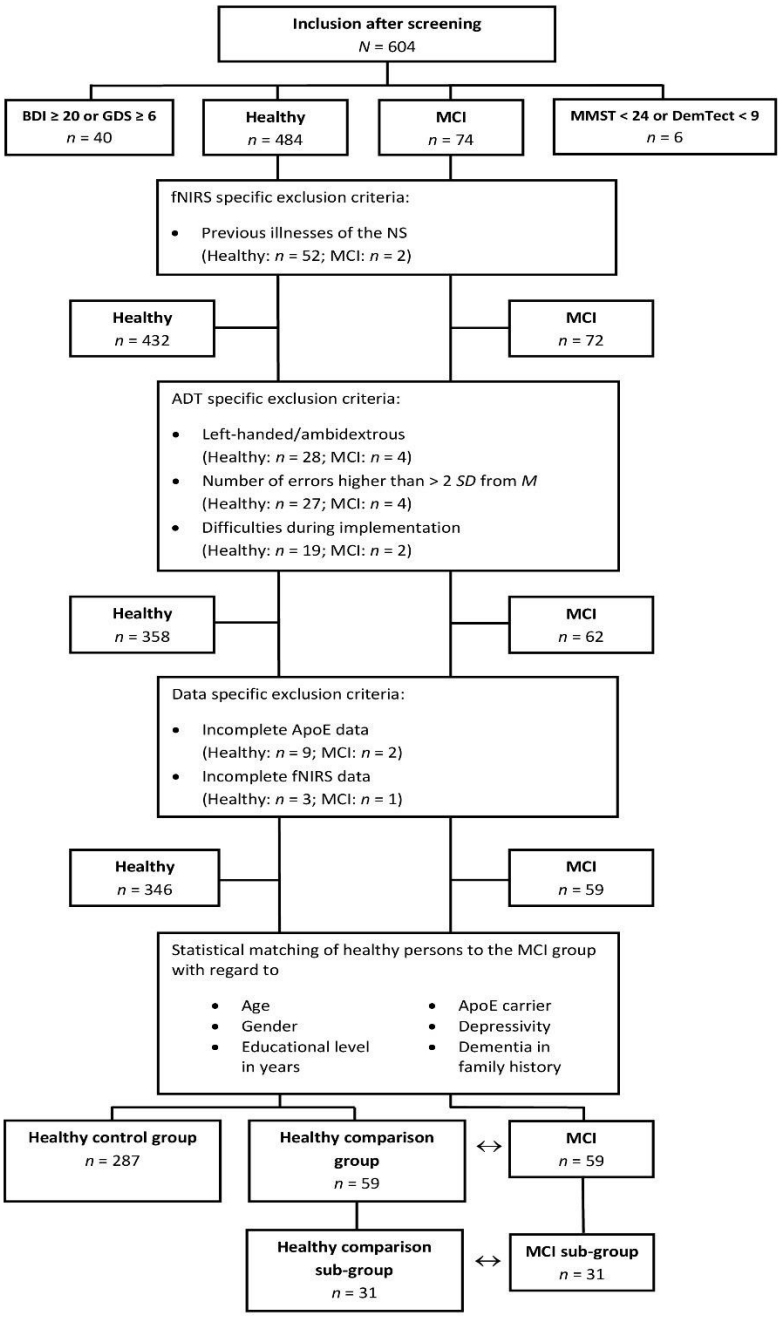

Figure 7. Course of exclusion for data analysis. BDI=Beck Depression Inventory-II (Beck et al., 1996); GDS=Geriatric Depression Screening Scale (Sheikh & Yesavage, 1986); MCI=Mild Cognitive Impairment; MMSE=Mini-Mental Status Examination (Folstein et al., 1975); DemTect=dementia detection test (Kalbe et al., 2004); fNIRS=functional Near-Infrared Spectroscopy; CNS=Central Nervous System; ADT=angle discrimination task; ApoE=Apolipoprotein-ε.

Table 7

Description of the two samples.

	MCI-group (*n* = 59)		Healthy comparison group (*n* = 59)		MCI vs. healthy comparison group		
	Male/Female		**Male/Female**		***Chi²***	***df***	***p***
	33/26		30/29		0.31	1	.58
	M	***SD***	***M***	***SD***	***t***	***df***	***p***
Age	74.1	1.6	73.6	1.5	-1.50	116	.14
Educational level	9.6	3.0	9.9	3.0	0.46	116	.65
BDI-II	5.6	3.5	6.0	4.8	0.46	106.74[a]	.64
GDS	1.3	1.2	1.4	1.5	0.41	111.78[a]	.69
MMSE	28.93	1.19	29.29	0.91	1.83	116	.07
DemTect	**15.19**	**2.31**	**16.14**	**2.12**	**2.33**	**116**	**.02**
ASI	12.82	10.61	15.86	11.66	1.47	114	.15
B-ADL	1.32	0.28	1.48	0.57	1.86	83.97	.07
CFT memory	54.97	10.70	57.58	7.50	1.52	114	.13
CFT visuoconstruction	70.20	10.12	71.00	9.37	0.44	116	.66
WMS-R digit span	**56.00**	**32.33**	**68.41**	**30.87**	**2.12**	**115**	**.04**
WMS-R block span	40.21	28.78	40.55	28.64	0.07	114	.95
VLMT immediate recall	**44.34**	**13.41**	**50.64**	**9.39**	**2.96**	**116**	**.004**
VLMT delayed recall	38.49	12.31	42.64	12.48	1.82	116	.07
VLMT recognition	**38.89**	**13.04**	**44.61**	**13.19**	**2.37**	**116**	**.02**
RWT verbal fluency	**43.10**	**26.75**	**55.49**	**26.91**	**2.51**	**116**	**.01**
RWT category fluency	**47.86**	**25.57**	**59.61**	**22.82**	**2.63**	**116**	**.01**
TAP tonic alertness	41.66	10.65	42.46	8.87	0.44	116	.66
TAP phasic alertness	48.58	11.93	46.93	10.76	-0.79	116	.43
TAP divided attention	46.25	15.01	50.56	14.45	1.58	115	.12
TAP compatibility	56.25	13.57	56.69	13.25	0.18	114	.86
TAP incompatibility	53.64	11.67	54.98	12.88	0.59	114	.56
TAP GoNoGo	48.51	10.19	48.52	9.47	0.01	116	.99

Note. Educational level=educational level in years; BDI-II=Beck-Depression-Inventory-II (Beck et al., 1996); GDS=Geriatric Depression Scale (Sheikh & Yesavage, 1986); MMSE=Mini-Mental-Status-Test (Folstein et al., 1975), DemTect=Dementia Detection Test (Kalbe et al., 2004), ASI=Anxiety Sensitivity Index (3rd version; Kemper, C. J., & Finnern, M., 2011), Bayer-Activities of Daily Living Scale (B-ADL; Hindmarch et al., 1998), Wechsler memory scale-revised (WMS-R; Härting et al., 2000), CFT=Rey Complex Figure Test (Meyers and Meyers, 1996), VLMT=Verbal learning and memory test (Helmstaedter et al., 2001), RWT=Regensburger Wortflüssigkeits-Test [Regensburger verbal fluency test] (Aschenbrenner et al., 2000), TAP=Testbatterie zur Aufmerksamkeitsprüfung [battery of tests for attentional performance] (Zimmermann and Fimm, 2009). [a]Correction due to heteroscedasticity.

Table 8

Description of the two subsamples matched on mean behavioral outcomes (reaction time [RT], number of errors [NE]).

	MCI group (*n* = 31)		Healthy comparison group (*n* = 31)		MCI vs. healthy comparison group		
	Male/Female		Male/Female		*Chi²*	*df*	*p*
	20/11		15/16		1.64	1	.200
	M	*SD*	*M*	*SD*	*t*	*df*	*p*
Age	73.90	1.66	73.74	1.32	-0.42	60	.673
Educational level	10.55	3.88	10.74	3.33	0.21	60	.834
BDI-II	4.97	3.05	6.26	5.08	1.21	49.14[a]	.231
GDS	1.35	1.11	1.42	1.34	0.21	60	.837
MMSE	29.10	1.17	29.29	0.94	0.72	60	.474
DemTect	15.65	1.94	15.94	1.86	0.60	60	.550
ASI	13.84	12.19	18.13	10.56	1.48	60	.230
B-ADL	**1.33**	**0.29**	**1.51**	**0.44**	**1.98**	**51.47[a]**	**.053**
CFT memory	55.26	11.75	57.22	5.76	.822	59	.414
CFT visuoconstruction	70.97	10.65	71.48	10.09	0.20	60	.845
WMS-R digit span	60.39	32.54	65.19	33.04	0.58	60	.566
WMS-R block span	43.43	28.90	43.29	29.56	-0.02	59	.985
VLMT immediate recall	**45.00**	**13.37**	**51.10**	**7.98**	**2.18**	**60**	**.033**
VLMT delayed recall	39.65	10.96	40.65	11.42	0.35	60	.726
VLMT recognition	39.87	13.47	44.65	13.42	1.40	60	.167
RWT verbal fluency	50.00	26.24	57.23	27.44	1.06	60	.294
RWT category fluency	51.10	27.42	55.94	19.22	0.80	60	.424
TAP tonic alertness	41.61	7.58	41.81	8.90	0.09	60	.927
TAP phasic alertness	47.77	10.88	46.48	10.51	-0.48	60	.637
TAP divided attention	**46.47**	**14.94**	**53.60**	**12.35**	**2.03**	**59**	**.047**
TAP compatibility	58.69	10.66	54.68	14.43	-1.25	60	.215
TAP incompatibility	55.77	10.59	54.55	14.81	-0.38	60	.709
TAP GoNoGo	50.65	11.26	49.44	10.52	-0.44	60	.664

Note. Educational level=educational level in years; BDI-II=Beck-Depression-Inventory-II (Beck et al., 1996); GDS=Geriatric Depression Scale (Sheikh & Yesavage, 1986); MMSE=Mini-Mental-Status-Test (Folstein et al., 1975), DemTect=Dementia Detection Test (Kalbe et al., 2004), ASI=Anxiety Sensitivity Index (3rd version; Kemper, C. J., & Finnern, M., 2011), Bayer-Activities of Daily Living Scale (B-ADL; Hindmarch et al., 1998), Wechsler memory scale-revised (WMS-R; Härting et al., 2000), CFT=Rey Complex Figure Test (Meyers and Meyers, 1996), VLMT=Verbal learning and memory test (Helmstaedter et al., 2001), RWT=Regensburger Wortflüssigkeits-Test [Regensburger verbal fluency test] (Aschenbrenner et al., 2000), TAP=Testbatterie zur Aufmerksamkeitsprüfung [battery of tests for attentional performance] (Zimmermann and Fimm, 2009). [a]Correction due to heteroscedasticity.

3.2.2.2 Clock-hand-angle discrimination task (ADT)

We used a modified version of the ADT (Lehmann et al., 2006; Vannini et al., 2004), to implement visual-spatial processing as described before (Haberstumpf et al., 2020). The participants were exposed to analogue clocks (yellow outlines/hand and black dial, see Figure 7) with a diameter of 18.5 cm on a black computer screen (18-inch diagonal display). The two hands of the clock varied in their angle to each other (40°, 60° or 80°) and in their length (short, middle, long), to modify the task difficulty (Vannini et al., 2004). The control task was a pointer-less clock. This resulted in 10 possible stimuli configurations, each presented 15 times in pseudorandomized sequence. The positioning of the hands was also alternated (=in total 150 stimuli).

The software *Presentation®* (Version 16.5, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) was used to design and produce the experiment and to record the reactions. While the subjects were placed at about 80 cm from the computer screen, they were instructed to press the "Left Arrow" button at a 60° angle of the hands using the right index finger. When one of the other angle sizes (40° or 80°) or the control condition appeared, the “right arrow” key should be pressed using the left middle finger (see Figure 8).

After the exercise runs had been successfully completed, in which each of the 10 stimuli combinations was presented once and had to be assigned correctly, the experiment began. After 10 seconds the first stimulus emerged on the black screen (duration of the stimulus presentation: 3 seconds), followed by an Inter-Stimulus-Interval (ISI; random variation between 2-4 seconds), during which a white fixation cross popped up in the middle of the monitor. The paradigm took a total of 15 minutes. Both RTs and the NE were recorded. During the task, the neuronal activity of the parietal cortex was recorded using fNIRS.

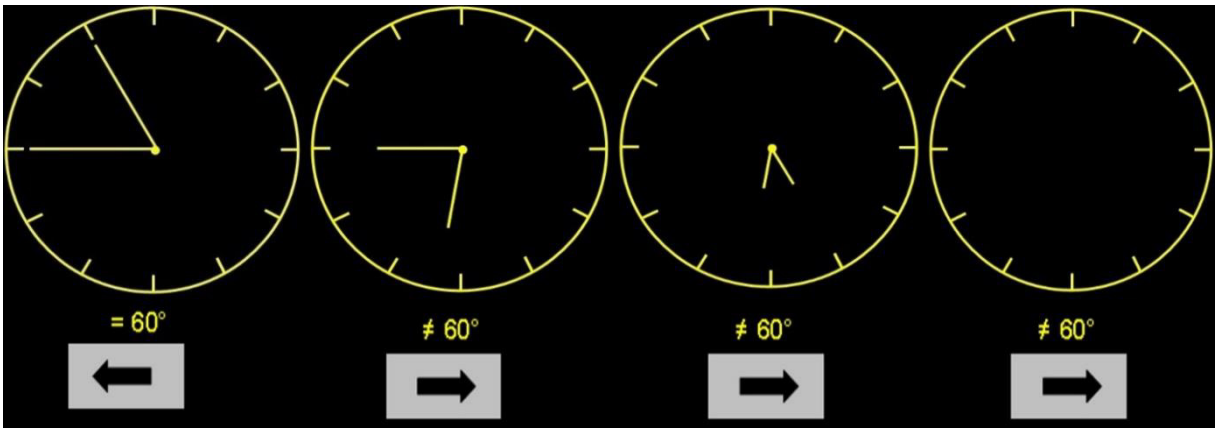

Figure 8. Sample stimuli of the clock-hand angle discrimination task (ADT) with instruction for the correct button press.

3.2.2.3 Functional near infrared spectroscopy (fNIRS)

The continuous wave fNIRS system ETG-4000 (Hitachi Medical Corporation, Tokyo, Japan) was used to measure the activity of the cerebral cortex. To ascertain the change in haemoglobin level, near-infrared light with two wavelengths (1: 695 nm±20 nm; 2: 830 nm±20 nm) was used and transmitted through the skull calotte to the parietal cortex with a sampling rate of 10 Hz. Parietal brain activity was measured for both hemispheres with identical sample sets, each consisting of eight laser emitters and seven photodetectors (arrangement 3x5), giving 22 channels in each case (channel=inter-optode distance of the emitters/detectors). Because of the 3 cm distance of the inter-optodes, the light entered about 1.5-2.5 cm deep into the parietal cortex (Hoshi, 2005).

An elastic hood was used to attach and link the two sample sets to the back of the subjects' heads. The international 10-20 system was used for positioning (Jasper, 1958). The electrode position Pz was used as a starting point to fix the emitters 17 and 27 on the right and left side. To reduce movement and muscle artifacts, participants were instructed not to move or bite their teeth together.

3.2.2.4 Data analysis

The statistical software *IBM SPSS* (Version 25, SPSS inc., USA) was used for the data analyses for both the behavioral parameters and the fNIRS data.

Behavioral parameters

There were two behavioral parameters that were captured: RT (=averaged over the individual conditions; in ms) and NE (=sum of errors and missings per condition). Since RTs are usually heavily skewed, we logarithmized the RT into ln(RT) as reported by Ratcliff (1993), for instance. Furthermore, a repeated measurement analysis of variance (ANOVA) was conducted with two intermediate subject factors: group (2: healthy comparison group, MCI) and gender (2: male, female). The pointer length represented the inner subject factor (3: short, middle, long).

At a significant alpha-level (α), which was set to .05, a post-hoc-*t*-tests with Bonferroni-corrected α was calculated (Holm, 1979). Sphericity was verified with the Mauchly's test and, if obligatory, the Greenhouse-Geisser-corrected values were submitted (Greenhouse & Geisser, 1959). The partial n^2 (n_p^2) was used to indicate the effect size of all analyses. Cohen's *d* was presented for *t*-tests.

Functional near-infrared spectroscopy (fNIRS)

Preparation of the fNIRS data

To smooth the data, the moving average filter with (time interval of 5 s) was used first. Next, slow drifts were patched using a high pass filter based on a cosine base function (high-pass filter: 0.08 Hz; low-pass filter: 0.5 Hz). Motion artifacts were reduced with a correlation-based method for signal enhancement, which was evolved by Cui, Bray, and Reiss (2010). This algorithm uses a linear combination of oxygenated and deoxygenated hemoglobin signals (oxy-Hb and deoxy-Hb) to eliminate large peaks due to head movement noise (and other white noise). As this recalculated value has the same properties as oxy-Hb, it was subsequently applied for further statistical analysis. The General Linear Model (GLM) was implemented for further data analysis of the fNIRS data. The implemented ordinary least-square regression model in which the hemodynamic response function (HRF) is determined by a Gaussian function with (peak time: 7.5 s), estimated beta weights. To determine a general, region-specific brain activity of the visual-spatial processing in the parietal cortex, the comparison between the experimental condition conditions (pointer length short vs. middle vs. long) and the control condition (= empty clock blade) was computed. Thus, we obtained an index for the activation of different brain regions.

Regions of Interest (ROI)

Because the channels of the parietal probe sets include a large area of the left and right hemisphere from the occipital to motor cortex, we defined Regions of Interest (ROIs) symmetrically over the left and right parietal cortex based on the results of our previous study in a sample of that age, consisting of channels #11, #12, #16, #20, #21, symmetrically on both hemispheres (for details see Haberstumpf et al., 2020 and Figure 9 for illustration). Referring to Okamoto et al. (2004), this area is part of the inferior (#11, #12) and the superior (#16, #20, #21) parietal cortex.

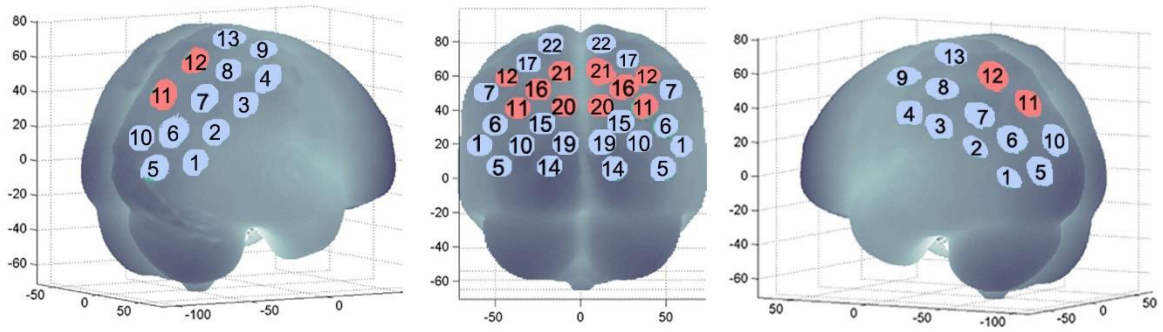

Figure 9. Graphical representation of the channel placement (blue) and the channels defined as Regions of Interest (ROI; red).

Statistical analyses

For the ROI analysis the beta weight of the GLM analyses of the corresponding channels were average for each condition and ROI per subject. To specify the effect between MCI participants and control group on the neuronal activation during the ADT we conducted a repeated measurement ANOVA with the between subject factor group (2: healthy control group, MCI participants). The internal subject factors were pointer length (3: short, middle, long), laterality (2: left, right), and brain region (2: superior, inferior). Additional single-channel GLMs were calculated. The same analyses were conducted for the above-described subsample.

Consistent with the behavioral data, we set a significance level of $p<.05$. The Mauchly's test was used to check the sphericity and the Greenhouse-Geisser correction was reported if necessary (Greenhouse & Geisser, 1959). The n_p^2 was used to indicate the effect size of all analyses. Significant results of the ROI analyses were corrected based

on the Bonferroni method for multiple testing with *α<.01 (p*<.05/5 ROIs) and followed up by post-hoc-*t*-tests if appropriate (Holm, 1979). For *t*-tests, Cohen's *d* was reported.

3.2.3 Results

3.2.3.1 Behavioral parameters

The analysis of the NE revealed significant main effects of the factors group as well as the pointer length (see Table 9).

Hence, MCI probands made significantly more errors as compared with the healthy comparison group (with MCI: *M*=2.53, *SD*=2.53 and healthy: *M*=1.46, *SD*=1.61).

In general, with decreasing pointer length, a higher NE was found for all probands (short vs. middle: *t*[117]=-6.65, *p*<.001, d_z=-0.54; short vs. long: *t*[117]=-7.71, *p*<.001, d_z=-0.75; middle vs. long: *t*[117]=-3.80, *p*<.001, d_z=-0.25; with short: *M*=3.18, *SD*=3.28; middle: *M*=1.67, *SD*=2.24; and long: *M*=1.13, *SD*=2.01).

There were no interaction effects.

Table 9

F-value, degrees of freedom (df), significance (p) and effect size (η_p^2) of the repeated measurement ANOVA for the number of errors analysis.

	F	df	*p*	η_p^2
Group	7.50	1.00; 116.00	**.007**	.061
Pointer	47.80	1.44; 167.48	**<.001**	.292
Group x Pointer	1.69	1.44; 167.48	.195	.014

Note. Pointer=pointer length. Greenhouse-Geisser-ε=.722. Bold *p*-values indicate significant results.

The analysis of the ln(RT) showed significant main effects group and pointer length and a significant interaction effect between both factors (see Table 10 and Figure 10). The interaction effect can be explained by slower reaction times for MCI patients within the middle and long pointer length conditions but not for the short pointer length condition (short: *t*[116]=-1.59, *p*=.114, d_z=-.29; with healthy: *M*=7.42, *SD*=0.16 and MCI: *M*=7.46, *SD*=0.16; middle: *t*[116]=-3.37, *p*=.001, d_z=-.62; with healthy: *M*=7.25,

SD=0.15 and MCI: *M*=7.35, *SD*=0.16; long: *t*[116]=-4.06, *p*<.001, d_z=-.75; with healthy: *M*=7.13, *SD*=0.15 and MCI: *M*=7.24, *SD*=0.14).

Table 10

F-value, degrees of freedom (df), significance (p) and effect size (η_p^2) of the repeated measurement ANOVA for the logarithmized reaction time analysis.

	F	df	*p*	η_p^2
Group x pointer	5.88	1.42; 164.16	**.008**	.048
Group	10.68	1.00; 116.00	**.001**	.084
Pointer	344.02	1.42; 164.16	**<.001**	.748

Note. Pointer=pointer length. Greenhouse-Geisser-ε=.708. Bold *p*-values indicate significant results.

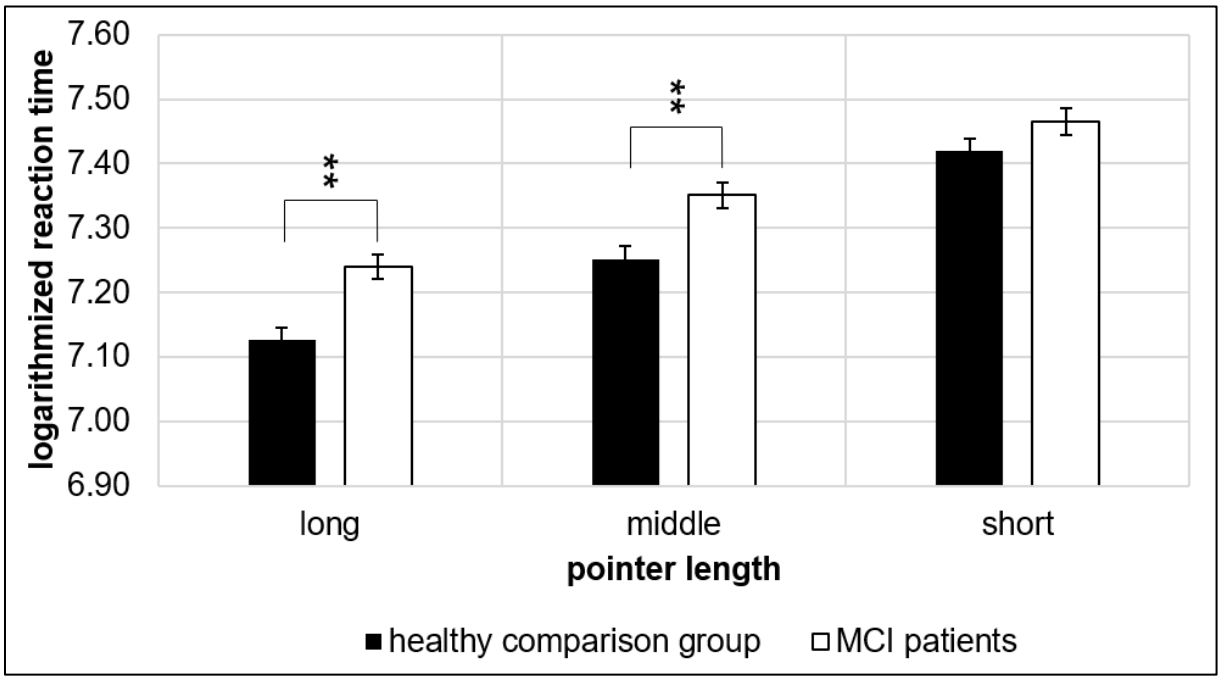

Figure 10. Interaction effect "pointer length x group" of the repeated measurement ANOVA concerning the logarithmized reaction time. Significant differences were noted (**=p<.001).

3.2.3.2 Neuronal activity measured with fNIRS

With regard to neuronal activity, a significant main effect of group (F(1, 116)=4.55, p=.035, η_p^2=.038) was observed. The subsequent mean value comparison indicated a generally decreased brain activity in the ROI of the MCI participants compared to the healthy participants (with MCI participants: M=0.03, SD=0.04 and healthy participants: M=0.05, SD=0.05).

The factor laterality also had a main effect (F[1.00, 116.00]=17.93, GG-ε=1.00, p<.001, η_p^2=.134). This was due to an increased activity in the right compared to the left hemisphere (with right hemisphere: M=0.04, SD=0.05 and left hemisphere: M=0.03, SD=0.05).

Moreover, an interaction effect "pointer length x brain region" could be revealed (F[1.84, 209.56]=4.84, p=.011, η_p^2=.04). Highly significant differences could be found between all three pointer lengths and both brain regions (see Table 11). However, the linear increase of parietal cortex activity in both brain regions with increasing task difficulty from long to short pointer length did not differ significantly (t[117]=1.82, p=.071, d_z=.07, with superior activation: M=0.01, SD=0.04, inferior activation: M=0.01, SD=0.04). Keeping the results from our behavioral data in mind (ln(RT)), analyses confirmed the linear increase of brain activity between both brain regions and the long and middle pointer length difference (t[117]=3.30, p=.001, d_z=.14, with superior activation: M=0.01, SD=0.03, inferior activation: M=0.00, SD=0.03; see Figure 11). For more details concerning the repeated-measurements ANOVA, see also Supplementary Table 1 in appendix[8].

[8] Please see chapter 6. (general thesis) for all supplementary tables of the **four** publications.

Table 11

Significant differences between the test pairs of the interaction effect "pointer length x brain region".

Pointer length	Brain region	*M*	*SE*	*t*	*p*	d_z
long	SPC	0.04	0.05	4.60	**<.001**	.02
	IPC	0.03	0.05			
middle	SPC	0.04	0.06	5.88	**<.001**	.24
	IPC	0.03	0.05			
short	SPC	0.05	0.06	4.65	**<.001**	.20
	IPC	0.04	0.06			

Note. SPC=superior parietal cortex, IPC=inferior parietal cortex, *M*=mean, *SE*=standard error. Df=117. Bold *p*-values indicate significant *t*-values.

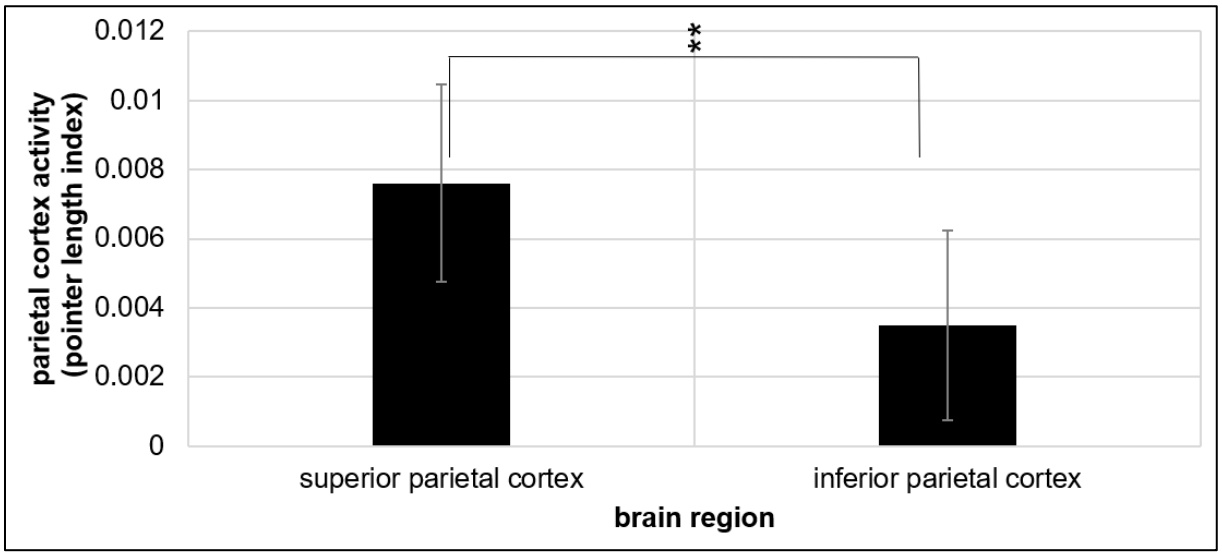

Figure 11. Linear increasing parietal cortex activity for the pointer length index (middle – long difference) regarding the interaction effect "pointer length x brain region". Significant differences were noted (**=p<.001).

Additionally, to the ROI analysis described above, we aimed to investigate the effects of MCI on a single channel level for the 5 ROI-channels (#11, #12, #16, #20. #21). Interestingly, channel wise repeated measurement ANOVAs revealed a significant interaction effect “laterality x group” in channel #21, which is localized in our defined ROI (F[1.00, 116.00]=5.87, p=.023, η_p^2=.04). Highly significant differences could be found between both groups in the right hemisphere (t[91.59]=3.00, p=.003, d_z=.55, with healthy: M=0.06, SD=0.07 and MCI: M=0.02, SD=0.04; see Figure 12). A further computed laterality index (right – left hemisphere) showed a significant decrease in laterality in the MCI group compared to the healthy control group for channel #21 (t[116]=2.31, p=.023, d_z=.42, with healthy: M=0.01, SD=0.04 and MCI: M=0.00, SD=0.02; see Figure 13).

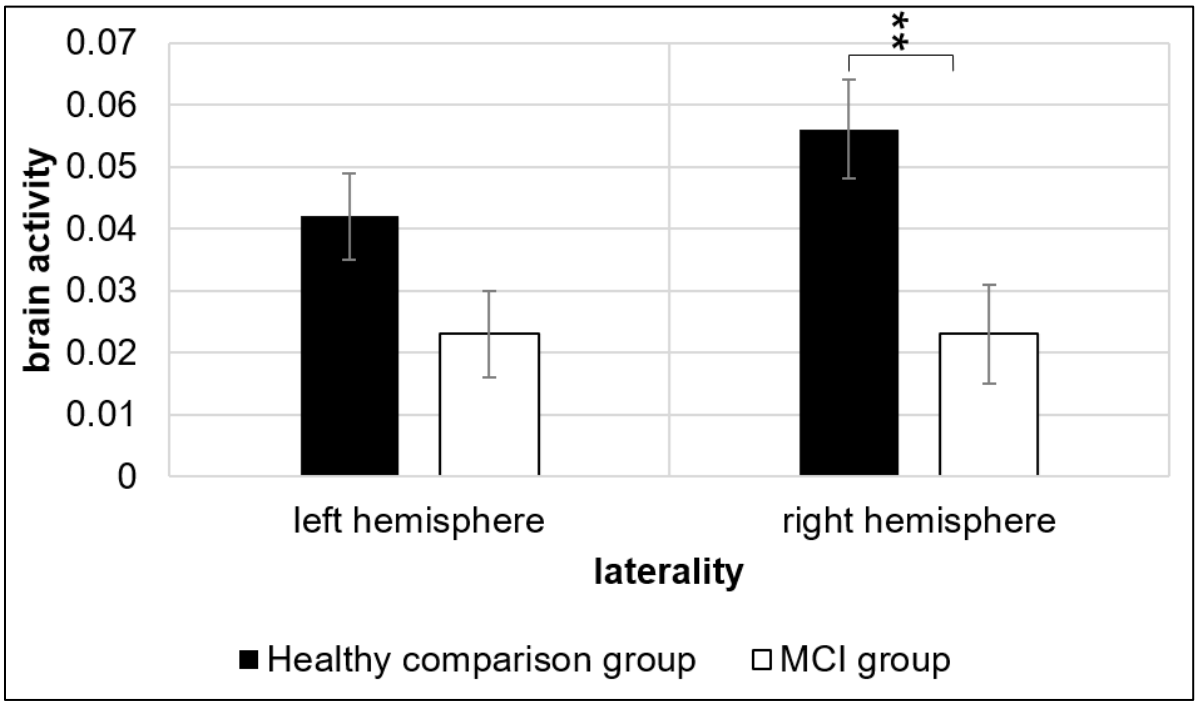

Figure 12. General Interaction effect “laterality x group” for channel #21. Significant differences were noted (**=p<.001).

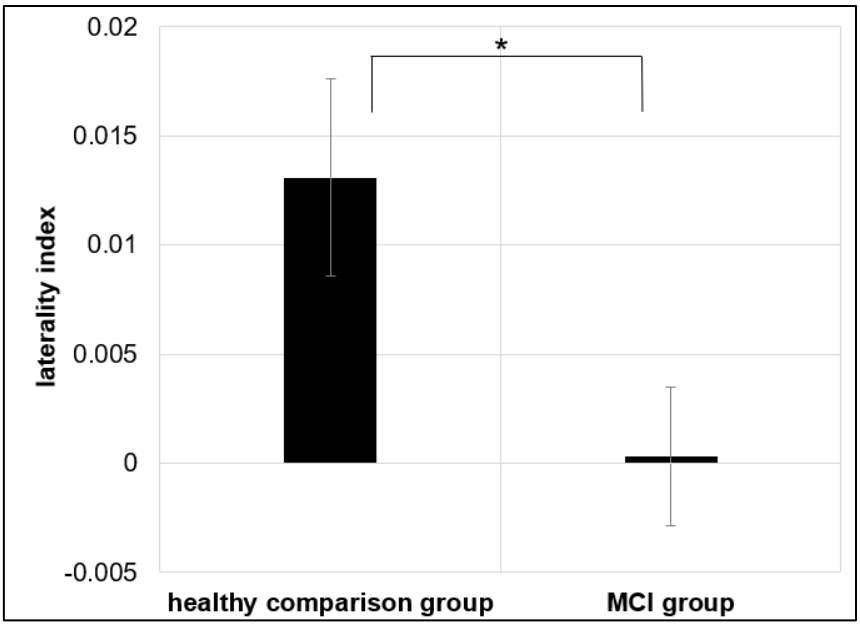

Figure 13. Laterality index of the interaction effect "laterality x group" for channel #21. Significant differences were noted (*=p<.05).

In detail, due to the concurrent observed behavioral deficits and neuronal hypoactivity in MCI participants, we matched a subgroup of *n*=31 MCI participants and *n*=31 healthy controls that did not differ significantly in behavioral performance (ln(RT) and NE) to reveal potential compensatory brain activity in the MCI participants (ln(RT): *t*[60]=-1.63, *p*=.108, d_z=-.41; NE: *t*[60]=-1.19, *p*=.238, d_z=-.30; see also section 2.[9]).

Concerning neuronal activity within our matched subsample, only significant main effects occurred. Similar to the previous analysis, the main effect group (*F*(1, 60)=5.73, *p*=.020, η_p^2=.087) was observed in the sense of parietal hypoactivity in MCI participants opposed to healthy participants (with MCI participants: *M*=0.02, *SD*=0.01 and healthy participants: *M*=0.06, *SD*=0.01).

Also, we found the significant main effect for laterality (F(1, 60)=6.71, p=.012, η_p^2=.101). Increased activity was again evident in the right hemisphere (with right hemisphere: M=0.043, SD=0.01 and left hemisphere: M=0.035, SD=0.01).

Moreover, we observed a highly significant main effect of brain region (*F*(1, 60)=16.89, *p*<.001, η_p^2=.220) with higher activity in the superior parietal cortex region within both

[9] Please note that this section now is numbered 3.2.2.

sample subgroups (superior activation*: M=0.05, SD=0.01*, inferior activation: *M=0.03, SD=0.01*).

Based on GLMs at the channel-wise level outside the ROI, MCI participants of the subsample showed parietal hypoactivity in every single of the remaining 17 channels, often combined with significant main effects of group affiliation. After Bonferroni α-adjustment (p<.003), no significant main effects remained (see Table 12).

Table 12

General Linear Models (GLMs) of the main effect subgroup performed for each channel to identify possible compensating mechanisms.

Channel	*F*	*p*	η_p^2	**Channel**	*F*	*p*	η_p^2
01	0.76	.387	.012	**10**	2.24	.140	.036
02	1.10	.299	.018	**13**	4.66	.035	.072
03	7.08	.010	.106	**14**	1.20	.277	.020
04	1.34	.251	.022	**15**	5.92	.018	.090
05	1.08	.303	.018	**17**	3.59	.063	.057
06	6.79	.012	.102	**18**	3.44	.072	.053
07	4.49	.038	.070	**19**	0.07	.794	.001
08	3.87	.054	.061	**22**	3.08	.084	.049
09	2.16	.147	.035	**-**	**-**	**-**	**-**

Note. df = 1, 60. No significant main effects remained after Bonferroni α-adjustment (p<.003).

3.2.4 Discussion

Several studies revealed behavioral and neuronal deficits in MCI patients as compared with healthy individuals. Especially deficits in visual-spatial functioning seemed to be characteristically. Thus, the ADT was often used to measure the visual-spatial performance. Nevertheless, studies applying the ADT paradigm during fNIRS implementation were limited in availability and hence were not reasonably interpretable because of the small number (Chrem Mendez et al., 2019; Lashley et al., 2018; Lawrence et al., 2017; Metzger et al., 2016; Yeung & Chan, 2020). In consequence,

we conducted a study with 59 MCI patients and 59 perfectly matched healthy controls (by age, gender, educational level, depressive stress, dementia history in the family and ApoE) which was successful in describing deficits in MCI at both the behavioral and neuronal level.

Firstly, and as expected, MCI patients showed behavioral deficits compared to the healthy controls, with higher NE over all conditions of pointer length and higher reaction times in the long and middle pointer length condition. Thus, the MCI participants found it more difficult to cope with the visual-spatial task. It appears plausible that affective-motivational aspects may contribute to the behavioral deficits of the MCI patients, as MCI can be a precursor of AD. The most frequent behavioral symptoms of MCI are apathy and loss of interest (Ramakers et al., 2010; van Dalen, Van Wanrooij, Moll van Charante, Richard, & van Gool, 2018). However, no significant differences in depressive symptoms were detectable between both subsamples which is why we excluded this explanation as single interpretation for our results (see also Table 7).

Secondly, fNIRS analyses revealed that the deficits on the behavioral level were accompanied by a significant reduction of parietal cortex activation in MCI patients. The fact that reduced parietal activity and visual-spatial performance losses occurred simultaneously suggests the assumption that our MCI participants were unable to compensate for deficits in visual-spatial processing. Therefore, their performance was worse than in the healthy sample.

In other studies, it is reported that MCI participants, compared to AD participants, are still able to compensate deficits in visual-spatial processing by stronger or additional activation of neuronal correlates (Bokde et al., 2008; for a review see Jacobs et al., 2012). In the study of Bodke et al (2008) the Petersen et al. (1999) criteria for MCI diagnosis were applied compared to the Portet et al. (2006) criteria used in our study. In our case, such compensatory mechanisms seemed to be unlikely because of the objective neuronal deficits. Yet there are further studies on visual-spatial processing in AD participants supporting the hypothesis of hypoactivity in the parietal lobe (Prvulovic et al., 2002; Thulborn, Martin, & Voyvodic, 2000; Vannini et al., 2008; Zeller et al., 2010). A look at participants with AD is of particular interest because up to 20% of all participants develop an AD from MCI (Bokde et al., 2008). An example is the study by Vannini et al. (2007), in which cerebral activity during the ADT of 18 MCI participants was compared with 13 matched healthy subjects. At baseline both groups showed

overlapping activation in the superior parietal structures involved in visual-spatial processing. However, at a 3-year follow-up, individuals who had progressed to AD showed increased brain activity in the left superior parietal cortex without concomitant changes on the behavioral level as compared with stable MCI patients. The authors interpreted this as a compensation mechanism. This means that MCI participants had to recruit more neuronal resources to cope with the visual-spatial task. In a later study, Vannini et al. (2008) matched 13 AD patients with 13 healthy controls and found out that, as compared with the healthy controls and with increasing task difficulty, AD patients showed both a parietal hypoactivity and a lower behavioral accuracy indicating that compensatory mechanisms were no longer possible.

Moreover, as tested within the MCI and healthy subsamples matched on terms of similar behavioral performance, significant parietal cortex hypoactivity again occurred in the MCI sample. This result further confirms our assumption that the MCI group has no compensation within parietal brain activation. Indeed, for future research, some more aspects may be considered to explain parietal hypoactivity in MCI participants with comparable behavioral performance as in the healthy comparison group. For example, one possible reason for the observed hypoactivity and the assumption of a lack of compensatory mechanisms in MCI participants could be models of compensatory mechanisms in other parts of the human brain known from aging research (Martins et al., 2015; Prvulovic et al., 2005). More in detail, the so-called Posterior-Anterior Shift in Aging Model (PASA) describes age-related increases in frontal activity with a simultaneous decrease in posterior brain activity (here: occipital lobe; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Dennis & Cabeza 2008; Grady et al., 1994). Positive correlations with performance benefits suggested underlying compensatory mechanisms. Thus, beyond the successful application of fNIRS to the parietal cortex, it may be interesting to compare these findings with those from, e.g., functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG) studies, as well as to measure covariances between activation patterns of different brain areas to further explore compensatory connectivity, e.g., via the ventral visual pathway (Prvulovic et al., 2002). Another example to explain the observed phenomenon besides mere compensation model approaches is that neural resources may play an important role. The CRUNCH model states that as cognitive impairment increases, more neural resources are required at even lower task loads (e.g.,

visuospatial tasks) to maintain behavioral performance, and resource limits are reached earlier than in healthier or younger individuals. At the “CRUNCH point”, cognitive load increases in a way resulting in a plateau or decreasing brain activity which further results in performance deficits (Cappell et al., 2010; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005). In turn, regarding our analysis, we could assume that our MCI participants were currently at the CRUNCH point, in the sense that although performance comparable to healthy individuals could still be achieved, deficits must soon be expected because brain activity just has reached its limit. Thus, if we assume that the MCI participants of the subsample already had fewer or limited resources at the investigation, an increase in task difficulty could result in both lower brain activation and performance deficits being evident in the MCI participants, leaving no subsample intersection of comparable performance between the highest-performing MCI participants and the lowest-performing healthy participants. All in all, this assumption emphasizes the relevance of longitudinal follow-up investigations.

Besides the above discussed methodological limitations, it should be mentioned that there is a lack of a uniform definition of MCI (Reischies & Bürker, 2005). The diagnostic criteria and the selected subcategories of the MCI vary across the studies, which makes the external validity and, thus, the generalizability of the findings more difficult (Janelidze & Botchorishvili, 2018). As MCI participants thus are a heterogeneous group, it cannot be precluded that, despite cognitive impairment, there are high-performers in the group of MCI participants who, for example, report high subjective impairment in addition to objective test and imaging deficits and as a result receive the MCI diagnosis, but show comparable performance with some healthy subjects. However, we defined MCI as usual, referring to the classification criteria by Portet et al. (2006). These criteria largely overlap with other commonly used MCI criteria such as those used by Petersen et al. (1999). These authors consider, for example, memory impairments with still intact cognitive functions for the diagnosis of MCI as compared to controls and AD patients. Moreover, our collective seemed to be comparable to other MCI samples (for example Bokde et al., 2008, with a MCI sample revealing a M=27.2 and ±1.5 SD in MMSE). Nevertheless, within our MCI patients a mean of 28.93 (±1.19 SD) in the Mini Mental State Examination (MMSE) could be found whereas Vannini et al. (2008) described a mean MMSE score of about 25.5 (±2.33 SD) in their ‘mild AD’

sample. Apparently, Vannini et al. (2008) investigated a much more diseased sample indicating caution when comparing studies on an objective level.

In conclusion, fNIRS can successfully be implemented in the measurement of visual-spatial processing in MCI patients and healthy elderly based on ADT. Our analysis revealed on the behavioral level that MCI patients made more errors and showed higher reaction times as compared to matched healthy individuals with increasing task difficulty. On the neuronal level, a hypoactivity in the parietal cortex could be found for MCI patients. Right hemispheric and superior parietal cortex regions appear to be generally more strongly associated with brain activity. Thus, it can be assumed that the MCI participants were no longer able to compensate for deficits in parietal activation by stronger activation and therefore showed measurable difficulties in performing the ADT. It would be advisable to conduct more studies as ours to gain a deeper understanding of the underlying mechanisms and to make use of the power of brain imaging techniques. Especially the more in-depth analysis of possible compensatory mechanisms in subsamples of comparable behavioral performance would be a gain in knowledge. Based on both these and previous findings in Haberstumpf et al. (2020), we suggest that the hemodynamic response during visual-spatial processing tasks, localized in the parietal cortex, is a reliable diagnostic biomarker of neurodegeneration not only for the diagnosis of MCI, but also for the (predictive) early detection of AD in high-risk groups such as those with MCI.

Contributors

Sophia Haberstumpf, Alexandra Seidel, and Martin J. Herrmann analyzed the data and wrote the first draft of the paper. Martin Lauer and Thomas Polak conducted and monitored medical investigations. Thomas Polak, Jürgen Deckert, and Martin J. Herrmann designed the study and were involved in data acquisition. All authors revised the paper, made considerable submissions, and agreed to the final paper to be published.

Declaration of competing interest

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3.2.5 References of Paper 2

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3.2.6 Implications for the third study

The second study confirmed the hypothesis that MCI patients showed significantly lower parietal cortex activation during the baseline fNIRS measurement of visual-spatial processing compared to a healthy control group. In addition, MCI patients made significantly more errors in all three difficulty levels of the ADT paradigm and had higher RTs in the long and middle pointer length conditions. Obviously, they had greater difficulty in processing the paradigm than the healthy study participants. Both the MCI patients and the healthy study participants showed significant right-hemispheric and superior parietal activation patterns, like the first study results. The parallel occurring activation and behavioral deficits in the MCI patients did not indicate compensatory processes. To gain more insights into possible underlying compensatory mechanisms, a subgroup comparison was performed, including only MCI patients and healthy study participants with comparable behavioral performance. However, this comparison also showed significantly lower parietal cortex activation in the group of MCI patients compared with the healthy sample. Thus, no evidence for compensatory mechanisms could be found in the parietal cortex.

Subsequent considerations led to the question to what extent an additional contribution neuropsychiatric diagnostic can provide for the early detection of MCI/AD beyond the use of imaging techniques. Is it possible to define pathological cognitive decline on a dimensional level beyond categorical diagnostic classifications by including the first follow-up and can this lead to even more reliable results? Can predictions of pathological cognitive decline be made, or at least changes detected? The aim for the third study was, therefore, to define latent cognitive domains within the total sample and to predict their change between the first two measurement time points based on possible risk factors.

3.3 Paper 3: Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research

Prediction of pathological cognitive decline

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Abstract

Objective: Alzheimer's disease (AD) is a growing challenge worldwide, which is why the search for early-onset predictors must be focused as soon as possible. Longitudinal studies that investigate courses of neuropsychological and other variables screen for such predictors correlated to mild cognitive impairment (MCI). However, one often neglected issue in analyses of such studies is measurement invariance (MI), which is often assumed but not tested for. This study uses the absence of MI (non-MI) and latent factor scores instead of composite variables to assess properties of cognitive domains, compensation mechanisms, and their predictability to establish a method for a more comprehensive understanding of pathological cognitive decline.

Methods: An exploratory factor analysis (EFA) and a set of increasingly restricted confirmatory factor analyses (CFAs) were conducted to find latent factors, compare them with the composite approach, and to test for longitudinal (partial-)MI in a neuropsychiatric test battery, consisting of 14 test variables. A total of 330 elderly (mean age: 73.78 $\pm$ 1.52 years at baseline) was analyzed two times (3 years apart).

Results: EFA revealed a four-factor model representing declarative memory, attention, working memory, and visual-spatial processing. Based on CFA, an accurate model was estimated across both measurement timepoints. Partial non-MI was found for parameters such as loadings, test- and latent factor intercepts as well as latent factor variances. The latent factor approach was preferable to the composite approach.

Conclusion: The overall assessment of non-MI latent factors may pose a possible target for this field of research. Hence, the non-MI of variances indicated variables that are especially suited for the prediction of pathological cognitive decline, while non-MI of intercepts indicated general aging related decline. As a result, the sole assessment of MI may help to distinguish pathological from normative aging processes and additionally may reveal compensatory neuropsychological mechanisms.

Keywords: latent factors; measurement invariance; composite; neuropsychiatric test battery; cognitive decline.

3.3.1 Introduction

Mild cognitive impairment (MCI) and Alzheimer's disease (AD). Due to the constantly aging society, neurodegenerative diseases such as dementia represent a growing challenge for health care systems worldwide (Abbott, 2011; Bickel, 2001; Prince et al., 2013). Affecting 60-70% of people suffering from dementia, one of the most usual forms is Alzheimer's disease (AD; World Health Organization [WHO], 2016). An early indicator is mild cognitive impairment (MCI), which often progresses into AD (Arnáiz & Almkvist, 2003). According to Petersen (2000), 10-15% of MCI patients convert into AD per year, and up to 15-20% of the general population express MCI symptomatology. Even though there is no cure available to date, early interventions can dampen the course of the disease (Mayeux, 2010; Winblad et al., 2006), which highlights the necessity of diagnostics in the early stages. Thus, finding variables with high predictive power for neuropsychiatric changes is a focus of MCI related research.

According to the consensus formulated in DSM-V and ICD-10 (American Psychiatric Association, 2014; World Health Organization [WHO], 2019), diagnostics of MCI and AD heavily rely on neuropsychiatric tests as their first symptoms are deficits in cognitive performance such as memory loss (Arnáiz & Almkvist, 2003; Jahn, 2013; Nestor et al., 2006; Riedel & Blokland, 2015). As a result, finding predictors for such neuropsychological symptoms may elude to targets for early interventions. The statistically and methodologically most efficient way to address this topic is analyzing longitudinal within-subject course data (Cooper et al., 2015; Hendrix et al., 2015; Makkar et al., 2020).

Shortcomings of the composite approach. A valid approach to increase robustness and significance of prediction analyses may be to create composite variables consisting of a sum- or average-score of potential predictors of interest. For example, multiple performance scores can be combined by forming a composite score. However, by simply adding the test scores, it is implicitly assumed that all scores are equally meaningful for the target construct (e.g., declarative memory). However, since the target construct is often a latent factor, it should be empirically verified that this assumption is indeed true. To do so, however, a latent factor approach would be more adequate. This problem is further complicated by the fact that the extent to which a predictor is relevant to the latent construct can vary across groups and over time. As a

result, both the classical composite approach and weighted composite approaches that impose fixed weights on scores within the composite (e.g., 1×immediate memory performance+0.3×working memory performance=latent memory ability) may fall short if the actual relationship of the manifest test scores differs from the weights chosen by the researcher (in the classical approach, each variable is multiplied by a weight of 1). Factor analyses may provide the most reliable weights for calculating composites. This may be particularly the case in longitudinal studies, as weights may change over time, which may affect the comparability of measurement occasions within the follow-up data. This effect ("response shift") has been described in other areas of research (e.g., Oort, 2005). However, different weights are not the only parameters that can change over time, which further complicates analyses and suggest new ways to examine course data in detail. For instance, if a sample achieved a mean score of 10 on a composite variable described by researchers as an indicator of memory at both the first and second measurement occasions, one would conclude that the sample's memory performance had not changed. However, this null finding could be misleading, as this sample's latent declarative memory performance may have decreased, even if this did not manifest in the composite variable due to compensatory mechanisms (e.g., coping strategies, test-memory effects). Thus, to estimate latent ability changes and to detect effect-concealing or inflating mechanisms, the intercorrelation matrix of different neuropsychiatric tests can be used. For example, an altered covariation between memory and attention scores at the second measurement occasion may indicate that the ability to modulate attention might make a decline in memory performance less noticeable. Also, memory abilities might have a lower covariance with other latent skills if its scores were affected by retest effects, while other neuropsychiatric domains were not. Hence, merit lies in the analysis of test score interplays rather than absolute values. The classical method to deal with such complex matrices between multiple test scores is the (confirmatory) factor analysis, which extracts latent abilities from manifest test scores and estimates changes in the intercorrelation of manifest and latent variables based on these data. In summary, this approach investigates the equivalence of parameters within a structural equation model (SEM) across groups/time and can find indicators of possible bias mechanisms that may distort the results of the composite approach. Measurement invariance (MI; no significant variation of a parameter across groups/time) of parameters would imply that the manifest sum score

approach would be largely unbiased. The following section gives interpretations for (non-)invariance for a subset of central parameters within such analyses.

Longitudinal MI. In most studies investigating MI, SEM comparing increasingly restricted confirmatory factor models is the method of choice. Due to its ability to integrate latent and observed variables out of many test variables, this approach is expected to offer an appropriate statistical method to reveal latent factor structures and to prove construct validity by factorial invariance measurements of neuropsychiatric test batteries across time, sample subgroups and different cognitive levels (Berndt & Williams, 2013; Kline, 2005; Mungas et al., 2011; Park & Festini, 2017; Rahmadi et al., 2018; Rowe, 2010; Schumacker & Lomax, 2004).

Intercepts. One often recognized MI parameter is the estimated intercept of single items/tests and latent means. In the context of regression (which reflects the relationship of a latent factor to its manifest indicators), intercepts reflect the (grand) mean score of a given population. Non-MI, e.g., in-/decreases in intercepts, may thus reflect sample-level in-/decreases of latent traits (latent trait level) or manifest test-performance (indicator level). In turn, non-MI of intercepts can be interpreted similarly to in-/decreases in composite scores: It indicates changes of ability (on a latent factor level) or test-performance (on the indicator level). Thus, this kind of invariance violation would not be a problem in longitudinal MI research but reflects an anticipated effect.

Variances. Another indicator for performance change are variances, as these may (inter alia) increase if at least two groups of individuals develop in different directions. In contrast, whole-population changes in one direction would only result in intercept but not variance changes. Therefore, non-MI of variances (on latent and indicator levels) would not be a problem but could indicate subpopulations within the sample.

From this perspective, an increase in latent factor score variance may highlight that some participants depict no change in the target construct or even increases while others suffered from decreases. On the other hand, decreasing variances over time may indicate retest effects that diminish inter-individual differences in performance capability or the diminishing influence of variance-inducing third variables such as trait anxiety (e.g., habituation effects) or simply normative aging processes that diminish smaller interindividual differences over time.

However, other mechanisms may lead to similar changes in variance. For instance, increases in variance may also be attributable to increasingly fluctuating cognitive

capabilities following cognitive decline and aging in general. Nonetheless, in the context of neuropsychological longitudinal MI research, non-invariance of variances may indicate that a certain domain is especially potent to distinguish healthy from abnormal courses or to at least indicate a certain cognitive domain to show some kind of aging-dependent variability.

Loadings. Another parameter that may show non-(MI) is the correlation of indicators and latent factors, which resembles weights within the composite approach. If loadings that previously were small enough to be neglected in increase to the extent that a new indicator should be added to the model or shifted from one latent factor to another, the factor structure may change in its entirety (Cheung & Rensvold, 2002; Oort, 2005).

In the context of neuropsychiatric measures, the neuronal bases of performance in psychometric tests may change (e.g., verbal skills deficits may affect memory performance and lead to a reorganization of the factor structure). However, this effect may also be observed in normative age-related processes.

Nonetheless, regardless of the etiology of the loading shifts, invariance across measurement occasions would be a requirement of the classical composite approach, as it implicitly assumes that all included variables contribute equally to the neuropsychiatric domain. Usually, weighted composite calculations are more beneficial. As weights of all variables entering a composite should reflect the loading of indicators on the latent factors, non-MI over time would imply that weights should also vary over time. Thus, non-MI is a general issue in this context and may highlight the shortcomings of classical composite approaches.

Longitudinal MI research based on neuropsychiatric test-batteries. In contrast to the vast number of longitudinal research papers implemented on the prediction and the course of MCI/AD, far fewer of these have focused on latent factor structures and factorial invariance underlying cognitive domains within neuropsychiatric test batteries to ensure generalizability (National Institute of Mental Health, 2011; Wicherts, 2016). Rather, some studies used the SEM approach to investigate between-group-MI (Avila et al., 2020; Mitchell et al., 2012; Mungas et al., 2011; Sayegh & Knight, 2014; Tuokko et al., 2009). Others investigated latent factors and tested for MI in neuropsychiatric test batteries without keeping the longitudinal aspect in mind (Ma et al., 2021).

To our knowledge, only a few longitudinal measurement invariance studies, including the within-group latent factor approach based on neuropsychiatric test batteries, were

published: For example, in a large multicenter sample of *N*=12020 cognitively healthy participants and participants with diagnosed MCI or dementia (age: ≥55 years; *M*=75.6 years), researchers derived a four-factor structure from a neuropsychiatric battery (12 test variables) including the factors memory, attention, executive function, and language (Hayden et al., 2011; Hayden et al., 2014). These factors remained invariant across the span of 1 year and predicted sample subgroups and cognitive impairment 3 years later. Moreover, Moreira et al. (2018) examined a two-factor model including memory performance and executive functioning in an elderly sample of 86 participants from a neuropsychiatric test battery. Defined factors remained invariant for two years. Similar studies concentrated on the two factors memory and executive functioning, extracted out of large test batteries over periods of up to eight years (Bertola et al., 2021; Williams et al., 2018).

Aims of the current study. As part of the prospective, observational, long-term follow-up "Vogel Study" of a large German sample (*M*=73.9 ± 1.55 years of age at first out of three visits; see also Polak et al., 2017; Haberstumpf et al., 2020; Katzorke et al., 2018; Katzorke et al., 2017; Zeller et al., 2019), this current analysis aims to investigate longitudinal MI in a sample of (mostly) healthy elderly (at the first measurement occasion) over 3 years. However, in contrast to between-group MI-testing, we hypothesize and aim for the absence of MI especially concerning variances of latent and manifest variables, as these may indicate at least two groups of participants differing in their performance trajectory over time. Other mechanisms that may also result in increased variance may hint towards the importance of affected variables as potential targets for future studies. An Increased variance may be result from the cognitive decline within the total sample (instead of within two distinct groups), which leads to more fluctuation in performance and thus longitudinal heteroscedasticity (Koscik et al., 2016). Nonetheless, non-MI would still provide for the insight that the affected variable is a valuable candidate for further investigation as it would have been indicated to be sensitive for cognitive decline or aging in general (see more on this in section 4[10]). This non-MI may thus single out promising variables for further analyses as they possibly differentiate normal from pathological cognitive changes. Moreover, general decreases in intercept estimates (in both latent and manifest variables) are also anticipated, reflecting sample based average changes in cognitive abilities on a

[10] Please note that this section now is numbered 3.3.4.

latent level and changes in average test performance in manifest test-scores. Additionally, MI of factor loadings is investigated to estimate possible shortcomings of the usual procedure to analyze sum-scores/composites.

3.3.2 Methods

3.3.2.1 Sample characterization

As described earlier in Polak et al. (2017), the Vogel Study was carried out with the authorization of the local ethics committee (vote no. 23/11) and complied with the Helsinki Declaration (World Medical Association, 2013). Residents (with or without origin) of the city of Würzburg born between April 1936 and March 1941 (age: 70-77 years) were included in the study. All of them were informed about the project. They gave their written consent to participate in the Vogel Study, which started in the year 2011 and has now completed two out of 3 measurement time points (visit 1 [V1], visit 2 [V2], and visit [V3]). The project intends a total study duration of 10 years with 6 years of observation per participant.

Participants were excluded if they 1) suffered of a severe internal, psychiatric, or neurologic disease within the last 12 months (e.g., brain infarction) or 2) had a severe and uncorrected impairment of vision or hearing on the first day of data collection. Thus, a total of *N*=604 subjects attended in the baseline examination of the Vogel Study.

At V2 approximately 3 years after V1, *n*=97 participants no longer participated in the study (*n*=507). This was, for example, due to death, the fulfillment of study exclusion criteria, study termination, relocation, or the deregistration of the telephone connection. For the current data analysis, depicted below, participants who did not perform the neuropsychiatric test battery (*n*=125) or exhibited more than 5 missings within the neuropsychiatric test battery (*n*=44) because of rejection or high-stress experience at baseline or first follow-up examination were excluded. Even though this indicates dropouts to be dependent on personality or ability traits (e.g., cognitive abilities may have been worse in those who died within the next three years as existing disorders may have had impact at V1 already), we assume that the remaining missings within the final dataset were random.

We then calculated Mahalanobis-distances (cut off: p <.001; *n*=4; Tabachnick & Fidell, 1996) as well as z-scores (cut off: ±3.29; *n*=4; Tabachnick & Fidell, 1996) for each neuropsychiatric test to find and subsequently exclude uni- and multivariate outliers pairwise.

Therefore, the remaining sample of this papers' final data set consisted of *n*=330 participants (age: 70-77 years with *M*=73.78±1.52 years at baseline examination; age: 73-81 years with M=77.67±1.60 years at first-follow up examination; *n*=138 females, *n*=192 males; see Figure 14). So far, as described above, we still are in preparation for the second follow-up examination and have no data available yet.

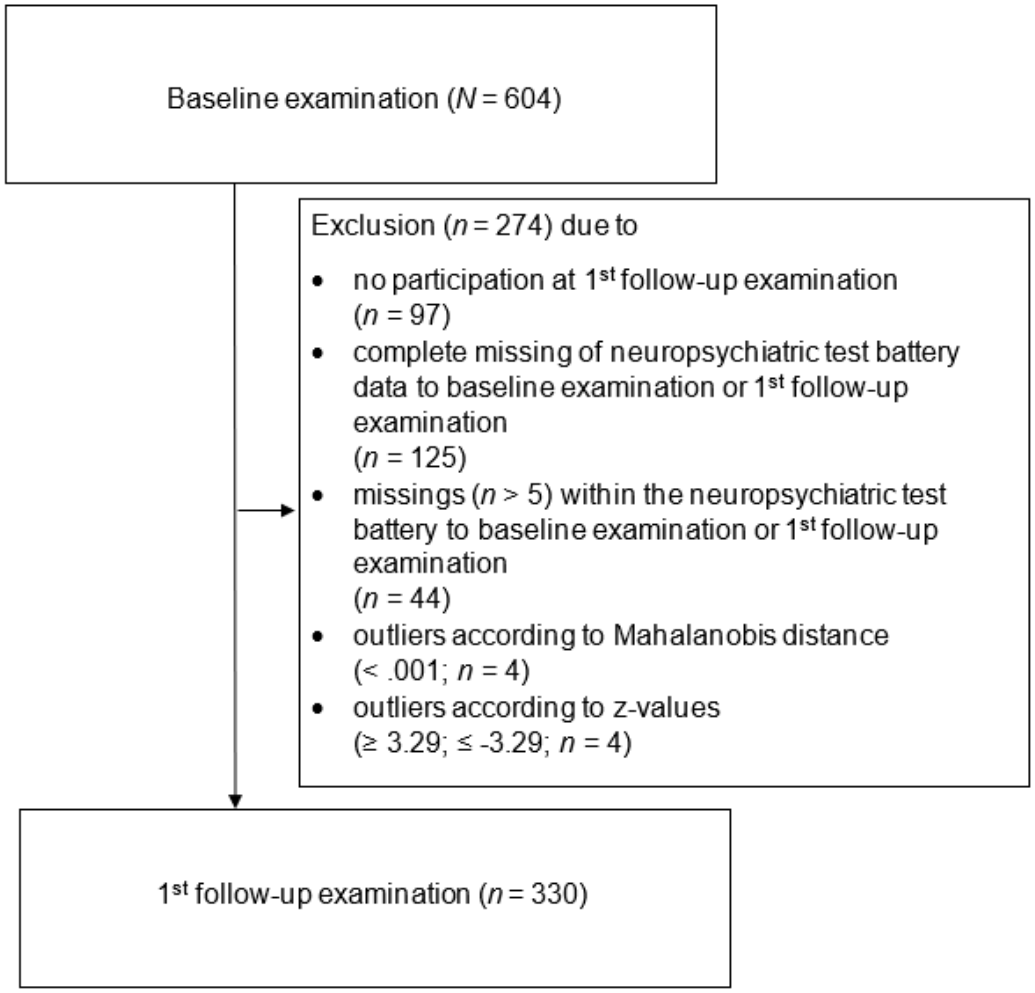

Figure 14. Course of exclusion for data analysis; CNS=Central Nervous System.

3.3.2.2 Neuropsychiatric test battery

Besides the examination of various demographic, anamnestic (e,g., lifestyle, medical history, etc.), affectivity, autonomy, blood, and lifestyle variables to characterize our sample, we conducted a neuropsychiatric test battery comprising of: a) the Verbal Learning And Memory Test (VLMT; Helmstaedter et al., 2001), b) the Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000), c) the Regensburger Verbal Fluency Test (RWT; Aschenbrenner et al., 2000), d) the Rey Complex Figure Test (CFT; Fimm & Zimmermann, 2001; Meyers & Meyers, 1996), and e) the battery of Tests for Attentional Performance (TAP; Fimm & Zimmermann, 2001). For a more detailed description of the general examination procedure within the Vogel Study, see our previous methods study (Polak et al., 2017).

The subsequent test scores were used in further latent factor analyses: VLMT immediate recall (sum score words), VLMT delayed recall (sum score reproduced words), VLMT recognition (sum score recognition word list), WMS-R digit span (sum score), WMS-R block span (sum score), RWT verbal fluency (sum score), RWT category fluency (sum score), CFT memory (sum score both reproduction times), CFT visuoconstruction (drawing score), TAP tonic alertness (median of reaction time [RT]), TAP phasic alertness (RT-parameter for phasic alertness), TAP divided attention (omission error), TAP GoNoGo (error number), TAP incompatibility (F-value of “field of vision x hand” interaction). Thus, the following latent factor analysis comprised of 14 test variables detached from 5 neuropsychiatric tests.

3.3.2.3 Statistical analyses

The data preparation, outlier detection, testing of prerequisite assumptions, and the EFA were conducted in IBM SPSS Statistics for Windows (version 25, SPSS inc., USA). Further CFA analyses were completed in R (lavaan package version 0.6-5; (Rosseel, 2012; Team, 2016). Predictive mixed models were also fitted via R (lme4 and lmerTest packages; Bates, Maechler, Bolker, & Walker, 2014; Kuznetsova et al., 2017; Kuznetsova et al., 2015).

Acceptable cut-offs for fit indices, e.g., the root mean square error of approximation (RMSEA) and comparative fit index (CFI), were set to <.05 and >.95, respectively. The alpha level to test for significance in χ^2-tests was set to <.05.

Regarding the SEM, standardizing manifest variables may lead to biased estimates in longitudinal data (Kline, 2005; Schumacker & Lomax, 2004). Also, some tests did not provide samples that qualified for T-value calculation in all ages of participants who were included in this study. To get an unbiased estimation of course effects, raw test-scores were used for further latent factor analyses (13 raw scores and 1 *F*-value for TAP incompatibility[11]).

Moreover, as unstandardized test scores exhibited substantial differences in their respective scales, those tests depicting variances greater than 10 times the magnitude of the smallest variance found in the dataset, were rescaled. This procedure is thought to diminish chances for Heywood cases and other estimation issues (Kline, 2005; Schumacker & Lomax, 2004). Finally, reaction-time-based variables were transformed via natural logarithm (TAP tonic and phasic alertness). However, no other transformation was carried out, which led to non-normality of several test scores. Even though this may, in theory, impair reliable estimation, several simulation studies reported only a small non-normality impact on standard errors (Lei & Lomax, 2005) or model fit (Gao et al., 2008). Furthermore, since the effect of non-normality may vary across different estimation methods, robust maximum likelihood estimation was used. This function leads to reliable model estimations considering misspecification, non-normality of data, and/or small sample sizes (Gao et al., 2020; Lai, 2018; Yilmaz, 2019).

Exploratory factor analysis (EFA)

To find a fitting latent factor structure, an EFA was carried out, including data of both measurement occasions. A parallel analysis was carried out to define the number of factors that were subsequently extracted after Varimax rotation. The Kaiser-Meyer-Olkin (KMO) criterium and Bartlett's test of sphericity were assessed to ensure suitable prerequisites for the analysis. Only those tests depicting rotated loadings of .4 or higher on only one factor were included in the final model.

[11]This test calculates an F-test to evaluate slowing in reaction time due to incompatible compared to compatible trials in a flanker task (the higher the percentage rank, the lower the incompatibility effect).

Invariance testing

The concluding factor structure, indicated by the EFA, was tested in a multigroup CFA using full information maximum likelihood estimation in the handling of missings, the lavaan-default “nlminb” optimization method, and robust maximum likelihood estimation (MLR) for the calculation of standard errors. Groups were defined by test sessions, which were 3 years apart, enabling a longitudinal interpretation of cross-group effects. Each participant remaining in the dataset was present on both occasions.

As stated before, MI is usually tested via increasingly restrictive CFAs. In this context, “restriction” refers to the fact that a given parameter is not allowed to vary across groups (measurement occasions): Suppose the fit between a predefined model and the actual data decreases by imposing such a restriction. In that case, this restriction seems to have violated the actual data structure in the sense that the data would be better represented by allowing varying parameters across groups, indicating non-MI.

Hence, each of the following models adds certain parameters to the previous models' restrictions. Comparing model fit across these, significant decreases in fit indices would indicate non-invariance (the restricted parameter varies over time). To test this, χ^2 statistics were calculated. These statistics indicate differences between one model and the model before (model 2 vs. 1, model 3 vs. 2, model 4 vs. 3). Following theoretical remarks, a total of four models was fit (Cheung and Rensvold, 2002; Dowling et al., 2010; Van de Schoot et al., 2012), including the following:

Configural model. In this model, only the factor structure (assignment of tests to latent factors) implied by the EFA was restricted for all variables. Otherwise, this model is built to freely estimate as many parameters as possible. However, to ensure the model to be identifiable, some restrictions need to be made. In this study, two separate approaches are discussed to give examples on possible modeling decisions concerning two different use cases.

First, to investigate measurement invariance with a focus on manifest-latent- factor-interaction, the loading of one indicator variable per factor was restricted to 1. Also, the means/intercepts of the latent factors were restricted to 0 to give the latent factors a metric. Since means of the latent factors are not allowed to differ from 0, changes within latent abilities will be propagated to manifest test score intercept differences over

time, enabling the investigation of test properties (i.e., how well they are suited to investigate latent ability changes). This approach was used at first.

In addition, one may consider the extraction of latent ability scores for further investigation (e.g., to use it as dependent variables within regression analyses or ANOVAs). Thus, for this goal, it is more beneficial to allow free latent score estimation at the second measurement occasion. To do so, in an exemplary use case, the configural model was later refitted with a restriction of latent variable means to 0 and latent variable variances to 1 for the first measurement occasion only. Furthermore, loadings of one manifest indicator variable per factor were restricted to be equal across both measurement occasions, which enabled the model to estimate latent factor means and variance freely at the second measurement. Thus, in this model, significance of changes over time can be easily assessed by investigation of latent variable estimates at V2 (intercepts are significant if they differ significantly from 0, variances are significant if they differ significantly from 1).

Regardless of these modeling choices, overall (absolute) fit of this kind of model indicates that the model structure (association of tests to a certain latent factor) is invariant over time. If this was violated, latent abilities would not be indicated by the same tests across time, which would imply severe issues with the composite approach and question the validity of course data in general.

Metric model. In the next model, investigating (construct-level) metric invariance, all loadings across groups/time were restricted to equal one another. The means of the factors themselves were still fixed to 0, while the loading of one indicator per factor was fixed to 1. In this model, invariance implies that manifest test scores equally indicate the given latent constructs over time. Violation of this loading invariance would imply that the weights of variables used for composite approaches must be adjusted over time.

Scalar model. The third, scalar model, added a cross-group restriction of manifest indicator intercepts. By doing so, the measurement model is identifiable without latent mean fixation. Thus, latent means were estimated freely instead of fixed to 0. In this model, non-MI across groups indicate changes in the difficulty of tests (changes in performance by participants). Furthermore, latent factor intercepts may be analyzed to find longitudinal decreases/increases in latent abilities. Violation of intercept invariance

would not pose a problem but may indicate anticipated effects of ability/performance decline.

Variance model. Finally, additionally to these restrictions, variances of latent factors were held constant across groups/time. Non-invariance in this model may reflect the presence of at least two groups of participants whose latent abilities evolve into different directions over time or the presence of other mechanisms that affect the overall variability of measured ability within the whole sample. Thus, violation of the invariance assumption would be in line with anticipated effects as this may highlight variables/parameters that could possibly be best suited for detection of early MCI related whole-sample or sub-sample-based changes (e.g., healthy vs. abnormal cognitive courses).

Composite approach

To assess the benefit of latent-factor-score analyzation with the more common composite approach, unweighted composite variables were calculated for comparison. To do so, the test score of each subject was standardized for each individual test by placing the score obtained in the context of an age- as well as gender- and education-matched norm sample (all test scores except the VLMT and CFT). In total, four composites were calculated before the context of the factor structure defined by the EFA by simply averaging test scores assigned to a common factor (see Figure 16). The models investigated the same $n = 330$ participants.

To then compare the benefit of the latent factor approach over the unweighted composites, as an example, a mixed effect regression model was fit once with the latent factor estimate for declarative memory as dependent variable and once with the respective composite as such. As a result, the two models can be compared directly by comparing the estimated effects of predictors (which are the same across both models) for these two dependent variables.

3.3.3 Results

3.3.3.1 Exploratory factor analysis

Both, the KMO criterium (.688) and Bartlett's test of sphericity ($\chi^2(91)=1974.583$, df=91, $p<.001$) implicated suitable prerequisites to conduct the analysis. Subsequently, a total of 5 factors was extracted following the suggestions of both Eigenvalue and parallel analysis. Estimations of factor properties, and a scree plot, are shown in Table 13 and Figure 15. Rotated loadings ≥.4 are displayed in Table 14.

Table 13

Estimations of factor properties.

	Eigenvalue	Explained Variance	Cumulative Explained Variance
Factor 1	2.463	17.591	17.591
Factor 2	2.007	14.339	31.930
Factor 3	1.827	13.052	44.982
Factor 4	1.705	12.176	57.158
Factor 5	1.091	7.792	64.950

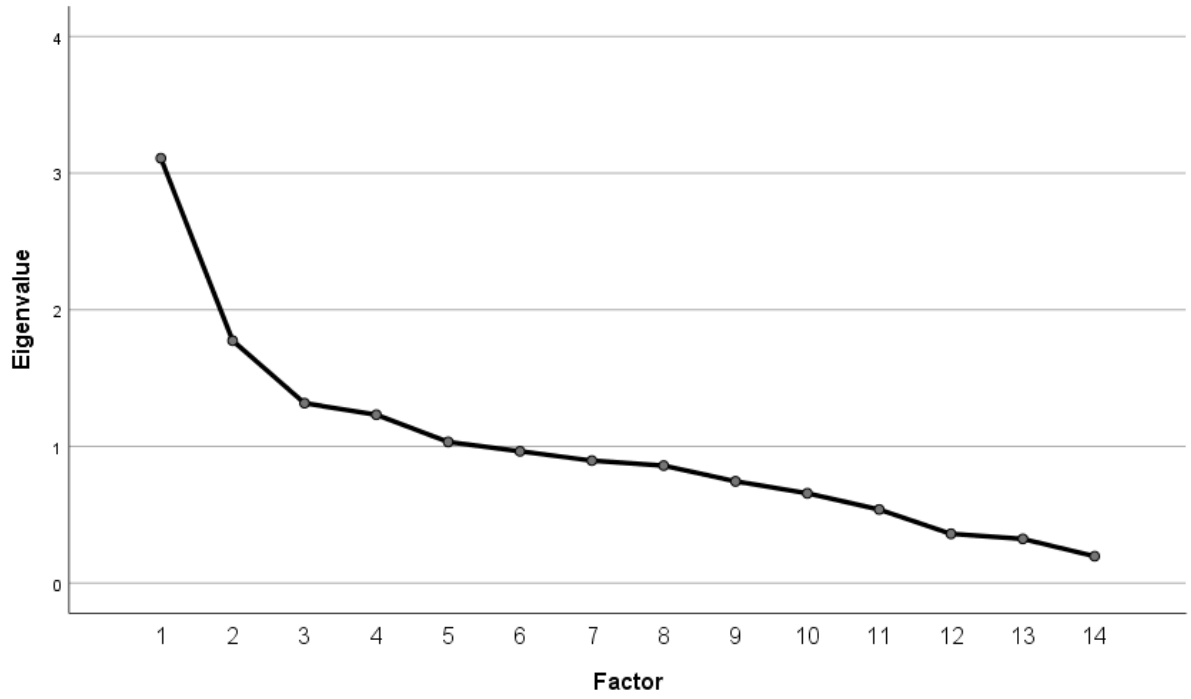

Figure 15. Scree plot showing the five-factor solution of the Exploratory Factor Analysis (EFA).

Table 14

Factor rotation of the five-factor solution of the Exploratory Factor Analysis (EFA).

Scale	Factor loadings after Varimax Rotation				
	1	2	3	4	5
VLMT immediate recall	.898	-	-	-	-
VLMT delayed recall	.888	-	-	-	-
VLMT recognition	.861	-	-	-	-
TAP tonic alertness	-	.997	-	-	-
TAP phasic alertness	-	.997	-	-	-
WMS-R digit span	-	-	.536	-	-
RWT verbal fluency	-	-	.833	-	-
RWT category fluency	-	-	.867	-	-
WMS-R block span	-	-	-	.565	-
CFT memory	-	-	-	.724	-
CFT visuoconstruction	-	-	-	.744	-
TAP compatible	-	-	-	-	.888
TAP divided attention	-	-	-	-	-
TAP GoNoGo	-	-	-	-	-

Note. EFA Coefficients ≥.40 are exhibited. VLMT=Verbal Learning an Memory Test (Helmstaedter et al., 2001); TAP=battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001); WMS-R=Wechsler Memory Scale-Revised (Härting et al., 2000); RWT=Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); CFT=Rey Complex Figure Test (Meyers & Meyers, 1996).

Cognitive domains were assigned to describe the factors as denominated in Table 15. However, only four factors of those implicated by the EFA were analyzed further as the fifth factor comprised only one indicator complicating estimation (Kline, 2005; Schumacker & Lomax, 2004).

Table 15

Designation of the four latent factors.

Latent Factors	Cognitive Domain	Included neuropsychiatric test scores
Factor 1	declarative memory	VLMT immediate recall, VLMT delayed recall, VLMT recognition
Factor 2	attention	TAP tonic alertness, TAP phasic alertness
Factor 3	working memory	RWT verbal fluency, RWT category fluency, WMS-R digit span
Factor 4	visual-spatial processing	CFT memory, CFT visuoconstruction, WMS-R block span

Note. VLMT=Verbal Learning an Memory Test (Helmstaedter et al., 2001); TAP=battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001); RWT=Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); WMS-R=Wechsler Memory Scale-Revised (Härting et al., 2000); CFT=Rey Complex Figure Test (Meyers & Meyers, 1996).

3.3.3.2 Measurement invariance testing

Four increasingly restricted models were fit and compared to analyze measurement invariance (see Table 16). Both the RMSEA and CFI indicated acceptable model data assuming that the assignment of manifest test scores to latent factors stays equal across time. Hence, the conceptual representation shown in Figure 16 represents the suitable structure for both measurement occasions. However, Table 16 further summarizes that factor loadings, test intercepts, latent means, and latent variances depict substantial non-MI over time.

Table 16

Confirmatory Factor Analyses (CFAs) for the sample of n=330 participants. Reported fit-parameters base on a robust maximum likelihood estimation.

CFA model	RMSEA	CFI	AIC	BIC	χ^2	df	*p*
Fixed structure	.049	.969	22068	22418	135.22	76	
+ Fixed loadings	.051	.963	22073	22392	154.33	83	.007**
+ Fixed intercepts	.080	.902	22182	22469	277.16	90	< .001
+ Fixed variances	.097	.849	22281	22550	384.20	94	< .001

Note. RMSEA=Root Mean Square Error of Approximation; CFI=Comparative Fit Index; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion.

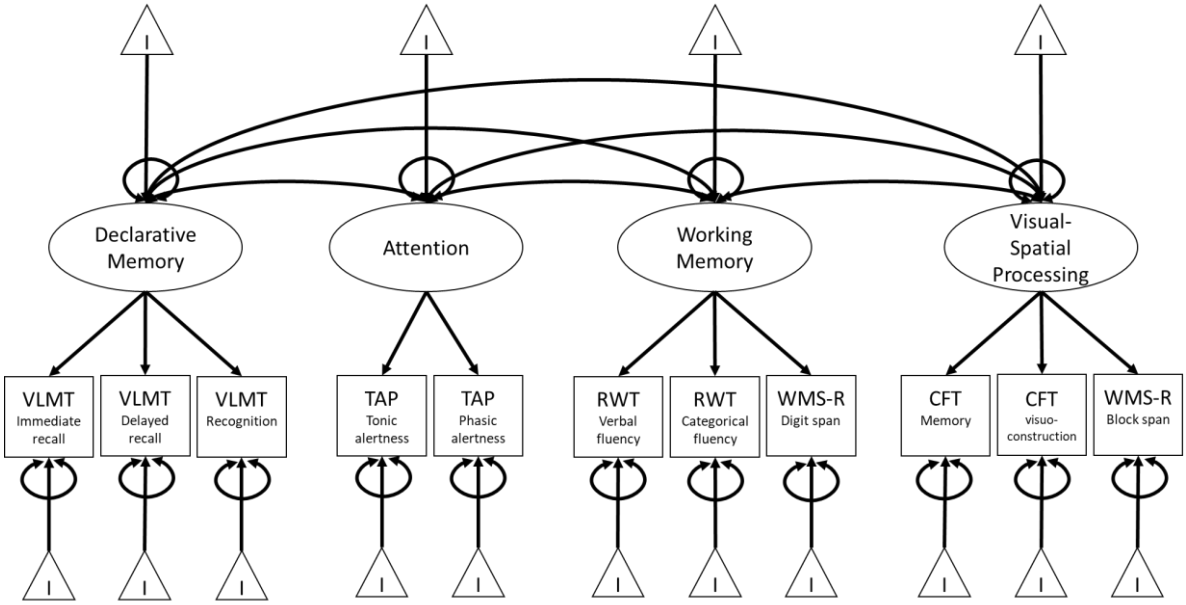

Figure 16. A conceptual model for the CFAs depicting estimated parameters. Oval variables depict latent factors, while rectangles reflect manifest test scores. Triangles represent intercepts.

However, as non-MI is not per se a property of the whole model but rather of certain parameters, further analyzes were carried out to clarify which (test-)parameters significantly changed over time and which did not. To assess this, the configural model yields the best insight as all the more restrictive models showed decreasing fit to the

data. Furthermore, as the configural model allows for the greatest number of freely estimated parameters, non-invariance in the data that would influence the fit indices of more restrictive models negatively should be reflected in significantly changing estimates over time. Table 17 summarizes the results by providing estimates across both measurement occasions. Furthermore, to provide information on the tendency of statistical significance of descriptive differences, the standard error of a variable's mean was multiplied by 1.96. By doing so, a 95% confidence interval (CI) was obtained. If the CI of either value (measurement occasion 1 or 2) included the estimated mean of the other measurement occasion, no significant difference was assumed. Please note that this comparison included two tests for each variable, which was not corrected for. Shading in Table 17 thus indicates trends (exploratory findings) but not confirmatory hypothesis testing as no specific assumption on non-MI of specific parameters was formulated beforehand.

Nonetheless, results indicate partial non-MI for loadings in VLMT recognition and immediate recall (declarative memory) and WMS-R block span (visual-spatial processing). Furthermore, VLMT immediate recall, VLMT recognition, and CFT visuoconstruction intercepts seem to decrease while CFT memory, tonic alertness, and WMS-R scores increase. Finally, VLMT delayed recall, RWT category fluency, and WMS-R digit span scores also seem to decrease in their variance over time, while two of three working memory relates scores RWT verbal fluency and CFT visuoconstruction increase in variance.

Table 17

Model parameters for a configural model.

Variables and Factors	Unstandardized loadings		Intercepts		Variances	
	V1	V2	V1	V2	V1	V2
VLMT Delayed Recall (F1)	1	1	6.004 (0.119)	5.437 (0.183)	2.461 (.383)	0.575 (.193)
VLMT Recognition (F1)	0.731 (.032)	.410 (.018)	5.391 (0.104)	4.858 (0.130)	1.692 (.192)	1.913 (.247)
VLMT Immediate Recall (F1)	0.810 (.031)	.620 (.027)	9.704 (0.098)	8.990 (0.171)	.829 (.119)	1.262 (.212)
TAP Phasic Alertness (F2)	1	1	23.128 (0.067)	23.172 (0.109)	.012 (.003)	3.423 (1.402)
TAP Tonic Alertness (F2)	1.754 (0.718)	2.840 (1.198)	26.653 (0.114)	26.974 (0.123)	.036 (.005)	0.979 (1.836)
RWT Verbal Fluency (F3)	1	1	2.701 (0.068)	2.672 (0.062)	.286 (.111)	.534 (.081)
RWT Category Fluency (F3)	1.090 (.146)	1.125 (.117)	3.534 (0.061)	3.533 (0.061)	.724 (.122)	.296 (.089)
WMS-R Digit Span (F3)	.799 (.145)	.829 (.138)	8.291 (0.117)	9.558 (0.107)	4.004 (.276)	3.263 (.277)
CFT Visuoconstruction (F4)	1	1	34.836 (0.107)	34.102 (0.160)	2.668 (.375)	4.216 (.793)
CFT Memory (F4)	1.389 (.357)	1.368 (.289)	7.259 (0.144)	7.811 (0.165)	4.62 (.617)	2.825 (1.157)
WMS-R Block Span (F4)	.490 (.112)	.217 (.050)	7.394 (0.078)	6.982 (0.079)	1.743 (.146)	1.894 (.157)

Note. V1=Visit 1, V2=Visit 2. Unstandardized estimates and Standard Errors (SEs; in parentheses) are reported. Light grey cell shadings reveal significant increases of estimates over time, dark grey cell shadings reveal significant decreases, which indicates non-MI.

Furthermore, in addition to the (manifest) indicator-level analyses of Table 17, latent factor estimates are summarized in Table 18. While indicator level estimations of Table 17 were made following the restriction of one indicator variable loading per factor to 1 and latent means to 0, results in Table 18 were produced by restricting the loading of one indicator per factor to the same value across groups while setting the latent means to 0 and the latent factor variance to 1 for the first measurement occasion, allowing for free estimation of these parameters at the second occasion. By doing this, free estimation of latent factor parameters could be ensured, which would be necessary for subsequent longitudinal prediction analyses using these latent factor scores as dependent variables. To demonstrate this idea, this model was used for parameter extraction, as it imposes the least restrictions while allowing free latent factor estimation.

Before the findings reported above, models fixating more parameters fit the data significantly worse. Hence, again, this model provides the most unbiased estimates. Table 18 highlights that the covariance between declarative memory and visual-spatial processing increases over time. Furthermore, intercepts decrease in declarative memory as well as in working memory. Finally, variances increased in both declarative memory and visual-spatial processing.

Table 18

Latent factor model parameters for a configural model.

		Covariances		Intercepts		Variances	
		V1	V2	V1	V2	V1	V2
Declarative Memory	**Attention**	-0.004 (0.054)	0.089 (0.136)	0	-0.568 (0.218)	1	9.737 (1.196)
	Working Memory	0.355 (0.052)	0.718 (0.181)				
	Visual-Spatial Processing	0.364 (0.070)	1.716 (0.369)				
Attention[12]	**Working Memory**	-0.244 (0.089)	-0.187 (0.093)	0	0.044 (0.128)	1	0.499 (.271)
	Visual-Spatial Processing	-0.179 (0.104)	-0.169 (0.096)				
Visual-Spatial Processing	**Working Memory**	0.343 (0.094)	0.478 (0.151)	0	-0.734 (0.193)	1	3.283 (.982)
Working Memory	-	-	-	0	-0.029 (0.092)	1	0.733 (.107)

Note. V1=Visit 1, V2=Visit 2. Unstandardized estimates and Standard Errors (SEs; in parentheses) of latent factor estimates are reported. Light grey cell shadings reveal significant increases of estimates over time, dark grey cell shadings reveal significant decreases, which indicates non-MI. These results indicate increases in the co-dependency of declarative memory and visual-spatial processing over time. Furthermore, it seems that the latent ability of declarative memory as well as visual-spatial processing decreased on average over time. Finally, the variance of declarative memory, working memory and visual-spatial processing increased as well.

[12] This factor is estimated by variables expressing reaction times. Thus, higher values indicate worse performance.

3.3.3.3 Comparison between the latent factor approach and the composite approach

Figure 17 illustrates the course of latent factor means and composites across V1-V2. Descriptively, both, the composite and latent factor approach indicate decreasing performance/ability scores for declarative memory over time. However, the latent factor approach indicates greater significance and effect size. Regarding attention, again, both approaches indicate a similar trend, this time towards increases in scores. Since attention scores are indexed by reaction time, depicted increases indicate decreases in reaction speed (thus, worse performance/capability) with a seemingly greater effect estimate in the composite approach. In working memory, the composite approach suggests increases in performance over time, while the latent factor approach shows no particular change. Finally, concerning visual-spatial processing, a significantly greater decrease in scores is shown in the latent factor as compared to the composite approach over time (indicating a decrease in processing capability).

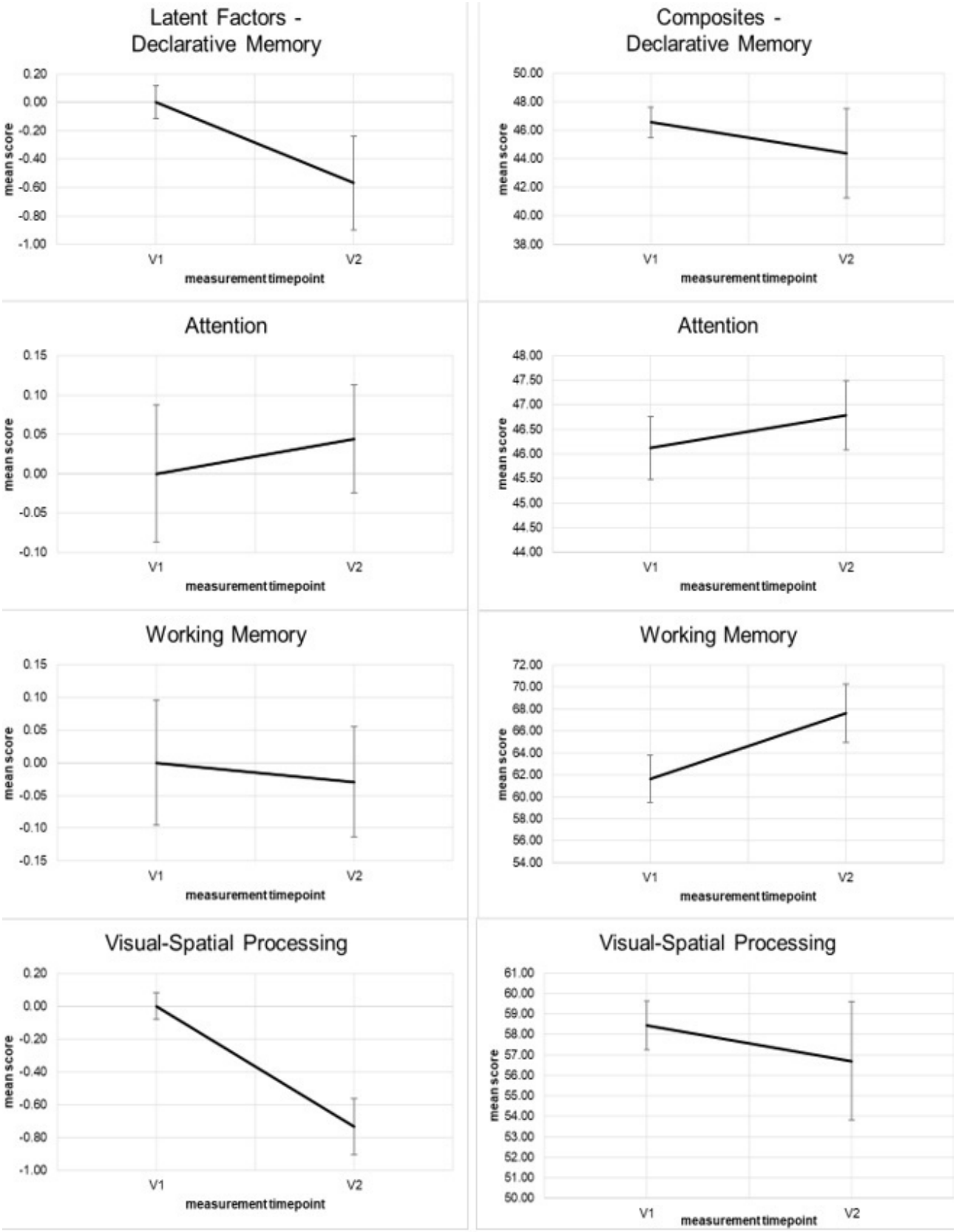

Figure 17. Latent factor approach (left column) compared with the composite approach (right column). V1=Visit 1, V2=Visit 2. Lines indicate mean (M), error indicators represent 95%-Confidence Interval (CI).

3.3.3.4 Example procedures for the prediction of latent ability scores

The current paper focuses on the general applicability of the SEM approach for describing the course of cognitive abilities and their decline. While the central part of this paper is based on the description of measurement invariance as a potential source of information for such questions, the estimated latent ability scores of the analysis can also be used directly to test specific predictor variables for their predictive ability. Two ways of doing this will be briefly described:

First, the predictor variables themselves can be included in the model. The SEM approach allows both latent and manifest scores to be predicted by both fixed (e.g., genetic vulnerabilities) and variable predictors (e.g., depression scores varying over each measurement occasion). Thus, for datasets with at least three measurement occasions (for linear trends; more may be needed for non-linear trajectories; e.g., Byrne & Crombie, 2003; Felt et al., 2017; Grimm & Ram, 2009), a latent growth curve model could be defined, in which second order latent factors are assumed that define a slope across the measurement occasions as well as an intercept, influencing the first order latent ability factors. At the same time, if one assumes that not all latent abilities (e.g., memory vs. visual-spatial processing) show the same slopes over time, a second-order latent slope and intercept could also be defined for each latent ability factor individually. These factors (slope and intercept) can, in turn, be predicted by predictor variables, making it possible to predict the temporal variation of latent factor scores with parameters such as genetic vulnerability factors. At the same time, the manifest variables measured per time point can also be predicted by influences that also change over time (e.g., BDNF levels, depression scores). This modeling approach establishes a link between measured values that would otherwise be mistakenly treated as between rather than within effects (e.g., the manifest test scores of a person in a test at two measurement times). However, such estimation would require significantly more study participants (Willett & Sayer, 1994), with the advantages of directly estimating the influence of predictors at the manifest and latent levels while simultaneously allowing for measurement invariance estimation.

As a second possibility, the latent factor scores could be read from the model and included as a dependent variable in a regression analysis or ANOVA. To illustrate this approach (which is also possible with the current dataset), a mixed model approach was chosen in which various predictor variables collected in the study were used as

independent variables. In contrast, the extracted latent factor scores were used as dependent variables.

The dependent latent factors were included with a random intercept for each subject and time as a fixed effect predictor (levels *one* and *two*, model 1). Due to their relevance in the literature (for an overview, see Xu et al., 2015) and supposedly low multicollinearity (or redundancy), the covariates age and gender (model 2), Brain-Derived Neurotrophic Factor (BDNF; quantified in serum by ELISA; model 3), depressiveness (measured by the Beck Depression Inventory-II [BDI-II]; Beck, Steer, & Brown, 1996; model 4), and vitamin B12 (quantified by blood plasma; model 5) were included as potential predictors (see Appendix for more details). Overall, one set of models was tested for each latent factor. The model with the highest fit index was subsequently chosen as the best model for the interpretation of fixed effects. Results revealed plausible predictive effects, mostly involving gender, age, and their respective interaction with time for all latent factors except for attention. For instance, concerning declarative memory, the best model revealed a significant main effect for age (β=-0.11, $t(299)=-2.340$, $p=.019$), time (β=-0.13, $t(299)=-2.898$, $p=.004$) and gender (β=0.44, $t(299)=4.765$, $p<.001$), indicating declining scores with higher age and over time as well as in men as compared to women.

To draw a comparison between the classical composite approach and the latent factor approach presented here, the same model was again fitted with an unweighted composite approach. Thus, the same predictors and their respective interactions were used with the composite *declarative memory* as dependent variable (see section 2.3.3. for details[13]). This mixed model, revealed only one effect for gender (β= 0.22, t(299)=2.483, p=.014), which was also less significant as compared to the latent factor approach. As a result, concerning the declarative memory domain, the same predictor model within the latent factor approach was able to find more significant and greater effects for the given list of predictors as compared to the composite approach.

[13] Please note that this section now is numbered 3.3.2.3.

3.3.4 Discussion

The current longitudinal analysis was performed to identify hints towards cognitive decline in a sample cohort totaling 330 individuals. As part of this, longitudinal MI of a test battery of 14 neuropsychiatric test variables was investigated across three years, which led to the identification of four stable latent factors of cognitive abilities: declarative memory, attention, working memory, and visual-spatial processing. Furthermore, predictive analyses using scores of these domains as a dependent variable indicated that latent ability scores increased significance of regression analyses in comparison to composite scores.

Longitudinal Measurement Invariance. To this day, there are only few studies available that analyzed longitudinal MI in neuropsychiatric test batteries and defined latent factor scores as dependent variables in the prediction of pathological cognitive decline. The SEM approach allows for concurrent testing of group/time-related differences in latent and manifest variables. Table 16 indicates that loadings of indicator variables significantly vary over time, leading to small but significant changes in model fit. Table 17 further clarifies this non-MI stems from VLMT, RWT, and WMS-R-related measures. In the context of the classical composite approach, this highlights a possible reason for null-findings: In the current study, the WMS-R block span test score becomes less indicative of the latent visual-spatial processing performance. Thus, if a researcher imposes the same weighting on this test score at both measurement occasions, the resulting trend over time may be biased.

To put the study results in a simple context, the following section compares approaches by using loadings of the configural model as weights while using actual mean standardized test scores (standardized to M=50, SD=10) of the 330 participants as variables. For unweighted composites, researchers may usually use the formula shown in equation (1):

$$(1 \times 73.95 + 1 \times 59.76 + 1 \times 41.74) - (1 \times 70.20 + 1 \times 66.0 + 1 \times 35.07) = 4.18 \quad (1)$$

Here, (1) indicates the implicitly imposed weight of 1 for each variable and other numbers reflecting the average test score. By subtracting the scores of the second measurement occasion from the first, the result reflects the mean change of the visual-spatial processing composite over time. A positive score indicates decreases over

time. However, Table 17 suggests that performances in the three tests are not equally relevant to the latent ability of visual-spatial processing. Thus, equation (2) modifies the previous approach by imposing different weights for each variable (according to Table 17):

$$(1 \times 73.95 + 1.389 \times 59.76 + 0.490 \times 41.74) - (1 \times 70.20 + 1.389 \times 66.0 + 0.490 \times 35.07) = -1.65 \qquad (2)$$

The result indicates an overestimation of the unweighted composite approach in comparison to the weighted one. The latter implies an overall increase in skill. However, equation (2) would be appropriate only if measurement invariance for factor loadings were given. Since Table 15 indicates otherwise, the formula is once again adapted by varying weights over time. The resulting equation is given in equation (3):

$$(1 \times 73.95 + 1.389 \times 59.76 + 0.490 \times 41.74) - (1 \times 70.20 + 1.368 \times 66.0 + 0.217 \times 35.07) = 9.31 \qquad (3)$$

Since equation (3) results from the model that fits the data best, we assume that its result is the most unbiased. Equation (1) would only be unbiased if all test scores were equally relevant/indicative/correlated to/of the target-construct (visual-spatial processing), while equation (2) would only hold if metric invariance was given. This example illustrates the value of SEM-driven course analyses and possible shortcomings of the most often used approach as equation (3) produced an effect more than double in size as the unweighted composite approach did.

The maximal misestimation due to non-MI is given by the sum of absolute factor loading differences between measurement occasions (Schmitt et al., 2011). For instance, in this study, the sum of for the factor visual-spatial processing equals 0.137 (|(0.410-0.487)|+|(0.620-0.540)|.

Furthermore, apart from changes in loadings over time, test intercepts also partially varied. For instance, WMS-digit span test intercepts significantly increased while WMS-block-span performance decreased (see Table 17). This result highlights that even though these two subscales were taken from one test-(battery), the performance trajectories were opposed to one another. Interestingly, this fits well with the factorial

structure. While both visual-spatial processing and declarative memory seem to pose as promising cognitive domains to assess early changes in abilities (indicated by Table 16), working memory was mostly characterized by invariance over time, which may be why mostly VLMT measures, along with WMS-block span showed decreasing intercepts in Table 17.

Course of latent factor scores. On a latent factor level, variances of declarative and working memory as well as visual-spatial processing increased over time, indicating the existence of at least one mechanism that may drive increases in sample-based variance statistics of latent ability scores. One explanation may lie in the existence of at least two groups that develop into different directions. At the same time, another possibility is given by the increasing inner-individual variance in “ability retrieval” in those who suffer from cognitive decline (memory capacitance may vary more greatly from day to day in those who show signs of an MCI than it does in healthy young adults). Either way, this indicates declarative memory, working memory, and visual-spatial processing to pose as early indicators for age-related changes in cognition.

Moreover, in the context of neuropsychiatric test scores, differences in covariances, including factor loadings and latent factor covariance, may reflect compensatory mechanisms between initially independent neuronal systems and functions. On that note, the connection between visual-spatial processing and declarative memory increased over time, possibly indicating at least one subsystem to rely on the other increasingly. Other interpretations may assume a third variable to produce these changes in covariance matrices. For instance, an uncontrolled third variable may affect both factors, thereby increasing their correlation over time. One such factor may be early signs of cognitive decline, which would be plausible given that only test intercepts of these two factors expressed non-MI. However, these interpretations are not yet reliable, basing them solely on the data of this one study. Further research and discussion are needed. Nonetheless, since covariance between those two factors that show the greatest changes in variance and intercepts increased, it would be plausible to assume that the connection between these constructs increases as a function of age and/or pathology-related cognitive decline.

Prediction of pathological cognitive decline. Finally, the current study provided a short example on the topic of latent score prediction based on covariates, psychometric parameters, and biomarkers.

Since the exemplary effects in latent factor score related analyses were generally more significant than in the composite models, these data highlight the possible benefit from investing in the more complex but possibly more reliable and valid SEM approach. This is especially relevant since the composite models produced effects that may not be plausible, such as increased working memory capability in older individuals.

Conclusions. Methodologically, it may be appropriate to calculate (weighted) composite variables instead of latent factors. However, it is important to note that composite variables do not adapt to the data over time. This indicates active neglect of compensation mechanisms, retest effects, habituation to test settings, the influence of increasingly severe disease, and many more factors of influence, as these may cause significant changes in the interdepend ability of neuropsychiatric functioning. For instance, loss of function in certain brain areas may affect the intercorrelation of neuropsychiatric domains by making them dependent on other compensating areas/functions. Moreover, psychological variables like trait anxiety may impair performance in the first measurement occasion to other extents as it does in the second due to habituation effects.

SEM, on the other hand, estimates such influences indirectly by addressing changes in the correlation matrix among manifest test scores obtained. As a result, changes in manifest scores, latent performances and their correlation can be addressed all at once. In fact, in this study, we found hints to either compensation mechanism or neurological change over time, as the covariance between visual-spatial processing and declarative memory increased. Since the variance of both latent factors also increased, while their intercepts decreased, these results may hint at least two sub-samples within the analyzed participants that showed different trajectories in their cognitive abilities across measurement occasions or a general decline in capabilities on these domains that results in increased inner-individual variability of skills (or a mix of both). However, this interpretation is speculative and needs clarification by identifying predictors for these latent score changes. The above-mentioned interpretation would become very plausible if the covariance pattern between both factors would decline to their baseline level after controlling for such predictors. Hence, again the SEM approach provides additional ways to gain more detailed insights into the data as the composite approach does. Moreover, in the example for one of the latent factors provided above, we were able to show that the composite approach

underestimated the effect of change over time by more than 50%, which again highlights possible shortcomings of the classical composite approach and may reveal mechanisms by which classical longitudinal analyses may have trouble finding reliable and significant change.

Ultimately, the exemplary prediction analysis depicted in this study provided further evidence of the superiority of the SEM approach over the composite approach, supporting the idea that this approach produces more reliable results.

To conclude our findings, this study was able to find four latent factors that are in line with previous research. Furthermore, by testing these factors for longitudinal measurement invariance, this study provides insights into calculating the extent of bias that may lead to inflation or false null-findings in the classical composite approach. In addition, even though measurement invariance was not present for most parameters, this study also discussed how this may be beneficial to understanding both normative and pathological aging. In sum, the SEM approach adds highly relevant information to the interpretation of longitudinal neuropsychiatric data.

Limitations. First, the generalizability of the factor structure may be impaired as the results are specific to the neuropsychiatric test battery used. Also, although supported by the residents' registration office, participant recruitment was not fully representative for the general population (Polak et al., 2017). In the case of the Vogel Study, participants had a relatively higher education level in comparison with the general German population (Statistisches Bundesamt, 2018).

Additionally, one problem of this latent factor model was the factor attention as it comprised only two manifest indicators, which may have significantly biased results for this domain (Kline, 2005). This may be one reason why no significant effect was present regarding this factor. Nonetheless, we do not anticipate significant misestimation of other factors and their indicators due to this issue.

Also, we want to note that the use of factor scores may propagate estimation errors within the SEM to the analysis of predictor variables which is an inherent risk to this approach and may lead to false results.

Due to relatively small sample size concerning the complex methodology, the precision of model estimation may have suffered. However, larger sample sizes may lead to smaller error terms and increased significance even for small non-invariance, which may also pose an issue as this may lead to overly sensitive analyses. As a result, we

argue to estimate the difference of effects due to variability of parameters (by using the formulas (1), (2) and (3)) to estimate the relevance of effects than to solely rely on significance. By doing so, greater sample sizes will lead to better estimation without introducing overinterpretation of significance.

Finally, the dataset included missings. Due to dropouts resulting from the longitudinal study setting and incomplete datasets, the sample size decreased from N = 604 participants at V1 to n = 330 at V2. Reasons for data exclusion may have correlated to cognitive ability and thus imply a selection bias for the remaining 330 participants, which indicates that the current study may have excluded such participants who had particularly bad courses. As a result, generalizability of results presented in this methods-focused paper may be considerably impaired. Within the remaining data set, only 0.0048% were missing implying no substantial influence on the estimation procedure within the SEM analysis.

Finally, as only n = 330 participants remained in the model, this study relied on the lower bound of necessary data to address such models as discussed in the current manuscript, even though more complex models like (second-order) latent growth curve models would be superior as they would be able to model the within-subject nature of the data more properly. Nonetheless, to our understanding, this sample size was sufficient for whole-model comparisons within the current approach.

Conflicts of interest / Disclosure

Jürgen Deckert is the co-recipient of a grant of the Bavarian State Government to BioVariance and an investigator in a European grant to P1Vital.

Contributors

Sophia Haberstumpf and André Forster equally contributed to data analysis and wrote the initial edition of the manuscript. Jonas Leinweber, Martin Lauer, and Thomas Polak executed and managed medical screenings. Martin Lauer, Thomas Polak, Jürgen Deckert, and Martin J. Herrmann made substantial contributions to concept and design. Stefanie Rauskolb and Michael Sendtner conducted neurobiological pre-analyses. The draft was critically revised by Martin J. Herrmann, Jonas Leinweber, Stefanie Rauskolb, Johannes Hewig, Michael Sendtner, Martin Lauer, Thomas Polak and Jürgen Deckert. All authors agreed to the final version.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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3.3.5 References of Paper 3

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3.3.6 Supplementary report on the predictive analyses

3.3.6.1 Supplementary information on the methods

For the predictive analysis following the latent factor approach as dependent variables and in addition to the covariates age and sex, we explicitly included the psychometric parameter depressiveness (see BDI-II; Beck, Steer, & Brown, 1996) as well as blood-derived biomarkers such as vitamin B12 and BDNF as independent variables. For BDNF extraction, we received the gracious support by Dr. S. Rauskolb and Prof. Dr. M. Sendntner, Institute of Clinical Neurobiology, University Hospital Wuerzburg as reported subsequently: Blood was withdrawn from the antecubital vein into vacuum tubes (S-Monovette 4.9 ml Z-gel, 03.1524, Sarstedt, Germany). After 60 minutes of clotting time, whole blood was centrifuged at 1100 x g for 15 minutes to separate the serum. Sera were collected in 100 µl aliquots to avoid several freezing cycles and were kept at -80°C before assaying. BDNF quantification by Enzyme-Linked Immunosorbent Assay (ELISA) was performed as previously described (Kolbeck et al., 1999; Rauskolb et al., 2010; see also http://dshb.biology.uiowa.edu) with the following modifications. MaxiSorp White Polystyrene plates (Nunc) were incubated overnight at room temperature with 2.5 µg/ml monoclonal antibody (mAb) #1 in coating buffer (50 milimol sodium hydrogen carbonate [$NaHCO_3$], 50 milimol sodium carbonate [Na_2CO_3], pH9.7). Following an overnight incubation, the plates were blocked at room temperature for 2 hours with 4% bovine serum albumin (BSA) in phosphate-buffered saline (PBS). Afterwards the plates were washed 3 times with PBS with Tween 20 (PBS-T, 0.1% Tween-20), and 150 µl of incubation buffer (0.1 mol KH_2PO_4, 0.1 mol Na_2HPO_4, pH7.6, 4% BSA) and 50 µl of either standards or diluted samples (both in extraction buffer) were added to the plate and incubated for 3 hours on a rotating platform. The standard was established using recombinant BDNF (provided by Prof. M. Sendtner, Institute of Clinical Neurobiology, University Hospital Wuerzburg) diluted in extraction buffer (0.05 mol $C_2H_3NaO_2$, 1 mol NaCl, pH4, 1% BSA). Serum samples were tested at 1:20 dilution. After five washes with PBS-T, 200 µl of horseradish peroxidase (HRP)-conjugated mAb-#9 diluted in incubation buffer (1:3333) was added to each well and incubated for 3 hours on a rotating platform. After five washes with PBS-T, BM Chemiluminescence ELISA Substrate (Roche) was added to the plate, and luminescence was measured with a microplate reader (Infinite M200 Pro, TECAN). Standards were measured in triplicates, samples in duplicates. The detection limit is

10 pg of BDNF per well. Recovery experiments indicated 90% recovery of known amounts of recombinant BDNF (30 pg) added to serum samples tested at the typical 1:20 dilution. The intra- and inter-assay coefficients of variation were found to be within 3.7% and 7%, respectively.

To conduct statistical analyses, the estimated latent factor scores for each participant at both measurement occasions were extracted after fitting the in the publication mentioned models investigating MI. The selection of potential predictors as well as the resulting set of models was also described in the publication (see chapter 3.3). Overall, one set of models was tested for each latent factor. Model comparisons were made using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). A model was deemed to fit the data best, if it performed significantly better than the once before and if no significantly better fitting model followed. This model was then used to test the effect of each predictor. Composite variables were calculated for comparison as also described in the publication and with the sample size of n=330 (see chapter 3.3).

3.3.6.2 Supplementary information on the results

The results for the latent factor declarative memory were already described within the manuscript in chapter 3.3.3.4.

Furthermore, exploratively, the investigation of the best model of attention (caution: inversed interpretation!) revealed a significant main effect of BDNF serum levels (β=-0.10, t(295)=-2.28, p=.023), indicating higher BDNF serum levels in participants with higher attention performance. In addition, a significant main effect of sex could be shown (β=0.18, t(295)=1.97, p=.05), revealing declined attention in women opposed to men. Refitting the same model with the composite variable no significant effects could be found.

The analysis of working memory, on the other hand, revealed a significant main effect of sex (β=0.28, t(296)=2.51, p=.013) indicating deceased working memory in men compared to women. This effect was not present in the composite approach (β=0.11, t(296)=1.09, p=.276). In the composite approach, only time was a highly significant predictor of an improving working memory performance, which did not seem plausible (β=0.20, t(296)=4.56, p<.001).

At last, concerning visual-spatial processing, a significant main effect of BDI-II scores (β=-0.10, *t*(294)=-2.00, *p*=.046) was present, indicating that more depressed individuals may in general score lower on this factor than others. Furthermore, a (highly) significant main effect of time (β=-0.41, *t*(294)=-10.66, *p*<.001) and sex (β=-0.21, *t*(294)=-2.15, *p*=.032) were found, indicating decreases of scores at V2 as well as in women as compared to men. Moreover, an highly significant interaction effect of sex and time was revealed, indicating that women's visual-spatial processing declines more drastically over time than men's (β=-0.24, *t*(294)=-2.99, *p*=.003). The same model with the composite variable as outcome revealed a similar main effect for sex (β=-0.24, *t*(294)=-2.70, *p*=.007) as well as increasing visual-spatial processing scores in higher age (β=0.10, *t*(294)=2.23, *p*=.027). In addition, since age's interaction with time was also significant, the model indicates more drastically decreasing scores in younger participants than older ones over time (β=0.12, *t*(294)=2.35, *p*=.019).

3.3.6.3 Supplementary information on the discussion

In our predominantly healthy sample sex revealed the highest predictive effect for a decline in all cognitive domains. While men performed better in the cognitive domains attention and visual-spatial processing, women performed better as compared to men in declarative and working memory. In line with this and as an exemplary, a current review highlights the relevance of sex-specific differences stating that women often show better performances in verbal memory (Nebel et al., 2018). We also tested verbal memory performance as part of our declarative and working memory factors to describe cognitive decline. Another review describes better visual-spatial performances in men, which is also consistent with our findings (Li & Singh, 2014).
Moreover, we found a possible relation between BDNF serum levels and the latent factor attention. The main effect suggested that individuals with higher BDNF serum levels showed higher attentional performance. However, it still is an exploratory finding within the study. This fits in the current research literature as lower BDNF serum levels frequently are associated with cognitive decline and neurodegenerative processes, respectively (Diniz & Teixeira, 2011; Ng et al., 2019; Qin et al., 2017). Nevertheless, no interaction effect could be found for any of the four latent factors tested. Recent studies found out that BDNF serum levels may also be elevated in individuals

diagnosed with MCI and that those individuals who later progress to AD show decreased BDNF levels (Balietti et al., 2018; B. Y. Kim et al., 2017; Laske et al., 2006). Hence, it is also possible that changes of the BDNF serum levels occur at late AD-stages (Ng et al., 2019). Longer observation periods of the study participants, especially the analyses of the pending V3, seem promising to detect further cognitive changes and to relate interactions between cognitive change and the BDNF serum level to each other.

At last, BDI-II scores showed a considerable impairing effect on visual-spatial processing, which reached significance and, hence, may indicate its potency to influence neurocognitive abilities as already described in chapter 1.2.3.

All in all, our results indicated sex and, as it is well-known, age to be the most important variables even though additional effects were present for BDNF and BDI-II scores. These results are in line with current meta-analytic results (J. Q. Li et al., 2016; Prado et al., 2019; Song et al., 2018).

3.3.7 Additional correlation analyses

Papers 1-3 (chapters 3.1-3.3) provide insights into pathological cognitive alterations in Vogel Study participants based on brain imaging and psychometric test diagnostics. Since the analysis of possible compensatory mechanisms and the associated role of the parietal cortex was discussed in the first two papers, an exploratory analysis of the associations between the four latent factors defined in paper 3 and the parietal cortex activation during the performance of the ADT with three difficulty levels during the fNIRS measurement will be performed. Moreover, detailed information on the anatomical location and functional connectivity of the four defined latent factors – also in relation to the parietal cortex - can be found in the general discussion (chapter 4.2.1).
To further relate the latent factors defined in Paper 3 (chapter 3.3) to the parietal cortex activation under the experimental conditions in the ADT paradigm during the fNIRS measurement in Studies 1 and 2 (chapters 3.1 and 3.2), the Pearson's correlation-coefficient was calculated between the previously defined ROI in the parietal cortex activity at each level of ADT difficulty with all of the four latent factors via *Jamovi* (version 1.6.23; the jamovi project, 2021). As in previous analyses, the significance level was set at $p < .05$ with a 95% CI.
The results of the correlation analyses can be found in Table 19.

Table 19

Correlation analyses between latent factors and the ADT experimental conditions.

	Declarative Memory		**Working Memory**		**Attention**		**Visual-Spatial Processing**	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Long pointer	0.05	.305	-0.06	.181	**0.10***	**.031**	**0.14****	**.002**
Middle pointer	0.03	.541	-0.07	.104	0.07	.117	**0.10***	**.034**
Short pointer	0.03	.480	-0.07	.133	0.07	.121	0.03	.465

Note. Pointer = pointer length. Bold values indicate significant factors ($p < .05$ = *; $p < .01$ = **). Due to the inclusion of reaction times, the latent factor attention was inverted for easier interpretation.

As can be shown by the correlation analyses, especially the experimental conditions in the ADT of the long pointer length, and in parts the middle pointer length, of the latent factors attention and visual-spatial processing were associated with parietal cortex activity. Therefore, the results from Table 19 imply an adequate discriminant and convergent validity of the applied methodological procedures for both the calculation of latent factors and the method of measuring visual-spatial processing via the fNIRS imaging technique in Studies 1 and 2.

3.3.8 Implications for the fourth study

The third study summarized 14 neuropsychiatric test variables on the four latent factors declarative memory, working memory, attention, and visual-spatial processing with adequate measurement (in-)variance across both measurement time points using the SEM approach. This approach was found to be statistically superior to the composite approach. Subsequently, the four latent factors were included as dependent variables in mixed models to generate predictive analyses. Most importantly, sex predicted decline in all four cognitive domains, with females performing better in declarative and working memory. Higher age also predicted sex-independent lower declarative memory performances. Evidence also emerged for predictive effects of lower BDNF serum levels on attention declines and of higher depressive symptomatology on lower visual-spatial processing. The results ultimately may indicate differences between normal aging and pathological neurodegenerative processes. Moreover, the covariance of latent factors suggested neuronal connectivity between factors and thus possible compensatory mechanisms, independent of causality and direction of effects. To sum up, the third study allowed the first predictions of pathological cognitive decline to be made. Even better predictions can thus be expected at the third and final measurement time point, the second follow-up visit. However, since the Vogel Study is a longitudinal study with 6 years of single case follow-up and a total duration of 10 years, participant dropouts must be expected across the measurement time points. It will therefore be interesting to assess the extent to which there are associations between dropout rates with early detection of pathological cognitive decline. Can dropouts be predicted, particularly by cognitive decline, and if so, what are the implications for further study progress and reporting? Thus, the fourth study aimed to predict, via MANCOVAs and multinomial logistic regressions, dropouts, "short" participation, and normal study participation on cognitive performance, dementia screenings, and autonomy in daily living parameters, as well as humoral and affective parameters.

3.4 Paper 4: Factors associated with dropout in the longitudinal Vogel Study of cognitive decline

Dropout prediction in the elderly

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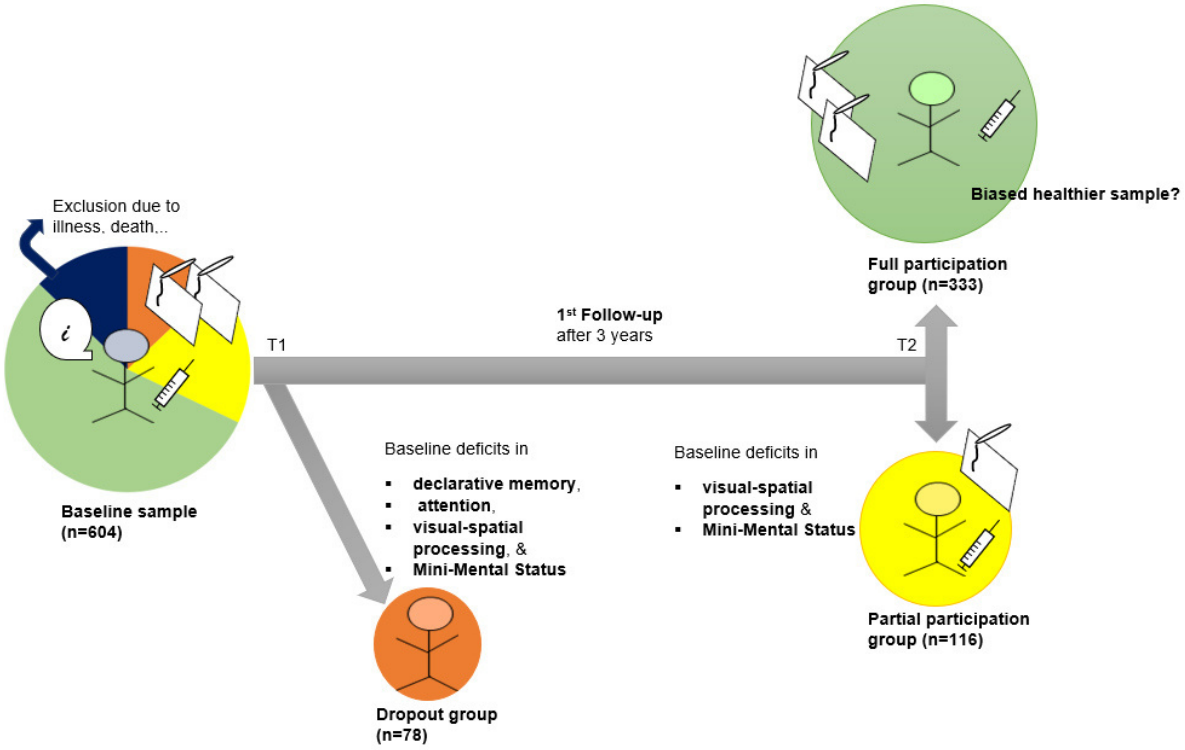
Abstract

Dementia, including Alzheimer's Disease (AD), is a growing problem worldwide. Prevention or early detection of the disease or a prodromal cognitive decline is necessary. By means of our long-term follow-up "Vogel Study", we aim to predict the pathological cognitive decline of a German cohort (mean age was 73.9 ± 1.55 years at first visit) with three measurement time points within 6 years per participant. Especially in samples of the elderly and subjects with chronic or comorbid diseases, dropouts are one of the biggest problems of long-term studies. In contrast to the large number of research articles conducted on the course of dementia, little research has been done on the completion of treatment. To ensure unbiased and reliable predictors of cognitive decline from study completers, our objective was to determine predictors of dropout. We conducted multivariate analyses of (co-)variance (MANCOVAs) and multinomial logistic regression analyses to compare and predict the subject's dropout behavior at the second visit 3 years after baseline (full participation, partial participation, no participation/dropout) with neuropsychiatric, cognitive, blood, and lifestyle variables. Lower performance in declarative memory, attention, and visual-spatial processing predicted dropout rather than full participation. Lower performance in visual-spatial processing predicted partial participation as opposed to full participation. Furthermore, lower performance in Mini-Mental Status Examination (MMSE) predicted whether subjects dropped out or participated partially instead of full participation. Baseline cognitive parameters are associated with dropouts at follow-up with a loss of impaired participants. We expect a bias into a healthier sample over time.

Graphical Abstract



Graphical Text

Longitudinal dropout behavior in the elderly. This study describes the predictive value of cognitive performance and dementia screenings in longitudinal dropout behavior (dropout, partial participation instead of full participation). Declines in declarative memory, attention, visual-spatial processing and the Mini-Mental-Status Examination increase the probability of study dropout 3 years after baseline and lead to a healthier, and therefore possibly biased sample.

Key points:

- Cognitive performance in declarative memory, attention, and visual-spatial processing can predict study dropout.
- Lower performance in Mini-Mental-Status Examination (MMSE) can predict study dropout.
- Baseline cognitive parameters can predict dropout behavior at follow-up with a loss of impaired participants and a bias into a healthier sample, respectively.

Keywords: Prediction, dropout, elderly, cognitive decline, mild cognitive impairment (MCI), Alzheimer's Disease.

3.4.1 Introduction

Alzheimer's Dementia (AD) is the most common form of dementia (60-70% of cases) and one of the most frequent neurodegenerative disorders (World Health Organization [WHO], 2019). An irreversible, progressive course is characteristic (Yang et al., 2018). Worldwide, around 50 million people have dementia (WHO, 2019). Experts estimate the number to be as high as 82 million by 2030 and an alarming 152 million by 2050, mainly due to the growing elderly population (WHO, 2019). The total cost of dementia in 2019 was estimated at around US$1 trillion and is expected to rise to US$2 trillion by 2030 (Handels et al., 2018; Reed et al., 2019; Alzheimer's Disease International [ADI], 2019). Currently, no curative drug therapy is available (Meyer et al., 2020).
Therefore, the prevention of the disease is mandatory. The exploration of risk factors and predictors of dementia or the characteristically prodromal cognitive decline could make this possible (Hickman et al., 2016; Jessen, 2019; Qian et al., 2017). Extensive reviews postulated the predictive validity for various risk factors, besides age (WHO, 2019). For example, early-life factors like the education level or family-related factors (Wang et al., 2019) and modifiable lifestyle factors such as alcohol consumption, physical activity, or the Body-Mass-Index (BMI) have the potential to be of predictive value (Li et al., 2020; Peters et al., 2019; Xu et al., 2015). Also, chronic or pre-existing diseases as heart, vascular or psychiatric diseases (Larsson & Markus, 2018), bio-physiological variables like the Brain-Derived Neurotrophic Factor (BDNF) and blood parameters, and genetics such as the phenotypes of Apolipoprotein-ε4ε4/ε3ε4 do play an important role (Sharma et al., 2020; Sun et al., 2015). Moreover, the cognitive performance level should be examined (Li et al., 2016; Song et al., 2018).
By means of our long-term follow-up "Vogel Study", we aim to predict a cognitive decline of a German cohort (>600 people, >70 years) over a total of 10 years, with 6 years of single participant observation and three visits. High dropout rates mean a loss of information and, therefore, biased predictions of cognitive decline and decreased statistical power. Hence, study completion is essential to find reliable predictors. A lack of understanding of the dropout behavior in our study even could increase the rate. Especially within samples of the elderly and subjects with chronic or comorbid diseases, dropouts are one of the biggest problems of long-term studies (Hill et al., 2016; Waring et al., 2005). Reasons for dropout vary and may occur due to illness, death, institutionalization, refusal of participation, failed contact, or lack of interest

(Burke et al., 2019; Coley et al., 2008). In contrast to the research conducted on the course of dementia, still only a few research has been conducted on study completion or predictors for dropout in longitudinal AD studies (e.g., Agogo et al., 2018; Coley et al., 2011; Das et al., 2018; Mehdipour Ghazi et al., 2019; Tan et al., 2018). Some revealed predictive factors influencing dropouts in longitudinal investigations of dementia/AD samples. For instance, researchers found out that a progressing cognitive impairment, more neuropsychiatric symptoms, or specific bio-physiological features are predictors for dropout using data of 35 US-American AD centers (Burke et al., 2019). Another study stated the relevance of weaker cognitive functioning using the Mini-Mental Status Examination (MMSE), symptoms of depression, higher age, and disability at baseline in a dementia prevention study (Beishuizen et al., 2017). Others found out that impaired cognitive functioning using the MMSE and dementia assessment scales and depressive symptoms could predict dropout in patients with mild cognitive impairment (MCI) and AD (Lo & Jagust, 2012). Moreover, the degree of need for care, the use of cholinesterase inhibitors or other drugs predicted dropout in another multicenter AD cohort (Coley et al., 2008). A further study investigated future dementia risk, evidenced by prior brain magnetic resonance imaging (MRI) scans, as a predictive factor associated with dropout (Glymour et al., 2012).

Based on recent findings considering the dropout behavior of the elderly, this study aimed to investigate our sample characteristics, examine the dropout behavior of the participants, and determine predictors of dropout. On these terms, we tried to find reliable predictors of cognitive decline from study completers.

3.4.2 Methods

3.4.2.1 Sample characterization

N=604 subjects (age: 70–77 years) participated in the baseline investigation of the “Vogel Study”, which is a long-term, observational, and prospective study including 2 follow-ups. With a total study duration of 10 years and 6 years of individual monitoring, the study aims to detect MCI or AD early and find predictors and risk factors of pathological cognitive decline. It was approved by the local ethics committee and was in accordance with the Helsinki Declaration (vote no. 23/11; World Medical Association, 2013). For participant recruitment, 5124 inhabitants of the city of

Würzburg, born between April 1936 and March 1941, were contacted by letter, and invited to our information session after receiving the contact information of 7875 age-appropriate inhabitant records from the registry department. Then, following the random and stepwise postal invitations of 200 potential participants each to information sessions, interested individuals were registered for the first screening.

The following exclusion criteria were applied: 1) a severe neurologic, psychiatric, or internal disease within the past year, 2) a severe, uncorrected, and impaired vision or hearing, and 3) the use of psychoactive medication at the baseline investigation. In addition, each subject confirmed the participation in the study in a written declaration of consent after receiving complete information. Hence, sample recruitment was done randomly to get a representative sample. However, it can be assumed that, for example, certain personality traits, the level of education, cognitive deficits, or socioeconomic status influence the willingness to participate in the study. The representativeness of the sample might therefore be restricted.

To control for confounding variables in statistical analyses and to ensure comparability with previous findings (Haberstumpf et al., in prep[14]; Haberstumpf et al., 2020; Katzorke et al., 2017; Katzorke et al., 2018; Polak et al., 2017; Zeller et al., 2019), we excluded *n*=65 participants due to a history of a central nervous system disease that may affect their cognitive performance (multiple sclerosis, epilepsy, pain syndrome, restless legs syndrome, stroke, head injury, traumatic brain injury, cerebral bleeding, transient ischemic attack, basal skull fracture). Furthermore, we excluded *n*=12 participants who died until the first follow-up because of the lack of information about the cause of death to avoid confounding variables. Until the first follow-up, we had a dropout group with a total of *n*=78 participants. Of those, *n*=56 participants did not participate anymore or dropped out due to a refusal to participate in further investigations, *n*=22 participants because they could no longer be reached (e.g., per phone, unknown removals). Those who participated fully (*n*=333) and partially (*n*=116; e.g., reduced neuropsychiatric diagnostics or domiciliary visits) remained, resulting in a total of *n*=527 participants until the completion of the first follow-up (see Figure 18). We examined demographic characteristics with frequency analyses, chi-square tests

[14] Please note that the paper 'Haberstumpf et al., in prep.' always refers to the paper 'Sophia Haberstumpf et al., 2021'. At the time of the accept of Paper 4, Paper 3 had not yet been accepted by the publisher.

(sex, type of housing), and one-way analyses of variance (ANOVAs; age, education level). Of *n*=271 males and *n*=256 females at first follow-up, more females were in the dropout and partial participation group at first follow-up than males, whereas more males participated fully (χ^2=8.24, *p*=.016). Groups also differed in age (*F*(2, 534)=5.61, *p*=.004, η^2=.02): Subjects with full participation (Mean [M]=73.72, Standard Deviation [SD]=1.55, *n*=333) were younger than dropouts (M=74.23, SD=1.44, *N*=78; *p*=.025) and subjects with partial participation (M=74.14, SD=1.55, *N*=126; *p*=.030). The dropout groups only tended to differ in education level (*F*(2, 520)=2.52, *p*=.081, η^2=.01; see Table 20). Moreover, groups did not differ in type of housing (alone/with relatives/other: χ^2=7.62, *p*=.106; room/apartment/house: χ^2=4.03, *p*=.673). Based on model assumptions and our previous work (Polak et al., 2017; see also the discussion section[15]), we applied sex, age (years) and education level (grades) as covariates for further analyses of the predictive value of neuropsychiatric tests and blood and lifestyle variables for predicting study dropout at first follow-up.

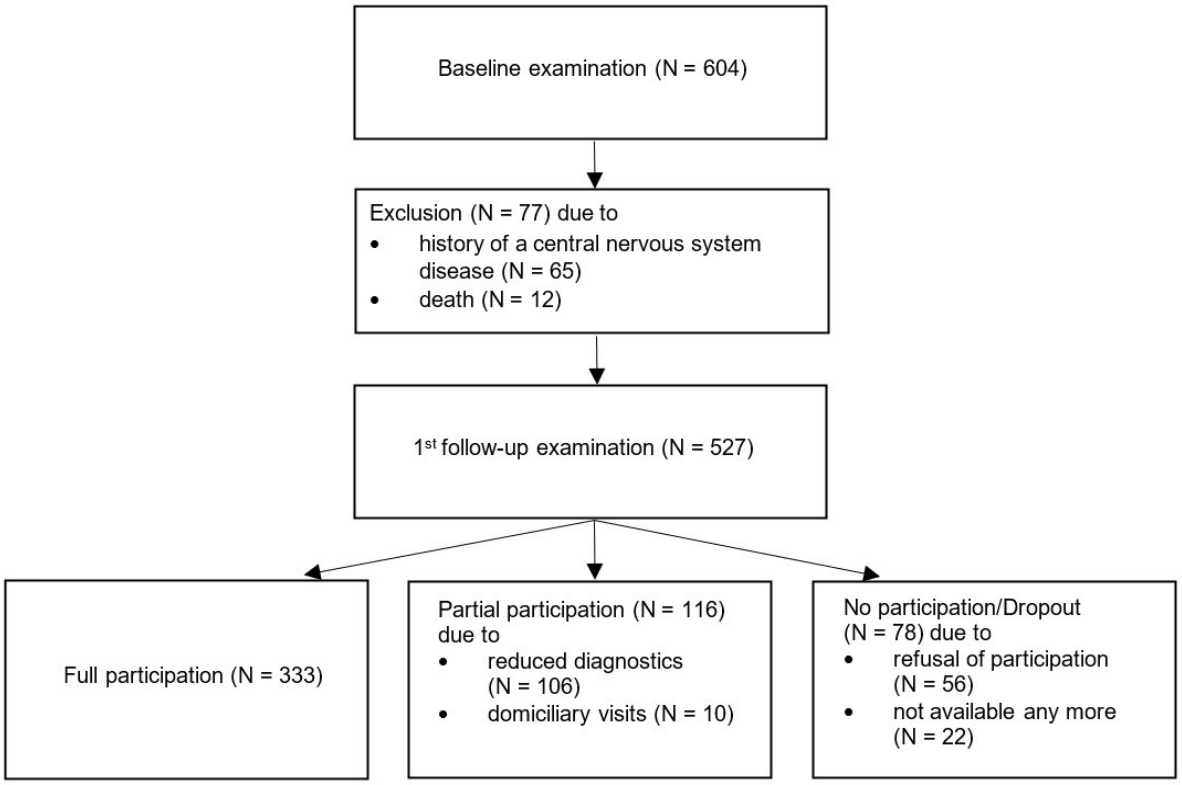


Figure 18. Course of exclusion for data analysis.

[15] Please note that this section now is numbered 3.4.4.

Table 20

Sample characterization.

	no participation/ dropout	partial participation	full participation	total sample
N	78	116	333	527
(male/female)	(35/43)	(49/67)	(187/146)	(271/256)
Age in years (range)	74.2 ± 1.44 (71-77)	74.2 ± 1.58 (70-77)	73.7 ± 1.55 (70-77)	73.9 ± 1.55 (70-77)
Education level N, %	77, 14.7	115, 22.0	331, 63.3	523, 100.0
Main school	35, 44.9	59, 50.9	140, 42.0	234, 44.4
Middle school	19, 24.4	31, 26.7	87, 26.1	137, 26.0
High school	11, 14.1	11, 9.5	35, 10.5	57, 10.8
University	12, 15.4	14, 12.1	69, 20.7	95, 18.2

Note. VLMT=Verbal Learning and Memory Test (Helmstaedter et al., 2001), WMS-R=Wechsler Memory Scale-Revised (Härting et al., 2000), TAP=battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001), RWT=Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000), CFT=Rey Complex Figure Test (Meyers & Meyers, 1996), RT=Reaction Time.

3.4.2.2 Neuropsychiatric diagnostics

We conducted different neuropsychiatric tests for the diagnostic characterization of our sample. Firstly, we measured cognitive performance with a specific test battery including the Verbal Learning and Memory Test (VLMT; Helmstaedter et al., 2001), the Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000), subtests tonic and phasic alertness of the battery of Tests for Attentional Performance (TAP; Fimm & Zimmermann, 2001), the Regensburger Verbal Fluency Test (RWT; Aschenbrenner et al., 2000), and the Rey Complex Figure Test (CFT; Meyers & Meyers, 1996).
We further investigated a participant's affectivity by using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the Geriatric Depression Screening Scale (GDS; Yesavage et al., 1982), and the Anxiety Sensitivity Index-3 (ASI-3; Reiss et al., 1986).
The state of neurodegeneration was assessed by using both the dementia detection test (DemTect; Kalbe et al., 2004) as well as the MMSE (Folstein et al., 1975) as dementia screenings.
A participant's autonomy in daily routine was objectified using the Bayer-Activities of Daily Living scale (B-ADL; Hindmarch et al., 1998). The B-ADL was assessed as an interview procedure, and the participants' functional level was therefore self-rated by them at the baseline.This was feasible due to the initial, mostly non-demented state of the participants.

3.4.2.3 Blood and lifestyle variables

We took blood as an empty-stomach blood test for routine and exploratory laboratory parameters (serum, ethylenediaminetetraacetate [EDTA] plasma) on baseline investigation (see Table 21) and obtained lifestyle variables based on anamnestic questions: We classified the education level by the participant's statements to their graduate level. Substance consumption variables describe the subject's dichotomous consumer behavior at baseline investigation (cigarettes, alcohol, caffeine). Finally, we asked for familial predispositions developing dementia/AD (e.g., known AD diagnosis in previous family generations) and calculated the body mass index (BMI).

Table 21

Blood analysis.

Collected blood parameters
Glucose (mg/dl)
Total cholesterol (mg/dl)
LDL-cholesterol (mg/dl)
HDL-cholesterol (mg/dl)
Triglycerides (mg/dl)
Leucocytes (n*1000/µl)
C-reactive protein (mg/dl)
Blood sedimentation rate – 1h (mm)
Blood sedimentation rate – 2h (mm)
Thyroid-stimulation hormone (ml U/l)
Vitamin B12 (pg/ml)
Folacin (ng/ml)
Homocysteine (µmol/l)
HbA1c (%)
BDNF (ng/ml)

Note. BDNF=Brain-Derived Neurotrophic Factor.

3.4.2.4 Data analysis

Cognitive performance

To quantify a participant's cognitive performance, we used the following 11 neuropsychiatric test variables of our 527 participants without a history of a central nervous system disease at baseline investigation: VLMT immediate recall (sum score words), VLMT delayed recall (sum score reproduced words), VLMT recognition (sum score recognition word list), WMS-R digit span (sum score), WMS-R block span (sum score), TAP tonic alertness (median of reaction time [RT]), TAP phasic alertness (parameter for phasic alertness), RWT verbal fluency (sum score) and RWT category fluency (sum score), CFT memory (sum score), CFT visuoconstruction (drawing score). Based on the theoretical background (National Institute of Mental Health, 2011) and preliminary Structural Equation Modeling (SEM) in a naturalistically smaller, more restricted sample described in Haberstumpf et al. (in prep), we identified 4 latent factors within our neuropsychiatric test variables that showed measurement invariance from baseline investigation to first follow-up. Hence, in our current analysis, we calculated values for each participant at baseline extracted by an Exploratory Factor Analysis (EFA), following Eigenvalue and parallel analysis (see Table 22). After Varimax rotation, factor loadings ≥ .4 were extracted in the model. All statistical requirements were met (Kaiser-Meyer-Olkin criterium: .758, Bartlett's test of sphericity: $\chi^2(55)=1486.78$, $p<.001$). Actual EFA revealed the same 4 factors for the baseline sample as described in Haberstumpf et al. (in prep), which simultaneously confirms the previously latent factors and their stability over time: declarative memory (consisting of all three VLMT scores), working memory (both RWT scores and WMS-R digit span), attention (TAP tonic and phasic alertness), and visual-spatial processing (both CFT scores and WMS-R block span).

Table 22

Neuropsychiatric factors defined by exploratory factor analysis (EFA).

Extracted factor	Test variables	Factor loadings after Varimax Rotation			
		1	**2**	**3**	**4**
Declarative Memory	VLMT immediate recall	.895	-	-	-
	VLMT delayed recall	.838	-	-	-
	VLMT recognition	.810	-	-	-
Attention	TAP tonic alertness	-	.748	-	-
	TAP phasic alertness	-	.688	-	-
Working Memory	WMS-R digit span	-	-	.624	-
	RWT verbal fluency	-	-	.779	-
	RWT category fluency	-	-	.808	-
Visual-Spatial Processing	WMS-R block span	-	-	-	.510
	CFT memory	-	-	-	.793
	CFT visuoconstruction	-	-	-	.727

Note. VLMT = Verbal Learning and Memory Test (Helmstaedter et al., 2001), WMS-R = Wechsler Memory Scale-Revised (Härting et al., 2000), TAP = battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001), RWT = Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000), CFT = Rey Complex Figure Test (Meyers & Meyers, 1996), RT = Reaction Time.

Statistical analysis

We analyzed demographical, neuropsychiatric, biological, and clinical data using baseline data and performed all computations in IBM SPSS Statistics for Windows (version 25). As possible, we presented data as M ± SD. The two-tailed α significance level was set at $p<.05$.

Multivariate analyses of covariance

We conducted multivariate analyses of covariance (MANCOVA) to compare the independent subject's dropout behavior (full participation, partial participation, and no participation/dropout) at first follow-up with diverse dependent variables to detect between-group differences, including the covariates sex, age, and education level. We specified the effects of our covariates by calculating correlations with dependent variables. Moreover, we used individual one-way ANOVAs and Bonferroni corrected post-hoc tests to examine differences for each group and avoid α-error-cumulation. Finally, we followed up significant MANCOVAs with multinomial logistic regression analyses.

Multinomial logistic regression analysis

We performed multinomial logistic regression analyses to examine the predictors of study dropout at the first follow-up investigation. We used our multinomial variable dropout behavior with three outcome categories (full participation, partial participation, and no participation/dropout) at first follow-up as the dependent variable. Predictors were treated as continuous variables. Exceptions were our covariate sex and our categorical variables familial predisposition for dementia/AD, cigarette consumption, alcohol consumption, and caffeine consumption. We entered all variables as main effects for univariate analyses. The relationship between our predictors and the variable dropout behavior was assessed by estimating Odds Ratios with 95%-Confidence Intervals (ORs, 95%-CI), indicating an increased probability of a subject's participation at the first follow-up investigation when OR>1. Otherwise (OR<1), our predictor variable will indicate an increased probability of a study dropout at the first follow-up investigation per every unit added.

3.4.3 Results

3.4.3.1 Multivariate between-group comparisons of baseline sample characteristics

Cognitive Performance

Using the multivariate Pillai's trace, we found significant effects between the 4 factors describing the participant's cognitive performance at baseline investigation and their dropout behavior at first follow-up (V=.06, $F(8, 1008)=3.58$, $p<.001$, $\eta^2=.028$; see Supplementary Table 10 in appendix). The univariate tests showed significant effects for 3 of the 4 factors: declarative memory ($F(2, 506)=3.73$, $p=.025$, $\eta^2=.015$), attention ($F(2, 506)=3.28$, $p=.038$, $\eta^2=.013$), and visual-spatial processing ($F(2, 506)=5.33$, $p=.005$ $\eta^2=.021$).

Bonferroni corrected post-hoc tests showed significant lower performances of declarative memory for participants who dropped out compared to those who participated fully at first follow-up (Mean Difference [MD]=-.33, $p=.020$). It also revealed significantly lower attention performances for participants who dropped out compared to full participants (MD=-.30, $p=.046$). Moreover, Bonferroni correction revealed significantly lower attention performances for partial participants compared with full participants at first follow-up (MD=-.39, $p=.032$). Significantly lower performances of visual-spatial processing for participants who dropped out compared to full (MD=.30, $p=.046$) and partial participants (MD=.29, $p=.023$) could also be found (see also Figure 19).

Highly significant group differences appeared for participants with higher education level performing better in declarative memory ($F(1, 506)=16.86$, $p<.001$, $\eta^2=.032$), working memory ($F(1, 506)=64.85$, $p<.001$, $\eta^2=.114$), and visual-spatial processing ($F(1, 506)=13.79$, $p<.001$, $\eta^2=.027$) as well as for female gender performing better in declarative memory ($F(1, 506)=67.63$, $p<.001$, $\eta^2=.118$) and male gender scoring higher in visual-spatial processing ($F(1, 506)=18.86$, $p<.001$, $\eta^2=.036$).

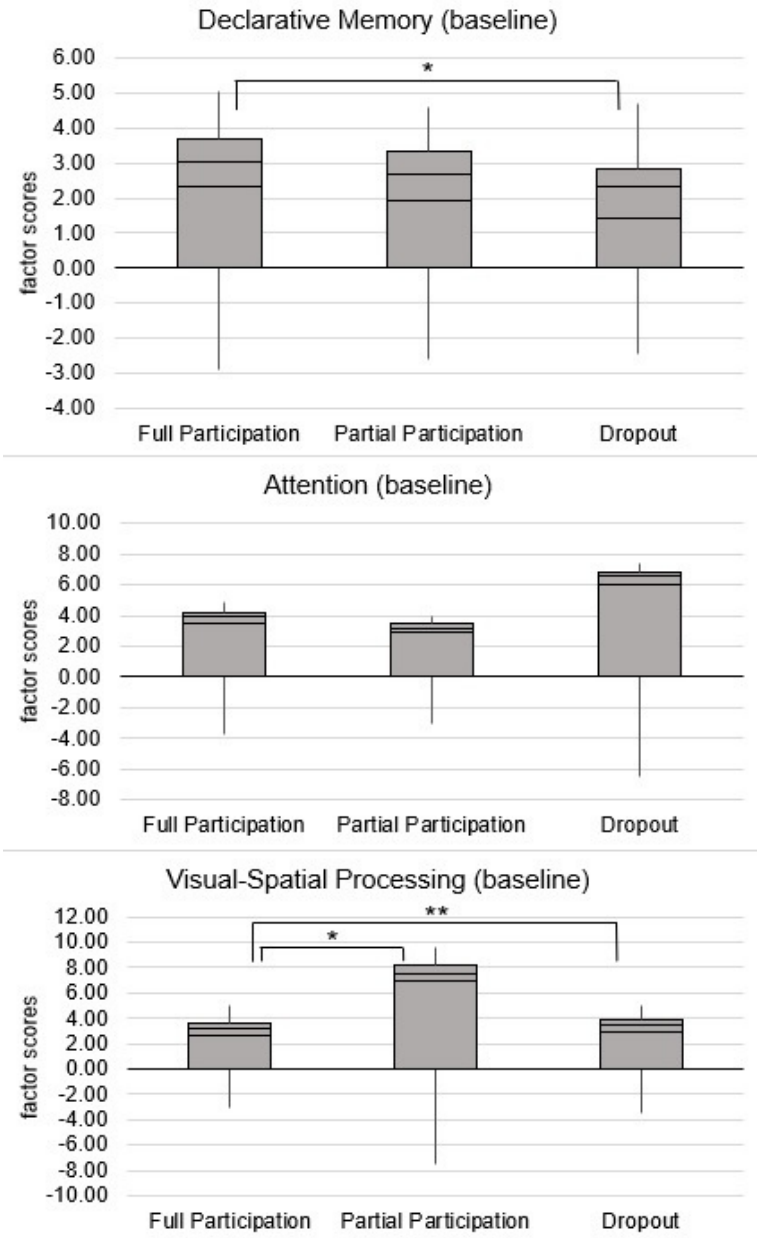


Figure 19. Significant factor scores of cognitive performances for subject's dropout behavior.

Affectivity

Pillai's trace showed a significant effect for the subject's dropout behavior on the psychiatric test scores measuring affectivity (BDI-II, GDS, ASI-3; V=.03, $F(6, 1012)=2.18$, $p=.043$, $\eta^2=.01$; see Supplementary Table 11 in appendix). However, univariate tests for all three affectivity test scores revealed no significant effects.

Dementia screenings

Pillai's trace revealed significant effects between dropout behavior at first follow-up investigation and the two cognitive test scores describing participant's state of neurodegeneration at baseline investigation (MMSE, DemTect; V=.04, $F(4, 1034)=5.36$, $p<.001$, $\eta^2=.02$; see Supplementary Table 12 in appendix). Both univariate analyses were significant (MMSE: $F(2, 517)=9.97$, $p<.001$, $\eta^2=.04$; DemTect: $F(2, 517)=3.80$, $p=.023$, $\eta^2=.01$).

Bonferroni corrected post-hoc tests showed highly significant lower performance in the MMSE performance for participants that dropped out compared to participants that participated fully at first follow-up (MD=-.64, $p<.001$) and significantly lower performance for subjects with partial instead of full participation at first follow-up (MD=.33, $p=.038$). Moreover, Bonferroni correction revealed significantly lower DemTect scores for subjects who dropped out compared to subjects with full participation at first follow-up (MD=-.73, $p=.021$; see also Figure 20).

Again, highly significant group differences could be revealed for higher educated participants reaching higher test scores in the MMSE ($F(1, 517)=18.46$, $p<.001$, $\eta^2=.034$) and the DemTect ($F(1, 517)=16.26$, $p<.001$, $\eta^2=.030$) as well as for better performances of the female gender in the DemTect ($F(1, 517)=16.67$, $p<.001$, $\eta^2=.031$).

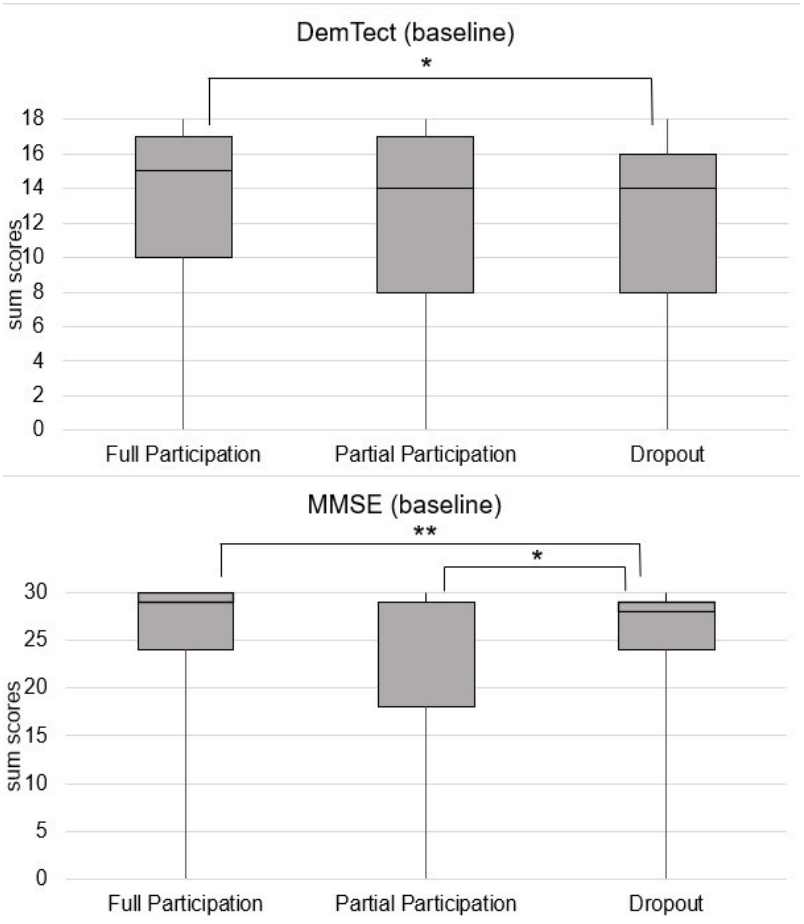


Figure 20. Significant sum scores of dementia screening diagnostics for subject's dropout behavior. DemTect=dementia detection test (Kalbe et al., 2004), MMSE=Mini-Mental State Examination (Folstein et al., 1975).

Autonomy in daily routine

Regarding participant's dropout behavior at follow-up investigation, no significant between-subjects effects could be found for B-ADL ($F(2, 517)=.059$, $p=.943$, $\eta^2=.00$; see Supplementary Table 13 in appendix).

Blood and lifestyle variables

Pillai's trace did not find any significant differences between blood and lifestyle factors and the participant's dropout behavior at first follow-up investigation (V=.06, F(32, 984)=9.7, p=.52, η^2=.03; see Supplementary Table 14 in appendix).

3.4.3.2 Prediction of dropout behavior at first follow-up investigation

Cognitive Performance

As can be seen in Supplementary Table 15 in appendix, individual multinomial logistic regression analysis (R^2=.10 (Cox-Snell); model $\chi^2(14)=52.02$, $p<.001$) revealed that study dropout could be predicted by 3 of the 4 factors. Lower performance in declarative memory at baseline significantly predicted dropout at first follow-up rather than full participation (b=-.38, Standard Error [SE]=.14, Wald$\chi^2(1)=7.18$, p=.007, OR=0.69). Also, analyses showed that lower performance in attention at baseline significantly predicted dropout at first follow-up instead of full participation (b=-.33, SE=.16, Wald$\chi^2(1)=4.13$, p=.042, OR=0.72). Additionally, deficits in visual-spatial processing significantly predicted dropout at baseline compared with full participation at first follow-up (b=-.37, SE=.14, Wald$\chi^2(1)=7.35$, p=.007, OR=0.69).

Referring to participants who *participated partially at* first follow-up, performance deficits could draw significant predictions for the factor *visual-spatial processing* (b=-.32, SE=.12, Wald$\chi^2(1)=7.29$, p=.007, OR=0.73).

Furthermore, our covariates male sex and higher age significantly predicted study dropout (sex: b=-.60, SE=.30, Wald$\chi^2(1)=3.96$, p=.047, OR=0.55; age: b=.16, SE=.13, Wald$\chi^2(1)=1.55$, p=.214, OR=1.17), but male sex was the only covariate predicting partial participation as opposed to full participation at first follow-up (sex: b=-.54, SE=.25, Wald$\chi^2(1)=4.68$, p=.030, OR=0.58). Unlike significant group differences in various test procedures (see Supplementary Table 10 in appendix), the education level could not significantly predict the dropout behavior.

Dementia screenings

As can be seen in supplementary Table 16 in appendix, subject's lower performance in MMSE predicted (highly) significant whether subjects dropped out (b=-.37, SE=.11, Waldχ^2(1)=11.19, p=.001) or participated partially at first follow-up (b=-.26, SE=.10, Waldχ^2(1)=6.44, p=.011) as opposed to full participation (R^2=.08 (Cox-Snell); model χ^2(12)=45.49, p<.001). Both covariates male sex and higher age (highly) significantly predicted dropout (sex: b=-.65, SE=.27, Waldχ^2(1)=5.87, p=.015; age: b=.25, SE=.09, Waldχ^2(1)=8.10, p=.004) or partial participation (sex: b=-.66, SE=.23, Waldχ^2(1)=8.42, p=.004; age: b=.20, SE=.07, Waldχ^2(1)=7.12, p=.008) rather than full participation at first follow-up. Again, no significant effects could be found for the education level as a predictor of dropout behavior compared to significant group differences in the dementia screenings (see Supplementary Table 12 in appendix).

3.4.4 Discussion

In this study, we investigated the predictive effects of several demographical, biological, and clinical variables assessed at the baseline investigation on dropout behavior at first follow-up in the elderly participants of the Vogel Study. Multinomial logistic regression analyses revealed that deficits in cognitive performance predict study dropout. More precisely, lower performance in declarative memory, attention, and visual-spatial processing at baseline investigation predicted dropout at first follow-up rather than full participation. Also, lower performance in visual-spatial processing at baseline investigation significantly predicted partial participation instead of full participation at first follow-up. However, as we saw in MANCOVA and logistic regression analysis, working memory could not predict dropout behavior. Concerning the covariates analyzed, older age at baseline and male sex predicted study dropout. In addition, the male sex decreased the likelihood of partial participation.

These results seem plausible, as lower performance in declarative memory, due to memory loss, could be one of the first signs of MCI or AD (Bryzgalov et al., 2018; Jahn, 2013; Nestor et al., 2006; Riedel & Blokland, 2015; Vakalopoulos, 2017). If we assume that participants with lower performance in declarative memory are beginning to suffer from MCI or dementia, this could explain dropout, and we must expect a smaller number of participants with diagnosed MCI or AD at the follow-ups. In reverse, the

long-term prediction of cognitive decline will get complicated. Researchers also suggest that declarative memory remains functional for a long time in neurodevelopmental disorders because of suspected compensatory mechanisms (Ullman & Pullman, 2015). Hence, lower performance in declarative memory could indicate the progression from prodromal symptoms to disease, which also increases the probability of dropout. Contrary, it is possible that the participant's routine with research methods, e.g., diagnostics, plays a role in further study participation. We assume that the probability of refusal thereby is smaller. Familiarity with cognitive tests, and therefore a higher retrieval frequency, affects memory performance more than memory age (Muller et al., 2014). Interestingly, research also discusses the relationship between memory and attention in AD in the sense of impaired attention performance accompanying memory deficits from early prodromal AD stages (Finke et al., 2013). Links between attention and visual-spatial processing performance are also conceivable: Poorer outcomes are possible due to visual search. The authors described both visuospatial attention and visual search deficits in early AD (Ramzaoui et al., 2018). Following memory research, visual-spatial impairment is an essential contributor to cognitive deficits and leads to the pathological development of dementia (Fernandez et al., 2018; Maharani et al., 2018, 2019). To strengthen findings concerning visual-spatial processing performance, other sensory impairments like auditory deficits should be assessed to predict dropout or cognitive decline (Zhao et al., 2015). We think that cognitive performance itself has a great potential to predict study dropout. Thus, it might be helpful to replicate our findings to specify the effect of our defined factors on dropout, expecting further effects for working memory as a predictor at a more progressive stage.

Our MANCOVAs showed no significant effects between affectivity test scores and dropout behavior, which is why we renounced regression analysis. Affective disorders are characterized by variability and instability over time (de la Vega et al., 2018). Therefore, it is difficult to predict the participant's health three years later. We had no information about the occurrence, remission rate, or chronification status of a participant's affective impairment. Furthermore, the ASI-3 is the only test we used to assess anxiety. This test measures anxiety as a trait. Traits are more stable over time than states, which is why we assume that a trait score is more suitable for prediction. It might be important to do more research with various appropriate diagnostics on this

topic, regarding their predictive potential (Beishuizen et al., 2017; Burke et al., 2019; Lo & Jagust, 2012).

Concerning the state of neurodegeneraiton, our statistical analyses showed that only the MMSE test score had a predictive effect on dropout behavior. Lower performance in MMSE predicted study dropout or partial participation rather than full participation at first follow-up. Confirmed by research that the MMSE is one of the most frequently used screening questionnaires for assessing cognitive impairment, we think this finding is highly reliable (Arevalo-Rodriguez et al., 2015). Possibly, these participants needed reduced neuropsychiatric diagnostics at first follow-up, domiciliary visits, moved to nursing homes, or were not accessible anymore. As already mentioned, other studies support the predictive value of the MMSE as a predictor for study dropout (Beishuizen et al., 2017; Lo & Jagust, 2012). Earlier MANCOVAs showed significant differences between study dropout and full participation at first follow-up concerning the subject's DemTect performance. However, the DemTect could not predict dropout. It is known that both DemTect and MMSE measure a similar construct but different cognitive domains (Beyermann et al., 2013).

Hence, we suggest that a subject's performance in these dementia screenings correlates with dropout (e.g., declarative memory $p < .029$, MMSE $p < .001$). Therefore, longitudinal research is particularly difficult since the sample that still participates fully at follow-up probably reflects a biased, healthier sample than expected in the future.

Regarding autonomy in daily routine, we found no significant effect for B-ADL as a predictor of dropout, although corresponding impairment may be a pre-clinical indicator of later MCI/AD progression and, thus, may also predict dropout (Cloutier et al., 2021).

Lastly, our MANCOVAs showed no significant effects between blood and lifestyle variables and dropout behavior. However, research focusing on blood and lifestyle variables seems very promising for general future dementia research and could be a chance to predict dropout (Masley et al., 2017; Preische et al., 2019).

Overall, also the findings concerning the covariates predicting dropout behavior delivered valuable information. First, older age predicted dropout or partial participation. In the current analysis, we examined a sample of older participants (aged ≥70 years), some of whom were in the risk group for developing MCI or AD. It is known that age is one of the strongest predictors of neurodegeneration and cognitive decline, respectively (Beishuizen et al., 2017; Podcasy & Epperson, 2016; Schneider et al.,

2015; Sengoku, 2020). Thus, if cognitively more impaired participants dropped out of the study or were too impaired for full participation, this would explain old age as a predictor. Second, sex is an often discussed and significant predictor of cognitive changes (Kim et al., 2015). In terms of AD, the female sex mainly predicts disease progression instead of the male sex (Li et al., 2016). Moreover, it is known that women have a higher lifetime risk of developing AD and are also more likely to be diagnosed with it (Li & Singh, 2014; Nebel et al., 2018; Podcasy & Epperson, 2016). Nevertheless, women mostly get older than men, which leads to the assumption that women fall ill at a comparatively later age than men (Beam et al., 2018). In our sample, women and men were of a similar age, and analyses revealed male sex as a predictor for study dropout. In line with other research literature, we suggest that this effect may be explained due to earlier death or by sex-specific distinctions in cognitive domains such as lower performance of men in declarative memory (Febo et al., 2020; Haberstumpf et al., in prep; Li & Singh, 2014; Muniz-Terrera et al., 2009; Nebel et al., 2018; Piccinin et al., 2013; Vega et al., 2010). Third, we saw that participants differed in educational level, but the educational level did not predict dropout behavior at first follow-up as can be revealed by the different statistical statistical procedure for the inclusion of the covariates in the MANCOVAs and regression analyses. We recommend study replications, as education level is also considered a promising predictor variable of cognitive decline and thus may also be relevant to long-term dropout behavior (Sharp & Gatz, 2011; Xu et al., 2015).

In sum, this analysis found out that a possible confound between cognitive impairments and study dropout should be considered. If the goal in future analyses is to identify and separate corresponding effects, appropriate statistical methods might be helpful. For example, Levin et al. (2000) applied discriminant analysis to detect cognitive decline in neuropsychological measures as a predictor for study attrition in a sample of patients with Parkinson's disease and possible dementia. Moreover, we suggest using such statistical methods that aim to control confounding variables, e.g., randomization, matching of samples, or the adjustment of confounding factors (Bernstein et al., 2021). From a more practical few, it may be helpful to apply retention tactics to reduce dropout rates in long-term studies. Actual reviews describe the association between the employment of diverse retention techniques and retention rates (Robinson et al., 2007; Robinson et al., 2015). We also tried to retain study participants in terms of the Vogel

Study. For instance, we provided study procedure information such as time schedules to all participants and educated them about follow-ups. Information events were provided. Our staff initiated contact regularly by phone and mail for new clinic appointments and informed them about findings and diagnoses. We tried to make adequate offers during the investigation appointments (e.g., drinks and food, regular breaks). Moreover, we tried to accommodate participants who were unable to come to the clinic themselves for an appointment, for example, due to illness, and visited them at home. All staff received regular and qualified training, were assigned to, and showed interest in the respective study participants. Since the clinic refunded parking tickets or postage fees, all study participants could be financially reimbursed.

Our study also had some limitations. First, despite a large sample size of participants in the Vogel Study, individual subsamples differ partly extensively. Hence, individual statistical results should be interpreted with caution. Second, we had to exclude diverse groups of participants because of a lack of information (see methods section[16]). Due to this, it could be possible that we also lost some helpful information. Moreover, in analyses as ours, numerous covariates, confounding or informing participant variables such as the socioeconomic status, transportation needs, and resources, support networks, motivations to participate in research, and research attitudes could be included. For future analyses, it would be helpful to investigate more of them and ask the participants for them, e.g., based on suitable questionnaires (Stites et al., 2021). Mainly since the onset of the corona pandemic in 2019 and associated contact restrictions, for example, lower social support and limitations in daily life are expected in our sample of elderly, which may have implications for cognitive decline and dropout rates. Third, we had some methodological issues. Testing the assumption of equality of covariance matrices using the Box's test for our MANCOVAs, we found highly significant results in all cases (p<.01). However, this small model accuracy can be explained by the model complexity. This finding is suggested usually in large samples producing greater (co-) variances (Tabachnick & Fidell, 2012). Therefore, probability values are more conservative, significant results can be relied on. Furthermore, the log-likelihood based Cox and Snell's pseudo-R^2 for both models were relatively small (R^2=.09 for cognitive performance factors, R^2=.08 for autonomy in daily routine

[16] Please note that this section now is numbered 3.4.2.

diagnostics). Converted into the effect size *f*, values of around .30 result. These numbers revealed a medium effect and is considered good (Cohen, 1992).

To sum up our research, we found out that the participant's performance in declarative memory, attention, visual-spatial processing, and MMSE are predictors for study dropout. We extended the literature by paying attention to cognitive decline not only as a dependent variable but rather as a predictor for dropout behavior in a longitudinal study. These findings may enable us to define new assumptions about the development of pathological cognitive deficits in research. Research should pay more attention to possible effects for subsequent results.

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Contributors

Sophia Haberstumpf analyzed the data and wrote the first draft of the publication. Jonas Leinweber, Martin Lauer, and Thomas Polak were responsible for medical investigations and proficient supervision. Jürgen Deckert, Thomas Polak, and Martin J. Herrmann were involved in study design and data acquisition. All authors critically revised the publication, made considerable suggestions, and approved to the final script to be published.

Conflicts of interest

Jürgen Deckert is the co-recipient of a grant of the Bavarian State Government to BioVariance and an investigator in a European grant to P1Vital.

Data availability statement

Data is available on request due to restrictions.

Ethics approval and patient consent statement

Please see Methods section.

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3.4.5 References of Paper 4

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3.4.6 Conclusions

In the fourth and final study, it was shown that performance deficits in the cognitive domains declarative memory, attention, and visual-spatial processing, as well as a lower total score in the dementia screening questionnaire MMSE, could significantly predict dropout in the Vogel Study sample. In addition, the extent to which losses of the impaired study participants can also be expected, especially for the last measurement time point of the Vogel Study, the second follow-up, and whether this results in a bias toward a healthier sample was discussed.

To sum up, all four studies of the present thesis have contributed to a significant gain in knowledge about pathological cognitive decline and thus to MCI/AD early detection research regarding imaging procedures and neuropsychiatric diagnostics as well as categorical and dimensional considerations.

4. General discussion

4.1 Summary

The present thesis intended to provide insight into pathological cognitive declines in participants who were primarily healthy at baseline in the longitudinal Vogel Study regarding the early detection of MCI or AD. All studies thus aimed to differentiate between study participants both categorically at the diagnostic level using fNIRS imaging and to identify early dimensional cognitive decline using neuropsychiatric testing to establish predictors of disease development and - among other issues - study retention behavior.

In the first study, healthy study participants completed an ADT on the day of the baseline survey to measure the hemodynamic response in the parietal cortex during visual-spatial processing by fNIRS. The results of the first study showed that neuronal brain activity increased significantly with increasing task difficulty. In addition, the right instead of the left cerebral hemisphere and the superior instead of the inferior parietal cortex showed significantly higher activation patterns. Behavioral results were also comparable in that RTs and NEs also increased with increasing task difficulty.

In the second study, the previous first analysis was extended by matching MCI patients with healthy study participants and comparing them as described. As expected, the results revealed significantly lower parietal cortex activation and mostly higher reaction times and error rates in MCI patients than in healthy study participants. As in the first study, higher right-lateral and superior brain activations were found in both groups of participants.

Overall, both studies thus confirmed the successful application of the fNIRS technique while performing ADT in both healthy elderly study participants and MCI patients. It further appeared that ADT processing was more difficult for MCI patients due to the simultaneously observable hemodynamic hypoactivation with the behavioral deficits in MCI patients. A subsequent subgroup analysis of both groups of participants, matched for comparable behavioral performance, also showed hypoactivation of the parietal cortex in MCI patients and thus also provided no evidence for compensatory mechanisms in this brain area.

The third study included for the first time the first follow-up of the longitudinal Vogel Study and considered dimensional pathological cognitive changes across both

measurement time points without the explicit consideration of diagnostic categories for the analysis of all study participants and identification of possible predictors of the baseline assessment for early detection of MCI and AD. To this end, the four latent factors declarative memory, working memory, attention, and visual-spatial processing were first extracted from 14 neuropsychiatric test variables with sufficient measurement (in-)variance using the SEM approach across the two measurement time points and then introduced as dependent variables in a mixed-model approach to perform predictive analyses. Compared with the composite approach, the SEM approach was found to be superior. In particular, sex was a predictor for all cognitive domains, with females showing better performance in the cognitive domain working and declarative memory. Also, age effects could be revealed for declarative memory. In addition, effects of the BDNF serum level on attention and of the depression screening procedure BDI-II on visual-spatial processing were discussed.

Finally, the defined latent factors of cognitive performance were used for our fourth study to predict the dropout behavior ("dropout", "partial participation", "full participation") of all study participants from baseline to first follow-up using MANCOVAs and multinomial logistic regression analyses, but also based on dementia and autonomy screenings, affective, humoral, and lifestyle variables. The results showed that especially cognitive performance deficits in declarative memory, attention, and visual-spatial processing as well as in the screening procedure MMSE could predict the dropout behavior of the study participants about three years later. The extent to which, due to the dropout of presumably impaired and thus highly relevant study subjects in the context of MCI and AD early detection research, a bias towards a healthier overall sample can be expected, especially for the later second follow-up measurement time point, and associated consequences were discussed.

Thus, the results of the four studies provide essential insight into MCI and AD early detection research and associated pathological cognitive changes detectable via imaging and neuropsychiatric testing diagnostics. In the following, these findings are discussed holistically and related to the current research literature. Existing limitations are discussed, and future perspectives are presented.

4.2 Implications

4.2.1 Comparing brain imaging methods with neuropsychiatric diagnostics

Following the four analyses presented, it is worthwhile to summarize the comparison of the first two studies, which detected altered brain activation patterns between our subject groups via fNIRS imaging, with study three, which focused on predicting cognitive decline based on neuropsychiatric test diagnostics.

As partly described in the introduction of the thesis, the first neuropathological changes in AD patients appear in the hippocampus, entorhinal cortex, and parietal, temporal, and frontal brain areas (Braak & Braak, 1995, 1998; Gómez-Isla et al., 1996; Petersen et al., 2006; Possin, 2010; Vlček & Laczó, 2014). Patients who developed early-onset AD or met the diagnostic criteria of MCI are likely to have earlier or greater brain atrophy in the parietal and occipital cortex, which in turn may be manifested via earlier visual-spatial deficits as opposed to memory deficits (G. B. Frisoni et al., 2007; Fujimori et al., 1998; Possin, 2010). Thus, neurodegenerative brain processes in the frontal cortex are expected to occur much later and may provide evidence for later AD progression in MCI patients. For example, Vlček and Laczó (2014) summarize in their review article several imaging studies that report the enormous relevance of the parietal cortex for MCI and early AD patients in terms of structural and metabolic changes, identifying these same changes particularly in those MCI patients who developed AD later. The approach in our first two fNIRS studies to measure different brain activation patterns between healthy study participants and MCI patients in the parietal cortex thus seemed appropriate and could also be successfully implemented.

Simultaneously, our third study allowed us to identify latent cognitive factors or domains equally important for the early detection of dimensional cognitive decline in our sample. However, despite factor analytic varimax rotation, we found that these cognitive domains were not wholly independent of each other. Furthermore, the values for covariance between the latent factors across the two measurement time points, baseline and first follow-up, also confirmed their connectivity. For example, we found that there was significantly greater connectivity between the declarative memory and visual-spatial processing factors across time (V1=1.198, SE=.311; V2=2.573, SE=.553) and that a further increase in connectivity in terms of involved compensatory mechanisms would be expected, especially at later measurement time points. This

finding seemed plausible, also considering the complexity of cognitive domains and their cerebral localization.

So, where precisely in the brain are the latent factors that were determined in Study 3 located? Does connectivity or a neuronal network exist between cognitive domains and specific brain areas, and how long does such functional integrity persist in the brain? How relevant are thus the latent factors from the third study to the parietal cortex imaging from the first two studies? What conclusions can therefore be drawn about possible compensatory mechanisms?

Declarative and working memory deficits are among the first impairments at AD onset (Jahn, 2013). Typically, memory is divided domain-specifically or content-wise into declarative (=explicit) and non-declarative (=implicit) memory, with **declarative memory** including both semantic factual knowledge and episodic, contextual information memory (see, e.g., Förstl, 2011). These functions are located in the medial temporal lobe with connections to the parietal pathways (S. W. Davis et al., 2018; Finke et al., 2013). In addition, retrieval processes from memory or memory deficits at the onset of AD are thought to be related to impaired selective attentional processes in the parietal cortex (Finke et al., 2013). For example, the dual-attentional-processes-hypothesis assumes that attentional processes are generated top-down via the dorsal parietal cortex and bottom-up via the ventral parietal cortex (Cabeza, 2008). This also explains progressive neuronal changes in the default mode network, which consists of interactions between the medial temporal lobe, medial prefrontal cortex, posterior cingulate cortex, ventral precuneus, and medial, lateral, and inferior parietal cortex and grows through childhood and adolescence into adulthood (Finke et al., 2013; Jahn, 2013).

The **working memory** is involved in solving tasks by storing and processing information (Chai et al., 2018). The best-known working memory model to date is the widely cited multicomponent model by Baddeley and Hitch (1974). After further development, this model includes, in addition to long-term memory, the components of the central executive (="control center"), the phonological loop (=verbal working memory), the visual-spatial notepad (=visual-spatial working memory), and the episodic buffer, thus expanding the view of working memory for the first time by more than a mere division into short-term and long-term memory (Baddeley, 2000; Chai et al., 2018). From this perspective, the phonological loop component seems to be

particularly relevant for the latent factor working memory defined in our analysis, as the inclusion of the test variables RWT word and category fluency and WMS-R number span addressed the participants' verbal working memory. From a current perspective, working memory appears to be similar to the concept of short-term memory but additionally emphasizes change processes of stored information that occur there (Baddeley, 2012; Chai et al., 2018). Numerous brain regions seem to be involved here, such as the frontoparietal brain network with prefrontal (e.g., central executive), cingulate (e.g., attentional control) and parietal brain regions (see "episodic buffer" above), subcortical regions such as the midbrain and cerebellum, which includes higher-order cognitive functions in addition to motor functions (e.g., working memory), but also, for example, the basal ganglia, caudate nucleus, and thalamus (Moore et al., 2013). The specific role of the prefrontal cortex in working memory is in sending top-down mechanisms to other brain areas (e.g., target behavior in the extrastriatal and premotor cortex), although the hippocampus and parietal cortex, for example, can also send top-down signals (D'Esposito & Postle, 2015; Eichenbaum, 2013; Ruff, 2013). So-called "connectivity shifts" have also been reported, e.g., by Oren et al. (2017), in the sense that parietal brain activity rather than activation of amygdala regions is traceable during emotional stimulus processing and altered working memory performance in samples of older participants.

Alertness processes, orientation, and executive functions are usually counted as part of the **attention** network (McDonough et al., 2019; Sarrias-Arrabal et al., 2020). Thus, considering the test variables of TAP tonic and TAP phasic alertness included in our latent factor attention, it is essential to consider alertness processes. Here, the alertness network consists of prefrontal and parietal brain regions, the thalamus, and cerebellum (="frontoparietal network"; Parks & Madden, 2013; Sarrias-Arrabal et al., 2020). In addition, particularly selective attentional processes are localized in the parietal cortex (Behrmann et al., 2004).

Onset deficits in **visual-spatial processing** in AD patients are often located in frontal, temporal, parietal and occipital brain regions, hippocampus, entorhinal and retrosplenial cortex (Christophel et al., 2012; Nachev & Husain, 2006; Possin, 2010; Vlček & Laczó, 2014). Especially medial temporal and parietal regions are affected in MCI patients (Vlček & Laczó, 2014). The organization can be equally, for example, top-down or bottom-up, dorsal-ventral, or egocentric and allocentric (Possin, 2010; e.g.,

see ventrodorsal pathway, chapter 1.2.2.4). Emphasis should also be placed primarily on possible connections between memory and visual-spatial processes. For example, Baddeley (2000) distinguishes between verbal and visual-spatial memory in that verbal and auditory information activates Broca's and Wernicke's areas (see above: phonological loop), visual-spatial information activates right hemispheric occipital regions. Especially for spatial working memory, connections to occipital and prefrontal brain areas are important (Grent-'t-Jong & Woldorff, 2007; Kobayashi, 2016).

All in all, it can be summarized that from the **parietal cortex**, there are connections between visual and attentional regions as well as prefrontal, temporal, and frontal regions (Caspers & Zilles, 2018). Furthermore, with about 20% of the total cerebral cortex, it represents a significant part of the human nervous system and is involved in somatic, visual, acoustic, and vestibular sensory information processing as well as spatial cognition and motor control (Behrmann et al., 2004; Kobayashi, 2016). Also, as described in chapter 3.3.7, the additional correlation analyses between the latent factors defined in Paper 3 (chapter 3.3) and the measured parietal cortex activation during the ADT investigation via fNIRS (chapters 3.1 and 3.2) support these findings from the literature in the sense that especially attentional and visual-spatial performances were associated with the activity in the parietal cortex region of our study participants. These results implied reliable latent factors as well as strenghtened the results from paper 1 and 2. Moreover, based on these results, one could hypothesize that other brain regions are more likely to be involved in memory performances, which is also consistent with the literature.

Due to its presented relevance and especially early neurodegenerative processes localizable in the cognitive domains of our sample, it seemed reasonable for our studies to consider the parietal cortex within the imaging studies for early detection. Previously undetected compensatory mechanisms do not necessarily mean that none could have been found throughout the cortex. It is possible that compensation took place in other brain areas or neuronal networks, possibly even overall, without involvement of the parietal cortex. Therefore, combining with other imaging techniques such as fMRI or EEG may be of interest for future research. For example, in addition to hemodynamic responses, oscillations detectable via EEG may also play a compensatory role. For example, in MCI and AD patients' samples, Babiloni et al. (2016) described less effective functional connectivity and aberrant cortical-neuronal

synchronizations between frontoparietal and frontotemporal brain areas during an EEG measurement. The authors interpreted this finding as evidence of dysfunctional neuroplasticity and prodromal AD in MCI patients. In addition, E. L. Dennis and Thompson (2014) referred to increased "compensatory connectivity" as a compensatory mechanism in AD patients in their review of studies that used fMRI to examine healthy study participants as well as MCI and AD patients.

Apart from the numerous studies on possible compensatory mechanisms, contrasting concepts such as the neural efficiency hypothesis may also be relevant. Lower brain activation in a corresponding area could thus be interpreted as a more efficient neuronal process that requires fewer cerebral resources (Chai et al., 2018; Merzagora et al., 2014; Vartanian et al., 2013).

The great potential of the four factors defined in our studies is also illustrated by the overlap of these factors with the diagnostic criteria for MCI/AD defined or internationally recognized in the previous research literature in ICD-10 (F06.7), DSM-5, or the Research Domain Criteria (RDoC) research domains (American Psychiatric Association, 2014; Dilling & Freyberger, 2016; National Institute of Mental Health, 2011). For example, ICD-10 requires patients to experience memory impairment (recall or relearning) lasting at least two weeks, attention deficits, or visual-spatial functional impairment. These three ICD-10 criteria alone comprise the four latent factors, and one of these impairments would be sufficient to assign MCI according to the list of criteria. Similarly, the presence of impairment in at least one cognitive domain is considered enough for an MCI diagnosis in the DSM-5, which at the same time is reminiscent of the rDoC research domains due to no deeper specialization of these domains. Similarly, the defined latent factors are comparable to the rDoC research domains, which, for example, propose declarative and working memory as independent memory domains, and attention and especially visual perception as cognitive domains. Moreover, years ago, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (=Alzheimer's Association; ADRDA) developed diagnostic criteria for possible AD, including the following cognitive domains that may reveal deficits in AD: memory, attention, language skills, visual perception, praxis abilities, orientation, problem solving, and social function, and (instrumental) activities of daily living. All our four defined latent factors are present in these cognitive domains defined by the

NINCDS-ADRDA Alzheimer's Criteria, requiring two or more impaired cognitive domains next to other criteria for the diagnosis of probable AD (McKhann et al., 1984). For all these reasons, especially the interrelations of cognitive domains and factors with the various brain areas involved, which can only be identified by imaging methods, the combination of neuropsychiatric diagnostics with imaging methods seems inevitable (e.g. fMRI for anatomical, EEG for functional connectivity). Furthermore, our approach of moving away from categorical-diagnostic classification to a dimensional understanding of pathological cognitive change seemed to be effective and successful in detecting early signs of neurodegenerative processes. Finally, such an approach may lead to more reliable prognoses and diagnoses, since the combination of both methods and thus the assessment of both cognitive function deficits and neurological biomarkers can, for example, exclude other somatic diseases and, thus, MCI as their consequence. This is because even the ICD-10 does not exclude a physical disorder for the diagnosis of MCI in the context of F06.7; reversibility - and thus a lower probability of AD development - is also possible. For example, after open-heart surgery, a patient could have memory deficits on a first measurement due to deficient oxygen saturation but return to age-appropriate memory on a second measurement (Anderson, 2019). Such a case could be excluded as an MCI patient via the additional collection of biomarkers (Anderson, 2019; Malek-Ahmadi, 2016).

4.2.2 Associations between latent factors and dropout behavior

Lastly, a summary comparison between the third and fourth studies will be made. Emphasis will be placed on the mutual relevance of exploring the measurement (in-)variance - including the defined latent factors - of dimensional cognitive decline and exploring potential predictors of dropout behavior in the context of our longitudinal Vogel Study.

First, it should be emphasized that via the fourth analysis, study dropouts could be predicted based on baseline cognitive performance deficits in declarative memory, attention, and visual-spatial processing, as well as lower MMSE scores at first follow-up. Despite comparatively high effect sizes (e.g., of the predictor worse *declarative memory* performance for a study dropout compared to full study participation: OR=0.69), it should be considered that the probability of a dropout increases according

to the OR per unit less on the corresponding cognitive domain. However, one unit corresponds to an immense change in cognitive performance due to our standardized data structure (here: EFA). Hence, the effect sizes should be interpreted, for example, by considering the distribution of the SDs of the factor scores. However, descriptive analyses of study participants' mean scores on the four domains of cognitive performance at V1 demonstrated that those who dropped out at V2 showed a cognitive performance that was up to two SDs lower than those who fully participated at V2. This finding, in turn, supports the predictive effect of the cognitive domains (e.g., declarative memory: participants who dropped out at V2: M = -0.24, participants who fully participated at V2: M = 0.06, with total M = 0.00, total SD = 1.00).

Nevertheless, it should be mentioned that for the analysis of dropout behavior at V2 only potential predictors of V1 were included. Data on the development or slope of cognitive performance over time toward V2 in terms of improvement or decline are not available and, therefore, cannot be interpreted.

All in all, the results regarding dropout behavior within our sample imply, on the one hand, the risk of losing parts of the actual "interesting" sample, namely the presumably AD sub-sample, by the end of the long-term study, on the other hand, reliable results on early detection should still be possible especially due to our dimensional analysis approach. Rather, the results imply the high relevance to consider the dropout behavior also at V3 to obtain more precise results.

Second, the fourth study of dropout behavior represents an important retrospective contribution to the third study exploring predictors of pathological cognitive decline. In the third study, study participants who dropped out at V2 had to be excluded from the data set for statistical-methodological reasons. However, remaining missings were assumed to be random (see, for example, choice of maximum likelihood estimation method). These assumptions were already discussed as a limitation in the third study due to the possibility of a cognitive selection bias within the sample (see 3.3). Study 4 supports this limitation, as the cognitive performance was suggested as a possible predictor for later study dropouts, giving reason to suggest that also the remaining missings in the data set were not completely at random.

Another significant limitation, but unfortunately common for longitudinal studies, is the knowledge gap of not determining the reason for dropout in every case (e.g., motivational deficit or death). It is possible that more information could have contributed

to more precise statistical analyses so that possibly, for example, humoral parameters could have been significant predictors.
However, the currently pending completion of the longitudinal Vogel Study with the second follow-up remains interesting to draw further conclusions such as whether effect sizes have changed or whether additional, distinct predictors of dropout behavior have emerged.
The general limitations of the thesis will be described hereafter.

4.3 Limitations

In addition to the limitations already described in the respective studies, some general limitations should also be mentioned here, which arose from the overall consideration of all four studies and have not been explicitly discussed in the individual studies.
On the one hand, when interpreting the study results, it must be considered that only the baseline measurement was included for the first two studies, while the first follow-up was already included for the last two studies. This allowed a dimensional view of cognitive decline from the third study onwards. Overall, while offering numerous and thus predominant interpretive advantages, this approach had the disadvantage of making it more difficult to compare the last with the first two findings. Moreover, there were altered sample compositions due to data missings and dropouts until the first follow-up. In addition to these temporal sample changes, information losses within the group of healthy study participants between the first two studies can also be assumed. In the second study, for the measurement of hemodynamic parietal cortex activation during ADT, the MCI patient group was matched with the same number of healthy study participants as a control group (n = 59 each), representing a healthy sample smaller by n = 228 study participants (n = 287 healthy study participants in the first study).
On the other hand, the management of comorbid conditions in MCI and AD patients should be mentioned. As is common in scientific studies, study participants who fulfilled the diagnosis of depression, for example, could not also fulfill the diagnosis of MCI or AD at any time point. Thus, this approach avoided erroneous interpretations and produced more reliable findings (e.g., difficulty concentrating as an ICD-10 symptom of depression ≠ pathological cognitive decline with a neurodegenerative cause).

However, it is known that MCI patients show increased depressive symptoms (Anderson, 2019). Some loss of information in the sense that possibly depressed patients with comorbid MCI/AD were excluded from relevant analyses can therefore be presumed.
In addition to the limitations described, however, numerous future perspectives arose from the thesis, which are discussed below.

4.4 Perspectives

All in all, the four studies presented in this thesis provided a deeper insight into the potential of early detection of pathological cognitive changes in an elderly participant group (≥ 70 years). The studies aimed to generate an increase in knowledge for possible preventive measures and thus to be able to reduce the risk of developing MCI or AD.
Future analyses should consider combining imaging with diagnostic procedures, as outlined in several times previously. Establishing a neuropsychiatric test battery suitable for the preventive domain also seems reasonable. This could ensure higher reliability and better comparability of studies. For example, Cicalese et al. (2020) recently established an “EEG-fNIRS hybridization technique” and, thus, reached higher study accuracy.
Thus, given the high number of potential predictors and risk factors presented in the results of the third and fourth studies, it seems reasonable to alter modifiable risk factors appropriately, even in healthy older people. To date, findings on common MCI/AD risk factors report overlapping but controversial risk factors, suggesting that these may have a highly individual impact on disease onset or progression. Lifestyle changes might therefore be able to transform risk factors into resilience factors, for example. In addition, studies three and four emphasized the high relevance of cognitive activity. Age-appropriate promotion of cognitive activity could, for example, reduce MCI/AD disease risk and/or even compensate for educational deficits, which play an equally important role in disease progression. In the future, given the potential of early MCI/AD detection, it would be conceivable to introduce financial support for preventive interventions in the relevant healthy age group.

Finally, and because of the currency in general, the impact of the current COVID-19 pandemic should not be dismissed for statistical implications both for the further completion of the Vogel Study and for other studies emerging in the current period from all research groups. It is to be expected that temporary contact restrictions impacted social contacts, caregiving, and nursing, and thus on the daily coping of many older people. This circumstance, in turn, may have had additional consequences for cognitive activity in terms of risk of earlier and more rapid disease progression in those affected.

In addition to risk factors that may have arisen, studies should also be methodologically adapted to pandemic conditions. In the example of our Vogel study, we extended our currently running third measurement point (V3) by the following questionnaire procedures: Würzburg Social Distancing Scale (unpublished), the Fear of COVID-19 Scale (Ahorsu et al., 2020), the Screen for Adult Anxiety Related Disorders scale (SCAARED; Angulo et al., 2017), the Patient Health Questionnaire – 9 items (PHQ-9; Kroenke & Spitzer, 2002), State-Trait-Anxiety Inventory (STAI; Spielberger et al., 1983). But the pandemic may also raise new differential diagnostic questions. For example, viruses, including COVID-19, can attack the CNS. In a small number of people who had already recovered, inflammatory processes were recently detected after a COVID-19 infection, which led to vascular abnormalities and thus to blood circulation disorders and even dementia symptoms (Förstl, 2021). Far more frequently, a "long COVID" syndrome ("post-acute COVID") has been observed in recovered patients, contributing to impaired mental performance in addition to chronic fatigue (Dani et al., 2021; Förstl, 2021). Moreover, under pandemic conditions, ensuring adequate medical care for affected elderly patients is a proven challenge (Förstl, 2021). Recently, the first S1 guidelines have been published as a guide to the management of post/long COVID syndrome (Koczulla et al., 2021). The rapid progress concerning treatment and aftercare for those affected is further supported by the expansion of outpatient care, including in the context of self-help groups, e.g., the *Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen* (NAKOS) or the *Verein Selbsthilfekontaktstellen Bayern e.V.* (SeKo).

However, current research on other forms of dementia similar to AD may also lead to differential diagnostic challenges in the future. For example, recent research on the limbic predominant age-related “Transactive response Deoxyribonucleic Acid (DNA)

binding Protein 43 kDa" (TDP-43) encephalopathy (="LATE-dementia/proteinopathy") may be mentioned (Neumann et al., 2006). Neurodegenerative processes progressively affect the amygdala, the hippocampus, and the middle frontal gyrus in three stages, usually causing hippocampal sclerosis. However, unlike AD patients, Aβ-plaques and tau-fibrils are not present despite the cognitive-amnestic decline (mainly episodic memory at a later stage; = "suspected non-Alzheimer's disease pathophysiology" [SNAP]). Nevertheless, due to the presumed prevalence of about 20-50% in the over 80-year-olds, the LATE-dementia seems to be a common form of dementia and thus should be considered for differential diagnosis (Nelson, 2021; Nelson et al., 2019; Wilson et al., 2015; Wilson et al., 2019; Wilson et al., 2013; Yu et al., 2015).

4.5 Final disclosure

In summary, the present thesis provided new and deeper insights into the pathological cognitive changes in Vogel Study participants and contributed to the prediction of MCI or AD. The results demonstrated possibilities and thus the potential for early detection of pathological neurological and cognitive changes in an older sample of study participants. Controversy remains regarding possible cerebral compensatory mechanisms, which should continue to be researched in the future. Combining research instruments and establishing standardized testing procedures are also challenges for future analyses. Finally, it remains to be considered that disorders such as MCI or AD always represent an interaction between internal and external factors - e.g., a balance between modifiable risk factors and social circumstances such as the COVID-19 pandemic.

„I feel as if I'm losing all my leaves. […] The branches, and the wind, and the rain. I don't know what's happening anymore."

- Quote by "Anthony" from the feature film "The Father" (F. Zeller, 2020).

Only through continued research interest, as it has been for more than a century, can future patients be treated professionally, qualified, and steadily better in addition to the early detection of neurodegenerative processes.

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6. Appendix

Supplementary Table 1

F-value, degrees of freedom (df), significance (p) and effect size (η_p^2) of the repeated measurement ANOVA for neuronal parietal activity.

	F	df	*p*	η_p^2
Group	4.55	1.00; 116.00	**.035**	.038
Pointer	6.00	1.82; 211.26	**.004**	.049
Laterality	17.93	1.00; 116.00	**.001**	.134
Brain region	28.98	1.00; 116.00	**<.001**	.200
Group x pointer	1.30	1.82; 211.26	.273	.011
Group x laterality	2.99	1.00; 116.00	.086	.025
Group x brain region	2.57	1.00; 116.00	.112	.022
Laterality x pointer	1.82	1.58; 182.73	.174	.015
Laterality x brain region	0.06	1.00; 116.00	.939	.000
Pointer x brain region	4.86	1.84; 213.73	**.010**	.040
Group x laterality x pointer	0.21	1.58; 182.73	.759	.002
Group x laterality x brain region	1.36	1.00; 116.00	.247	.012
Group x pointer x brain region	0.90	1.84; 213.73	.402	.008
Laterality x pointer x brain region	0.15	1.73; 200.76	.831	.001
Group x laterality x pointer x brain region	2.18	1.73; 200.76	.123	.018

Note. Pointer = pointer length.

Supplementary Table 2

Mixed-model comparisons of Declarative Memory.

Model	AIC	BIC	χ^2	df	p (>χ^2)
DM1	2629.5	2647.1			
DM2	2600.4	2635.5	37.1459	4	1.681E-07***
DM3	2600.9	2644.9	3.4385	2	0.1792
DM4	2600.5	2653.2	4.4083	2	0.1103
DM5	2604.4	2665.9	0.1603	2	0.923

Note. DM=Declarative Memory, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion.

Supplementary Table 3

Mixed-model comparisons of Attention.

Model	AIC	BIC	χ^2	df	p(>χ^2)
AT1	1318.9	1336.5			
AT2	1322.9	1358.1	3.9687	4	0.41026
AT3	1319.1	1363	7.8371	2	0.01987*
AT4	1320.7	1373.4	2.3888	2	0.30289
AT5	1322.5	1384	2.2136	2	0.33062

Note. AT=Attention, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion.

Supplementary Table 4

Mixed-model comparisons of Visual-Spatial Processing.

Note. VSP=Visual-Spatial Processing, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion.

Model	AIC	BIC	χ^2	df	$p(>\chi^2)$
VSP 1	1859.3	1876.8			
VSP 2	1851.2	1886.4	16.0394	4	0.002967**
VSP 3	1850.8	1894.7	4.4825	2	0.106325
VSP 4	1848.6	1901.3	6.1641	2	0.045866*
VSP 5	1850.8	1912.3	1.762	2	0.414375

Supplementary Table 5

Mixed-model comparisons of Working Memory.

Model	AIC	BIC	χ^2	df	$p(>\chi^2)$
WM1	1222.1	1239.7			
WM 2	1218.2	1253.4	11.9321	4	0.01786*
WM 3	1220.3	1264.3	1.862	2	0.39415
WM 4	1220.1	1272.8	4.2453	2	0.11972
WM 5	1222.8	1284.3	1.3083	2	0.51989

Note. WM=Working Memory, AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion.

Supplementary Table 6

Best Mixed-models for the fixed effects of Declarative Memory for the latent factors and composite approach.

DM	Estimate	SE	df	*t*	*p*	Beta
(Intercept)	-0.165/ 46.011	0.104/ 0.982	296/ 296	-1.582/ 46.856	.115/ <.001***	0.03/ 0.02
Gender	0.999/ 4.896	0.21/ 1.972	296/ 296	4.765/ 2.483	<.001***/ .014*	0.44/ 0.22
Time	-0.3/ -1.249	0.103/ 1.194	296/ 296	-2.898/ -1.046	.004**/ .296	-0.13/ -0.06
Age	-0.16/ -0.091	0.068/ 0.642	296/ 296	-2.34/ -0.142	.020*/ .887	-0.11/ -0.006
Gender:Time	0.518/ -1.109	0.208/ 2.397	296/ 296	2.49/ -0.463	.013*/ .644	0.23/ -0.05
Time:Age	-0.071/ 0.689	0.068/ 0.78	296/ 296	-1.054/ 0.883	.293/ .378	-0.05/ 0.05

Note. DM=Declarative Memory, SE=Standard Error. Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

Supplementary Table 7

Best Mixed-models for the fixed effects of Attention for the latent factors and composite approach.

AT	Estimate	SE	df	*t*	*p*	Beta
(Intercept)	0.052/ 46.373	0.032/ 0.314	295/ 295	1.621/ 147.806	.106/ <.001***	0.01/ 0.009
Gender	0.128/ 0.72	0.065/ 0.637	295/ 295	1.966/ 1.131	.050/ .259	0.18/ 0.11
Time	0.034/ 0.46	0.039/ 0.27	295/ 295	0.852/ 1.707	.395/ .089	0.05/ 0.07
Age	0.008/ 0.266	0.021/ 0.205	295/ 295	0.36/ 1.296	.719/ .196	0.02/ 0.06
BDNF	-0.002/ -0.003	0.001/ 0.009	295/ 295	-2.278/ -0.288	.023*/ .774	-0.1/ -0.01
Gender:Time	0.017/ 0.517	0.08/ 0.548	295/ 295	0.214/ 0.944	.831/ .346	0.02/ 0.08
Time:Age	0.026/ 0.252	0.026/ 0.176	295/ 295	1.026/ 1.43	.306/ .154	0.06/ 0.06
Time:BDNF	0.002/ -0.001	0.001/ 0.008	295/ 295	1.612/ -0.091	.108/ .927	0.09/ -0.004

Note. AT=Attention, SE=Standard Error, BDNF=Brain-Derived Neurotrophic Factor, BDI-II=Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

Supplementary Table 8

Best Mixed-models for the fixed effects of Visual-Spatial Processing for the latent factors and composite approach.

VSP	Estimate	SE	df	*t*	*p*	Beta
(Intercept)	-0.383/ 57.283	0.062/ 0.931	294/ 294	-6.195/ 61.531	<.001***/ <.001***	-0.02/ -0.02
Gender	-0.272/ -5.151	0.127/ 1.905	294/ 294	-2.15/ -2.704	.032*/ .007**	-0.21/ -0.24
Time	-0.527/ -1.325	0.049/ 1.116	294/ 294	-10.662/ -1.188	<.001***/ .236	-0.41/ -0.06
Age	0.002/ 1.356	0.04/ 0.609	294/ 294	0.052/ 2.227	.958/ .027	0.003/ 0.1
BDNF	0.002/ 0.028	0.002/ 0.027	294/ 294	1.192/ 1.06	.234/ .290	0.06/ 0.05
BDI-II	-0.022/ -0.155	0.011/ 0.162	294/ 294	-2.003/ -0.955	.046*/ .340	-0.1/ -0.04
Gender:Time	-0.302/ -3.384	0.101/ 2.283	294/ 294	-2.987/ -1.482	.003**/ .139	-0.24/ -0.16
Time:Age	0.041/ 1.715	0.032/ 0.73	294/ 294	1.283/ 2.35	0.20*/ .019*	0.05/ 0.12
Time:BDNF	0.002/ 0.012	0.001/ 0.032	294/ 294	1.469/ 0.369	.143/ .712	0.06/ 0.02
Time:BDI-II	-0.012/ -0.048	0.009/ 0.194	294/ 294	-1.443/ -0.249	.150/ .803	-0.06/ -0.01

Note. VSP=Visual-Spatial Processing, SE=Standard Error, BDNF=Brain-Derived Neurotrophic Factor, BDI-II=Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

Supplementary Table 9

Best Mixed-models for the fixed effects of Working Memory for the latent factors and composite approach.

WM	Estimate	SE	df	*t*	*p*	Beta
(Intercept)	-0.012/ 64.297	0.046/ 1.148	296/ 296	-0.266/ 56.019	.791/ <.001***	0.02/ 0.009
Gender	0.233/ 2.518	0.093/ 2.305	296/ 296	2.51/ 1.092	.013*/ .276	0.28/ 0.11
Time	-0.021/ 4.517	0.023/ 0.99	296/ 296	-0.905/ 4.562	.366/ <.001***	-0.02/ 0.2
Age	-0.046/ -0.377	0.03/ 0.75	296/ 296	-1.507/ -0.503	.133/ .616	-0.08/ -0.02
Gender:Time	-0.074/ -1.208	0.046/ 1.989	296/ 296	-1.597/ -0.608	.111/ .544	-0.09/ -0.05
Time:Age	0.002/ 0.361	0.015/ 0.647	296/ 296	0.13/ 0.558	.896/ .577	0.004/ 0.02

Note. WM=Working Memory, SE=Standard Error. Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

Supplementary Table 10

MANCOVA comparison of cognitive performance at baseline and dropout behavior at first follow-up investigation.

Factors	Covariates	Dropout (N = 74)	Partial participation (N = 109)	Full participation (N = 329)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
Declarative memory		-0.24 ± 1.16	-0.01 ± 0.96	0.05 ± 0.97	**3.73 (2, 506)**	**.025**	**.015**
	Sex				67.63 (1, 506)	<.001	.118
	Age				3.81 (1, 506)	.052	.007
	Education level				16.86 (1, 506)	<.001	.032
Working memory		-0.10 ± 0.83	-0.15 ± 1.06	0.07 ± 1.01	1.56 (2, 506)	.212	.006
	Sex				3.65 (1, 506)	.057	.007
	Age				0.01 (1, 506)	.914	<.001
	Education level				64.85 (1, 5068)	<.001	.114
Attention		-0.22 ± 1.00	0.14 ± 1.65	-0.01 ± 0.66	**3.28 (2, 506)**	**.038**	**.013**
	Sex				3.01 (1, 506)	.083	.006
	Age				2.43 (1, 506)	.119	.005
	Education level				0.98 (1, 506)	.323	.002
Visual-spatial-processing		-0.23 ± 0.96	-0.25 ± 1.37	0.13 ± 0.82	**5.33 (2, 506)**	**.005**	**.021**
	Sex				18.86 (1, 506)	<.001	.036
	Age				0.39 (1, 506)	.534	.001
	Education level				13.79 (1, 506)	<.001	.027

Note. Multivariate Pillai's trace $V = .06$, $F(8, 1008) = 3.58$, $p < .001$, $\eta^2 = .028$. Bold values indicate significant factors ($p < .05$).

Supplementary Table 11

MANCOVA comparison of affectivity at baseline and dropout behavior at first follow-up investigation.

Affectivity test scores	Covariates	Dropout (n = 74)	Partial participation (n = 113)	Full participation (n = 326)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
BDI-II		5.73± 4.46	7.44 ± 5.54	6.04 ± 5.73	2.12 (2, 507)	.121	.008
	Sex				15.65 (1, 507)	<.001	.030
	Age				.60 (1, 507)	.440	.001
	Education level				3.24 (1, 507)	.072	.006
GDS		1.45 ± 1.45	1.72 ± 1.97	1.34 ± 1.79	1.68 (2, 507)	.188	.007
	Sex				1.34 (1, 507)	.247	.003
	Age				1.26 (1, 507)	.262	.002
	Education level				.61 (1, 507)	.436	.001
ASI-3		14.34 ± 10.33	16.13 ± 13.27	17.64 ± 13.98	1.84 (2, 507)	.160	.007
	Sex				.29 (1, 507)	.591	.001
	Age				.203 (1, 507)	.653	.001
	Education level				.27 (1, 507)	.601	.001

Note. Multivariate Pillai's trace $V = .03$, $F(6, 1012) = 2.18$, $p = .043$, $\eta^2 = .01$; BDI-II = Beck Depression Inventory–II (Beck et al., 1996), GDS = Geriatric Depression Screening Scale (Yesavage et al., 1982), ASI-3 = Anxiety Sensitivity Index–3 (S. Reiss et al., 1986).

Supplementary Table 12

MANCOVA comparison of dementia screenings at baseline and dropout behavior at first follow-up investigation.

Autonomy test scores	Covariates	Dropout (n = 77)	Partial participation (n = 115)	Full participation (n = 331)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
MMSE		**28.65 ± 1.32**	**28.92 ± 1.66**	**29.26 ± .99**	**9.97 (2, 517)**	**<.001**	**.034**
	Sex				1.12 (1, 517)	.291	.002
	Age				3.75 (1, 517)	.053	.007
	Education level				18.46 (1, 517)	<.001	.034
DemTect		**15.47 ± 2.43**	**15.90 ± 2.41**	**16.18 ± 1.99**	**3.80 (2, 517)**	**.023**	**.014**
	Sex				16.67 (1, 517)	<.001	.031
	Age				2.44 (1, 517)	.119	.005
	Education level				16.26 (1, 517)	<.001	.030

Note. Multivariate Pillai's trace $V = .04$, $F(4, 1034) = 5.36$, $p < 0.001$, $\eta^2 = .02$; MMSE = Mini-Mental State Investigation (M. F. Folstein et al., 1975), DemTect = dementia detection test(Kalbe et al., 2004). Bold values indicate significant factors ($p < .05$ and $p < .01$).

Supplementary Table 13

MANCOVA comparison of autonomy in daily routine at baseline and dropout behavior at first follow-up investigation.

Autonomy test scores	Covariates	Dropout (n = 77)	Partial participation (n = 115)	Full participation (n = 331)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
B-ADL		1.45 ± .46	1.46 ± .56	1.45 ± .60	.06 (2, 517)	.943	<.001
	Sex				1.47 (1, 517)	.227	.003
	Age				2.20 (1, 517)	.139	.004
	Education level				.72 (1, 517)	.397	.001

Note. B-ADL = Bayer-Activities of Daily Living scale (I. Hindmarch et al., 1998).

Supplementary Table 14

MANCOVA comparison of blood and lifestyle indicators at baseline and dropout behavior at first follow-up investigation.

Blood and lifestyle indicators	Covariates	Dropout (n = 67)	Partial participation (n = 99)	Full participation (n = 293)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
Glucose (mg/dl)		96.66 ± 21.59	98.95 ± 20.88	95.02 ± 17.40	1.57 (2, 453)	.208	.007
	Sex				12.51 (1, 453)	<.01	.027
	Age				1.17 (1, 453)	.280	.003
	Education level				8.31 (1, 453)	.004	.018
Total cholesterol (mg/dl)		209.70 ± 38.48	216.83 ± 45.64	216.26 ± 40.59	1.34 (2, 453)	.264	.006
	Sex				55.12 (1, 453)	<.001	.108
	Age				4.50 (1, 453)	.034	.010
	Education level				.01 (1, 453)	.926	<.001
LDL-cholesterol (mg/dl)		122.73 ± 33.77	128.62 ± 39.22	129.92 ± 36.22	1.43 (2, 453)	.240	.006
	Sex				27.88 (1, 453)	<.001	.058
	Age				5.95 (1, 453)	.015	.013
	Education level				.07 (1, 453)	.797	<.001
HDL-cholesterol (mg/dl)		63.07 ± 18.06	64.19 ± 15.36	63.95 ± 17.96	1.43 (2, 453)	.240	.003
	Sex				52.23 (1, 453)	<.001	.103
	Age				1.66 (1, 453)	.198	.004
	Education level				.48 (1, 453)	.490	.001
Triglycerides (mg/dl)		119.45 ± 52.97	120.71 ± 58.08	116.26 ± 53.26	.46 (2, 453)	.630	.002
	Sex				2.28 (1, 453)	.132	.005
	Age				.51 (1, 453)	.475	.001
	Education level				.11 (1, 453)	.744	<.001
	Age				.32 (1, 453)	.571	.001

Continuation of Supplementary Table 14

MANCOVA comparison of blood and lifestyle indicators at baseline and dropout behavior at first follow-up investigation.

Blood and lifestyle indicators	Covariates	Dropout (n = 67)	Partial participation (n = 99)	Full participation (n = 293)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
Leucocytes (n*1000/µl)		6.03 ± 1.51	6.13 ± 1.57	5.95 ± 1.63	.52 (2, 453)	.597	.002
	Sex				3.26 (1, 453)	.072	.007
	Age				3.86 (1, 453)	.050	.008
	Education level				.09 (1, 453)	.770	.002
C-reactive protein (mg/dl)		.25 ± .34	.28 ± .33	.21 ± .30	2.08 (2, 506)	.126	.009
	Sex				.67 (1, 453)	.414	.001
	Age				1.14 (1, 453)	.287	.003
	Education level				.36 (1, 453)	.552	.001
Blood sedimentation rate – 1h (mm)		10.45 ± 6.81	10.80 ± 7.81	9.69 ± 6.60	.21 (2, 453)	.812	.001
	Sex				40.16 (1, 453)	<.001	.081
	Age				.32 (1, 453)	.571	.001
	Education level				1.01 (1, 453)	.316	.002
Blood sedimentation rate – 2h (mm)		24.57 ± 13.44	25.59 ± 14.72	23.03 ± 13.64	.32 (2, 453)	.726	.001
	Sex				48.53 (1, 453)	<.001	.097
	Age				.26 (1, 453)	.614	.001
	Education level				1.11 (1, 453)	.293	.002
Thyroid-stimulation hormone (ml U/l)		1.71 ± 1.01	1.56 ± .97	1.52 ± .84	1.26 (2, 453)	.283	.006
	Sex				.39 (1, 453)	.535	.001
	Age				1.33 (1, 453)	.249	.003
	Education level				1.49 (1, 453)	.223	.003

Continuation of Supplementary Table 14

MANCOVA comparison of blood and lifestyle indicators at baseline and dropout behavior at first follow-up investigation.

Blood and lifestyle indicators	Covariates	Dropout (n = 67)	Partial participation (n = 99)	Full participation (n = 293)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
Vitamin B12 (pg/ml)		442.97 ± 278.55	468.37 ± 203.92	450.19 ± 265.67	.20 (2, 453)	.822	.001
	Sex				4.82 (1, 453)	.029	.011
	Age				.88 (1, 453)	.350	.002
	Education level				.00 (1, 453)	.987	<.001
Folacin (ng/ml)		10.70 ± 4.64	10.92 ± 4.57	10.96 ± 4.10	.07 (2, 453)	.937	<.001
	Sex				8.94 (1, 453)	.003	.019
	Age				10.06 (1, 453)	.002	.022
	Education level				.38 (1, 453)	.540	.001
Homocysteine (µmol/l)		15.77 ± 4.46	13.78 ± 3.72	14.67 ± 7.47	.82 (2, 453)	.443	.004
	Sex				2.46 (1, 453)	.118	.005
	Age				6.17 (1, 453)	.013	.013
	Education level				.00 (1, 453)	.954	<.001
HbA1c (%)		5.74 ± .53	5.75 ± .55	5.79 ± .49	.37 (2, 453)	.691	.002
	Sex				.02 (1, 453)	.902	<.001
	Age				1.68 (1, 453)	.195	.004
	Education level				2.57 (1, 453)	.110	.006
BDNF (ng/ml)		90.13 ± 36.48	98.50 ± 33.23	97.17 ± 34.04	1.67 (2, 453)	.189	.007
	Sex				9.59 (1, 453)	.002	.021
	Age				.07 (1, 453)	.792	<.001
	Education level				1.32 (1, 453)	.252	.003

Continuation of Supplementary Table 14

MANCOVA comparison of blood and lifestyle indicators at baseline and dropout behavior at first follow-up investigation.

Blood and lifestyle indicators	Covariates	Dropout (n = 67)	Partial participation (n = 99)	Full participation (n = 293)	Group differences		
		M ± SD	M ± SD	M ± SD	F (df_H, df_E)	*p*	η^2
BMI (kg/m²)		**26.80 ± 3.88**	**26.83 ± 3.84**	**25.84 ± 3.66**	**4.00 (2, 453)**	**.019**	**.017**
	Sex				16.29 (1, 453)	<.001	.035
	Age				.17 (1, 453)	.678	<.001
	Education level				7.82 (1, 453)	.005	.017

Note. Multivariate Pillai's trace V = .07, F(32, 878) = 9.8, p= .503, η^2 = .03; BDNF = Blood Derived Neurotrophic Factor, BMI = Body-Mass-Index. Bold values indicate significant factors (p < .05).

Supplementary Table 15

Multinomial logistic regression analysis for cognitive performance at baseline investigation and dropout behavior at first follow-up investigation.

	b (SE)	Wald χ^2 (df = 1)	*p*	95% CI for Odds Ratio		
				Lower	Odds Ratio	Upper
No participation at 1st follow-up vs. full participation at 1st follow-up						
Cognitive performance						
Declarative memory	**-0.38 (.14)**	**7.18**	**.007**	0.519	0.685	0.903
Working memory	-0.21 (.15)	1.94	.164	0.609	0.814	1.088
Attention	**-0.33 (.16)**	**4.13**	**.042**	0.528	0.722	0.988
Visual-spatial processing	**-0.37 (.14)**	**7.35**	**.007**	0.526	0.689	0.902
Covariates						
Sex (male/female)	-0.60 (.30)	3.96	.047	0.306	0.550	0.991
Age (years)	0.23 (.09)	6.83	.009	1.060	1.262	1.503
Education level	0.16 (.13)	1.55	.214	0.912	1.173	1.508
Partial participation at 1st follow-up vs. full participation at 1st follow-up						
Cognitive performance						
Declarative memory	-0.13 (.13)	1.02	.314	0.691	0.882	1.126
Working memory	-0.19 (.12)	2.30	.129	0.649	0.828	1.057
Attention	-0.12 (.12)	1.05	.306	0.893	1.131	1.432
Visual-spatial processing	**-0.32 (.12)**	**7.29**	**.007**	0.577	0.727	0.916
Covariates						
Sex (male/female)	-0.54 (.25)	4.68	.030	0.356	0.581	0.356
Age (years)	0.14 (.08)	3.49	.062	0.993	1.150	1.331
Education level	-0.11 (.12)	0.82	.364	0.716	0.900	1.130

Note. R^2 = .10 (Cox-Snell). Model $\chi^2(14) = 52.02$, $p < .001$. Bold values indicate significant factors ($p < .05$ and $p < .01$).

Supplementary Table 16

Multinomial logistic regression analysis for dementia screenings at baseline investigation and dropout behavior at first follow-up investigation.

	b (SE)	Wald χ^2 (df = 1)	*p*	95% CI for Odds Ratio		
				Lower	Odds Ratio	Upper
No participation at 1st follow-up vs. full participation at 1st follow-up						
Autonomy in daily routine						
MMSE	**-.37 (.11)**	**11.19**	**.001**	.55	.69	.86
DemTect	-.09 (.06)	1.88	.170	.81	.92	1.04
Covariates						
Sex (male/female)	-.65 (.27)	5.87	.015	.31	.52	.88
Age (years)	.25 (.09)	8.10	.004	1.08	1.28	1.52
Education level	.06 (.12)	.27	.606	.84	1.06	1.35
Partial participation at 1st follow-up vs. full participation at 1st follow-up						
Autonomy in daily routine						
MMSE	**-.26 (.10)**	**6.44**	**.011**	.63	.77	.94
DemTect	-.02 (.06)	.14	.710	.88	.98	1.09
Covariates						
Sex (male/female)	-.66 (.23)	8.42	.004	.33	.52	.81
Age (years)	.20 (.07)	7.12	.008	1.05	1.22	1.41
Education level	-.14 (.11)	1.82	.178	.70	.87	1.07

Note. R^2 = .08 (Cox-Snell). Model $\chi^2(12) = 45.66$, $p < .001$; MMSE = Mini-Mental State Investigation(M. F. Folstein et al., 1975), DemTect = dementia detection test (Kalbe et al., 2004), B-ADL = Bayer-Activities of Daily Living scale (I. Hindmarch et al., 1998). Bold values indicate significant factors ($p < .05$ and $p < .01$).

7. Publications

12/2021

Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy. *Journal of Psychiatric Research*, *146*, 31-42. https://doi.org/10.1016/j.jpsychires.2021.12.021.

12/2021 – shared first-authorship

Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. *Journal of Neuropsychology*, *n/a*(n/a). https://doi.org/https://doi.org/10.1111/jnp.12269.

09/2021

Haberstumpf, S., Leinweber, J., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Factors associated with dropout in the longitudinal Vogel Study of cognitive decline. *European Journal of Neuroscience*, 1-14. https://doi.org/10.1111/ejn.15446.

10/2020

Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia, 148*, 107650. https://doi.org/10.1016/j.neuropsychologia.2020.107650.

8. Statement of individual author contributions and of legal second publication rights (as of September 28, 2021)

8.1 Papers

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Graduate School
Life Sciences

"Dissertation Based on Several Published Manuscripts"
Statement of individual author contributions and of legal second publication rights

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia, 148*, 107650. doi:https://doi.org/10.1016/j.neuropsychologia.2020.107650.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	TP, JD, MJH	-	-	-	-
Data Collection	ML, TP	-		-	-
Data Analysis and Interpretation	SH	AS	MJH	-	-
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	SH	AS	MJH	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Leinweber, J., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Factors associated with dropout in the longitudinal Vogel Study of cognitive decline. . *European Journal of Neuroscience*, 1-14. doi:10.1111/ejn.15446.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	TP, JD, MJH	-	-	-	-
Data Collection	JL, ML, TP, MJH	-	-	-	-
Data Analysis and Interpretation	SH	-	-	-	-
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	SH	-	-	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., Herrmann, M.J. (n.d.). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. Under review.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	ML, TP, JD, MJH	-	-	-	-
Data Collection	JL, ML, TP	SR, MS	-	-	-
Data Analysis and Interpretation, Revision	SH, AF	JL, MJH, SR, JH, MS, ML, TP, JD	-	-	-
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	SH, AF	-	-	-	-

Explanations: Sophia Haberstumpf and André Forster contributed equally to this work.

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (n.d.). Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy. Under review.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	TP, JD, MJH	-	-	-	-
Data Collection	ML, TP, JD, MJH	-	-	-	-
Data Analysis and Interpretation	SH	AS	MJH	-	-
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	SH	AS	MJH	-	-

Explanations (if applicable): -

The doctoral researcher confirms that she/he has obtained permission from both the publishers and the co-authors for legal second publication.

The doctoral researcher and the primary supervisor confirm the correctness of the above mentioned assessment.

Sophia Haberstumpf	28.09.2021	Höchberg	[redacted]
Doctoral Researcher's Name	Date	Place	Signature
Prof. Dr. phil. Martin J. Herrmann	[redacted]		
Primary Supervisor's Name	Date	Place	Signature

8.2 Figures

Julius-Maximilians-
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Graduate School
Life Sciences

"Dissertation Based on Several Published Manuscripts"
Statement of individual author contributions to figures included in the manuscripts

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia, 148*, 107650. doi:https://doi.org/10.1016/j.neuropsychologia.2020.107650.

Figure	**Author Initials,** Responsibility decreasing from left to right				
1	SH	-	-	-	-
2	SH	AS	MJH	-	-
3	SH	MJH	AS	-	-
4	SH	-	-	-	-
5	SH	-	-	-	-
6	SH	-	-	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Leinweber, J., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Factors associated with dropout in the longitudinal Vogel Study of cognitive decline. *European Journal of Neuroscience*, 1-14. doi:10.1111/ejn.15446.

Figure	**Author Initials,** Responsibility decreasing from left to right				
1	SH	-	-	-	-
2	SH	-	-	-	-
3	SH	-	-	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., Herrmann, M.J. (n.d.). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. Under review.

Figure	**Author Initials,** Responsibility decreasing from left to right				
1	SH, AF	-	-	-	-
2	SH, AF	-	-	-	-
3	SH, AF	-	-	-	-
4	SH, AF	-	-	-	-
5	SH, AF	MJH	-	-	-

Explanations: Sophia Haberstumpf and André Forster contributed equally to this work.

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (n.d.). Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy. Under review.

Figure	**Author Initials,** Responsibility decreasing from left to right				
1	SH	MJH	-	-	-
2	SH	AS	MJH	-	-
3	SH	MJH	AS	-	-
4	SH	-	-	-	-
5	SH	-	-	-	-
6	SH	-	-	-	-
7	SH	-	-	-	-

I also confirm my primary supervisor's acceptance.

Sophia Haberstumpf	28.09.2021	Höchberg	[redacted]
Doctoral Researcher's Name	Date	Place	Signature

8.3 Tables

Julius-Maximilians-
UNIVERSITÄT
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Graduate School
Life Sciences

"Dissertation Based on Several Published Manuscripts"
Statement of individual author contributions to tables included in the manuscripts

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2020). Neuronal correlates of the visual-spatial processing measured with functional near-infrared spectroscopy in healthy elderly individuals. *Neuropsychologia, 148*, 107650. doi:https://doi.org/10.1016/j.neuropsychologia.2020.107650.					
Table	**Author Initials,** Responsibility decreasing from left to right				
1	SH	-	-	-	-
2	SH	-	-	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Leinweber, J., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (2021). Factors associated with dropout in the longitudinal Vogel Study of cognitive decline. *European Journal of Neuroscience*, 1-14. doi:10.1111/ejn.15446.					
Table	**Author Initials,** Responsibility decreasing from left to right				
1	SH	-	-	-	-
2	SH	-	-	-	-
3	SH	-	-	-	-
Appendix	SH	-	-	-	-

Explanations (if applicable): -

Publication (complete reference): Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., Herrmann, M.J. (n.d.). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. Under review.

Table	**Author Initials,** Responsibility decreasing from left to right				
1	SH, AF	-	-	-	-
2	SH, AF	-	-	-	-
3	SH, AF	-	-	-	-
4	SH, AF	-	-	-	-
5	SH, AF	-	-	-	-
6	SH, AF	-	-	-	-
Appendix	SH, AF	-	-	-	-

Explanations: Sophia Haberstumpf and André Forster contributed equally to this work.

Publication (complete reference): Haberstumpf, S., Seidel, A., Lauer, M., Polak, T., Deckert, J., & Herrmann, M. J. (n.d.). Reduced parietal activation in participants with mild cognitive impairments during visual-spatial processing measured with functional near-infrared spectroscopy. Under review.

Table	**Author Initials,** Responsibility decreasing from left to right				
1	SH	-	-	-	-
2	SH	-	-	-	-
3	SH	-	-	-	-
4	SH	-	-	-	-
5	SH	-	-	-	-
6	SH	-	-	-	-
Appendix	SH	-	-	-	-

I also confirm my primary supervisor's acceptance.

Sophia Haberstumpf 28.09.2021 Höchberg [redacted]

Doctoral Researcher's Name Date Place Signature

9. Affidavit/Eidesstattliche Erklärung

Affidavit

I hereby confirm that my thesis entitled “Pathological cognitive decline in the elderly participants of the Vogel Study” is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

_____ _____

Place, Date Signature

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation „Pathologische kognitive Verschlechterung bei den älteren Probanden der Vogel-Studie“ eigenständig, d.h. insbesondere selbstständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

_____ _____

Ort, Datum Unterschrift

10. Curriculum Vitae