Visual attentional assessment in mild cognitive impairment and Alzheimer's disease based on a theory of visual attention

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List of abbreviations and technical terms

α	top-down control (PR)
AAL	automated anatomical labeling
AChE	acetylcholine esterase
AChEI	acetylcholine esterase inhibitor/s
AD	Alzheimer's disease
Ang-SMG	angular and supramarginal gyri of the parietal cortex (parts of TPJ)
ANOVA	analysis of variance
ApoE4	apolipoprotein E ε4 allele/s
Aβ	β-amyloid
C	visual perceptual processing speed (WR)
canthomeatal line	line connecting the lateral corner of the eye (external canthus) with the central point of the external auditory meatus (ear canal)
CBF	cerebral blood flow
CDR	Clinical Dementia Rating (severity of disease)
CDT	Clock Drawing Test
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease (neuropsychological test)
cm	centimeter/s
et al.	et alii (and others)
et seq. / seqq.	et sequentes (and the following)
f	female
^{18}FDG-PET	^{18}fluoro-deoxy-glucose positron emission tomography
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
HC	healthy control subject/s
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision (World Health Organization)
IPL	inferior parietal lobe
IPS	intraparietal sulcus
K	VSTM storage capacity (WR)
M	arithmetic mean
m	male
MBq	megabecquerel
MCI	mild cognitive impairment
mg	milligram
min	minute
ml	milliliter
mm	millimeter
MMSE	Mini Mental Status Examination (cognitive screening)
MNI	Montreal Neurological Institute
ms	millisecond/s
MWT-B	Mehrfachwahl-Wortschatz-Intelligenz-Test B (verbal intelligence screening)
n/ N	number
NaSSA	noradrenergic and specific serotonergic antidepressant
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association
NTVA	neural TVA
p	level of significance
p. / pp.	page/s
PC	personal computer
PET	positron emission tomography
pMTG	posterior middle temporal gyrus (part of TPJ)
PR	partial report paradigm (TVA-based)
r	correlation coefficient
r^2	explained variance
ROI	region of interest
RT	reaction time
SD	standard deviation
SE	standard error
sec	second/s
SPECT	single photon emission computed tomography
SPL	superior parietal lobe
SPM	Statistical Parametric Mapping
SSRI	selective serotonin reuptake inhibitor
t_0	perceptual threshold (WR)
TAP	Test for Attentional Performance (RT-based)
TPJ	temporo-parietal junction
TVA	theory of visual attention
VSTM	visual short-term memory
w_i	laterality index of attentional weighting (PR)
WR	whole report paradigm (TVA-based)

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1. Introduction

Research in the field of aging and dementia is a main concern as the population of elderly people is growing continuously due to increasing life expectancy and thus an accumulative number of people who live well beyond 65 years of age run a risk of developing age-associated neurodegenerative disorders of cognitive function, such as Alzheimer's disease (AD), emerging as a major health problem. Rising rates of prevalence and incidence with age (Bickel, 2000; Gao, Hendrie, Hall, & Hui, 1998; Hebert, Beckett, Scherr, & Evans, 2001; Kukull et al., 2002) are countered by prospects of effective therapies that, at least, might be able to slow or delay the progression to AD and the course of AD, respectively. Based on the assumption that earlier identification of people at risk of AD will lead to better cognitive outcome by e.g. medical interventions, research has focused on methods to identify cognitive disorders at the prodromal stage of the illness, the stage of mild cognitive impairment (MCI; Petersen et al., 1999). In particular, the amnestic form of MCI is generally considered a transitional stage between normal ageing and a diagnosis of clinically probable AD (Petersen, 2000) and therefore a subject of intense investigation.

The present work is based on growing evidence that deficits in visual selective attention occur early in the progression to AD (Foldi, Lobosco, & Schaefer, 2002) and therefore might be present as the first non-memory deficits (Perry & Hodges, 1999) at the early prodromal MCI stage. Despite intensive research done in this field (Amieva, Phillips, Della Sala, & Henry, 2004b; Bäckman et al., 2004; Balota & Faust, 2002; Parasuraman & Haxby, 1993; Perry & Hodges, 1999) there is still ongoing debate as to whether certain aspects of visual selective attention are particularly vulnerable or preserved, especially at the stage of MCI, and whether attentional functioning might be qualitatively and/ or quantitatively different from attentional performance at the AD stage on the one hand or normal functioning on the other hand. To date, a huge variety of studies presented results on visual attentional functions in MCI and/ or AD patients which are heterogeneous due to several reasons:

a) Heterogeneity in the etiology and application of clinical criteria especially with regard to the various concepts of MCI lead to difficulties in gathering from results of different studies.

b) Furthermore, results derived from different paradigms for attentional assessment are not highly comparable when they varied with respect to task, task difficulty, stimuli, stimuli presentation conditions, automation (e.g. manual versus computerized tests), or response measurement (e.g. reaction time (RT) or error rate).

c) Cognitive impairment in general and cognitive slowing in particular are predominantly associated with deceleration in motor response and therefore often measured by manual response times like it is done, for example, in the established clinical diagnostic tool 'Test for Attentional Performance' (TAP; Zimmermann & Fimm, 1993). With the application of such a motor response dependent tool, it has to be taken into account that general cognitive slowing might lead to a distortion of the evaluation of other cognitive functions like short-term memory capacity or top-down control, which would undermine the theoretical independence of attentional functions. Reversely, even selective deficits in motor speed would not unambiguously point to reduced processing capacity as the underlying cause might be due to predominantly prevailing motor disturbances. Therefore, attentional assessment in elderly healthy subjects as well as in patients suffering from cognitive degeneration like AD should preferably be based on theoretically and empirically independent attentional components.

d) As even patients in the early stage of AD show remarkable cognitive and memory impairment, the application of exclusively easy and intuitive tasks including simple instructions would allow comparing attentional functions of distinct stages in the course of AD. In TAP subtests like the 'Go/No-go' or the 'Working memory' task (Zimmermann & Fimm, 1993) instructions would presumably be too difficult to follow for probable AD patients or contrariwise, the experimenter could hardly control for comprehension of the task.

To overcome these shortcomings, this present work was designed to investigate selective visual attentional functions in MCI and AD patients compared to healthy control subjects based

on Bundesen's theory of visual attention (TVA; Bundesen, 1990, 1998). This theoretical framework allows the assessment of several latent, mathematically independent and quantitative parameter estimates which are derived from two highly comparable paradigms – computerized whole report and partial report of briefly presented visual letter arrays.

Before describing the theoretical and mathematical framework of TVA in more detail, a short overview of the studies presented in the chapters 4 to 6 is provided in the next section.

2. Synopsis

In the following sections, English summaries of the three studies presented in this dissertation are given. For a detailed German synopsis of the present work, see chapter 8 (pp. 118 et seqq.).

Research in the field of aging and dementia is a main concern as the population of elderly people is growing continuously due to increasing life expectancy and thus, an accumulative number of people who live well beyond 65 years of age run a risk of developing age-associated neurodegenerative disorders of cognitive function, such as Alzheimer's disease (AD), emerging as a major health problem.

The present work is based on growing evidence that deficits in visual selective attention occur early in the progression to AD (Foldi et al., 2002) and therefore might be present as the first non-memory deficits (Perry & Hodges, 1999) at the early prodromal stage of mild cognitive impairment (MCI; Petersen et al., 1999). The present dissertation was performed to contribute to the still ongoing debate as to whether certain aspects of visual selective attention are particularly vulnerable or preserved, especially at the stage of MCI, and whether attentional functioning might be qualitatively and/ or quantitatively different from attentional performance at the AD stage on the one hand or normal functioning on the other hand.

As theoretical basis, Bundesen's theory of visual attention (TVA; Bundesen, 1990, 1998) was employed to assess several latent, mathematically independent and quantitative parameter estimates which are derived from two highly comparable paradigms – computerized whole report and partial report of briefly presented visual letter arrays. Central conclusions arising out of TVA-based investigations (e.g., Bublak et al., 2005; Bublak, Redel, & Finke, 2006; Duncan et al., 1999; Duncan et al., 2003; Finke et al., 2006; Gerlach, Marstrand, Habekost, & Gade, 2005; Habekost & Bundesen, 2003; Habekost & Rostrup, 2006; Peers et al., 2005) point at four central strengths of this tool for attentional assessment – the quality criteria sensitivity, specificity, reliability and validity.

2.1. Study 1

In AD, the amyloid cascade hypothesis (Hardy & Selkoe, 2002) assumes that rising plaque and tangle burden invokes loss of nerve cells through direct and indirect effects on synaptic, neuronal and neuritic function (see e.g. Cirrito et al., 2005), resulting in progressive intellectual decline. Thus, sensitive biomarkers loading functionally on the neural alterations invoked by AD from early on, might improve the possibility to identify at risk subjects in time, providing a chance for effective treatment (Shah et al., 2008). The first study (see chapter 4, pp. 31 et seqq.) examined whether cognitive parameters for estimating the capacity of visual attention might serve that purpose.

Based on Bundesen's (1990) TVA, visual information uptake was analyzed in 18 subjects with probable AD, 18 subjects with amnestic MCI, and 18 healthy elderly control subjects. Groups were matched for gender, age, and education. From a whole report task requiring verbal report of briefly presented letters, four parameters were derived, characterizing different aspects of visual processing capacity: perceptual threshold t_0, iconic memory μ, processing speed C, and visual short-term memory (VSTM) storage capacity K.

Comparison of these attentional parameters between groups revealed an elevation of the perceptual threshold already in MCI subjects, while processing speed and VSTM storage capacity showed a significant decline for AD patients, only. AD patients on medication with acetylcholine esterase inhibitors had higher processing speed, but were still below the level of MCI patients. Perceptual threshold values were significantly correlated with disease duration, but not with cognitive measures. Conversely, speed and VSTM were significantly related to cognitive scores, but not to disease duration. In particular, VSTM storage was related to neuropsychological tasks applying visual material (picture naming and visuo-construction), while speed showed an additional relationship also to measures of verbal memory.

These results indicate a staged pattern of deficits affecting pre-attentive visual processing in MCI, and attentive processing in AD. They fit into the amyloid cascade hypothesis according

to which the neuropathology of AD is characterized by a net accumulation and deposition of β-amyloid (Aβ) in the initial phase, giving rise to neuronal and neuritic dysfunction. Later, gradual neuronal loss and transmitter disturbances finally cause the increasing intellectual decline during further progression of the disease. A threshold elevation may thus be considered as a possible index of impaired neuronal functioning prior to cell death, while speed and VSTM deficits may be indicative already of a substantial loss of neuronal cell assemblies and a degeneration of neurotransmitter systems.

2.2. Study 2

AD is the most frequent form of dementia which appears both as a familial and a sporadic variant. In the by far more frequent sporadic form, a genetic risk factor is also implicated, in that carriers of the apolipoprotein E ε4 allele (ApoE4) have a 3 to 15 times higher risk of developing the disease, compared to non-carriers (Blennow, de Leon, & Zetterberg, 2006). Using an identical TVA-based partial report paradigm as in the present study, Finke et al. (2006) had found a close relationship between the severity of the underlying genetic pathology in another neurodegenerative, namely Huntington's, disease and the direction and degree of spatial attentional weighting. Sensitive tools for assessing selective visual attention might serve as early cognitive markers in the course of AD and therefore enhance the identification rate of at-risk subjects at the MCI stage (Shah et al., 2008) as well as of subjects with underlying genetic risk (ApoE4). The second study (see chapter 5, pp. 60 et seqq.) aimed at examining whether attentional parameters of visuospatial and task-related selection are appropriate means for that purpose.

Visual selective attention was investigated in 32 patients with amnestic MCI, 16 patients with probable AD, and 36 healthy elderly control subjects. Groups were matched for age, gender and educational level. In combination with Bundesen's (1990) TVA, two mathematically independent and quantitative parameter estimates were derived from a partial report of briefly

presented letter arrays: top-down control of attentional selection, representing task-related attentional weighting for prioritizing relevant visual objects, and spatial distribution of attentional weights across the left and right visual hemifield.

Compared to controls, MCI patients showed significantly reduced top-down controlled selection which further deteriorated in AD subjects. Moreover, attentional weighting was significantly unbalanced across hemifields in MCI and tended to be more lateralized in AD. The majority of patients was biased to the left. Across MCI and AD patients, ApoE4 carriers revealed a leftward spatial bias. The leftward bias was the more pronounced the younger the ApoE4-positive patients and the earlier disease onset. ApoE4-negative subjects showed balanced attentional weighting.

These results indicate that impaired top-down control may be linked to early dysfunction of cortico-cortical networks connecting parietal and frontal lobes. Accompanying, an early interhemispheric asymmetry in temporo-parietal cortical interactions might cause a pathological spatial bias. As the inheritance of ApoE4 is associated with an interhemispheric imbalance in parietal cortical interactions, a pathological spatial bias may function as early cognitive marker for detecting subjects at risk for probable AD.

2.3. Study 3

In the latter study, the TVA-based partial report paradigm proved to be a sensitive tool for verifying that both, deficits in task-related selection and a pathological attentional imbalance, are already present at the early stage of amnestic MCI and increase further at the AD stage (see second study, chapter 5, pp. 60 et seqq.). It was hypothesized that these deficiencies in selective attention may result from an early disconnection syndrome and an interhemispheric imbalance in cortical interactions, respectively, in the fronto-parietal attention network, before gradual neuronal loss leads to further decline in selective attentional and intellectual functions at later stages.

In the third study (see chapter 6, pp. 93 et seqq.), these hypotheses were tested by investigating the relationship of both partial report parameters, top-down control α and especially the laterality index of attentional weighting w_λ, to regional glucose metabolism measured by resting-state positron emission tomography (PET) in a sample of 30 amnestic MCI or mild AD patients.

Hypometabolism across all patients was slightly increased in the left hemisphere. Interestingly, the more reduced the metabolism in the left temporo-parietal junction (TPJ) the more pronounced was the top-down control deficit. Accordingly, hypometabolism in the left TPJ predicted the magnitude of the spatial bias. Furthermore, relative hypometabolism in the left TPJ and left inferior parietal lobe (IPL) as compared to the right TPJ and right IPL, respectively, was correlated with direction and degree of spatial bias.

Taken together, PET imaging results support the hypotheses that, one the one hand, early deficits in task-related weighting may result from a fronto-parietal disconnection syndrome already at the stage of MCI. On the other hand, very early AD seems to be also associated with an interhemispheric imbalance of metabolism, particularly in the temporo-parietal cortices, resulting in a correspondingly directed and distinctive visuo-spatial attentional bias.

2.4. Conclusions and outlook

This dissertation intended to investigate the probable valuable contribution of the whole and partial report of briefly presented letter arrays based on Bundesen's theory of visual attention (TVA; Bundesen, 1990, 1998; Bundesen, Habekost, & Kyllingsbaek, 2005) in assessing amnestic MCI and AD patients in comparison to healthy elderly control subjects.

The results of the three presented studies suggest a staging model of visual selective attentional impairments in MCI and AD. Deficits of pre-attentive processing (perceptual threshold t_0), task-related (top-down control α) and spatial weighting (laterality index of attentional weighting w_λ) were already detectable in MCI patients, while aspects of processing capacity

(perceptual processing speed *C* and VSTM storage capacity *K*) were still intact. At a later stage of the disease, further deterioration of top-down control α and increasing lateralization of spatial weighting w_λ accompanied impairments in perceptual processing speed *C* and VSTM storage capacity *K*.

In conclusion, the TVA-based assessment of selective visual attention proved to be a sensitive diagnostic tool for revealing subtle deficits already at the stage of MCI which might exhibit the capability of an early cognitive marker for the identification of subjects at risk of AD. To address this question, this survey needs to be complemented by longitudinal studies.

3. Theory of visual attention (TVA)

The theory of visual attention (TVA) by Claus Bundesen (Bundesen, 1990, 1992, 1998; Bundesen et al., 2005) is a formal computational theory integrating both, aspects of early (e.g., filter theory by Broadbent, 1958; feature integration theory by Treisman & Gelade, 1980) and late visual attentional selection (Deutsch & Deutsch, 1963) into one unified mechanism of visual recognition and attentional selection. Accordingly, in TVA, selection and recognition are assumed to characterize the same processing operation and therefore occur at the same time. As a result, an object in the visual field is selected when it is recognized, and vice versa.

As TVA was developed from Luce's (1959) choice model (see also Bundesen, Pedersen, & Larsen, 1984; Bundesen, Shibuya, & Larsen, 1985), which was integrated in the framework of the race model (Bundesen, 1987) on the one hand, and from a fixed-capacity four-parameter independent race model (FIRM; Shibuya & Bundesen, 1988), these models will not be discussed here. TVA is a mathematical model with strong relations to the biased competition account of attentional selection proposed by Desimone and Duncan (Desimone, 1998; Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997). For a detailed mathematical description of TVA, see Bundesen (1990, 1998), Duncan et al. (1999), or Kyllingsbæk (2006).

3.1. Basic assumptions and equations

Perceptual categorizations are at the basis of visual recognition and attentional selection in TVA. Visual information intake is a process by which evidence is accumulated that a visual perceptual unit in the visual field, object *x*, belongs to a certain perceptual category *i* (the class of all objects that exhibit a certain common feature) and is characterized by a certain perceptual feature *j* (e.g. a specific color, shape, movement, or spatial location). According to that, a set of red objects would be indicative of a perceptual categorization with regard to color; in view of shape, a letter set of the character *Z* could be exemplified.

The probability that a specific categorization is selected is dependent on both, the strength of the sensory evidence that object *x* belongs to a particular category *i* and the strength of the sensory evidence that *x* bears a certain perceptual feature *j*. The representation of relatively weaker or stronger sensory evidence is not on equality with conscious recognition and attentional selection. Decisions on the affiliation of an object to a specific perceptual category are computed before the start of the selection process. As a consequence, the object *x* can only be identified or selected (which is synonymous in TVA) as belonging to category *i*, when it is encoded into a capacity-limited visual short-term memory (VSTM) store. To consider this matter from another angle, an object *x* is assumed to be represented in the VSTM store when some categorization of object *x* entered this store.

According to TVA, objects in the visual field are processed in parallel and compete for selection, that is, 'conscious' representation within the information processing system. The selection mechanism is temporally restricted so that only those objects may be reported from a briefly presented visual display which sampled categorizations are completely encoded into VSTM, before the decay of the sensory representation of the visual stimulus array and before the VSTM is completely filled with other elements. If the perceptual categorization of object *x* is not completely processed/ sampled or if it was sampled but the VSTM store is filled up with *K* other elements, not containing a representation of object *x*, the categorization of object *x* will be lost. Thus, object *x* won't be selected into VSTM and won't be identified unless there are less than *K* elements represented in VSTM store. Parameter *K*, an estimation of VSTM storage capacity, represents the maximum number of objects that can be consciously maintained in parallel in VSTM (expressed in number of elements). Typically, parameter *K* reaches between three to four elements in healthy subjects (Bundesen et al., 1984; Bundesen et al., 1985; Finke et al., 2005). Objects (i.e. targets) that entered the VSTM store are correctly identified with a probability close to 100% regardless of whether other elements in the visual field are encoded or not. Thus, the maximum number of elements represented in VSTM

store, parameter *K*, is independent of display size (Bundesen et al., 1984; Bundesen et al., 1985).

It is important to differentiate between the limited capacity of the VSTM store with regard to the number of objects, *K*, that might be represented at the maximum, and the non-limited amount of object categorizations, provided the following prerequisites are established: a) categorizations of object *x* can always enter the VSTM as long as the corresponding object is already encoded into VSTM (irrespective of whether it is filled completely with *K* elements) and therefore represented with one or various categorizations; b) the categorization of object *x* can be sampled and represented in VSTM in case of less than *K* encoded elements. These assumptions are in line with a study by Luck and Vogel (1997) who were able to demonstrate that VSTM capacity must be interpreted as integrated objects bearing e.g. several features or categorizations that are bound together and related to one single object representation instead of individual unconnected features.

3.1.1. Single stimulus identification

When a single object is considered, the probability of correct object identification is a function of exposure duration. It can be modeled by an exponential growth function originating from a threshold value t_0, beneath which nothing is perceived, rising steeply with increasing presentation time, and approaching an asymptote when additional presentation time does not yield any further effect on report probability. The slope of this function at its origin reflects processing speed which is determined by the available capacity of attention (see Kyllingsbaek, 2006, for a mathematical description). An illustration of this process is given in the second study of this dissertation (see Figure 4, p. 44).

Given that *x* is the only object in the visual display, this single element's processing rate v_x determines the speed of the object's race towards VSTM and equals the *basic sensory effectiveness* of object *x*, denoted s_x (Bundesen, 1990, 1998) The sensory effectiveness of an object s_x

is determined by several influences such as stimulus discriminability, contrast and spatial location in relation to fixation (see also section 5.3.3.3, pp. 72 et seq.).

3.1.2. Selection from multi-element displays

In the case of multiple objects present in the visual field, two limiting factors emerge: a) the amount of the attentional capacity available and b) the capacity of the VSTM store (about four objects in healthy young subjects; see Cowan, 2001). The first constraint implies allocation of attention across all objects, which reduces the capacity each object receives and thereby decreases the processing speed for each object. The second constraint relates to the termination of the selection process, which occurs when the VSTM store is completely filled.

Thus, according to TVA, which considers the competition between multiple objects for selection as a race towards VSTM, the efficiency of visual processing is primarily characterized by two components: visual processing speed and the VSTM storage capacity. These components can be assessed by a whole report task, in which letter arrays are briefly presented, either masked or unmasked, and subjects have to report as many letters as possible. A subject's performance can then be modeled by four parameters: perceptual processing speed C (i.e. the slope of the exponential growth function), VSTM storage capacity K (i.e. the asymptote of the function), a perceptual threshold t_0, and an estimation of iconic memory μ (or visual persistence) derived from unmasked displays (Kyllingsbaek, 2006). For a detailed illustration of the exponential growth function see Figure 4 (p. 44).

3.1.2.1. Equation 1 – rate equation

As the selection of a visual object is synonymous with its encoding into a VSTM store with limited capacity, the probability of selection is determined a) by an object's *processing rate v*, which depends on the *attentional weight w* it receives, and b) by the capacity of the VSTM store (if the store is filled, the selection process terminates). When an object is presented in

the visual field and is assigned to a certain perceptual category *i*, the hazard function of this process is assumed to be: $v(x,i) = \eta(x,i)\beta_i \frac{w_x}{\sum_{z \in S} w_z}$ (equation 1; Bundesen, 1990).

The strength of the sensory evidence that element *x* belongs to category *i* is represented by $\eta(x,i)$, β_i is a perceptual decision bias associated with category *i* ($0 \leq \beta_i \leq 1$), and w_x and w_z are attentional weights of elements *x* and *z*, respectively. *S* is the set of all elements in the visual field. The denominator of the third factor represents the *relative* attentional weight of object *x* (in reference to the sum of attentional weights for all elements in the visual field). Consequently, the third factor of the rate equation indicates the portion of the total available capacity that is allocated to object *x* (e.g. Bundesen, 1990).

With regard to central TVA parameters, it should be mentioned that perceptual processing speed *C* is defined as the sum of *v* values across all perceptual categorizations of all elements in the visual field while VSTM storage capacity *K* corresponds to the asymptote of the growths function relating mean number of reported visual objects to exposure duration. Parameter *K* represents the maximum number of reported elements on any single trial at any exposure duration (e.g. Duncan et al., 1999). Further details are provided in chapter 4.3.3 (pp. 42 et seq.) of the second study.

3.1.2.2. Equation 2 – weight equation

Due to the limitation of VSTM capacity to *K* distinct elements, the resulting parallel race for selection (see also the 'biased competition model' by Desimone & Duncan, 1995) among objects in the visual display can be biased such that some objects are favored for selection/ encoding into VSTM, especially if display elements outnumber VSTM capacity *K*. According to the TVA model, to each element in the visual field a corresponding *attentional weight w* is assigned. The probability of a non-selected visual object to be encoded into VSTM depends on the relative attentional weight of that specific object in relation to the summed attentional weights of all other non-selected objects in the visual display (see equation 1; Bundesen, 1990). Attentional weights are derived from *pertinence values*, π_j (Bundesen, 1998; Kyl-

lingsbaek, 2006). Every perceptual category *j* is assigned a pertinence value π_j, which is a measure reflecting the current importance of attending to elements that belong to category *j*. The attentional weight of every object *x* in the visual field is determined by the second central equation of TVA: $w_x = \sum_{j \in R} \eta(x, j)\, \pi_j$ (equation 2; Bundesen, 1990).

R is the set of all perceptual categories, $\eta(x,j)$ is the strength of the sensory evidence that element *x* belongs to category *j*, and π_j is the pertinence value of category *j* (Bundesen, 1990).

Importantly, further central TVA-based parameters are derived from attentional weights *w*, which are estimated separately for each object in the visual display. Parameter top-down control α, reflecting task-related weighting for prioritizing relevant visual objects for processing, indicates whether attentional weights for targets (T) are greater than the weights for distractors (D) and is defined as the ratio w_D / w_T. The spatial distribution of attentional weights across the left and right hemifields, parameter w_λ, is derived from separate attentional weights for the left (w_{left}) and the right visual hemifield (w_{right}). Parameter w_λ is defined as the ratio w_{left} / (w_{left} + w_{right}). See chapter 5.3.3 (pp. 70 et seqq.) for additional information.

3.2. A neural theory of visual attention (NTVA)

TVA (Bundesen, 1990) is able to account for a broad range of data from the experimental psychological literature on visual selective attention. The neural theory of visual attention (NTVA; Bundesen et al., 2005) also bridges the gap to neurophysiology by explaining a wide range of attentional effects derived from single cell recordings, and by making explicit assumptions about a neural interpretation of its parameters. For example, processing speed is assumed to reflect the number and activation of cortical neurons representing visual objects, while VSTM storage is thought to represent the function of neuronal populations arranged in a feedback circuitry to actively maintain object representations (Bundesen et al., 2005).

Parameter top-down control α and the spatial distribution of attention w_λ are both derived from attentional weights that are computed for each element in the visual display. In terms of

NTVA (Bundesen et al., 2005), attentional weights are assumed to be represented as cortical activation in a saliency map which may be located in the widely interconnected pulvinar nucleus of the thalamus. Via attentional weights, the reallocation of attention is controlled by dynamic remapping of receptive fields of cortical neurons. The higher the attentional weight of a visual object, the more neurons are assigned to that object. Consequently, selective processing of a prioritized object results from the amount of processing capacity allocated to this element which is dependent on the attentional weight of that object (Bundesen et al., 2005). In healthy subjects, more processing resources are dedicated to important objects, i.e. targets in contrast to distractors, indicating intact top-down control α (Desimone & Duncan, 1995). Accordingly, the parameter spatial distribution of attentional weights w_λ might reflect the distribution of interhemispheric cortical activity (Desimone & Duncan, 1995; Peers et al., 2005).

3.3. TVA-based attentional assessment

The whole report paradigm as well as the partial report paradigm are the central experimental applications of Bundesen's TVA (Bundesen, 1990) in the studies of the present dissertation.

3.3.1. Whole and partial report paradigms

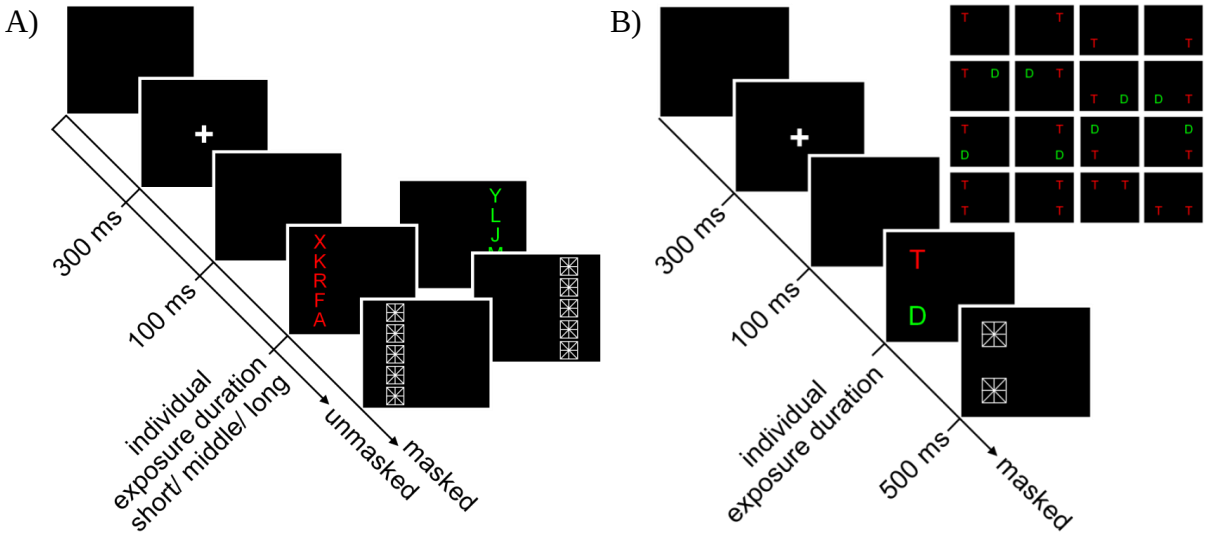


Figure 1: Schematic illustration of the TVA-based (A) whole and (B) partial report paradigms

(A): Different trial types with presentation of five equidistant letters (either red or green, respectively) in columns on the left or the right of the fixation cross are shown. (B): 16 different trial types were presented: 4 single target (depicted as 'T', always red), 8 target plus distractor (depicted as 'D', always green) and 4 dual target conditions.

We used a whole report task (Figure 1 A), in which letter arrays are briefly presented, either masked or unmasked, and subjects have to report as many letters as possible (for the exact whole report instructions, see Instruction 1 and Instruction 2, p. 126). The whole report task, procedure, stimuli and apparatus are described in detail in the first study of this dissertation (see chapter 4.3.2, pp. 39 et seqq.).

The whole report task was combined with Bundesen's TVA (see e.g. Bundesen, 1990) in order to assess four mathematically independent and quantitative parameter estimates describing facets of visual information intake in general and specific aspects of processing capacity: a) parameter t_0 (expressed in milliseconds), the estimated threshold value (minimum presentation time) beneath which nothing is perceived; b) parameter μ (also expressed in milliseconds), the iconic memory buffer estimated from the difference in accuracy between unmasked and masked displays; c) parameter *C*, an estimation of visual perceptual processing speed reflecting the rate of information uptake during visual processing (expressed in numbers of elements processed per second); and d) parameter *K*, an estimation of VSTM storage capacity representing the maximum number of objects that can be consciously maintained in parallel in VSTM (expressed in number of elements; see also chapter 4.3.3, pp. 42, et seq.).

Besides the whole report task, a task was employed requiring partial report of briefly presented letters, based on Bundesen's (1990) TVA (see Figure 1 B). Subjects were instructed to report only pre-defined target letters while ignoring green distractor letters. For detailed information on test instructions, see Instruction 3 and Instruction 4 (p. 127). Details on the partial report assessment (task, procedure, stimuli and apparatus) are provided in the second study of this dissertation (see chapter 5.3.2, pp. 68 et seqq.).

The partial report paradigm allowed deriving two independent quantitative parameter estimates for characterizing specific aspects of attentional weighting, such as task-related weighting for prioritizing relevant visual objects for processing (top-down control α) and the spatial

distribution of attentional weights across the left and right hemifields, parameter w_λ (for more detailed information, see chapter 5.3.3, pp. 70 et seqq.).

3.3.2. Advantages

The TVA-based approach permits parametric estimates to be derived from performance in two psychophysical tasks that reflect both, aspects of processing capacity (e.g., perceptual processing speed *C* and VSTM storage capacity *K*), assessed by a whole report task, and spatial (parameter laterality of attentional weighting w_λ) as well as task-related (parameter top-down control α) aspects of attentional weighting, evaluated by a partial report experiment.

In both highly identical paradigms (identical stimuli, similar tasks), subjects are simply asked to 'Report as many letters as possible' (whole report) and to 'Report red (target) letters only' (partial report), respectively, with the experimenter typing in all reported letters. Even cognitively severely impaired patients like neglect patients (Bublak et al., 2005; Duncan et al., 1999) or Huntington's disease patients (Finke et al., 2006) were able to complete both, the whole and partial report task.

In general, whole and partial report can be considered as simple psychophysical tasks which were already successfully applied to several clinical populations like focal brain-damaged patients including partly subjects with subclinical attention deficits (Bublak et al., 2005; Gerlach et al., 2005; Habekost & Bundesen, 2003; Habekost & Rostrup, 2006; Peers et al., 2005), neglect patients (Bublak et al., 2005; Duncan et al., 1999), patients suffering from simultanagnosia (Duncan et al., 2003), Huntington's disease (Finke et al., 2006) as well as MCI and AD (Bublak et al., 2006). Central conclusions arising out of TVA-based investigations (i.e. studies mentioned above) point at four central strengths of this tool for attentional assessment – the quality criteria sensitivity, specificity, reliability and validity.

Notably, TVA-based attentional assessment completely abandons RT-based measurement. Thus, confounds by motor dysfunction are ruled out. Accordingly, parameters are derived

from raw data accuracy measurement of correctly reported letters. Therefore, interpretation of *all* parameter values is legitimate even if e.g. slowing of mental processing speed would be the underlying symptom of a patient.

A further advantage of both paradigms is the fact that task difficulty is adapted to each of the subjects by individual adjustment of exposure duration which permits to control for comparable task demands, for instance, when assessing healthy subjects, MCI and AD patients within one scope of research question, as presented in this dissertation.

4. Study 1: Visual processing capacity in MCI and AD

In this study, attentional functions of visual information intake and processing capacity were analyzed in a whole report task (WR) in patients with amnestic mild cognitive impairment (MCI) and Alzheimer's disease (AD).

4.1. Abstract

The present study analyzed visual information uptake based on Bundesen's (1990) theory of visual attention (TVA) in 18 subjects with probable Alzheimer's disease (AD), 18 subjects with amnestic mild cognitive impairment (MCI), and 18 healthy elderly control subjects. Groups were matched for gender, age, and education. From a whole report task requiring verbal report of briefly presented letters, four parameters were derived, characterizing different aspects of visual processing capacity: perceptual threshold t_0, iconic memory μ, processing speed C, and visual short-term memory (VSTM) storage capacity K.

Comparison of these attentional parameters between groups revealed an elevation of the perceptual threshold already in MCI subjects, while processing speed and VSTM storage capacity showed a significant decline for AD patients, only. AD patients on medication with acetylcholine esterase inhibitors had higher processing speed, but were still below the level of MCI patients. Perceptual threshold values were significantly correlated with disease duration, but not with cognitive measures. Conversely, speed and VSTM were significantly related to cognitive scores, but not to disease duration. In particular, VSTM storage was related to neuropsychological tasks applying visual material (picture naming and visuo-construction), while speed showed an additional relationship also to measures of verbal memory.

These results indicate a staged pattern of deficits affecting pre-attentive visual processing in MCI, and attentive processing in AD. They fit into the amyloid cascade hypothesis according to which the neuropathology of AD is characterized by a net accumulation and deposition of β-amyloid (Aβ) in the initial phase, giving rise to neuronal and neuritic dysfunction. Later,

gradual neuronal loss and transmitter disturbances finally cause the increasing intellectual decline during further progression of the disease. A threshold elevation may thus be considered as a possible index of impaired neuronal functioning prior to cell death, while speed and VSTM deficits may be indicative already of a substantial loss of neuronal cell assemblies and a degeneration of neurotransmitter systems.

4.2. Introduction and aim of the study

Alzheimer's disease (AD) is the most frequent cause of dementia and has a prevalence that exponentially increases with age, so that up to one third of individuals aged above 80 years are affected (Blennow et al., 2006). It takes a slowly progressive course, typically with episodic memory impairment as the first ostensible cognitive sign. AD neuropathology is characterized by an increasing load of senile plaques and neurofibrillary tangles in the brain, due to an imbalance between the production and clearance of β-amyloid (Aβ).

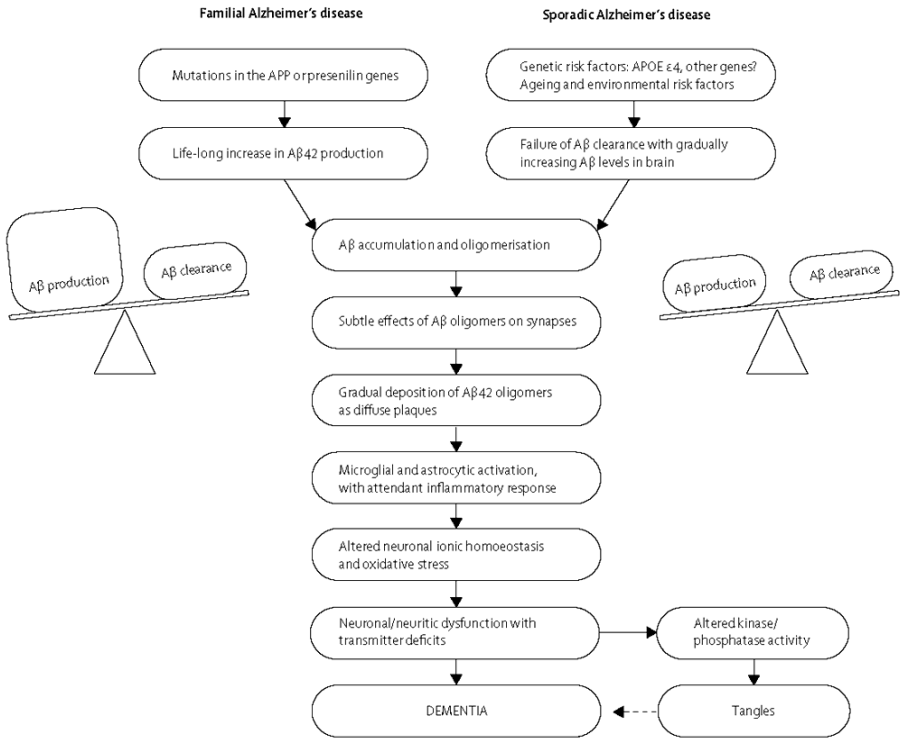


Figure 2: Amyloid cascade hypothesis in Alzheimer's disease

"According to this hypothesis, the central event in the disease pathogenesis is an imbalance between Aβ production and clearance, with increased Aβ production in familial disease and decreased Aβ clearance in sporadic disease. Aβ oligomers could directly inhibit hippocampal long-term potentiation and impair synaptic function, in addition to the inflammatory and oxidative stress caused by aggregated and deposited Aβ. These processes impair neuronal and synaptic function with resulting neurotransmitter deficits and cognitive symptoms. Tau pathology with tangle formation is regarded as a downstream event, but could contribute to neuronal dysfunction and cognitive symptoms" (see p. 4 in Blennow et al., 2006; see also Hardy & Selkoe, 2002).

The amyloid cascade hypothesis (Hardy & Selkoe, 2002) assumes that rising plaque and tangle burden invokes loss of nerve cells through direct and indirect effects on synaptic, neuronal and neuritic function (see e.g. Cirrito et al., 2005), resulting in progressive intellectual decline (see Figure 2). Presumably, the pathological load starts years before the clinical onset but remains undetected until a critical threshold is reached and the first symptoms arise (Gauthier et al., 2006; Nestor, Scheltens, & Hodges, 2004). This transitional stage, when slight cognitive deficits already exist but do not yet exert adverse effects on activities of daily living, is termed "mild cognitive impairment" (MCI). MCI not necessarily leads to dementia, with some subjects remaining stable or even returning to normal over time. However, it represents an at-risk state with more than half of the subjects converting to dementia within five years (Gauthier et al., 2006; Levey et al., 2006; Nestor et al., 2004). In particular, for AD the amnestic type of MCI is known to bear a high risk for progression to dementia, especially so, if additional deficits of non-memory domains are also present (Alexopoulos et al., 2006; Alladi et al., 2006; Gauthier et al., 2006).

Attention is one of the cognitive domains most likely to be affected already at early stages of AD (Foldi et al., 2002; Perry & Hodges, 1999, 2003). This is allegeable considering several important features of AD neuropathology. For example, large cortical neurons get preferentially lost, inducing a cortico-cortical disconnection (Delatour, Blanchard, Pradier, & Duyckaerts, 2004) that not only affects hippocampal functions, but also destroys the neural network nodes supporting attentional functions (Sorg et al., 2007). In particular, accumulation of plaques and tangles in visual association areas (Braak, Braak, & Kalus, 1989) may underlie deficits of visual attention. Finally, degeneration of the basal nucleus results in decline of corticopetal cholinergic input (Coyle, Price, & DeLong, 1983; Mesulam, 2004). As cholinergic projections attain to virtually all cortical regions and are able to modulate the processing of sensory stimuli (Sarter & Bruno, 2000; Sarter, Hasselmo, Bruno, & Givens, 2005), their loss additionally contributes not only to learning, but also to attentional deficits. Importantly, all

these features described can already be found in MCI patients (Herholz, 2008; Herholz et al., 2005; McKee et al., 2006). Thus, sensitive biomarkers loading functionally on the neural alterations invoked by AD from early on, might improve the possibility to identify at risk subjects in time, providing a chance for effective treatment (Shah et al., 2008). The present study examines whether cognitive parameters for estimating the capacity of visual attention might serve that purpose.

A decisive progress in this direction has already been made by the assessment of visual perceptual speed based on the so-called inspection time paradigm (Deary, 2001; Vickers, Nettelbeck, & Willson, 1972). In this task, subjects are presented with, for example, a π-like shape that has two arms of different lengths, and have to decide which one (left or right) is the longer. By assessing performance accuracy as a function of presentation time in this task, an estimation of the speed of visual information uptake is derived. Inspection time (IT) has been shown to be significantly increased in Parkinson's disease (Johnson et al., 2004), and in both subjects with AD (Deary, Hunter, Langan, & Goodwin, 1991) and with MCI (Bonney et al., 2006). Pharmacological studies have confirmed a strong relationship between perceptual speed, as assessed by IT, and the functional state of the cholinergic system (Hutchison, Nathan, Mrazek, & Stough, 2001; Nathan & Stough, 2001; Stough, Thompson, Bates, & Nathan, 2001).

However, studies using the IT approach have also raised some unresolved issues. For example, although a relationship to intelligence is well established (Deary, 2001; Grudnik & Kranzler, 2001; Schweizer & Koch, 2003), the exact role of the cognitive mechanisms reflected by IT is not sufficiently understood (Burns & Nettelbeck, 2003; Deary, 2000). In addition, it has become increasingly clear that IT has a more complex psychological nature than initially thought and might encompass not only a pure speed component, but also other aspects such as perceptual thresholds or even higher-level functions related to memory, attention, and cognitive control (Nettelbeck, 2001).

A theoretical framework that is more explicit with respect to the integration of different components of visual information intake is the theory of visual attention (TVA) proposed by Bundesen (1990, 1998). TVA is a computational model of visual selective attention with a strong association to the biased competition framework (Desimone, 1998; Desimone & Duncan, 1995; Duncan et al., 1997). According to TVA, visual information intake is a process by which evidence is accumulated that a visual object "x" belongs to a certain category "i" (e.g. red objects) and bears a certain feature "j" (e.g. shape). As a result of this process the object can be identified, which in TVA is synonymous with its selection or – in TVA terms – encoding into a visual short-term memory (VSTM) store. When a single object is considered, the probability of correct identification is a function of exposure duration. It can be modeled by an exponential growth function originating from a threshold value t_0, beneath which nothing is perceived, rising steeply with increasing presentation time, and approaching an asymptote when additional presentation time does not yield any further effect on report probability. The slope of this function at its origin reflects processing speed which is determined by the available capacity of attention (see Kyllingsbaek, 2006, for a mathematical description).

In the case of multiple objects present in the visual field, two limiting factors emerge: a) the amount of the attentional capacity available and b) the capacity of the VSTM store (about 4 objects in healthy young subjects; see Cowan, 2001). The first constraint implies allocation of attention across all objects, which reduces the capacity each object receives and thereby decreases the processing speed for each object. The second constraint relates to the termination of the selection process, which occurs when the VSTM store is completely filled.

Thus, according to TVA, which considers the competition between multiple objects for selection as a race towards VSTM, the efficiency of visual processing is primarily characterized by two components: visual processing speed and the VSTM storage capacity. These components can be assessed by a whole report task, in which letter arrays are briefly presented, either masked or unmasked, and subjects have to report as many letters as possible. A subject's per-

formance can then be modeled by four parameters: processing speed (i.e. the slope of the exponential growth function), VSTM storage capacity (i.e. the asymptote of the function), a perceptual threshold, and an estimation of iconic memory (or visual persistence) derived from unmasked displays (Kyllingsbaek, 2006).

TVA is able to account for a broad range of data from the experimental psychological literature on visual selective attention. It also bridges the gap to neurophysiology by explaining a wide range of attentional effects derived from single cell recordings, and by making explicit assumptions about a neural interpretation of its parameters. For example, processing speed is assumed to reflect the number and activation of cortical neurons representing visual objects, while VSTM storage is thought to represent the function of neuronal populations arranged in a feedback circuitry to actively maintain object representations (Bundesen et al., 2005).

In recent years, the TVA based approach has been successfully applied to several clinical populations (Bublak et al., 2005; Duncan et al., 1999; Gerlach et al., 2005; Habekost & Bundesen, 2003; Habekost & Rostrup, 2006, 2007; Peers et al., 2005). In particular, in a previous study assessing the subcortical dementia of Huntington's disease, both the speed of processing and the VSTM storage capacity were reduced and this decline was significantly related to the disease stage (Finke et al., 2006).

In the present study, the same methodology was applied to AD as a cortical dementia, in order to examine whether there would be a systematic decrease of processing capacity at different stages of the disease, that is, amnestic MCI and dementia. In addition, perceptual threshold and iconic memory parameters were also assessed, so as to obtain a more complete picture of the factors contributing to the purported impairment of visual information intake during the course of AD. In general, for all aspects, an incremental decline in MCI compared to healthy subjects was expected, and in AD compared to MCI subjects.

4.3. Method

4.3.1. Subjects

Overall, 54 subjects – 18 patients with probable AD, 18 MCI patients, and 18 healthy control subjects – participated in this study. The three groups were matched for gender ($\chi^2(2)= .15$; $p > .90$), age ($F(2, 53) = .35$; $p > .70$), and education ($F(2, 53) = 1.09$; $p > .30$). Disease duration (time since symptom onset) tended to be longer in AD than in MCI subjects ($t(34) = 1.87$, $p < .10$). Demographic data are summarized in Table 1. Patients were recruited from the Memory Clinic of the Department of Psychiatry, Technical University, Munich, Germany; control subjects by word-of-mouth and notice board advertising.

All patients underwent a standardized diagnostic assessment comprising medical history (both patient and informant interview); medical, neurological, and psychiatric examination; neuropsychological assessment using the test battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP, German version; Thalmann and Monsch (1997); see Test 1, pp. 141 et seqq.), which includes the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the Clock Drawing Test (CDT; Shulmann et al. (1993), see Test 2, pp. 155 et seq.), rating of the overall severity of cognitive deficits using the Clinical Dementia Rating scale (CDR; Morris (1993), see Test 3, pp.157 et seqq.), structural brain imaging (MRI), and blood tests. The results of the neuropsychological testing are also provided in Table 1. Details for individual MCI and AD subjects are provided in Table 8 (p. 128).

Table 1: WR: Demographic and neuropsychological data for MCI and AD patients and healthy controls

See also Table 8 (p. 128).
Values represent mean scores (and standard deviations).
AD: subjects with probable Alzheimer's disease; MCI: subjects with mild cognitive impairment; HC: healthy control subjects; CDR: clinical dementia rating; MMSE: Mini Mental State Examination; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; n.a.: not applied.
**: AD versus MCI, $p < .01$; *: AD versus MCI, $p < .05$; +: AD versus MCI, $p < .08$
§§: MCI versus HC, $p < .01$;
[a]: Values represent median (and range);
[b]: Norm values taken from the CERAD manual.
[c]: Cut-off score

	AD	**MCI**	**HC**
Gender (male / female)	7 / 11	8 / 10	7 / 11
Age (years)	68.3 (9.0)	69.8 (5.0)	68.0 (6.0)
Education (years)	9.9 (1.5)	10.8 (1.9)	10.6 (2.0)
MMSE (max. 30)	22.5 (2.4)**	27.4 (1.2)§§	29.0 (1.1)
Disease duration (years)	3.4 (1.9)+	2.5 (1.2)	-
CDR sum score[a]	4.3 (3.5-7.0)**	2.0 (0.5-3.5)	-
CERAD total score	66.0 (10.8)**	83.5 (13.0)	n.a.
Category Fluency (animals)	13.9 (5.7)**	18.3 (5.7)	21.3 (5.5)[b]
Boston Naming (max. 15)	12.6 (2.2)	13.0 (2.4)	14.0 (1.1)[b]
Word list learning (max. 30)	10.8 (2.8)**	15.2 (3.9)	20.1 (3.7)[b]
Delayed recall (max. 10)	1.4 (1.2)**	3.9 (1.6)	6.9 (2.0)[b]
Recognition (max. 20)	16.8 (1.7)**	18.3 (1.8)	19.4 (0.9)[b]
Visuoconstruction (max. 11)	8.3 (1.7)*	9.7 (1.7)	10.4 (0.9)[b]
Clock drawing (max. 6)[a]	4.0 (1-5)**	2.0 (1-4)	3[c]

Diagnosis of probable AD was made following the diagnostic criteria of the ICD-10 classification of mental and behavioral disorders for dementia (Bramer, 1988), and the NINCDS-ADRDA criteria (see list of abbreviations, p. VIII) for the diagnosis of AD (McKhann et al., 1984). Diagnosis of MCI met the criteria for amnestic MCI (Gauthier et al., 2006; see also Sorg et al., 2007), which include reported and neuropsychologically assessed memory impairments, largely preserved activities of daily living (B-ADL; Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998), excluded dementia according to ICD-10 criteria, and CDR (global score) of 0.5 (questionable dementia). Exclusion criteria for entry into the study were other neurological, psychiatric, or systemic diseases (e.g. stroke, depression, alcoholism), or clinically notable MRI (e.g. stroke lesions) which could be related to cognitive impairment. None of the subjects had diabetes mellitus, and none received antidepressant medication. Two MCI sub-

jects received anti-hypertensive medication. Eleven of the subjects with probable AD were treated with acetylcholine esterase inhibitors (AChEI). All patients were able to fixate adequately, understand, and follow verbal instructions, and concentrate on the task for the duration of the experiment. All healthy control subjects were without memory complaints, were unrelated to the patients, and had no history of neurological or psychiatric disease.

All patients and control subjects taking part in this study were right-handed (according to the Edinburgh Handedness Inventory, Oldfield, 1971), and had normal or corrected to normal vision. Subjects were treated in full agreement with the Declaration of Helsinki II, and gave written informed consent in accordance with the Human Research Committee guidelines of the Klinikum Rechts der Isar, Technical University, Munich.

4.3.2. Whole report paradigm

The whole report paradigm was applied in a manner analogous to that introduced by Duncan et al. (1999) and adopted in several previous studies of our own group (Bublak et al., 2005; Finke et al., 2006; Finke et al., 2005).

4.3.2.1. Task

A schematic illustration of an experimental trial is shown in Figure 3. On each trial, subjects were briefly presented with five equidistant target letters. They were arranged in a vertical column, which was displayed to either the left or the right of a fixation cross (see Figure 3). Subjects were instructed to maintain fixation and, after the letters had been presented, to verbally report all the letters they were fairly sure they had recognized. Letters could be reported in any order, and there was no emphasis on speed of report. The experimenter entered the reported letter(s) on the computer keyboard and initiated the next trial after the subject had indicated that he/she was ready. For detailed information on test instructions, see Instruction 1 and Instruction 2 (p. 126).

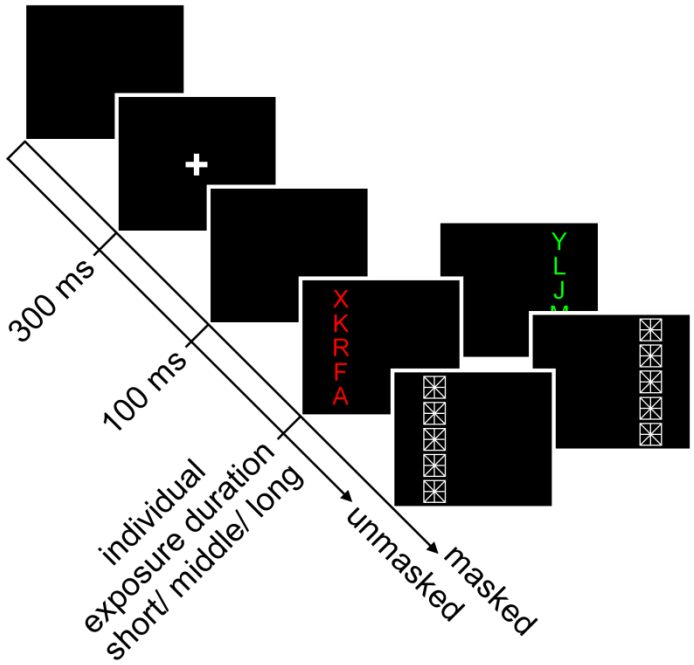


Figure 3: WR: Schematic illustration of the whole report task
Different trial types with presentation of five equidistant letters (either red or green, respectively) in columns on the left or the right of the fixation cross are shown.

4.3.2.2. Procedure

The letter arrays were presented for three different exposure durations, and were either masked or unmasked. Owing to visual persistence, the actual exposure durations are usually prolonged in unmasked as compared to masked conditions (Sperling, 1960). Thus, by orthogonally combining the three exposure durations with the two masking conditions, six different 'effective' exposure durations resulted. These were expected to generate a broad range of performance, so that coverage of the whole curve relating report accuracy to effective exposure duration would be possible.

The three exposure durations were determined individually for each subject in a pre-test phase and then introduced into the experimental assessment phase. This was done to permit adjustment of baseline performance for all subjects, so as to support maximum validity of parameter estimation. Note that presentation time selection by itself is not a determinant of the parameters obtained; rather, it provides just a means for optimal modeling of a subject's performance.

During the pre-test, the individual presentation time was determined at which a subject could report, on average, one letter per trial correctly (i.e. 20% report accuracy) in a series of 24 masked trials (12 for each hemifield) presented with a fixed exposure duration (e.g. 300 ms). This presentation time was then used as the intermediate exposure duration in the experimental session, together with a shorter (about half as long, e.g. 157 ms) and longer (about twice as long, e.g., 600 ms), exposure duration (with each exposure duration adjusted to the screen refresh rate). The average "short" presentation time was *M = 140 ms* (*SD = 29.1*) for healthy control subjects, *M = 162 ms* (*SD = 56.9*) for MCI subjects, and *M = 198 ms* (*SD = 64.4*) for AD subjects. "Intermediate" presentation times were on average *M = 274 ms* (*SD = 61.0*) for healthy subjects, *M = 317 ms* (*SD = 117.8*) for MCI subjects, and *M = 387 ms* (*SD = 134.0*) for AD subjects. And "long" presentation times were *M = 547 ms* (*SD = 127.2*) for healthy control subjects, *M = 597 ms* (*SD = 188.7*) for MCI subjects, and *M = 713 ms* (*SD = 172.1*) for AD subjects. The most frequently used set of presentation times was (157 ms, 300 ms, 600 ms), applied to about half of the subjects (13 healthy control subjects, 5 MCI subjects, and 10 AD subjects). Individual exposure durations for all three subject groups are listed in Table 9 (p. 129).

The whole report task comprised 192 trials, separated into four blocks of 48 trials each. Within each block, the twelve different trial conditions (2 hemifields x 3 exposure durations x 2 masking conditions) of the experiment were presented equally often and in randomized order. Each subject received the same letter displays in the same random order. The test lasted about half an hour, with breaks between blocks adapted to a subject's needs.

4.3.2.3. Stimuli

The letters presented on each trial were either all red or all green and appeared at high contrast on a black background. For a given trial display, letters were randomly chosen from the alphabet excluding 'C, D, G, I, O, Q, U, V', with a particular letter appearing only once. Letter size was 0.5° of visual angel in height and 0.4° in width. Masks consisted of letter-sized

squares (of 0.5°) filled with a "+" and an "×" and presented for 500 ms at each letter location. The distance of the letter column from the vertical meridian was 2.5° of visual angle.

4.3.2.4. Apparatus

The whole report task was conducted in a dimly lit room. Stimuli were presented on a personal computer with a 17'' monitor (1024 x 768 pixel screen resolution; 70 Hz refresh rate). Viewing distance was about 50 cm. All patients were tested on location in the Memory Clinic, while the control subjects were assessed in an external psychology lab under identical conditions.

4.3.3. Estimation of TVA parameters

Parameters were estimated applying the algorithms described in detail by Kyllingsbaek (2006) and used in several recent studies (Bublak et al., 2005; Duncan et al., 1999; Finke et al., 2006; Finke et al., 2005; Habekost & Bundesen, 2003). Generally, based on the basic equations (see sections 3.1.2.1 and 3.1.2.2, pp. 24 et seqq.) provided by TVA (see Bundesen, 1990; Bundesen et al., 2005; Kyllingsbaek, 2006), a subject's accuracy of letter report as a function of effective exposure duration is modeled by an exponential growth function, according to a maximum likelihood method. Two defining characteristics of this function are the slope at its origin and its asymptote. They represent two important TVA parameters, the meaning of which is described below.

According to TVA, in masked conditions, the effective exposure duration of the stimulus display is the difference $t–t_0$, with t being the display presentation time and t_0 the estimated *minimal effective exposure duration* below which information uptake from the display is assumed to be zero. Under non-masked stimulus conditions, owing to visual persistence, an effective exposure duration of μ milliseconds is added to $t–t_0$. TVA assumes that, for a given subject, t_0 and μ are constant across experimental conditions (see e.g. Bundesen, 1990).

Thus, essentially, fitting of the raw data is based on estimating four parameters which define the exponential growth function: a) parameter t_0 (expressed in milliseconds), the estimated threshold value (minimum presentation time) beneath which nothing is perceived (i.e. probability of report equals 0); b) parameter μ (also expressed in milliseconds), the iconic memory buffer estimated from the difference in accuracy between unmasked and masked displays; c) parameter *C*, an estimation of visual processing speed (rate of information uptake, expressed in numbers of elements processed per second), reflecting the slope of the exponential growth function at its origin at the coordinate (t_0, 0); and d) parameter *K*, an estimation of VSTM storage capacity (the maximum number of objects that can be represented simultaneously at a time in VSTM, expressed in number of elements), reflecting the asymptote of the exponential growth function.

4.4. Results

4.4.1. Raw data

Figure 4 illustrates the qualitative pattern of performance for three representative subjects, one for each of the three groups. As indicated by the histograms (Figure 4 A-C), for each subject, the number of letters reported correctly increased systematically with increasing exposure duration. However, both the AD and the MCI subject's letter identification performance was markedly reduced compared to the healthy control subject at the shortest exposure durations, with a relatively large proportion of zero letter reports. In the right panels of Figure 4 (D-F), the black dots represent the observed number of correctly reported letters [Mean(obs)] as a function of the effective exposure duration. As can be seen, within the earlier section of the ascending curve relating performance to presentation time, the performance increment with increasing stimulus exposure is more pronounced in the healthy subject, but less so especially in the AD patient.

4.4.2. TVA parameter estimates

For each subject, the accuracy of letter report as a function of effective exposure duration was modeled by a TVA-based function representing the best fit of the raw data according to a maximum likelihood method (see e.g. Ross, 2000). This theoretically derived function is shown as a solid line for the representative subjects in Figure 4 [*Mean(theo)*].

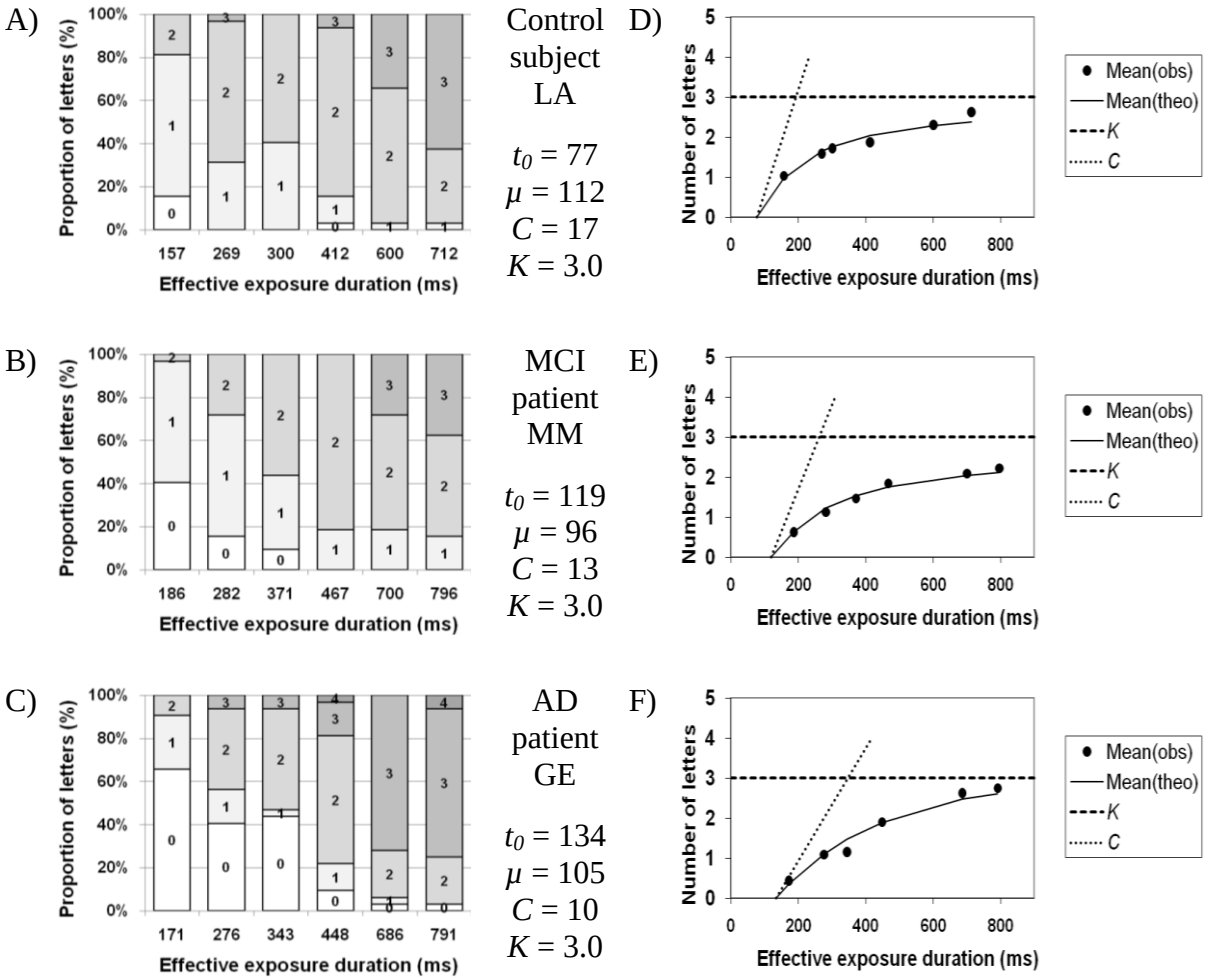


Figure 4: WR: Whole report performance of a representative subject for each group: One healthy control subject (LA), one MCI patient (MM), and one AD patient (GE)
The left panels (A–C) show the percentage of trials with 0, 1, 2, 3 or (in the AD patient) 4 correct letters reported, plotted as a function of effective exposure duration. In the right panels (D–F), the mean number of correctly reported letters is shown as a function of effective exposure duration. Solid curves represent the best fits of the TVA-based model to the observed values. The resulting estimates of visual short-term memory storage capacity *K* are marked by a dashed horizontal line (asymptote of the curve), the estimates of visual perceptual processing speed *C* are shown as a dotted tilted line (slope of the curve at t_0). Numerical values of these parameters, as well as of the estimated threshold t_0 and of iconic memory duration μ are also provided.

Overall, there was a close correspondence between the theoretically and the empirically obtained mean scores in the three groups. Across subjects, the average Pearson product-moment correlation between the observed values and the TVA best data fits in each of the three groups was r = .93 (SD = .08) for the AD group, r = .96 (SD = .02) for the MCI group, and r = .95

(SD = .04) for the group of healthy control subjects. Thus, overall, the TVA model accounted for more than 86% of the variance in the performance of the whole report task.

In Figure 4, the theoretically derived function [*Mean(theo)*] shows the typical course already known from previous studies (e.g. Duncan et al., 1999; Finke et al., 2005). However, in both patients, the function originates at a longer exposure duration compared to the healthy subject. Also, the slope of the function (dotted tilted line) at the point (t_0, 0) is less steep in the AD patient compared to the other two subjects, indicative of a somewhat reduced processing speed *C*. As exposure duration increases to a few hundred milliseconds, though, all three curves approach a similar asymptotic level of about 3 reported letters. Accordingly, the three dashed horizontal lines indicating the subjects' predicted VSTM storage capacity *K*, are at about the same level.

As for the representative cases shown in Figure 4, the four parameters (t_0, μ, *C and K*) were derived individually for each of the 54 subjects tested by modeling his/ her performance in the whole report task. The numerical parameter estimates obtained in this way for each subject (see Table 10, pp. 130 et seq.) allowed for statistical analysis at the group level. Planned comparisons between groups (healthy control subjects versus MCI patients, and MCI versus AD patients) were conducted using t-tests for independent samples.

4.4.2.1. Perceptual threshold: Parameter t_0

Figure 5 presents the group means for the threshold parameter t_0, separately for each group. Subjects with MCI displayed a significantly elevated threshold compared to healthy control subjects (M = 106.1 ms, SD = 64.8 versus M = 75.5 ms, SD = 39.2; $t(34) = -1.72$, $p < .05$, one-tailed), but the difference between MCI subjects and AD subjects (M = 106.1 ms, SD = 64.8) versus M = 114.9 ms (SD = 51.1)) was non-significant ($t(34) = .45$, $p > .30$).

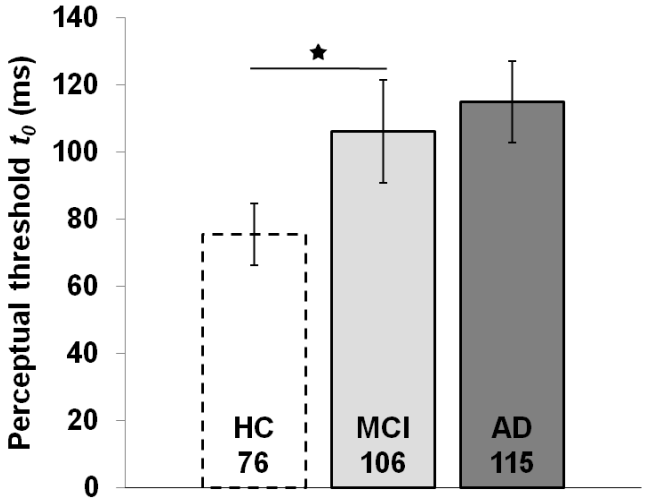


Figure 5: WR: Mean values of the estimated perceptual threshold t_0 for healthy controls (HC), MCI and AD subjects
Error bars indicate the standard error of the mean.

4.4.2.2. Iconic memory: Parameter μ

Figure 6 shows group means for the iconic memory parameter μ. There were no statistically significant differences in this parameter, neither between MCI and healthy control subjects (M = 91.6 ms, SD = 31.8 versus M = 102.7 ms, SD = 39.5; $t(34) = .93$, $p > .15$), nor between MCI and AD subjects (M = 91.6 ms, SD = 31.8 versus M = 97.6 ms, SD = 62.9; $t(34) = .36$, $p > .35$).

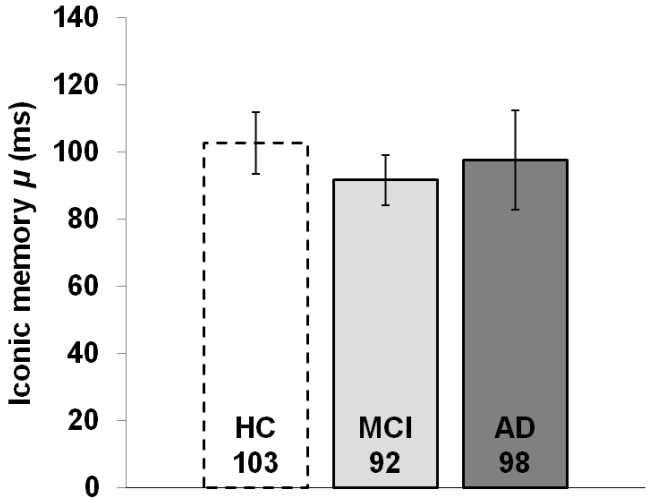


Figure 6: WR: Mean values of the estimated iconic memory μ duration for healthy controls (HC), MCI and AD subjects
Error bars indicate the standard error of the mean.

4.4.2.3. Processing speed: Parameter *C*

Figure 7 presents the group means for the speed parameter *C*.

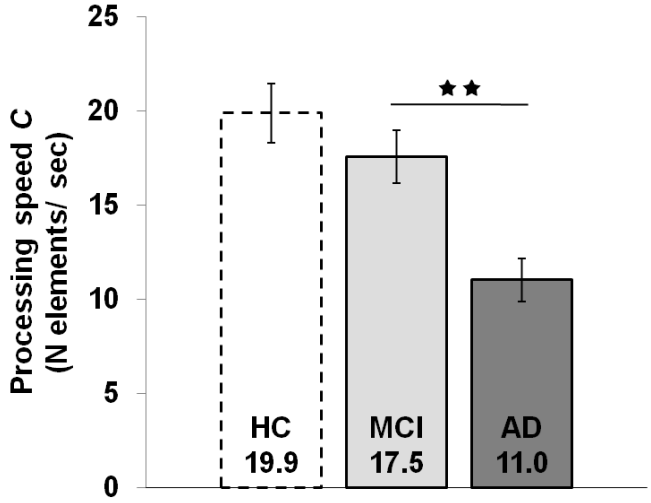


Figure 7: WR: Mean values of the estimated processing speed *C* for healthy controls (HC), MCI and AD subjects
Error bars indicate the standard error of the mean.

While MCI subjects were comparable to healthy control subjects in processing speed (M = 17.5 elements/ sec, SD = 6.0 versus M = 19.9 elements/ sec, SD = 6.6; $t(34) = 1.11$, $p > .10$), they were able to process a significantly larger number of items per second than AD subjects (M = 17.6 elements/ sec, SD = 6.0 versus M = 11.0 elements/ sec, SD = 4.9; $t(34) = -3.57$, $p < .01$, one-tailed).

4.4.2.4. VSTM storage capacity: Parameter *K*

Figure 8 presents the group means for the VSTM parameter *K*. As for the speed parameter, MCI subjects did not differ significantly from healthy control subjects in terms of VSTM storage capacity (M = 2.9 elements, SD = .4 versus M = 3.0 elements, SD = .4; $t(34) = .88$, $p > .15$); however, MCI subjects' capacity was larger than that of AD subjects (M = 2.9 elements, SD = .4 versus M = 2.5 elements, SD = .6; $t(34) = -1.89$, $p < .05$, one-tailed).

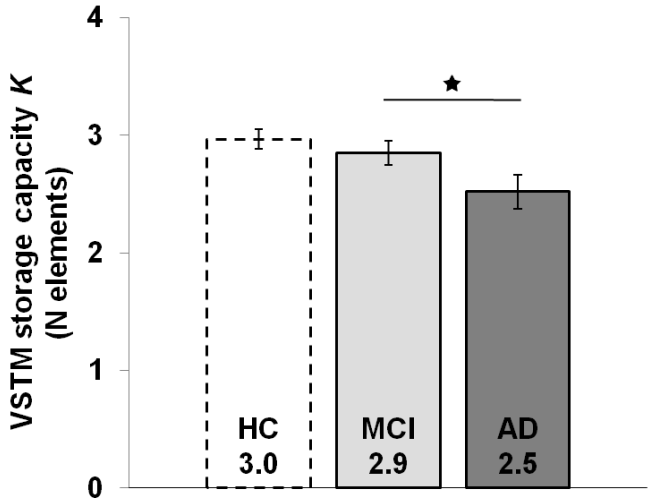


Figure 8: WR: Mean values of the estimated visual short-term memory storage capacity *K* for healthy controls (HC), MCI and AD subjects
Error bars indicate the standard error of the mean.

Taken together, analysis of the TVA parameters indicated an elevation of the perceptual threshold already in MCI, but a significant decline in processing speed and VSTM storage capacity only in AD.

4.4.3. Effect of acetylcholine esterase inhibitor medication

As mentioned above, 11 AD subjects received acetylcholine esterase inhibitors (AChEI) at the time of testing. Therefore, medicated and non-medicated AD subjects were compared with respect to the two parameters for which significant differences had been found compared to MCI: processing speed *C* and VSTM storage capacity *K*. Medicated and non-medicated subjects were comparable in terms of age ($t(16) = 1.05$, $p > .30$), gender ($\chi^2(2) = .08$; $p > .75$), and education ($t(16) = -.20$, $p > .80$).

For processing speed *C*, there was a significant difference (Figure 9). Non-medicated AD patients had lower processing speed than AChEI-medicated patients (M = 8.1 elements/ sec, SD = 4.0 versus M = 12.9 elements/ sec, SD = 4.7; $t(16) = -2.24$, $p < .05$; two-tailed). Non-medicated patients also exhibited lower VSTM storage capacity compared to medicated patients (M = 2.2 elements, SD = .7 versus M = 2.7 elements, SD = .5), though this difference was not statistically reliable ($t(16) = -1.54$, $p > .15$).

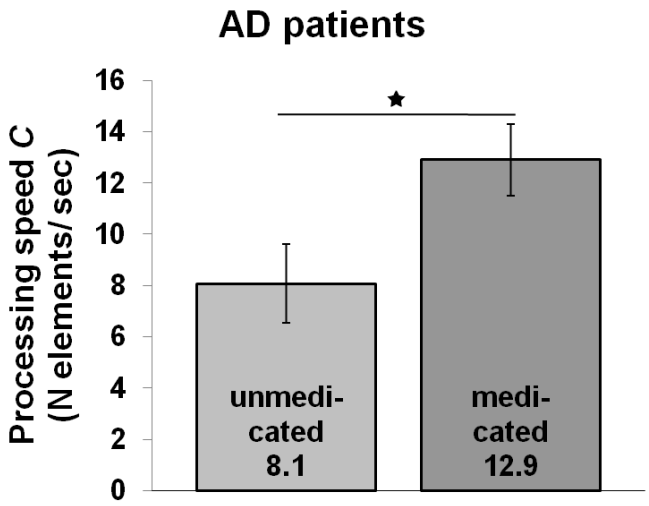


Figure 9: WR: Mean values of the estimated processing speed *C* for medicated and non-medicated subjects with probable Alzheimer's disease
Medication refers to acetylcholine esterase inhibitors. Error bars indicate the standard error of the mean. (HC = level of healthy control subjects; MCI = level of MCI patients).

With respect to processing speed, medicated AD patients still differed significantly from MCI subjects ($t(27) = -2.20$, $p < .05$; two-tailed).

4.4.4. Relationship to disease duration

Across both clinical groups (i.e. MCI and AD patients), correlations between the three affected TVA parameters (t_0, *C*, and *K*) and disease duration were calculated, that is, time since symptom onset.

For t_0, the correlation with disease duration was significant ($r = .34$, $p < .05$; two-tailed), indicating a modest association that points to an increase of the perceptual threshold with longer lasting disease. In contrast, *C* and *K* were not associated with disease duration ($r = .02$, $p > .90$, and $r = -.09$, $p > .55$, respectively).

4.4.5. Relationship to indices of cognitive function

We also calculated correlations between the three affected TVA parameters (t_0, *C*, and *K*) and three global cognitive measures – namely: CDR score, MMSE and CERAD total score (which does not include the MMSE; see Chandler et al., 2005) – across both clinical subject groups.

The perceptual threshold parameter t_0 was not associated with any of these measures (all $p > .40$; two-tailed). However, processing speed C was significantly related to CDR ($r = -.55$, $p < .01$), the MMSE score ($r = .59$; $p < .01$) and the CERAD total score ($r = .42$, $p < .05$). VSTM storage capacity K was also significantly related to CDR ($r = -.39$, $p < .05$), and the CERAD total score ($r = .40$, $p < .05$), while the association to the MMSE score was somewhat weaker ($r = .33$, $p < .06$).

Interestingly, with respect to the CERAD, VSTM storage capacity K was related only to those subtests providing visual material (i.e. picture naming and visuo-construction; $r = .49$, $p < .01$ in both cases). In contrast, processing speed C was significantly correlated not only with these measures ($r = .33$, and $r = .39$, respectively, both $p < .05$), but also with the verbal memory measures (learning, delayed recall, and recognition; all $r > .35$, all $p < .05$).

4.5. Discussion

The present study analyzed visual information uptake based on Bundesen's (1990) theory of visual attention (TVA) in AD, MCI, and healthy elderly control subjects. From a whole report task requiring verbal report of briefly presented letters, four parameters were derived, characterizing different aspects of visual processing capacity: perceptual threshold t_0, iconic memory μ, processing speed C, and VSTM storage capacity K. Comparison of these attentional parameters between groups revealed an elevation of the perceptual threshold already in MCI subjects, while processing speed and VSTM storage capacity showed a significant decline for AD patients only. The reduction in processing speed was especially pronounced in non-medicated AD patients, proving a strong relation of processing speed to the functional state of the cholinergic system.

This staged pattern of performance deficits revealed in the present study is striking, because it is the first, to my knowledge, to assess basic aspects of visual information uptake in both MCI and AD patients. It is well established that AD is accompanied by abnormalities in attentional

processing of visual stimuli. For example, Schlotterer et al. (1984) found Alzheimer patients to require more time than age-matched controls to identify letters, and to be susceptible to interference from a backward pattern mask for a longer time interval. Consistent with this, Gilmore et al. (2005) have shown that AD patients have to rely on higher contrast stimuli than healthy subjects for identifying rapidly flashed masked letters with comparable accuracy. Also, Kavcic & Duffy (2003) disclosed an impaired temporal dynamics of visual perceptual processing in the attentional-blink paradigm using rapid serial visual presentation of alphanumeric stimuli. However, MCI patients were not assessed in these studies, so that a direct comparison between deficits at different stages of AD was not possible. Conversely, Perry & Hodges (2003) found a normal attentional blink in MCI, while Bonney et al. (2006) reported prolonged inspection times in MCI subjects, but both studies had not included patients with dementia.

Relying on the conceptual strength of TVA in the present study, qualitative as well as quantitative differences could be described between MCI and AD subjects with respect to separable components of visual information intake. The data point to the possibility that the identified impairments follow an orderly progression, such that simpler aspects of visual processing like a perceptual threshold are affected at an earlier disease stage (MCI), and before significant cognitive decline has emerged, while more complex aspects like processing speed and short-term storage decline at a later stage when intellectual functions have already deteriorated (dementia). Based on TVA and its neural interpretation (NTVA; Bundesen et al., 2005), this differentiation can be discussed with respect to deficits at early (pre-attentive) versus late (attentive) stages of visual processing.

4.5.1. Deficits of pre-attentive processing

According to TVA, during the first stage of visual processing, perceptual units (objects) in the visual field are matched to representations in visual long-term memory (categories). This is a massively parallel process that results in the computation of evidence values, each providing a

measure for the degree of the match between a given object and a long-term memory representation. This first stage does not enable object identification. For example, in whole report of letters, the strength of the evidence that a given letter is an 'E' may equal the strength of the evidence that the letter is an 'F'. Evidence values are affected by the objective conditions of the visual environment like stimulus visibility (e.g. contrast), by the quality of the visual patterns to be matched, and by the reliability of long-term memory representations (this description follows Kyllingsbaek, 2006). As a result, pathology of both peripheral and central components of the retino-calcarine pathway could contribute to deficits arising at this first stage.

With respect to peripheral pathology, an extensive neuro-ophthalmic investigation by Rizzo et al. (1992) has provided evidence that, compared to pathologic changes in visual association cortex, retinal or optic nerve pathology are negligible for explaining visual deficits in AD (see Rizzo, M., Anderson, Dawson, & Nawrot, 2000, for a similar conclusion). Recently, however, retinal abnormalities have been reported to occur in early AD (Berisha et al., 2007), so that it is conceivable that an elementary deficit like an elevated threshold would be related to such abnormalities. However, what argues against this assumption is that any retinal pathology would be expected to also affect iconic memory duration, which was not supported by the present results. Moreover, in the study of Berisha et al. (2007), retinal pathology was associated with visual field defects. However, there was no evidence for the presence of scotoma in the participants of this study. Therefore, the identified elevation of the visual threshold is suggested to be related to central, rather than to peripheral, pathology.

As regards central pathology, an elevated visual threshold could result from alterations in early visual areas in and around the striate cortex. On this assumption, feature detectors that provide the 'building-blocks' for constructing visual patterns would be degraded. Consequently, the patterns to be compared to visual long-term memory representations might be compromised, impeding the matching process. This interpretation is compatible with the available

evidence that neurofibrillary tangle burden, although relatively minor in area 17, is considerable in areas 18 and 19 (Braak et al., 1989; Lewis, Campbell, Terry, & Morrison, 1987). Moreover, this pathology is notable already in pre-clinical AD subjects (McKee et al., 2006), supporting the present finding of a threshold increase in MCI patients.

An alternative account could be that long-term memory representations of letters, assumed to reside in the fusiform gyrus of the left hemisphere (Polk et al., 2002), might be degraded directly. That is, the disturbance of the matching process would result from the memory rather than pattern construction. Consistent with this, tangle burden has been found to be particularly marked in infero-temporal areas (Lewis et al., 1987), and cortical degeneration to be more pronounced in the left hemisphere (Thompson et al., 2003).

4.5.2. Deficits of attentive processing

TVA conceives of the second stage of visual processing as a race in which categorizations derived from the first stage compete for representation in VSTM. Entry to VSTM is synonymous with selection. Its result is the identification of a subset of visual elements from the visual field (e.g. that a given letter is an 'E'). Thus, in terms of TVA, those elements are selected that won the race for VSTM representation as a result of receiving the highest processing rate (Bundesen et al., 2005; Kyllingsbaek, 2006). The processing rate for each element is a function of both the evidence value derived from the first stage and an attentional weight assigned to the element. The weights stem from the available (limited) attentional capacity that is distributed across all the elements in the visual field. Thus, under the conditions of a whole report task where no element in the display is prioritized according to an a-priori criterion, it can be assumed that processing speed (i.e. the sum of the processing rates for each display element) essentially reflects the amount of available attentional capacity.

According to the neural interpretation of TVA (NTVA; Bundesen et al., 2005), allocation of attentional capacity to a visual object is synonymous with the recruitment of cortical neuronal populations representing the object. While the number and activation levels of these neurons

reflect processing speed, VSTM storage is realized by feedback loops that sustain the activation of neural units representing a subset of objects within reverberatory circuits (Bundesen et al., 2005). Thus, from a neuroanatomical and neurophysiological perspective, these visual functions arise from both the pure number of available neurons and their responsiveness. Hence, while a rather local pathology could explain the threshold elevation discussed above, more widespread alterations are likely to underlie the decline of VSTM storage capacity and processing speed. Given this, it appears plausible that these aspects show significant decline at an advanced disease stage (as seen in the present study) when AD pathology has already paved the way for substantial loss of neurons, cortico-cortical and cortico-subcortical disconnection, as well as destruction of neurotransmitter systems.

In line with this, in subjects with acquired brain damage, Habekost & Rostrup (2007) found severe reductions of processing speed and VSTM capacity after white matter lesions affecting long-range anterior-posterior or cortico-thalamic connections. In a study with patients suffering from focal brain lesions, Peers et al. (2005) reported damage to the temporo-parietal region to be associated with significant speed and VSTM deficits. This region is also known to be heavily affected by AD pathology during the course of the disease (Blennow et al., 2006). Moreover, temporo-parietal hypometabolism has been identified to predict progression from MCI to dementia with high accuracy (Chetelat et al., 2003). For VSTM storage, fMRI evidence suggests that bilateral activity in posterior regions, more specifically in the intraparietal and the intraoccipital sulcus, is correlated with the number of objects held in VSTM (Todd & Marois, 2004). This suggests that the significant VSTM decline found in AD subjects in the present study is related to advanced cortical pathology in posterior, especially temporo-parietal regions. For visual perceptual processing speed, on the other hand, there is also conclusive evidence that it heavily relies on the activity of the cholinergic system (Hutchison et al., 2001; Nathan & Stough, 2001; Stough et al., 2001). Interestingly, and in full agreement with this assumption, higher processing speed in AD patients on cholinomimetic medication

was found. Nevertheless, these patients' speed was still below the level of the MCI patients. Thus, the speed decline identified in this study might reflect a deficit in cholinergic innervation, which is also known as a neuropathological hallmark of AD (Mesulam, 2004).

4.5.3. Relationship to other clinical and cognitive measures

The results of the analysis of correlations between disease-related TVA parameters and other clinical and cognitive measures are compatible with the suggested neurocognitive interpretation of the deficits. Although these correlations were only moderate, they showed a distinctive pattern: Perceptual threshold values were significantly (though moderately) correlated with disease duration, but not with cognitive measures; conversely, speed and VSTM were significantly related to cognitive scores, but not to disease duration. This is what would be expected if measures of the perceptual threshold depicted the gradual accumulation of tangle and plaque deposits, which characterizes the pre-clinical stage of AD until the advent of MCI (Blennow et al., 2006). On the other hand, cognitive decline to dementia may follow a non-linear and perhaps less systematic trend due to several influencing risk and protective factors (Jarvik et al., 2008), so that other measures (processing speed and VSTM capacity) depicting the progressive degradation of the neural machinery underlying cognition are not closely associated with disease duration as such. In this regard, there may be a difference to a subcortical dementia such as Huntington's disease, for which speed and VSTM measures were found to be linked to disease duration (Finke et al., 2006). In this case, onset of cortical pathology may occur at later stages of the disease, giving rise to the link between duration and cognitive decline.

We found significant associations with cognitive tasks, both within the visual domain and beyond. In particular, VSTM storage was related to neuropsychological tests involving visual material (picture naming and visuo-construction), while speed showed an additional relationship to measures of verbal memory. Similar relationships have already been documented in earlier studies. For example Cronin-Golomb et al., (1995) reported that visual dysfunction oc-

curs in conjunction with cognitive decline in AD. An extensive investigation in AD patients (Rizzo, M., Anderson, Dawson, & Nawrot, 2000) showed significant associations between overall cognitive status and the performance in both perceptual and attentional visual tasks. Finally, modest relationships between a measure of processing speed (inspection time) and verbal memory measures have also been revealed for MCI subjects (Bonney et al., 2006).

Such an association between vision and cognition can be interpreted in one of three ways. First, it is possible that general cognitive decline, producing difficulties in performing any task, also gives rise to problems with visual tasks. However, this is unlikely to apply to the present findings, given the simplicity of the whole report task. This task, which does not need a complex instruction and does not require the subject to engage in a complex mapping of stimuli to (key press) responses, makes minimal cognitive demands and can even be performed by patients with Huntington's disease at a progressed stage (Bublak et al., 2006; Finke et al., 2006). Moreover, the individual performance pattern (see Figure 4, p. 44 for examples) demonstrates that AD patients produce results that show a similar, systematic increase in performance with longer presentation times as for healthy control subjects. This would not be expected in a cognitively demanding task that poses difficulties for subjects with intellectual decline.

As a second possibility is that visual deficits could affect the performance of a variety of cognitive tasks, especially if these tasks use visual stimulus material. Such an interpretation is supported by recent data of Cronin-Golomb et al. (2007) who demonstrated that simply enhancing stimulus strength can improve cognitive performance. This was true, however, only for relatively simple tasks with a clear visuo-cognitive component (picture naming, reading, face recognition), but not for a more complex reasoning task (Raven matrices). Such an account may also explain the current finding of an association between VSTM capacity and both picture naming and visuo-construction scores. VSTM storage may be required in these tasks for at least two reasons: either because more complex pictures comprising several com-

ponents (e.g., drawing a wire cube) have to be processed, or because visual scanning is necessary. Likewise, these functions may also depend on processing speed, consistent with the association of the TVA speed parameter with the scores in these tasks. The association of speed to the verbal memory measures may then be due to the fact that subjects had to read the words during encoding.

A third explanation may invoke common underlying pathology. On this account, correlations between certain parameters and tasks would result from the fact that both measures depend on the integrity of the same brain regions. For example, visuo-constructive tasks and picture naming may require spatial shifts of attention, so that performance involves posterior parietal functions in both cases. This region may also play a role in VSTM storage, as discussed above, and may be associated with these tasks for this reason. With regard to processing speed, if this function critically depends on the cholinergic system, as supported by the present results, then the association with memory could be explained by the fact that this system also contributes to learning and memory formation (Mesulam, 2004). In addition, one would expect the speed parameter to be correlated with a broad range of cognitive functions, due to the widespread cortical effects of the cholinergic system.

Thus, more generally, the TVA parameters assessed in the present study may just be considered as neurocognitive markers for the functional integrity of the different cerebral systems and regions that are most prominently affected by AD pathology: posterior cortical areas in the temporal, parietal, and occipital lobe, and the cholinergic corticopetal projection system.

4.5.4. Limitations

The current study has a number of limitations that are worth mentioning. First, the presentation of results focused on the main line of the effects. There were numerical differences that did not reach statistical significance (in particular, differences between MCI and healthy control subjects with respect to parameters *C* and *K*) which might have turned out significant with a larger sample of subjects. However, even if such effects reached significance, they would

not contradict the conclusions drawn so far. In fact, the gradual transition from the MCI to the dementia stage of AD would imply a substantial overlap between both groups, as was quite evident in the present patient samples as well. The current results merely suggest that an elevated threshold marks the MCI stage, while a speed decline unambiguously indicates the dementia stage, notwithstanding the fact that more subtle differences may also be present. Nevertheless, the present findings would have to be replicated in further studies to underpin the robustness of the effects revealed.

A second limitation of this study derives from the fact that it is based on a cross-sectional approach, comparing different groups of subjects at different stages of cognitive decline. This approach needs to be complemented by longitudinal studies to examine whether the staged pattern of deficits identified does also hold for the individual progression of the disease.

Third, despite the significant group differences in the mean parameter estimates, there was also substantial overlap between groups with respect to the individual parameter values. Therefore, it remains an open issue whether parametric assessment based on TVA can be used for diagnostic decisions at the level of individual patients. Note, however, that the diagnostic potential of this approach may significantly improve by taking into account additional measures – such as TVA-based assessment of attentional weighting (Bublak et al., 2005; Finke et al., 2006; this was not examined in the present study), or functional neuroimaging (e.g., positron emission tomography, PET) data.

4.5.5. Conclusions

Besides the presence of a memory disorder, AD is also characterized by deficits in visual perception and attention that can be related to the neuropathology predominantly affecting posterior cortical areas. Visuo-cognitive impairments have been revealed in a broad range of tasks, involving visual search (Tales, Haworth et al., 2005), visual short-term memory (Alescio-Lautier et al., 2007), and visual perception (Rizzo, M., Anderson, Dawson, & Nawrot, 2000). It has also been suggested that deficits in visual memory can predict the advent of AD

long before a diagnosis can be made (Kawas et al., 2003). Efficiency of visual information uptake may contribute critically to such deficits. The present study, which was designed to analyze different components of visual processing capacity, revealed an incremental pattern of modified parameters that was associated with different disease stages and could be explained by differential impairments of pre-attentive and, respectively, attentive stages of visual processing. These findings are compatible with the amyloid cascade hypothesis of AD (Blennow et al., 2006; Hardy & Selkoe, 2002), according to which the AD neuropathology is characterized by a net accumulation and deposition of Aβ in the initial phase, giving rise to neuronal and neuritic dysfunction. At later stages, gradual neuronal loss and transmitter disturbances finally cause the increasing intellectual decline during further progression of the disease. The threshold elevation found in this study may thus be considered as a possible index of impaired neuronal functioning prior to cell death, while speed and VSTM deficits may be indicative already of a substantial loss of neuronal cell assemblies and a degeneration of neurotransmitter systems, in particular the cholinergic system. Thus, TVA-based assessment could provide appropriate neurocognitive markers of both a dysfunctional and a degenerated cortex, tracking the cerebral decomposition over the course of Alzheimer's disease.

5. Study 2: Visual attentional selection in MCI and AD

In the second study, visual attentional functions of spatial and task-related selection were investigated in a partial report task (PR) in patients with amnestic mild cognitive impairment (MCI) and Alzheimer's disease (AD).

5.1. Abstract

The present study investigated visual selective attention in 32 patients with amnestic mild cognitive impairment (MCI), 16 patients with probable Alzheimer's disease (AD), and 36 healthy elderly control subjects. Groups were matched for age, gender and educational level. In combination with Bundesen's (1990) theory of visual attention (TVA), two mathematically independent and quantitative parameter estimates were derived from a partial report of briefly presented letter arrays: top-down control of attentional selection, representing task-related attentional weighting for prioritizing relevant visual objects, and spatial distribution of attentional weights across the left and right hemifield.

Compared to controls, MCI patients showed significantly reduced top-down controlled selection which further deteriorated in AD subjects. Moreover, attentional weighting was significantly unbalanced across hemifields in MCI and tended to be more lateralized in AD. The majority of patients was biased to the left. Across MCI and AD patients, carriers of the apolipoprotein E ε4 allele (ApoE4) revealed a leftward spatial bias. The leftward bias was the more pronounced the younger the ApoE4-positive patients and the earlier disease onset. ApoE4-negative subjects showed balanced attentional weighting.

These results indicate that impaired top-down control may be linked to early dysfunction of cortico-cortical networks connecting parietal and frontal lobes. Accompanying, an early interhemispheric asymmetry in temporo-parietal cortical interactions might cause a pathological spatial bias. As the inheritance of ApoE4 is associated with an interhemispheric imbalance in

parietal cortical interactions, a pathological spatial bias may function as early cognitive marker for detecting subjects at risk for probable AD.

5.2. Introduction and aim of the study

Alzheimer's disease (AD) is the most frequent form of dementia characterized by progressive cortical degeneration starting in mediotemporal regions and proceeding to parietal and frontal areas (Braak & Braak, 1990; Braak, Braak, & Bohl, 1993; Whitwell et al., 2007). It appears both as a familial and a sporadic variant. The familial form is rare, with a prevalence below 0.1%, and represents an autosomal dominant disorder with onset before age 65 years, mostly caused by mutations of the highly homologous presenilin genes. In the by far more frequent sporadic form, a genetic risk factor is also implicated, in that carriers of the apolipoprotein E ε4 allele (ApoE4) on chromosome 19 have a 3 (in heterozygotes) to 15 times (in homozygotes) higher risk of developing the disease, compared to non-carriers. In both variants, the neuropathological basis of AD is an accumulation of β-amyloid (Aβ) either due to a life-long over-production (familial variant) or a failure of the clearance (sporadic form) of Aβ (Blennow et al., 2006).

Mild cognitive impairment (MCI) is considered as the prodromal phase of dementia in most patients. It is defined as a transitional state between the normal alterations of cognitive and functional abilities in elderly subjects and the significant decline associated with probable dementia (Gauthier et al., 2006; Nestor et al., 2004). In particular, MCI of the amnestic type bears a high risk for subjects to develop AD (Gauthier et al., 2006). According to Petersen et al. (1999), it is diagnosed on presentation of subjective memory complaints, preferably corroborated by an informant, the presence of objective memory impairment, as assessed by neuropsychological testing, essentially normal functional abilities, and the absence of dementia. It has been claimed by some authors that the initial memory disturbance in AD is at least accompanied if not preceded by early deficits of selective attention (Foldi et al., 2002; Perry &

Hodges, 1999). Thus, sensitive tools for assessing selective attention might serve as early cognitive markers in the course of AD and therefore enhance the identification rate of at-risk subjects at the MCI stage (Shah et al., 2008). The present study aims at examining whether attentional parameters of visuospatial and task-related selection are appropriate means for that purpose.

Deficits of visuospatial attention are well established in AD, and have been extensively studied using spatial cueing and visual search tasks (for review, see Parasuraman, Greenwood, & Sunderland, 2002). AD patients have been shown to suffer from a reduced spatial attentional window (Rizzo, M., Anderson, Dawson, Myers et al., 2000) and to present difficulties in disengaging attention from invalidly cued locations (Tales, Snowden, Haworth, & Wilcock, 2005). Recently, Drago et al. (2008) reported that the capacity to reallocate spatial attention is especially hampered when it had been directed towards the left. Similarly, Foster et al. (1999) had already found that AD patients had more difficulty in detecting targets on the right in a visual search task. In fact, a lateral bias of spatial attention, either towards the left or the right hemifield, seems to occur in a substantial number of cases, with some studies even showing signs of hemispatial neglect (Bartolomeo et al., 1998; Ishiai et al., 2000; Mendez, Cherrier, & Cymerman, 1997; Venneri, Pentore, Cotticelli, & Della Sala, 1998). Typically, however, the spatial bias is more subtle and disclosed under conditions of double simultaneous stimulation only, when stimuli within both hemifields compete for selection (Bublak et al., 2006). It is an open issue whether a spatial bias of attention is already present at the MCI stage. Thus, the first aim of the current study was to investigate the evidence of spatially lateralized attentional processing in both MCI and AD subjects.

Visual search tasks have also revealed impairments in task-related selection, that is, deficits of filtering out irrelevant distractors during target processing. For instance, Baddeley et al. (2001) found AD patients to be somewhat more susceptible to interference from similar distractors than control subjects. Amieva et al. (1998) have reported deficient inhibitory mechan-

isms in the widely used trail making test, which may be the result of a profound impairment of executive functions in AD, present already at early stages (Amieva, Phillips, Della Sala, & Henry, 2004a; Levinoff, Li, Murtha, & Chertkow, 2004; Minati, Edginton, Bruzzone, & Giaccone, 2009). In contrast to inferences from rather indirect measures of task-related selection (defined by, e.g., distractor similarity or error type differences), the second goal was to analyze the effect of distractor interference by direct comparison of performance between trials with a single target presented on its own and trials with an additional distractor.

To investigate these issues, a task requiring partial report of briefly presented letters (i.e. report only pre-defined target letters, but not distractor letters) was employed, based on Bundesen's (1990) formal theory of visual attention (TVA). The TVA-based approach permits parametric estimates to be derived from performance in this simple psychophysical task that reflect both spatial and task-related aspects of attentional processing. In this way, comparability of conditions was ensured for interpreting separate aspects of selective attention in both MCI and AD subjects; for a recent summary for TVA-based studies with neurological and psychiatric patients, see Habekost and Starrfelt (2009). A further, critical advantage of this paradigm is that it does not rely on response time-based assessment (as many previous studies did), thereby eliminating a general slowing of motor performance as a potentially confounding factor. Thus, by individually adjusting the (brief) stimulus presentation times, a comparable task difficulty is ensured across subjects. In a previous study, this approach had already been, successfully, applied to investigate patients with a subcortical type of dementia, Huntington's disease (Finke et al., 2006). Furthermore, a related TVA-based whole report paradigm (in which subjects had to report as many letters from a briefly presented array as possible) had proved to be sensitive to revealing visual attentional capacity reductions in both MCI and AD patients (Bublak et al., 2009). Therefore, this method deemed to be appropriate for assessing spatial and task-related aspects of attentional processing in subjects at different stages of cortical degeneration, that is, amnestic MCI and probable AD.

TVA is a mathematical model with strong relations to the biased competition account of attentional selection proposed by Desimone and Duncan (1995); for a detailed mathematical description of TVA, see Bundesen (1990, 1998), Duncan et al. (1999), or Kyllingsbæk (2006). For a neural interpretation of TVA, see Bundesen et al. (2005). On this account, visual objects in the visual field are processed in parallel and compete for selection, that is, 'conscious' representation within the information processing system. The resulting race among objects can be biased such that some objects are favored for selection, based either on stimulus-driven, 'bottom-up' or on intentional, 'top-down' factors. In TVA, selection of a visual object is synonymous with its encoding into a visual short-term memory (VSTM) store with limited capacity. The probability of selection is determined a) by an object's processing rate *v*, which depends on the attentional weight (*w*) it receives, and b) by the capacity of the VSTM store (if the store is filled, the selection process terminates). TVA provides parameters for characterizing specific aspects of attentional weighting, such as task-related weighting for prioritizing the processing of relevant visual objects (top-down control) and the spatial distribution of attentional weights across the left and right hemifields. Independent quantitative estimates of these two aspects of attentional weighting are derived from subjects' performance in the partial report task. In this task, subjects have to report target objects only, which are pre-specified (e.g., with respect to color), whilst ignoring distractors.

Thus, the present study provides an extension of a previous TVA-based investigation of visual processing capacity in MCI and AD using a (non-selective) whole report task, which, however, does not allow for aspects of the selective weighting of stimuli to be examined (Bublak et al., 2009). The partial report paradigm was applied in patients with amnestic MCI, probable AD, and healthy control subjects. In patients, the possible influence of genetic risk on attentional weighting was also assessed by comparing carriers and non-carriers of ApoE4 alleles. Using an identical TVA-based partial report paradigm, Finke et al. (2006) had found a close relationship between the severity of the underlying genetic pathology in another neurodege-

nerative, namely Huntington's, disease and the direction and degree of spatial attentional weighting. Therefore, it was examined whether ApoE4 carriers in the present clinical groups might exhibit more pronounced deficits in spatial and/ or task-related attentional weighting than clinical non-carriers of the ApoE4 allele.

5.3. Method

5.3.1. Subjects

48 patients with the clinical diagnosis of amnestic mild cognitive impairment (MCI) or probable Alzheimer's disease (AD), respectively, were recruited from the Memory Clinic of the department of Psychiatry, Technische Universität München, Germany. 32 MCI patients (17 male, 15 female; mean age 69.0 years; mean educational level 10.8 years) took part in the study. The AD patient group consisted of 5 men and 11 women (mean age 67.1 years; mean education 9.8 years). All patients were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Written informed consent according to the Helsinki II declaration was obtained from all subjects or, respectively, their legal representatives, and the study was formally approved by the ethics committee of the University of Munich. All subjects had normal or corrected-to-normal vision. All patients were able to fixate adequately, understand, and follow the verbal task instructions as well as work concentrated for about 30 minutes, and did not suffer from color blindness. No subjects in the clinical group displayed any salient and considerable visual deficits typical of posterior cortical atrophy.

All patients had undergone a standardized diagnostic assessment including medical history (both patient and informant interview), medical, neurological, and psychiatric examination, neuropsychological assessment using the test battery of the Consortium to Establish a Registry for Alzheimer's Disease - Neuropsychological Battery (CERAD-NP, German version; Thalmann and Monsch (1997); see Test 1, pp. 141 et seqq.) including the Mini-Mental State

Examination (MMSE; Folstein et al., 1975), and the Clock Drawing Test (CDT; Shulmann et al. (1993), see Test 2, pp. 155 et seq.) as well as rating the overall severity of cognitive deficits with regard to activities of daily living using the Clinical Dementia Rating (CDR; Morris (1993), see Test 3, pp.157 et seqq.), structural brain imaging (MRI), and blood tests.

All AD patients fulfilled the criteria of probable dementia (CDR global score ≥ 1) of the Alzheimer type based on the diagnostic criteria of the ICD-10 classification of mental and behavioral disorders for dementia (Bramer, 1988), and the NINCDS-ADRDA criteria for the diagnosis of AD (McKhann et al., 1984). All MCI patients fulfilled the following inclusion criteria: cognitive impairment affecting at least the memory domain (amnestic MCI patients, single or multiple domains) according to Petersen (2000; Petersen et al., 1999), largely preserved activities of daily living (Bayer ADL scale; Hindmarch et al., 1998), no dementia according to ICD-10 criteria, and questionable dementia indicated by CDR global score of 0.5. Exclusion criteria for participation in this study were other neurological or systemic diseases like stroke or substance abuse or clinically notable MRI pointing to cognitive deficits.

None of the MCI patients was medicated with antidementives, but 11 (69%) AD patients were treated with acetylcholine esterase inhibitors (AChEI). Due to mild symptoms of depression, 9 MCI (28%) and 3 (19%) AD patients received antidepressant medication. Distributions of antidepressant medication in MCI patients resembled those in AD subjects ($p > .45$). Furthermore, two MCI and three AD patients suffered from diabetes mellitus, 9 MCI and 6 AD patients received antihypertensive medication.

Table 2: PR: Overview of biographical and clinical details for MCI and AD patients and healthy controls

See also Table 11 (pp. 132 et seq.).

CDR: Clinical Dementia Rating Scale, global score (Morris, 1993); p: level of significance; M (SD): mean score and standard deviation; Age in years; Education in years; Handedness: according to the Edinburgh Handedness Inventory (Oldfield, 1971); R: right-hander; MMSE: Mini Mental State Examination (Folstein et al., 1975), 30-0 points, cut-off ≤ 23; CERAD: The Consortium to Establish a Registry for Alzheimer's Disease (Thalmann & Monsch, 1997), total score; n.a.: not applied; CDT: Clock Drawing Test, 0-6 points, cut-off ≥ 3 (Shulman, Shedletsky, & Silver, 1986); CDR sum: sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4: apolipoprotein E4 genotype, positive (+), negative (-).

	AD (n = 16, CDR ≥ 1)	**MCI (n = 32, CDR = 0.5)**	**Control (n = 36)**	***p***
Age, M (SD), range	67.1 (8.6) 55.8 – 81.5	69.0 (7.6) 45.9 – 79.9	67.2 (6.6) 50.0 – 82.0	> .55
Gender (male/ female)	5 / 11	17 / 15	16 / 20	> .35
Education, M (SD), range	9.8 (1.3) 9 – 13	10.8 (1.9) 9 – 13	10.5 (2.1) 7 – 13	> .20
Handedness	all R	all R	all R	
MMSE, M (SD), range	22.8 (2.3) 19 – 25	27.4 (1.3) 25 – 30	29.0 (1.0) 27 – 30	**< .01**
CERAD, M (SD), range	68.0 (10.0) 51 – 84	82.9 (10.5) 54 – 112	n.a.	**< .01**
CDT, M (SD), range	3.2 (1.1) 1 – 5	2.0 (.9) 1 – 4	n.a.	**< .01**
CDR sum, M (SD), range	4.4 (.6) 3.5 – 5.0	2.0 (.7) 1.0 – 3.5	n.a.	**< .01**
Age at onset, M (SD), range	64.5 (9.1) 52.1 – 78.4	66.2 (7.9) 43.6 – 76.8	-	> .50
Disease duration, M (SD), range	3.3 (2.0) 0.8 – 8.0	2.7 (1.5) 0.5 – 7.8	-	> .25
ApoE4 genotype	10 +/ 4 - 2 n.a.	18 +/ 11 - 3 n.a.	n.a.	> .75

As can be seen in Table 2, ApoE4 genotype was assessed for a subset of 29 MCI (18 ApoE4 carriers) and 14 AD (10 ApoE4 carriers) patients. Distributions of the ApoE4 genotype were comparable in MCI and AD patients.

A control group of 36 healthy older subjects (16 male, 20 female; mean age 67.2 years; mean education 10.5 years; all right-handed) was recruited by word-of-mouth recommendation, flyers and notices. None of the control subjects reported a neurological or psychiatric history. All subjects had normal or corrected-to-normal vision. MCI and AD patients as well as con-

trol subjects did not differ significantly from each other with regard to Age [$F(2, 81) = .58$, $p > .55$], Education [$F(2, 81) = 1.50$, $p > .20$] or Gender [$\chi^2(2) = 2.08$, $p > .35$].

Further biographical and detailed clinical information of each subject group is listed in Table 2 (for details of individual MCI and AD subjects see Table 11, pp. 132 et seq.). All three groups differed significantly from each other with regard to MMSE score. Furthermore, MCI patients were significantly less impaired than AD patients in the overall level of functioning according to CERAD (total score excluding MMSE, Chandler et al., 2005), in the CDT and the CDR (sum of category scores). Estimates of disease onset (based on the date of the first documentation of the MCI diagnosis) and disease duration were comparable across patient groups.

5.3.2. Partial report paradigm

The stimuli and the general method were similar to those introduced by Duncan et al. (1999) and identical to several previous studies of our research group (Bublak et al., 2005; Finke et al., 2006; Finke et al., 2005).

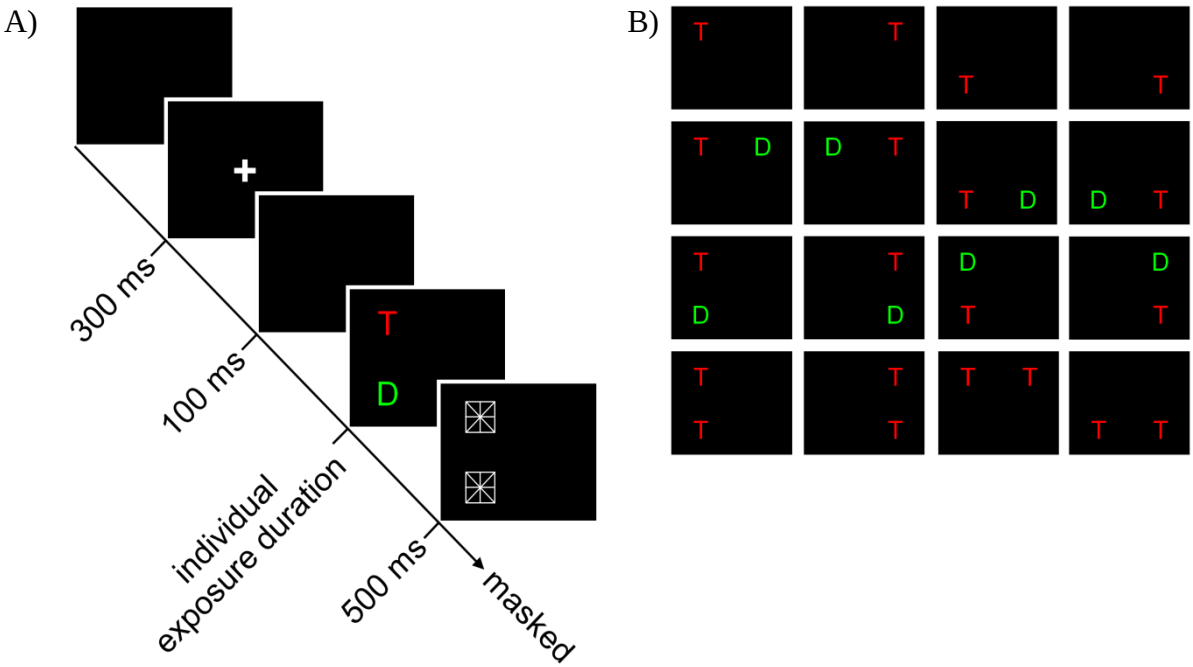


Figure 10: PR: Illustration of (A) the partial report paradigm with (B) 16 different trial types
4 single target (depicted as 'T', always red), 8 target plus distractor (depicted as 'D', always green) and 4 dual target conditions.

5.3.2.1. Task

In Figure 10, the sequence of events on an experimental trial (A) and the different trial types (B) are illustrated. Subjects were asked to maintain fixation before being presented with one or two letters on four possible equidistant positions round the fixation cross. The subjects' task was to verbally report only red target letters they felt relatively sure they had recognized, and to ignore green distractor letters. Verbal report of individual letters was performed in arbitrary order and without stress on report speed. The experimenter entered the reported letter(s) on the keyboard and then started the next trial as soon as the subject was ready. For detailed information on test instructions, see Instruction 3 and Instruction 4 (p. 127).

5.3.2.2. Procedure

First, subjects were instructed to fixate a central white cross (0.3° visual angle) presented for 300 ms (see Figure 10 A). Then, after a gap of 100 ms, red and/or green letters (0.5° high x 0.4° wide) were presented on a black background for a predetermined exposure duration. Subjects were instructed to maintain fixation on the fixation cross until the presentation of the letter(s). Prior to the start of the experiment proper, a short practice session was conducted which served to determine the individual presentation durations (besides validating intact visual functions in all subjects).

For the specification of the individual exposure durations, an initial test phase consisting of 32 masked trials was used, aiming for about 80% accuracy on single letter trials. In the experiment itself, all stimuli displays were presented for the individually adjusted exposure duration. A mean exposure duration of 452 ms (SD = 171, range: 100-743) was used for AD patients, of 330 ms (SD = 114, range 143-600) for MCI patients, and of 200 ms (SD = 69, range: 71-357) for control subjects. Exposure durations of individual subjects are listed in Table 12 (p. 134).

The total number of trials was 288, divided into blocks of 48 trials each. Within each block, the sixteen different trial types of the experiment (4 single target, 8 target-plus-distractor, and

4 dual target conditions) were presented equally often (with 18 trials each) and in randomized order. On each trial, a single red target (letter), or a target plus a green distractor (letter), or two red targets (see Figure 10 B) were presented at the corners of an imaginary square with an edge length of 5°, centered on the screen. Two stimuli were presented either horizontally (row display) or vertically (column display), but never diagonally. Stimuli were displayed randomly at all possible positions in pre-specified combinations as well as with respect to visual hemifield in order to avoid anticipatory responses by the subjects.

5.3.2.3. Stimuli

The letters for a given trial were randomly chosen from the prefixed set 'ABEFHJKLMNPRSTWXYZ', with the same letter appearing only once in a trial display. Each subject received the same letter displays in the same random order. Stimuli were all masked by squares of 0.5° filled with a '+' and an 'x', which were presented for 500 ms at each stimulus location after stimulus presentation.

5.3.2.4. Apparatus

Stimuli were presented on a personal computer with a 17'' monitor (1024 x 768 pixel screen resolution; 70 Hz refresh rate). Viewing distance was about 50 cm. The patients were tested in hospital, and the control subjects in a university laboratory. At all locations, experiments were conducted in a dimly lit room under identical conditions.

5.3.3. Estimation of TVA-based parameters

The individual assessment of performance accuracy across the different partial report conditions (see Figure 10 B) was modeled by a TVA-based algorithm using a maximum likelihood method (e.g. Ross, 2000). Detailed descriptions of the model fitting procedure, which was largely identical with that used by Duncan et al. (1999), and the software used, can be found in Kyllingsbæk (2006). By fitting TVA to individual (partial report) raw data sets, several parameter estimates can be derived, in particular: parameters for characterizing specific aspects of attentional weighting, such as task-related weighting for prioritizing relevant visual objects

for processing (top-down control) and the spatial distribution of attentional weights across the left and right hemifields. Additionally, parameter estimates for sensory effectiveness reflecting the processing rate for each hemifield are provided.

The qualitative pattern of each group's performance was quantitatively described by a TVA-based model that produced individual estimates of attentional weights w_i separately for each of the four display locations and separately for targets and distractors. Similarly, individual estimates of sensory effectiveness A_i for each display location (irrespective of the displayed letter being a target or distractor) were derived.

The mean scores for the different partial report conditions and those predicted based on the best fits of the TVA model parameters showed a high correspondence, with a mean correlation of r = .87 (SD = .11) for controls, of r = .92 (SD = .11) for MCI patients and of r = .95 (SD = .04) for AD patients. The predicted values accounted for r^2 = 77% (SD = .17) of the variance of the observed mean score in controls, for r^2 = 85% (SD = .16) in MCI patients and r^2 = 91% (SD = .07) in AD patients.

5.3.3.1. Task-related weighting

Parameter α, reflecting the efficiency of top-down control, indicates whether attentional weights for targets (T) are greater than the weights for distractors (D; averaged across locations, respectively) and is defined as the ratio w_D / w_T. Thus, lower α values indicate more efficient top-down control. Unselective processing, by contrast, would give rise to equally weighted target and distractor processing, increasing α to approach 1. A value of α greater than 1 would indicate that the subject actually prioritizes the task-irrelevant distractors.

5.3.3.2. Spatial weighting

The spatial distribution of attentional weighting, w_λ, is estimated from performance in conditions in which subjects have to report stimuli presented either unilaterally, on either side of the visual field, or bilaterally, in the left and right visual hemifields. From the accuracy of target identification, separate attentional weights are derived for the left (w_{left}) and the right he-

mifield (w_{right}). In TVA, the absolute attentional weighting has no meaning; only relative intra-individual values can be compared. Therefore, a laterality index was computed from the raw data of the *w* estimates: parameter w_λ, reflecting the laterality of the spatial distribution of attentional weights. The laterality index of attentional weighing w_λ is defined as the ratio w_{left} / (w_{left} + w_{right}). Hence, a value of w_λ = 0.5 indicates balanced weighting (w_{left} = w_{right}), values of w_λ > 0.5 indicate a leftward and values of w_λ < 0.5 a rightward spatial bias, because weights for objects to the left of fixation would be higher than those for objects to the right, or vice versa. As a result, for example a value of .63 would indicate a leftward spatial bias, a value of .37 would represent a spatial bias of comparable degree, however to the opposite, right, hemifield. In AD with bilateral neurodegenerative processes, single patients might show a dysbalance to either hemifield, that reflects either predominantly right-sided or left-sided neural damage, rather than suffering from a systematic spatial bias to a specific hemifield. Thus, the absolute deviation of w_λ from the optimum value 0.5 in *any* direction was also computed, Dev(w_λ), as an index of the subject's general ability to attend equivalently to both hemifields (see also Finke et al., 2005). Note that in the two examples given above, this absolute deviation from 0.5, the imbalance index of attentional weighting Dev(w_λ), would be equally severe and indicated by a value of .13.

5.3.3.3. Sensory effectiveness

In TVA, the probability of identifying an object depends not only on its relative attentional weight (i.e. the weight allocated to a given object relative to the weights assigned to the other objects), but also on the sensory effectiveness *A* of an object (Duncan et al., 1999), which is independent of its attentional weight (rather, it depends on factors such as stimulus discriminability, contrast, and retinal eccentricity). Parameter *A* is assumed to reflect the total processing rate for each hemifield, rather than how capacity is divided between the different objects in a display. Conceptually, the estimates of *A* are measures of basic sensory effective-

ness and thus are related to accuracy on a single element presented alone, rather than to performance losses in multi-element displays.

According to TVA, a spatial bias may be caused by attentional weights being reduced for one compared to the other hemifield (Duncan et al., 1999), unbalancing the competition between objects on left and the right side. Alternatively, a spatial bias might be due to basic sensory effectiveness being reduced for one hemifield, leading to an imbalance in sensory processing between hemifields (see equation 2, section 3.1.2.2, p. 25; Bundesen (1990)). To decide between these possibilities (analogously to the definition of w_i), values of A_{right} and A_{left} are calculated, that is, the mean values of sensory effectiveness for the upper and lower positions in the left and the right hemifield, respectively. In addition, a laterality index for sensory effectiveness (A_i) is computed as the ratio A_{left} / (A_{left}+A_{right}). Thus, a laterality value above 0.5 reflects a lateralization of sensory effectiveness to the left (i.e. higher effectiveness in the left hemifield), and a value below 0.5 a lateralization to the right visual hemifield. In order to test for sensory accuracy loss in *either* of the two hemifields, the absolute deviation of A_i from the balanced value 0.5 in *any* direction was computed, Dev(A_i), as an index of a given subject's general degree of balance/ imbalance in sensory effectiveness between the two hemifields.

5.4. Results

This section is divided into two subsections, the first presenting the results on task-related weighting and the second the findings on spatial weighting and associated sensory effectiveness. Each subsection starts with a description of the qualitative pattern of performance produced by each subject group in the partial report task. Next, the TVA-model estimates of the parameters for top-down control of attention, for spatial laterality and balance/imbalance of attentional weighting, and for the corresponding sensory effectiveness parameters are presented for each subject group, and compared among groups. Subsequently, the intercorrelations of both partial report parameters are reported for each subject group. For addi-

tional information about the clinical relevance of the TVA parameters, their relationship with external clinical measures and cognitive tests is also documented. Furthermore, in order to assess whether the parameters are related to possible underlying gene-associated pathology, the effect of ApoE4 genotype (carriers versus non-carriers) on the parameter values is examined.

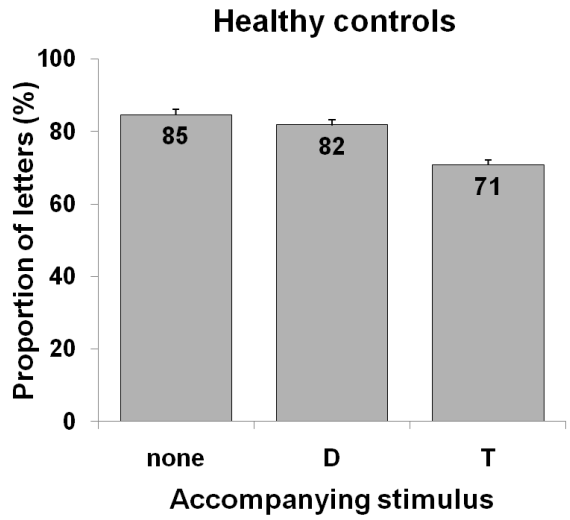
5.4.1. Task-related weighting

In this section, findings are present which pertain to the ability to perform top-down controlled visual selection under conditions in which distractor information is present, starting with the raw data results followed by the estimates of the corresponding (top-down control) parameter α.

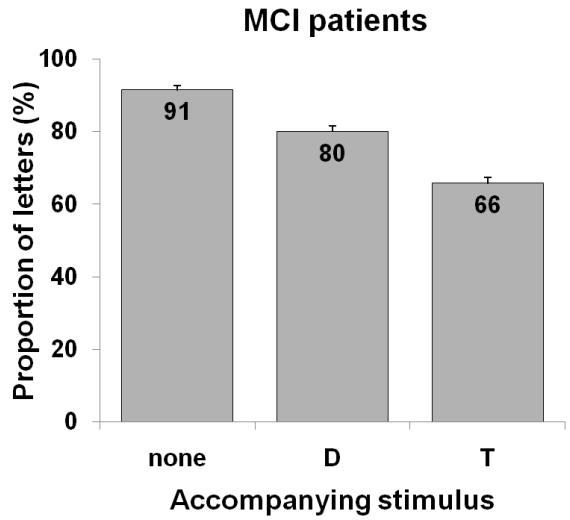
5.4.1.1. Raw data

Top-down control of attention refers to the capability of task-related selection, that is, of prioritizing the visual processing of targets over that of distractors. To illustrate top-down control, Figure 11 shows the mean proportion of target letters correctly identified, by patients and controls, separately for conditions with single target letters, targets accompanied by distractors, and targets accompanied by a second target. As the interest here is in a general estimate of top-down control in the whole visual field, averaged values across hemifields are presented.

A)



B)



C)

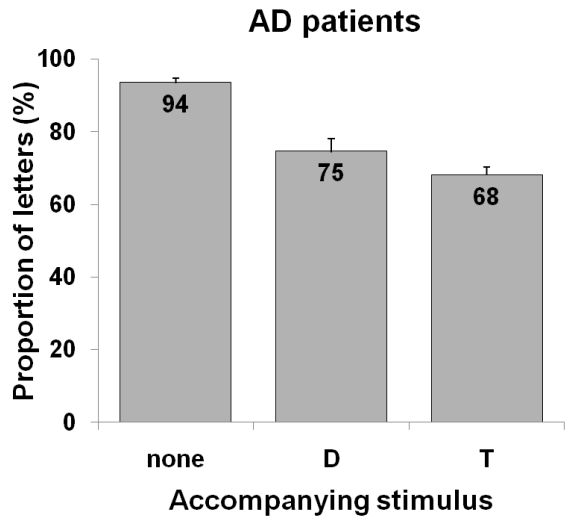


Figure 11: PR: Mean proportion of correctly reported letters (in %) of (A) control subjects, (B) MCI subjects and (C) AD patients in the single target (none), the target + distractor (D), and the target + target (T) conditions across both hemifields
Error bars show standard errors of the mean.

In order to compare the efficiency of top-down controlled selection across the three subject groups, the relative performance in the target plus distractor condition is critical. In normal subjects, performance in this condition nearly equals that for single targets (3% difference) and is clearly higher than that for dual targets (11%). Thus, they efficiently prioritize targets over distractors. In the MCI patients, the accuracy in the distractor condition further approaches that for dual targets (14% difference; in contrast to 11% difference to the single target condition), in contrast to controls. Thus, this group seems to attribute higher attentional weights to irrelevant distractors compared to normal controls. In AD patients finally, accuracy in distractor conditions nearly equals that in dual target conditions (7% difference; in contrast to 19% difference to the single target condition). Therefore, distractors and additional targets interfere with AD patients' performance to a comparable degree, indicative of rather non-selective processing.

As selectivity is reflected in performance on target plus distractor displays compared to the single target condition (baseline), a raw data selectivity index was calculated which equals the ratio of mean accuracy for target plus distractor arrays divided by the mean accuracy for single target displays. The lower this ratio, the lower the relative performance in the target plus distractor condition and, hence, the lower the efficiency of top-down control. An ANOVA was conducted on these raw data selectivity indices, with the single (between-subject) factor Group (controls, MCI and AD patients). The Group effect was highly significant [$F(2, 81) = 21.42$; $p < .01$]. T-tests revealed that controls (M = .97, SD = .05) and MCI patients (M = .88, SD = .10) differed significantly [$t(66) = 4.74$, $p < .01$], as well as MCI and AD patients (M = .80, SD = .14) [$t(46) = 2.31$, $p < .05$]. This staged decrease of the raw data selectivity index value points to a progressive deficit in prioritizing the processing of targets over that of distractors in MCI and, more markedly, AD patients.

5.4.1.2. TVA parameter estimates

From the raw data of the *w* estimates (for more details see chapter 5.3.3.1, p. 71), the parameter efficiency of top-down control α was calculated and compared across subject groups.

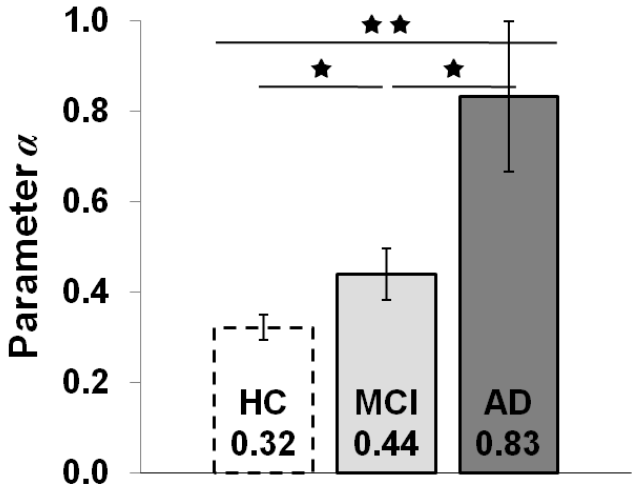


Figure 12: PR: Mean values of parameter top-down control α for healthy controls (HC), MCI and AD patients
Error bars represent standard errors of the mean.

An ANOVA of the parameter efficiency of top-down control α with the between-subject factor Group (MCI, AD, HC) and the within-subject factor Side of Visual Field (left, right) revealed a highly significant effect of Group [$F(2, 81) = 12.37$, $p < .01$]. The main effect of Side and the interaction were not significant [all $p > .25$]. As depicted in Figure 12, post-hoc tests revealed that top-down control was impaired in both, MCI [$t(66) = 1.83$, $p < .05$] and AD patients [$t(50) = 2.97$, $p < .01$], compared to healthy subjects. The decline was staged, i.e. values of AD patients were worse than that of MCI patients [$t(46) = 2.19$, $p < .05$]. Parameter estimates for individual MCI and AD patients are provided in Table 13 (pp. 135 et seqq.).

5.4.2. Spatial weighting and sensory effectiveness

First, visual field differences related to the spatial laterality and imbalance indices of attentional weighting are reported, as well as that of sensory effectiveness across the left and the right hemifields, starting with the presentation of raw data results followed by the parameter estimates.

5.4.2.1. Raw data

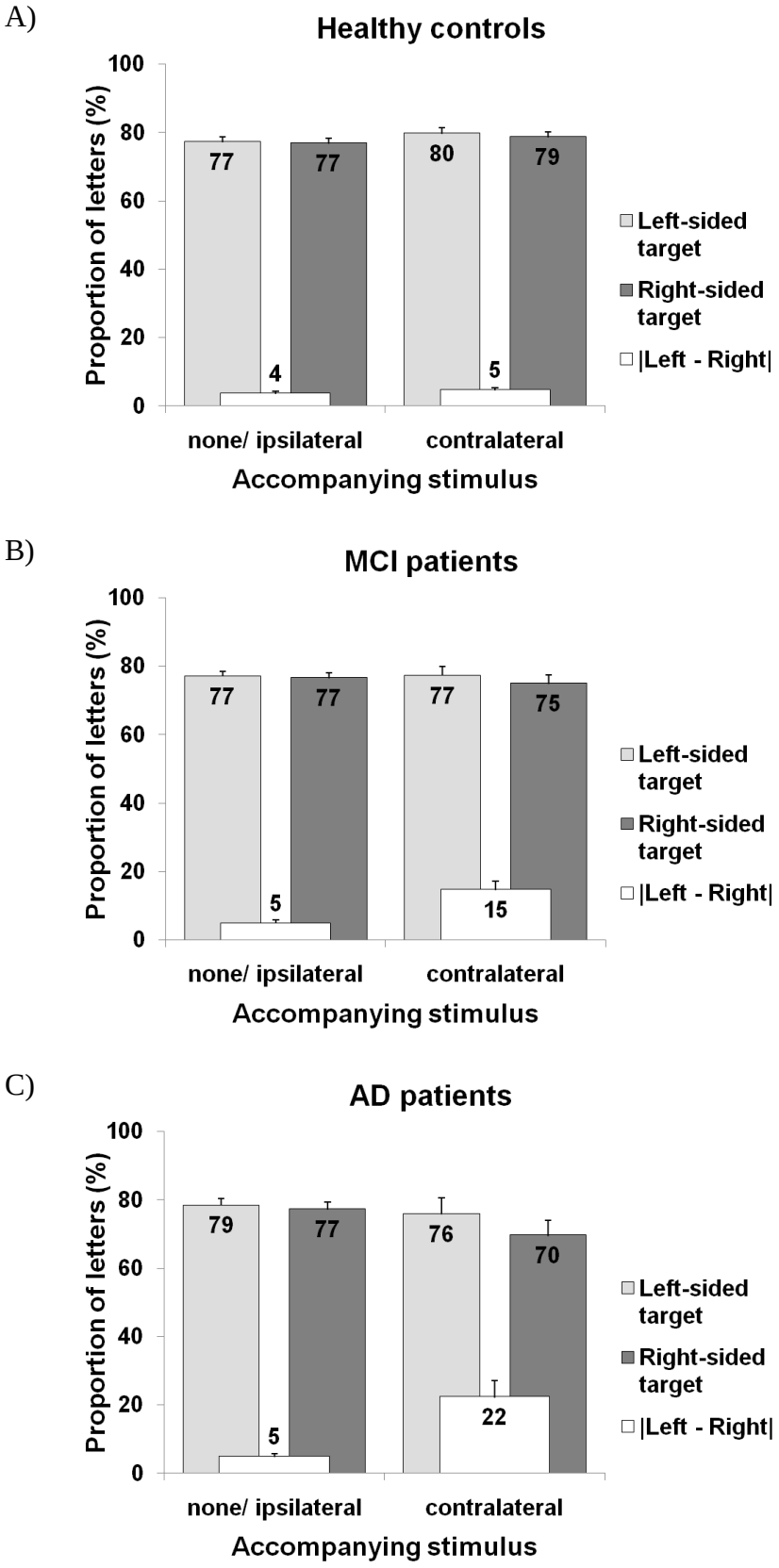


Figure 13: PR: Mean proportion of correctly reported letters (in %) of (A) control subjects, (B) MCI subjects and (C) AD patients in unilateral stimulus conditions (accompanying stimulus: none/ ipsilateral) and bilateral stimulus conditions (contralateral)
The white bars indicate the averaged individual hemifield differences in the respective conditions. Error bars represent standard errors of the mean.

To illustrate attentional weighting and sensory effectiveness across the two hemifields, Figure 13 shows the mean proportion of target letters correctly identified by patients and controls in each hemifield, separately for experimental conditions with unilateral stimuli (average of single targets and targets accompanied by ipsilateral targets or distractors) and bilateral stimuli (average accuracy of targets accompanied by a contralateral stimulus).

Performance for unilateral stimulus conditions was examined to assess the general sensory effectiveness, that is, basic sensory efficiency of visual processing of a single target stimulus at a given exposure duration. In unilateral displays, this basic efficiency is assumed to be *independent* of the spatial attentional weighting across the two hemifields. In the unilateral presentation conditions (none, ipsilateral distractor, ipsilateral target), both controls and patients exhibited only minor hemifield differences, indicating a balanced sensory effectiveness.

The laterality of attentional weighting is a measure of the spatial distribution of attentional weights across the left versus the right visual hemifield. Therefore, the bilateral stimulus conditions with (row) displays containing a stimulus in each hemifield are crucial for the TVA-based estimation of the attentional weighting parameter. In these conditions, spatial attentional weights have to be distributed across the left *and* the right visual hemifield, with the weight allocation determined by a competitive process between the two hemifields. If attentional weights are biased towards one hemifield, performance in the bilateral (compared to the unilateral) target condition will suffer more for a target presented in the hemifield with relatively low attentional weights, compared to a target in the hemifield with high weights. In bilateral presentation conditions, healthy controls showed no obvious hemifield differences. In contrast, MCI patients showed slightly better performance in the left compared to the right hemifield, indicating that objects on the left side received higher attentional weight and affected accuracy for right side stimuli more than vice versa. AD patients showed an even more pronounced leftward bias.

It is worth noting that the standard error of the mean in bilateral conditions was quite large in MCI patients, and even larger in AD patients, compared to healthy subjects, indicating a remarkable variance in performance. In order to examine whether this variance reflects individually enhanced spatial attentional biases either to the left or the right hemifield, the average accuracy differences between the left and the right hemifield, $|accuracy_{left} - accuracy_{right}|$, were computed. These hemifield differences are illustrated, separately for each group and the different conditions, by the white bars in Figure 13. In unilateral conditions, no significant differences between groups were found [$F(2, 81) = 1.11$; $p > .30$]. In bilateral conditions, however, the groups differed significantly [$F(2, 81) = 12.62$; $p < .01$], with enhanced values in MCI [$t(66) = 3.82$; $p < .01$] and AD patients [$t(50) = 3.66$; $p < .01$] compared to controls.

These results suggest that MCI and AD patients suffered from biased spatial attentional weighting (either directed to the left or to the right visual hemifield in the individual patients) in conditions with bilaterally presented stimuli. Since no comparably enhanced visual field differences were revealed in unilateral stimulus conditions, the basic sensory effectiveness of visual processing seemed to be non-lateralized.

5.4.2.2. TVA parameter estimates

Three laterality indices were computed from the raw data of the *A* and *w* estimates (for more details, see chapters 5.3.3.2 and 5.3.3.3, pp. 71 et seq.): the laterality index of sensory effectiveness A_λ, the laterality index of attentional weighting w_λ and the imbalance index of attentional weighting Dev(w_λ). For detailed parameter values in all subject groups, see Table 3. Parameter estimates for individual MCI and AD patients are provided in Table 13 (pp. 135 et seqq.).

Table 3: PR: TVA partial report parameters of MCI and AD patients and controls
See also Table 13 (pp. 135 et seqq.).
A_{left}/ A_{right}: basic sensory effectiveness in the left and right hemifield, respectively; A_λ: laterality index of sensory effectiveness; w_λ: laterality index of attentional weighting; Dev(w_λ): imbalance index of attentional weighting; **: highly significant difference compared to controls ($p < .01$). Values represent mean scores (and standard deviations).

	A_{left}	A_{right}	A_λ	w_λ	Dev(w_λ)
AD	3.08 (.81)	3.05 (1.04)	.51 (.07)	.56 (.19)	.16 (.11)**
MCI	3.20 (1.76)	2.83 (.91)	.52 (.08)	.51 (.14)	.11 (.09)**
Controls	2.79 (.92)	2.68 (.83)	.51 (.05)	.49 (.06)	.05 (.04)

An ANOVA of sensory effectiveness parameters *A*, with the between-subject factor Group (HC, MCI, AD) and the within-subject factor Side of Visual Field (left, right), revealed neither main effect to be significant, Group [$F(2, 81) = .95$, $p > .35$] and Side [$F(1, 81) = 2.00$, $p > .15$], nor the Group x Side interaction [$F(2, 81) = .79$, $p > .45$]. Similarly, the index for the laterality of sensory effectiveness A_λ did not differ significantly between subject groups [$F(2, 81) = .21$; $p > .80$]. Neither the control group's nor the patients' index differed significantly from 0.5, which indicates equal sensory effectiveness on both sides (all $p > .20$).

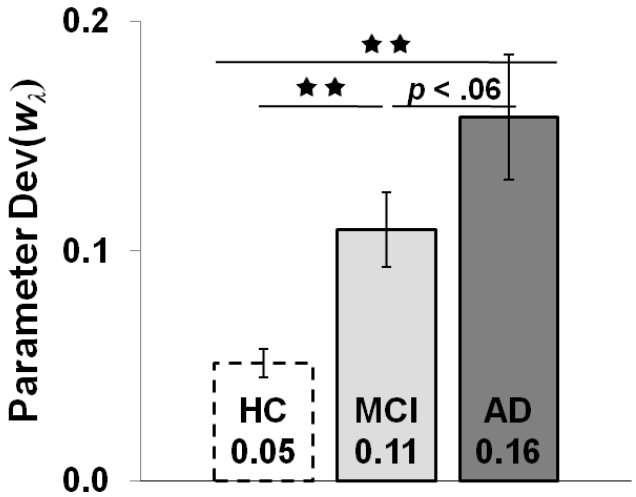


Figure 14: PR: Mean values of the imbalance index of attentional weighting Dev(w_λ) for healthy controls (HC), MCI and AD patients
Error bars show standard errors of the mean.

The parameter laterality of attentional weighting w_λ did not differ significantly among groups [$F(2, 81) = 1.95$; $p > .10$], and none of the group mean values differed significantly from the unbiased value 0.5 (all $p > .15$). These results indicate that there was no specific bias in the sense of a general leftward or rightward preference in the patient groups.

However, a significant group effect was found for the deviation from the optimum value, that is, the imbalance index Dev(w_i) [$F(2, 81) = 11.07$, $p < .01$]. As depicted in Figure 14, post-hoc comparisons revealed highly significant differences between healthy control subjects and both MCI [$t(66) = 3.27$, $p < .01$]) and AD patients [$t(50) = 3.75$, $p < .01$]). Furthermore, AD patients tended to show even more increased values compared to MCI patients [$t(46) = 1.60$, $p < .06$] indicating a more severe imbalance of attention. Thus, rather than suffering from a *directed* imbalance towards one *specific* hemifield, the patients displayed a more general inability to distribute attention across both hemifields, with a preference for the right *or* the left on the level of the single cases.

Based on the range of the imbalance index Dev(w_i) in healthy subjects, the 90th percentile was selected to indicate a pathological spatial imbalance (Dev(w_i) $\geq .11$) in patients. On this criterion, 12 MCI (38%; 7 left, 5 right) and 9 AD patients (56%; 7 left, 2 right) suffered from a pathological imbalance of attentional weights, predominantly directed to the left visual hemifield (67%), though, to a smaller portion, also directed to the right (33%).

In order to rule out probable sensory confounds with the imbalance index Dev(w_i), this index was correlated with the corresponding parameter indicating imbalance of sensory effectiveness Dev(A_i). Non-significant correlations were obtained for all subject groups (controls: $r = -.05$, $p > .75$; MCI: $r = -.17$, $p > .35$; AD: $r = -.02$, $p > .90$). Thus, the pathological imbalance of spatial weighting is not attributable to a more fundamental sensory imbalance.

5.4.3. Parameter inter-correlation

No significant correlation was found between the imbalance index of attentional weighting Dev(w_i) and the efficiency of top-down control α within single groups (all $p > .25$). These results indicate that partial report parameters are independent of each other in healthy controls as well as in both clinical groups.

5.4.4. Relationship of partial report parameters to external clinical measures

Furthermore, the relationship of both partial report parameters, imbalance index of attentional weighting Dev(w_λ) and the efficiency of top-down control α, with external criteria was examined, including age, age at onset and disease duration since estimated symptom onset in both patient groups and across all patients. Neither of these correlations reached significance (all $p > .10$).

5.4.5. Relationship of partial report parameters to measures of cognitive function

Across both clinical groups, 46 MCI and AD patients (clinical indices of two AD patients were not available), Spearman correlations were calculated between the pathological imbalance of spatial attentional weighting Dev(w_λ) and the decreased efficiency of top-down control α, to external clinical criteria, the CERAD battery (total score excluding MMSE; see Chandler et al., 2005), the CDR sum of boxes score, MMSE, and CDT. After correction for multiple comparisons, a significant negative correlation between Dev(w_λ) and the CERAD total score ($r_S = -.34$, $p < .05$) was revealed. Thus, the more pronounced the general cognitive decline, the more severe the inability to pay equal attention to both visual hemifields. In contrast, parameter selectivity of top-down control α was significantly positively related to the CDR score ($r_S = .34$, $p < .05$). This result suggests that the degree of impairment in top-down selection corresponds to the progressive stage of AD severity according to CDR. All other correlations were non-significant.

5.4.6. Effect of ApoE4 genotype

In order to test whether the partial report parameters are related to a possibly underlying gene-associated pathology (as has been found for spatial attentional weighting in Huntington's disease, Finke et al., 2006) the effect of ApoE4 genotype (1-2 allele carriers denoted as $ApoE4^+$ versus $ApoE4^-$) on the parameter values was analyzed.

ApoE4 status was available in 43 patients. For further analyses, the combined patient group was used in order to enhance sample size. The patients were divided into two subgroups, 28 $ApoE4^+$ and 15 $ApoE4^-$ patients. Clinical details are reported in Table 4, separately for each of the groups under study.

Table 4: PR: Clinical characteristics of ApoE4 subgroups
$ApoE4^+$: ApoE4 gene carriers; $ApoE4^-$: ApoE4 non-carriers; AChEI: acetylcholine esterase inhibitors; SSRI: selective serotonin reuptake inhibitors; NaSSA: noradrenergic and specific serotonergic antidepressant; see also Table 2 (p. 67).

	$ApoE4^+$ (n = 28)	**$ApoE4^-$** (n = 15)	***p***
Age, **M (SD), range**	68.4 (6.2) 56.1 – 79.0	68.1 (10.1) 45.9 – 81.5	> .85
Gender (male/ female)	12 / 16	9 / 6	> .25
Education, **M (SD), range**	10.6 (1.9) 9 – 13	10.2 (1.8) 9 – 13	> .45
Diagnosis	18 MCI, 10 AD	11 MCI, 4 AD	> .50
Handedness	all R	all R	
MMSE, **M (SD), range**	25.8 (2.4) 20 – 29	26.5 (2.7) 19 – 30	> .40
CERAD, **M (SD), range**	78.3 (9.1) 54 – 90	78.8 (16.4) 51 – 112	> .90
CDT, **M (SD), range**	2.4 (1.1) 1 – 5	2.3 (1.2) 1 – 4	> .75
CDR sum, **M (SD), range**	2.8 (1.3) 1.0 – 5.0	2.7 (1.3) 1.0 – 5.0	> .75
Age at onset, **M (SD), range**	65.3 (7.1) 53.4 – 76.5	65.2 (9.9) 43.6 – 78.4	> .95
Disease duration, **M (SD), range**	3.1 (2.0) .5 – 8.0	2.9 (1.2) 1.1 – 5.4	> .70
Medication: **Antidementive**	19 AChEI (68%)	13 AChEI (87%)	> .15
Medication: **Antidepressant**	6 SSRI, 1 NaSSA (25%)	1 SSRI, 1 NaSSA, 1 tricyclica (20%)	> .70

$ApoE4^+$ and $ApoE4^-$ subgroups were matched with regard to all variables listed in Table 4 (all $p > .15$). A trend-level difference between ApoE4 subgroups was revealed with regard to the spatial laterality index of attention w_λ [$t(41) = 1.62$, $p < .06$]. A significant deviation from the optimal unbiased w_λ value 0.5 was only present in $ApoE4^+$ patients [$t(27) = 2.61$, $p < .01$], in-

dicating a pathological leftward spatial bias in contrast to the balanced distribution of attention in ApoE4$^-$ patients [$t(14) = .31$, $p > .75$] (see Figure 15).

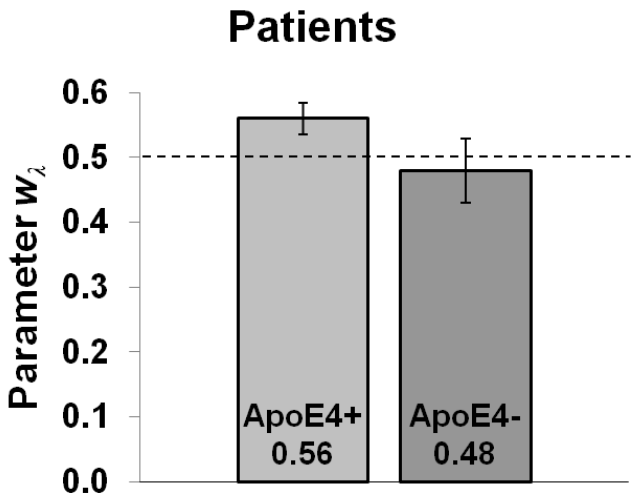


Figure 15: PR: Effect of ApoE4 genotype (ApoE4$^+$: gene carrier; ApoE4$^-$: non-carrier) on parameter laterality of attentional weighting w_λ in a combined group of MCI and AD patients
The dashed line represents the unbiased w_λ value 0.5. Error bars indicate standard errors of the mean.

As can be seen from Figure 16, age and the spatial laterality index of attention w_λ were significantly correlated in ApoE4$^+$ patients (n = 27, $r = -.33$, $p < .05$) and a trend level correlation was found between parameter w_λ and disease onset ($r = -.30$, $p < .07$). These correlations indicate that ApoE4$^+$ patients with an early onset show a more pronounced leftward spatial bias. This result was revealed after the exclusion of one outlier value (3 standard deviations above mean) produced by MCI patient AW ($w_\lambda = .13$).

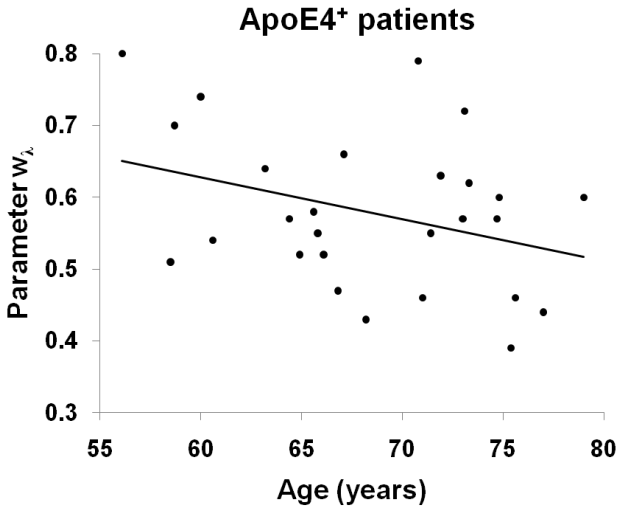


Figure 16: PR: Scatterplot relating the spatial laterality index of attentional weighting w_λ to age in ApoE4$^+$ patients

5.5. Discussion

The aim of the present study was to investigate the functions of spatial and task-related attentional weighting by means of a partial report task based on Bundesen's (1990) theory of visual attention (TVA) in amnestic MCI and probable AD patients compared to a healthy elderly control group. The partial report task required the verbal report of briefly presented target letters (and to-be-ignored distractors) and allowed the derivation of two independent quantitative parameter estimates from the qualitative performance pattern: task-related efficiency of top-down control α and spatial imbalance of attentional weighting Dev(w_λ). MCI and AD patients were impaired in both attentional functions compared to healthy controls. Early deficits of both parameters α and Dev(w_λ) at the MCI stage further deteriorated at the stage of AD. In apolipoprotein E ε4 allele (ApoE4) carriers, earlier disease onset was associated with a more pronounced leftward spatial bias w_λ.

Thus far, to my knowledge, there have been no reports of both spatial and task-related aspects of visual attentional weighting in MCI as well as AD patients, although it is widely accepted that early AD is marked by visuospatial (Parasuraman et al., 2002) and executive deficits (Perry & Hodges, 1999).

The imbalance index of attentional weighting Dev(w_λ) and the efficiency of top-down control α were uncorrelated for each group, indicating that these indices represent distinct attentional deficiencies with possibly different underlying neuropathological mechanisms. In support of this, Bublak et al. (2005), who employed the same partial report task, observed the following double dissociation: One patient with a right inferior parietal lesion suffered from impaired laterality of attentional weighting w_λ, while efficiency of top-down control α was intact. The second patient with a superior frontal brain lesion displayed the reverse pattern, with impaired top-down control and balanced spatial weighting.

5.5.1. Impairments in task-related weighting

Frontal lobe pathology is generally not seen in the early stages of AD (Braak & Braak, 1990; Braak et al., 1993; Whitwell et al., 2007). However, it has been repeatedly suggested that the frontal lobes might be functionally disconnected from other relevant extrastriate, parietal and hippocampal areas (see review by Delbeuck, Van der Linden, & Collette, 2003; Grady et al., 2001; Sorg et al., 2007). Correspondingly, a number of studies suggest that impairment in top-down processing might be even a very early feature in the course of AD (Azari et al., 1992; Perry & Hodges, 1999). The results of the present study were in line with this assumption. The task-related selection, that is, the efficiency of top-down control α, was impaired early at the MCI stage and deteriorated further in the later stages of disease progression.

Neuropathology in AD is mainly characterized by neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are prevailing in associative areas, that is, the parietal and frontal lobes, and in large cortical neurons mediating cortico-cortical connections (Pearson et al., 1985), while neuritic plaques seem to accumulate at the ends of cortico-cortical tracts (De Lacoste & White, 1993). Both pathological markers give rise to a selectively distributed neocortical disconnection syndrome in AD (Delbeuck et al., 2003; Sorg et al., 2009), disrupting, among others, functional connectivity between frontal and parietal cortices in AD (Azari et al., 1992; Horwitz et al., 1987). The diminished anterior-posterior connectivity in AD was corroborated by Collette et al. (2002), who examined inhibitory processing and selective attention in AD patients with either parietal and temporal hypometabolism or with additionally reduced metabolism in frontal areas. Both AD groups were impaired in all executive tasks, irrespective of the presence or absence of frontal lobe hypometabolism. Consequently, executive impairments in AD seem to be predominantly caused by disruptions of the fronto-parietal attention network, rather than frontal lobe dysfunction, and therefore might occur early, that is, at the MCI stage of the disease. At the later AD stage, increasing burden of neuritic plaques and neurofibrillary tangles cause substantial loss of neuronal cell assemblies in parietal

and frontal cortex (Braak & Braak, 1990, 1991; Whitwell et al., 2007), which is in accordance with further deterioration of top-down control selectivity in AD compared to MCI patients. By using a comparable TVA partial report task, Peers et al. (2005) revealed that, in patients with frontal lobe lesions, deficits in the efficiency of top-down control α were predicted by lesion volume. Consequently, the staged decline of efficiency of top-down control α, as revealed in the present study, might result from early cortico-cortical disconnection in the fronto-parietal attention network at the MCI stage and a later additional loss of nerve cells in corresponding association areas at the stage of AD.

5.5.2. Impairments in spatial weighting

In the current clinical samples, a pathological spatial deviation of attention Dev(w_λ) to either hemifield was obtained in both MCI and AD patients, although the patients' performance was absolutely balanced across both hemifields in unilateral stimulus conditions. Any unilateral right- or left-sided sensory loss was excluded by a balanced laterality index of sensory effectiveness A_λ across the left and right visual hemifield and non-significant correlations between imbalance of attentional weighting Dev(w_λ) and the corresponding imbalance index of sensory effectiveness Dev(A_λ) in all subject groups. Additionally, the spatial bias exhibited by the clinical groups in this study is also not attributable to an inability to maintain central fixation during the partial report task. Any systematic gaze deviation to either hemifield would have resulted in higher accuracy and enhanced values of sensory effectiveness of visual processing for one or the other hemifield and would, thus, have affected the absolute accuracy differences between the left and the right hemifield in unilateral conditions as well as the laterality index of sensory effectiveness A_λ.

Significant accuracy asymmetries in patients were present in bilateral presentation conditions only, which accords with the view that visual extinction is at the basis of the patients' visuospatial bias, a symptom mainly found in unilaterally brain damaged patients. Extinction is defined as the inability to process a stimulus in the right visual hemifield in presence of another

stimulus in the left hemispace, or vice versa, despite preserved visual sensory processing (Driver & Vuilleumier, 2001). In manifest neglect, the patient would be completely unaware of all stimuli presented in the contralesional hemifield.

These findings are consistent with the assumption that parietal lobe degeneration in AD is bilateral on the one hand (Braak & Braak, 1990), however, probably also not absolutely balanced in individual patient's brains. Neural degeneration in AD might be slightly intensified in the left compared to the right hemisphere, as indicated by various measures of brain activity (Desgranges et al., 1998; O'Brien et al., 1992; Volkow et al., 2002) and pre- (Thompson et al., 2003; Ueyama et al., 1994) and post-mortem (Li et al., 2000) brain volume measurements. Accordingly, Bartolomeo et al. (1998) and Venneri et al. (1998) reported visual spatial neglect of the right hemifield in single cases with cortical atrophy and hypoperfusion predominantly in the left posterior regions. However, leftward neglect in patients with predominantly right-hemispheric degeneration has also been reported (Ishiai et al., 2000; Mendez et al., 1997; Venneri et al., 1998). Group studies (Bublak et al., 2006; Ishiai et al., 2000; Maruff, Malone, & Currie, 1995; Meguro et al., 2001; Mendez et al., 1997) found left- or right-sided spatial bias in line bisection, reaction times, discrimination and visual search tasks in up to 75% of AD patients. Since potential lateralizations at the early MCI stage of the disease are presumably even more subtle than those in the later AD phase, highly sensitive, experimentally-based, paradigms are needed to reveal small but indicative deficits. The present TVA-based partial report results resembled these findings even at the early stage of the disease, since in 38% of MCI and 56% of AD patients a pathological spatial bias prevailed. About 2/3 of these patients showed leftward spatial lateralization and about 1/3 a spatial bias towards the right visual field.

Although AD does often not lead to clinically manifest hemineglect symptoms according to a classical test of figure copying, visual search paradigms using picture material can reveal hemispatial omissions in the majority of patients (i.e. Meguro et al., 2001). In this study, AD pa-

tients' enhanced rightward omissions were correlated with lower parietal cerebral blood flow (CBF), as measured with single photon emission computed tomography (SPECT), in the left hemisphere compared to the right, and patients with predominantly leftward omissions showed the opposite CBF pattern. Accordingly, it is feasible that in the current clinical groups the present pathological laterality of spatial attention w_λ might be associated with and result from an underlying interhemispheric imbalance in (temporo-)parietal cortical interactions in such a way that a more pronounced leftward spatial bias would be associated with distinct leftward parietal impairment and vice versa. Further imaging (e.g., positron emission tomography, PET) studies are necessary to investigate this issue. The staged increase in pathological spatial bias from MCI to AD patients in this study might result from an early imbalance in parietal cortical interactions and, at the later AD stage, additional parietal degeneration through neuronal loss. Support for the latter assumption is provided by a TVA-based partial report study by Peers et al. (2005). In this study, patients with parietal lobe lesions revealed a lateral spatial bias, which was associated with lesion volume.

5.5.3. Effect of ApoE4 genotype

One major influence on spatial attention in AD might stem from genetic influences. This is suggested by findings in several fluoro-deoxy-glucose PET (FDG-PET) studies in healthy subjects (Reiman et al., 1996; Small et al., 2000; Small, Mazziotta et al., 1995) as well as MCI and AD patients (Mosconi et al., 2005; Mosconi, Nacmias et al., 2004; Mosconi, Perani et al., 2004), which showed that the dose of ApoE4 allele influences the typical age-related decline in parietal, temporal and posterior cingulate cerebral glucose metabolism progresses. Healthy monozygous ApoE4$^+$ subjects with subjective memory impairments (Small, La Rue et al., 1995) as well as homozygous ApoE4$^+$ subjects without memory complaints (Reiman et al., 1996) were found to display significantly lower parietal metabolism compared to ApoE4$^-$ subjects and a significantly enhanced parietal asymmetry with a more pronounced hypometabolism in the left hemisphere. Furthermore, in healthy subjects at genetic risk, lower baseline

metabolism in left posterior cingulate, inferior parietal and lateral temporal regions predicted the greatest portion of metabolic decline after two years (Small et al., 2000). Interestingly, using an identical partial report paradigm, Finke et al. (2006) had found a close relationship between the severity of the underlying gene-associated pathology in the neurodegenerative Huntington's disease and the degree of leftward spatial attention. In the present study, the findings of Finke et al. (2006) could be replicated in a combined clinical group of MCI and AD patients, suggesting more pronounced leftward spatial bias in ApoE4^{+} patients with earlier disease onset. The correlation was lower in the present study, which is most probably related to the deeper impact of the underlying gene-associated pathology in Huntington's disease. Since interactive effects of ApoE4 genotype and (onset) age have been documented (Mosconi et al., 2005; Mosconi, Sorbi et al., 2004), it would be important to examine systematically, in larger samples, whether distinct effects of ApoE4 genotype in patients with early and with late (onset) age would be found on, for instance, the parameter laterality of attention w_{λ}.

5.5.4. Limitations of the study

As a cross-sectional study design was used, neither conclusions on the predictive value of one or both partial report parameters can be drawn with regard to conversion from MCI to AD nor on the course of partial report parameters in the individual progression of AD. Therefore, this survey needs to be complemented by longitudinal studies.

5.5.5. Conclusions

The TVA-based partial report task proved to be a sensitive tool for assessing selective visual attention already at an early stage of the progression to AD. Both, deficits in task-related selection and a pathological attentional imbalance, are already present at the early MCI stage, besides the presence of memory impairments, and they increase further at a more advanced stage of the disease. These findings are compatible with the hypotheses that early impairments in task-related and spatial weighting result from a disconnection syndrome and an interhemis-

pheric imbalance in cortical interactions, respectively, in the fronto-parietal attention network. At later stages, gradual neuronal loss causes further decline in selective attentional and intellectual functions. The present results point to the efficiency of top-down control and to the spatial imbalance of visual attention as potential early cognitive markers. Both attentional parameters can be taken into account as sensitive measures of neuronal dysfunction prior to cell decline. The fact that the pathological spatial imbalance of attentional weighting was associated with the presence of ApoE4 and early disease onset, may even determine the partial report procedure as efficient diagnostic tool for early identification of subjects at risk for AD.

6. Study 3: Spatial weighting and interhemispheric metabolic imbalance across MCI and AD

In the third study, the relationship of the spatial distribution of attentional weights across the left and right hemifield was analyzed with regard to interhemispheric metabolic imbalances as measured by ^{18}Fluoro-deoxy-glucose positron emission tomography (FDG-PET) in temporo-parietal cortices (TPJ, temporo-parietal junction) in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD).

6.1. Abstract

In mild to moderate Alzheimer's disease (AD), deficits of visuospatial attention and task-related selection are well established. Furthermore, the partial report paradigm based on the theory of visual attention (TVA) proved to be a sensitive tool for verifying that both, deficits in task-related selection and a pathological attentional imbalance, are already present at the early amnestic stage of mild cognitive impairment (MCI) and increase further at the AD stage (see second study, chapter 5, pp. 60 et seqq.). It was hypothesized that these deficiencies in selective attention may result from an early disconnection syndrome and an interhemispheric imbalance in cortical interactions, respectively, in the fronto-parietal attention network, before gradual neuronal loss leads to further decline in selective attentional and intellectual functions at later stages.

In the present study, these hypotheses were tested by investigating the relationship of both partial report parameters, top-down control α and especially the laterality index of attentional weighting w_λ, to regional glucose metabolism measured by resting-state positron emission tomography (PET) in a sample of 30 amnestic MCI or mild AD patients.

Hypometabolism across all patients was slightly increased in the left hemisphere. Interestingly, the more reduced the metabolism in the left temporo-parietal junction (TPJ) the more pronounced was the top-down control deficit. Accordingly, hypometabolism in the left TPJ together with the left inferior parietal lobe (IPL) predicted the magnitude of the spatial bias.

Furthermore, relative hypometabolism in the left TPJ and left IPL as compared to the right TPJ and right IPL, respectively, was correlated with direction and degree of spatial bias.

Taken together, PET imaging results support the hypotheses that, one the one hand, early deficits in task-related weighting may result from a fronto-parietal disconnection syndrome already at the stage of MCI. On the other hand, very early AD seems to be also associated with an interhemispheric imbalance of metabolism, particularly in the temporo-parietal cortices, resulting in a correspondingly directed and distinctive visuo-spatial attentional bias.

6.2. Introduction and aim of the study

In the latter study (see chapter 5, pp. 60 et seqq.), functions of spatial and task-related attentional weighting were assessed by means of a partial report task based on Bundesen's (1990) theory of visual attention (TVA) in amnestic mild cognitive impairment (MCI) and probable Alzheimer's disease (AD) patients compared to healthy elderly controls. The TVA-based partial report task proved to be a sensitive tool for assessing selective visual attention already at an early stage of the progression to AD. The findings of the latter study corroborated that patients in the early stage of MCI were impaired in both, task-related efficiency of top-down control α and spatial imbalance of attentional weighting Dev(w_i) compared to control subjects. Thus, on the one hand, MCI subjects were impaired in their ability to prioritize prespecified target letters over task-irrelevant distractor letters. On the other hand, in MCI patients, a pathological spatial imbalance of attention towards either hemifield was revealed. Compared to healthy controls, most of these patients suffered from a pathological spatial bias directed to the left visual hemifield, though a smaller portion of patients showed a rightward spatial lateralization.

The findings in view of parameter top-down control α are compatible with the hypothesis that early impairments in task-related weighting might result from a cortico-cortical disconnection syndrome (see e.g. Delbeuck et al., 2003; Sorg et al., 2009) in the fronto-parietal attention

network, which was corroborated by a ^{18}fluoro-deoxy-glucose positron emission tomography (^{18}FDG-PET) study by Collette et al. (2002). In this study, AD patients with either parietal and temporal hypometabolism or with additionally reduced metabolism in frontal areas were impaired in various executive tasks, irrespective of the presence or absence of frontal lobe hypometabolism. As a result, cortico-cortical disconnectivity between frontal and parietal cortices might be at the bottom of deficits in top-down controlled selection (see chapter 5.5.1, pp. 87 et seq., for a detailed discussion). As a consequence, the first aim of the third study was to investigate whether the TVA-based assessment in combination with resting-state ^{18}FDG-PET would reveal evidence for a functional disconnection syndrome between frontal and parietal cortices in early AD.

The second and main goal of the present study was derived from the finding that already MCI patients suffered from impaired spatial allocation of attentional weights which was interpreted as being probably caused by an interhemispheric (temporo-)parietal imbalance in cortical interactions. In line with this hypothesis are findings of a visual search study by Meguro et al. (2001), revealing that AD patients' enhanced rightward omissions were correlated with lower parietal cerebral blood flow (CBF) in the left hemisphere compared to the right, and vice versa. The fact that temporo-parietal hypometabolism is a main indicator of AD (see e.g. review by Mosconi, 2005) supported the view of parameter laterality of attentional weighting w_λ as potentially early cognitive marker of subjects at risk for AD. In this study, a more pronounced leftward spatial bias was expected to be associated with relative left-hemispheric hypometabolism in (temporo-)parietal cortex compared to the metabolic rate in homologous right-hemispheric regions and vice versa. For a more thorough discussion and detailed argumentation, see chapter 5.5.2 (pp. 88 et seqq.).

Thus, the present study expands the investigation of the previously presented second study of this dissertation (see chapter 5, pp. 60 et seqq.) by relating TVA parameters for spatial and task-related attentional selection to ^{18}FDG-PET imaging data. The TVA-based partial report

paradigm (and whole report paradigm) was applied in patients who were predominantly diagnosed with amnestic MCI – only some patients were diagnosed with probable AD – in order to be able to account for behavioral-metabolic coherences in early AD.

6.3. Method

6.3.1. Subjects

A subgroup of those patients who participated in the second study (for details on diagnostic assessment, exclusion and diagnostic criteria, see chapter 5.3.1, pp. 65 et seq.) took part in this third study because only individuals of the original sample underwent FDG-PET imaging, resulting in 23 MCI and 7 AD patients (11 male, 19 female; mean age 67.5 years; mean education 10.3 years; all right-handed). The patient sample was supposed to represent early AD because the majority (77%) consisted of MCI patients. None of the MCI patients was medicated with antidementives, but 6 AD patients were treated with acetylcholine esterase inhibitors (AChEI). Due to mild symptoms of depression, 8 MCI patients and 1 AD patient received antidepressant medication. Furthermore, 1 MCI patient suffered from diabetes mellitus, 5 MCI and 2 AD patients received antihypertensive medication.

The age, gender and education matched control group for the TVA-based (whole and) partial report assessment was identical to the group of control subjects assessed for the second study and consisted of 36 healthy older subjects (16 male, 20 female; mean age 67.2 years; mean education 10.5 years; all right-handed). All control subjects were neurologically and psychiatrically healthy, were not medicated and had no cognitive symptoms. All subjects had normal or corrected-to-normal vision. Patients and control subjects did not differ significantly from each other with regard to Age [$F(1, 65) = .04$, $p > .80$], Education [$F(1, 65) = .08$, $p > .75$] or Gender [$\chi^2(1) = .41$, $p > .50$]. Further biographical and clinical information of each subject group is listed in Table 5 (for demographic details of individual MCI and AD subjects, see Table 14, p. 138).

Table 5: TVA-PET: Overview of biographical and clinical details across MCI and AD patients and healthy controls

See also Table 14 (p. 138).

CDR: Clinical Dementia Rating Scale, global score (Morris, 1993); *p*: level of significance; M (SD): mean score and standard deviation; Age in years; Education in years; Handedness: according to the Edinburgh Handedness Inventory (Oldfield, 1971); R: right-hander; MMSE: Mini Mental State Examination (Folstein et al., 1975), 30-0 points, cut-off ≤ 23; CERAD: The Consortium to Establish a Registry for Alzheimer's Disease (Thalmann & Monsch, 1997), total score; n.a.: not applied; CDT: Clock Drawing Test, 0-6 points, cut-off ≥ 3 (Shulman et al., 1986); CDR sum: sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4: apolipoprotein E4 genotype, positive (+), negative (-).

	MCI and AD (n = 30, CDR ≥ .5)	**Control (n = 36)**	***p***
Age, M (SD), range	67.5 (7.9) 45.9 – 79.9	67.2 (6.6) 50.0 – 82.0	> .80
Gender (male/ female)	11 / 19	16 / 20	> .50
Education, M (SD), range	10.3 (1.8) 9 – 13	10.5 (2.1) 7 – 13	> .75
Handedness	all R	all R	
MMSE, M (SD), range	26.2 (2.4) 20 – 30	29.0 (1.0) 27 – 30	**< .01**
CERAD, M (SD), range	81.1 (11.5) 54 – 112	n.a.	
CDT, M (SD), range	2.4 (1.1) 1 – 5	n.a.	
CDR sum, M (SD), range	2.6 (1.1) 1.0 – 5.0	n.a.	
Age at onset, M (SD), range	64.7 (8.3) 52.1 – 76.8	-	
Disease duration, M (SD), range	2.8 (1.6) 0.5 – 7.8	-	
ApoE4 genotype	19 +/ 8 -/ 3 n.a.	n.a.	

All participants gave informed consent to taking part in the TVA-based assessment and resting-state ^{18}FDG-PET. The ethics committee of the Technical University of Munich and the radiation protection authorities approved the study protocol. The TVA procedure and the PET acquisition were performed within an interval of a few days.

For the comparison of patient baseline PET data with an age-matched control group a pre-existing PET database of 23 healthy volunteers was applied. This group had been acquired previously for clinical and scientific purposes in the dementia research unit and consisted of subjects without cognitive symptoms, neurological, psychiatric, or systemic diseases. The ethics committee of the Technical University of Munich and the radiation protection authorities

approved the PET protocol for the healthy control group. PET examinations of the control group had been performed following the identical protocol as for the patient group.

6.3.2. Whole and partial report paradigm

Please note that the TVA-based whole report paradigm was primarily applied in order to control for possible non-lateralized influences of distinct components of processing capacity on aspects of both, task-related and spatial weighting. Task, procedure, stimuli and apparatus of the whole report assessment were identical to the testing in the first study described in this dissertation (see chapter 4.3.2, pp. 39 et seqq.). The average "short" presentation time used in the whole report paradigm was M = 167 ms (SD = 58) across MCI and AD patients and M = 135 ms (SD = 29) for healthy control subjects. "Intermediate" presentation times were on average M = 325 ms (SD = 120) across MCI and AD patients, and M = 265 ms (SD = 58) for healthy subjects. And "long" presentation times were M = 618 ms (SD = 191) across MCI and AD patients, and M = 528 ms (SD = 188) for healthy subjects. Individual exposure durations for the combined patient group and control subjects are listed in Table 15 (p. 139).

The main focus of this study was the partial report assessment which was identical to the examination in the second study (see chapter 5.3.2, pp. 68 et seqq.). A mean exposure duration of 360 ms (SD = 138) was used across MCI and AD patients, of 200 ms (SD = 69) for control subjects. Exposure durations of individual subjects are listed in Table 15 (p. 139).

6.3.3. Estimation of TVA-based parameters

Parameter estimates derived from the whole report, perceptual processing speed *C* and VSTM storage capacity *K*, were computed as presented in the first study (see chapter 4.3.3, pp. 42 et seq.). The estimation of the partial report parameters top-down control α, characterizing task-related weighting for prioritizing relevant visual objects for processing, and the spatial distribution of attentional weighting w_λ across the left and right visual hemifield were conducted as described in the second study (see chapter 5.3.3, pp. 70 et seqq.).

6.3.4. ^{18}FDG-PET measurement

^{18}FDG-PET was used for data assessment in MCI and AD patients. An age-matched control group of healthy volunteers was composed of a pre-existing PET database.

6.3.4.1. Between-group and between-hemisphere comparisons

Images were acquired on a Siemens 951 R/31 PET scanner. For all patients, PET imaging began 30 minutes after injection of an intravenous bolus of 370 Megabecquerel (MBq) of ^{18}FDG. Subjects were positioned with the head parallel to the canthomeatal line within the gantry. During data acquisition, patients were at rest with their eyes closed. Three frames of ten-minute duration were acquired and averaged to a single frame. Image data were acquired in 2-dimensional mode with a total axial field of view of 10.5 cm and no inter-plane gap space. Attenuation correction was performed by a standard ellipse-fitting method. Details of the imaging procedure can be found in a report by Drzezga et al. (2005). Images were normalized to a standard template in Montreal Neurological Institute (MNI) space using a non-linear algorithm implemented in Statistical Parametric Mapping (SPM) 5 (http://www.fil.ion.ucl.ac.uk/spm/) and smoothed using a 12x12x12 mm^3 Gaussian kernel. Individual global counts were proportionally scaled to a mean value of 50 mg/ 100 ml/ min. The smoothed images were further analyzed within the framework of the general linear model (Friston et al., 1995).

In a first step, global effects of the presence of amnestic MCI and AD on glucose metabolism were investigated by comparing PET images from the combined patient group with images of 23 healthy age-matched controls. A two-sample Student's t-test on each voxel was performed, accepting differences that passed a threshold of $p < .01$, false-discovery-rate-corrected (FDR-corrected) for multiple comparisons, as significant. Regions differing between the groups were supposed to be those most affected by disease progression and expected any effects of clinical scores to be found within these areas. This was done mainly to ensure that the sample in this study was representative of MCI and AD in general.

Further, a group-level map of disease-mediated interhemispheric asymmetry was created. In order to be able to compare homologous structures in both hemispheres, PET images needed to be adjusted to make them symmetrical across the central commissure. For this purpose, all patients' images (which had previously been normalized to MNI space) were averaged to create a patient-specific template and averaged this template with a duplicate that had been flipped across the y-z-plane to make it symmetrical. The patients' and controls' native images were then normalized to this symmetrical template, effectively creating symmetrical images that still retained individual variations in metabolism. Again, a two-sample Student's t-test was used to find regions of significant hypometabolism (at $p < .01$, FDR-corrected, and a minimum of 200 contiguous voxels) in patients compared to controls. These hypometabolic areas were used as a mask within which to search for disease-related interhemispheric metabolic asymmetry. To test for these imbalances in metabolism, a duplicate of each image was created that was then flipped along the y-z-plane and subtracted the original image from its flipped duplicate, yielding images of metabolic difference across hemispheres. Using these images, a one-sample t-test was performed on each voxel to find unbalanced regions (at $p \leq .05$, FDR-corrected, and 50 contiguous voxels).

6.3.4.2. Multiple regression model of PET-based measurements onto TVA parameters

As the next step, a multiple regression model of TVA parameters onto PET images was created. Although at least four main parameters (laterality of attention weighting w_λ, top-down control α, perceptual processing speed C and visual short-term memory (VSTM) storage capacity K) can be derived from the TVA-based whole and partial report paradigms, the main interest was taken in the laterality index of attentional weighting w_λ, which was expected to be related to hypometabolism in temporo-parietal regions (see Meguro et al., 2001). In addition, it was analyzed whether top-down control α might be predominantly associated with metabolism in temporo-parietal cortex, besides frontal areas (see Collette et al., 2002; Delbeuck et al., 2003).

Since the measure of spatial laterality of attention w_λ ought to be used with as few confounds from other factors as possible, the contribution of the parameters processing speed *C*, VSTM storage capacity *K* and top-down control α to parameter w_λ were extracted by using Gram-Schmidt orthogonalization, yielding four orthogonal TVA regressors. Analogous procedures were executed with regard to parameter top-down control α. The participants' age was used as covariate of no interest. The hypothesis focused on the relationship between parameter w_λ and metabolism in four homologous left and right temporo-parietal regions putatively related to impairments in spatial attention: the angular and supramarginal gyri of the parietal cortex (Ang-SMG) as well as the posterior middle temporal gyrus (pMTG) as representatives of the temporo-parietal junction (TPJ), along with the inferior parietal lobule (IPL) and the superior parietal lobule (SPL). TPJ was separated into two regions of interest (ROIs) to get more spatially specific results. Initially, analyses were restricted to these regions by anatomically defining ROIs using the Automated Anatomical Labeling (AAL) tool (Tzourio-Mazoyer et al., 2002). Additionally, a whole-brain analysis was used to look for correlations outside of the ROIs defined in this study. Please note that whole-brain analyses were not corrected for multiple comparisons ($p < .001$, cluster threshold: minimum of 50 contiguous voxels). Consequently, a larger alpha error (i.e. $p > .05$) cannot be excluded. Therefore, correlations revealed by whole-brain analyses might not be considered as rigorous and straight compared to ROI results.

Next, in order to further evaluate the contribution of spatially non-lateralized attention mechanisms, analogous analyses were performed for the remaining TVA parameters perceptual processing speed *C*, VSTM storage capacity *K*, and top-down control α.

6.3.4.3. Metabolic laterality index

Finally, to test the hypothesis that it is the relative hypometabolism of one brain structure compared to its contralateral homologue, rather than metabolism of that single brain structure, which causes spatial lateralization towards one or the other hemifield, mean values from the

four ROIs in both hemispheres were extracted. For each ROI, a metabolic laterality index was created by dividing average metabolism in the right ROI by the sum of metabolism in left and right homologous ROIs, i.e. using the formula $\text{ROI laterality index} = \frac{\text{right ROI metabolism}}{\text{right ROI metabolism} + \text{left ROI hypometabolism}}$. Then, it was checked up on significant relations between the ROI indices and the partial report laterality parameter of attentional weighting w_λ, using Pearson's correlations. To test whether the laterality parameter w_λ is related to imbalanced metabolism in the visual system, the same procedure was performed for primary visual areas along the calcarine sulcus, again as derived from the AAL tool.

6.4. Results

This chapter is divided in three sections, the first describing the results on pathological hypometabolism across MCI and AD patients, the second presenting results on task-related weighting and the third on spatial weighting in relation to PET metabolism. Subsequently, the inter-correlations of the main four TVA parameters (w_λ, α, C and K) and relevant metabolic laterality indices are reported for patients and healthy subjects.

6.4.1. AD-typical hypometabolism across MCI and AD patients

Regions of significant hypometabolism across MCI and AD patients compared to the normal controls' PET images are shown in Figure 17.

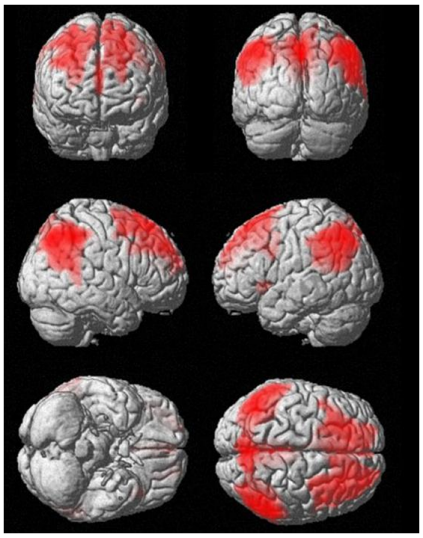


Figure 17: TVA+PET: Regions of significant hypometabolism across MCI and AD patients as compared to healthy controls
$p < 0.01$, FDR-corrected, cluster threshold: minimum of 200 contiguous voxels;

Patients showed bilaterally distributed hypometabolism centered on posterior cingulate gyrus/ precuneus (largest group differences), lateral superior parietal lobes, dorsolateral frontal lobes and anterior cingulate cortex.

6.4.2. Task-related weighting and frontal/ temporo-parietal hypometabolism

Parameter top-down control α was negatively correlated with ROI-metabolism in the left Ang-SMG and the left pMTG, indicating reduced top-down controlled selection with diminished metabolism in left TPJ (see Figure 18 A).

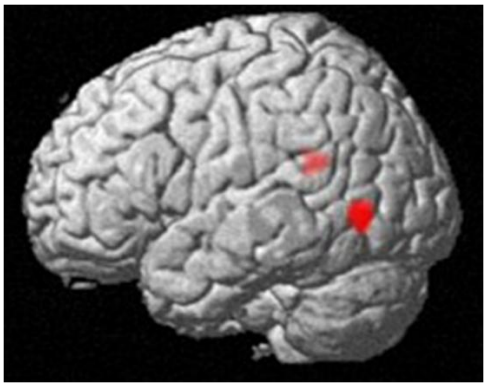
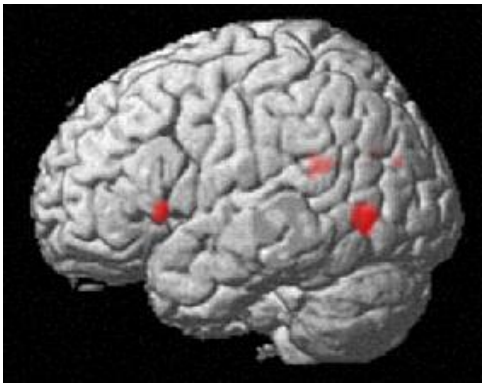
A)  B) 

Figure 18: TVA+PET: Left-hemispheric hypometabolic regions showing a negative correlation (A) in the ROI and (B) in the whole-brain analysis with parameter top-down control α across MCI and AD patients
Whole-brain analysis: $p < 0.001$, uncorrected, cluster threshold: minimum of 50 contiguous voxels;

Whole-brain analyses with a more liberal threshold were conducted to avoid excluding potentially relevant regions and revealed the same left posterior maxima of correlation with para-

meter α, as in the ROI analysis with further maxima found in the left inferior frontal cortex and the left precuneus (see Figure 18 B). The more reduced left-hemispheric metabolism in TPJ, inferior frontal lobe and precuneus, the more impaired was top-down control α.

6.4.3. Spatial weighting and temporo-parietal hypometabolism

A significant group effect was found for parameter laterality of attentional weighting w_λ [$t(64) = 2.83$, $p < .01$]. Across MCI and AD patients (M = .55, SD = .11), parameter w_λ deviated significantly from the optimal unbiased w_λ value 0.5 [$t(29) = 2.46$, $p < .05$], indicating a pathological leftward spatial bias. In contrast, healthy controls (M = .49, SD = .06) showed balanced spatial weighting [$t(35) = 1.40$, $p > .15$]. The laterality index of sensory effectiveness A_λ in the patient group (M = .52, SD = .08) did not differ significantly from the value 0.5 [$t(29) = 1.40$, $p > .15$], which indicates equal sensory effectiveness on both sides of the visual field. Therefore, the pathological spatial bias w_λ in the clinical group is not attributable to a more fundamental sensory bias. For detailed information concerning individual parameter values, see Table 16 (p. 140).

In line with the behavioral results, six clusters of significant hemispheric differences were revealed within those regions showing hypometabolism in the patient group. Five of these regions were situated in the left hemisphere, indicating that metabolism in those left-hemispheric structures was reduced compared to the same structures in the right hemisphere. The five clusters of left hypometabolism were in the posterior cingulate, the superior, middle, and inferior frontal gyri, and the inferior parietal lobule. The single cluster of relative right hypometabolism was in the precuneus.

Furthermore, a significant negative correlation of parameter laterality of attentional weighting w_λ with metabolism in the left pMTG was found, near the maximum for parameter top-down control α. Therefore, lower metabolism in the left TPJ was associated with a more pronounced leftward spatial bias. Parameter w_λ did not correlate with the symmetrical right TPJ or with the inferior or superior parietal lobules of either hemisphere. In the whole-brain analysis (see

Figure 19), correlations with the laterality parameter w_λ were restricted to the left temporal and parietal lobes, centered on TPJ (Ang-SMG and pMTG). No other areas showed any significant correlations. Therefore, parameter laterality of attentional weighting w_λ seemed not to be related to the metabolic rate of the visual system, for instance.

Figure 19: TVA+PET: Left-hemispheric hypometabolic regions showing a negative correlation with the spatial laterality index of attentional weighting w_λ across MCI and AD patients
$p < 0.001$, uncorrected, cluster threshold: minimum of 50 contiguous voxels;

Finally, the relationship of parameter laterality of attentional weighting w_λ to the laterality index of relative regional metabolism in ROIs was investigated across MCI and AD patients. The metabolic laterality index was significantly correlated with parameter w_λ in the Ang-SMG and the pMTG (TPJ; $r = .43$, $p < .01$; see Figure 20 A), i.e. regions which were already identified to significantly correlate with parameter w_λ in the unilateral analysis.

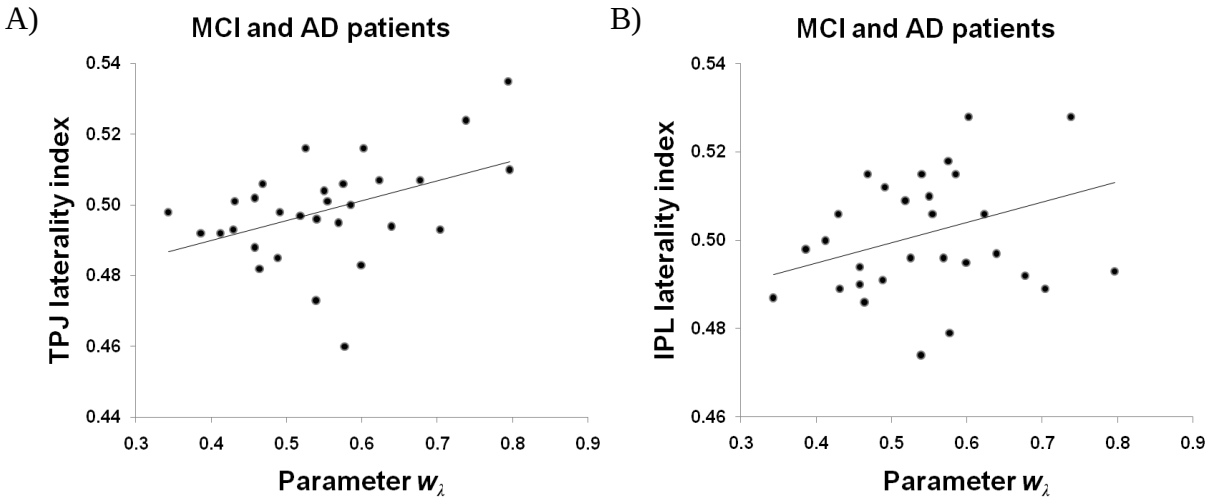


Figure 20: TVA+PET: Positive correlation of the spatial laterality index of attentional weighting w_λ to corresponding interhemispheric metabolic (A) TPJ and (B) IPL laterality indices across MCI and AD patients

TPJ: temporo-parietal junction; $\text{TPJ laterality index} = \frac{\text{right TPJ metabolism}}{\text{right TPJ metabolism} + \text{left TPJ metabolism}}$; IPL: inferior parietal lobe; $\text{IPL laterality index} = \frac{\text{right IPL metabolism}}{\text{right IPL metabolism} + \text{left IPL metabolism}}$;

Additionally, the metabolic laterality index for the IPLs correlated significantly with the laterality index of attention w_λ (r = .35, p < .05; see Figure 20 B), even though the left IPL alone was not correlated with parameter w_λ. The metabolic laterality index of the visual cortex was not correlated with parameter w_λ, indicating that the spatial distribution of attention seems to be independent of interhemispheric metabolic imbalances in the visual system, but dependent on relative metabolism in homologous temporo-parietal cortical regions.

6.4.4. Parameter inter-correlation

Given the adjacent metabolic maxima in the left pMTG for both, parameter spatial laterality index of attention w_λ and parameter top-down control α, a special interest was taken in investigating whether these parameters were associated with each other.

No significant correlations were found between all TVA parameters (see Table 6), laterality index of attentional weighting w_λ, top-down control α, perceptual processing speed C and visual short-term memory storage capacity K, in both, patients and healthy controls (all p > .13).

In healthy subjects, two trend-level correlations between parameters w_λ and C and parameters w_λ and K, respectively, were revealed (all p < .10), indicating that a slight leftward spatial bias

was associated with enhanced general processing capacity, i.e. faster processing speed and higher VSTM storage capacity.

Table 6: TVA-PET: TVA parameter inter-correlations and relationship to metabolic TPJ- and IPL laterality indices

w_λ: laterality index of attentional weighting; α: top-down control; C: perceptual processing speed (N elements/ sec); K: visual short-term memory storage capacity (N elements);
TPJ: temporo-parietal junction; IPL: inferior parietal lobe; $\text{TPJ laterality index} = \frac{\text{right TPJ metabolism}}{\text{right TPJ metabolism} + \text{left TPJ metabolism}}$;
$\text{IPL laterality index} = \frac{\text{right IPL metabolism}}{\text{right IPL metabolism} + \text{left IPL metabolism}}$; **: $p < .01$; *: $p < .05$;

Parameter inter-correlations	***α***	***C***	***K***	**TPJ laterality index**	**IPL laterality index**
MCI and AD					
w_λ	-.06	-.15	-.19	**.43****	**.35***
α	-	.00	-.10	-.18	-.32
C	-	-	.28	-.25	-.06
K	-	-	-	-.18	-.08
TPJ laterality index	-	-	-	-	**.75****
Controls					
w_λ	.14	*.29*	*.28*	-	-
α	-	.11	.05	-	-
C	-	-	.10	-	-

Across MCI and AD patients (for individual parameter values, see Table 16, p. 140), significant positive correlations were solely revealed between the laterality index of attentional weighting w_λ and both, TPJ (Ang-SMG and pMTG) and IPL laterality indices. Both metabolic indices were positively inter-correlated. This inter-correlation also subsisted when posterior cingulate metabolism was used as a covariate of no interest in order to control for disease severity. None of the other correlations calculated between TVA parameters and metabolic indices reached the level of significance. These results indicate that direction and degree of the spatial laterality index of attentional weighting w_λ rest upon analogous interhemispheric imbalances in both, TPJ and IPL regions, and are independent of non-lateralized attentional mechanisms such as task-related selection (top-down control α) and processing capacity, perceptual processing speed C and VSTM storage capacity K.

Notably, parameters *C* and *K* were not correlated with any ROI and did not show significant correlations elsewhere in the whole-brain analysis.

6.5. Discussion

The present study was conducted to investigate the relationship between components of selective visual attention, as assessed by a partial report task based on Bundesen's (1990) theory of visual attention (TVA), and the regional ^{18}FDG-PET metabolism in early AD patients (about 80% amnestic MCI and 20% probable AD patients). From the partial report task, two independent quantitative parameter estimates were derived: task-related efficiency of top-down control α and the spatial laterality index of attentional weighting w_λ. In early AD, left-hemispheric hypometabolism in temporo-parietal (and frontal) areas predicted deficient top-down controlled selection. Furthermore, hypometabolism in the left temporo-parietal junction (TPJ) as well as interhemispheric metabolic imbalances in homologous regions of the TPJ and the inferior parietal lobe (IPL), respectively, were significantly correlated in degree and direction with spatial attentional weighting w_λ.

PET imaging data affirmed that the present clinical sample can be considered as representative group of early AD patients (majority of MCI patients), since hypometabolic regions in the current sample are typically anticipated at an early stage of the disease (Drzezga et al., 2003; Drzezga et al., 2005; Herholz, 1995). Furthermore, TVA-based capacity-reflecting parameters, perceptual processing speed *C* and VSTM storage capacity *K*, were not correlated with any ROI and did not show significant correlations elsewhere in the whole-brain analysis, as expected due to the nonspecific regional character of lesions associated with structural limitations in attentional processing capacity (Bundesen et al., 2005). Both parameters, *C* and *K*, had no effect on top-down control α or the spatial laterality index of attentional weighting w_λ, nor on the metabolic measures. Previous findings are in line with the present results, attributing deficits in general processing capacity mainly to lesion volume and wide-ranging dis-

ruptions of white matter cortico-cortical fibers (Habekost & Rostrup, 2007; Habekost & Starrfelt, 2009; Peers et al., 2005), instead of circumscribed (e.g. metabolic) alterations in distinct regions. Importantly, top-down control α and the laterality parameter w_λ were uncorrelated for each group, corroborating (see also chapter 5.5, pp. 86 et seq.) that both parameters are present as distinct and independent attentional indices, reflecting possibly different underlying neuropathological mechanisms. This issue will be discussed in the next sections.

6.5.1. Task-related weighting and frontal/ temporo-parietal hypometabolism

Neurofibrillary tangles and neuritic plaques give rise to a selectively distributed neocortical disconnection syndrome in AD (Delbeuck et al., 2003; Sorg et al., 2009), disrupting, among others, functional connectivity between frontal and parietal cortices in AD (Azari et al., 1992; Horwitz et al., 1987). A FDG-PET study by Collette et al. (2002) was in line with the hypothesis of diminished anterior-posterior connectivity. In this study, AD patients with either parietal and temporal hypometabolism or with additionally reduced metabolism in frontal areas were similarly impaired in several executive tasks, irrespective of the presence or absence of frontal lobe hypometabolism. The current results on the relationship of parameter top-down control α with hypometabolism in predominantly left-hemispheric posterior regions (left TPJ, composed of Ang-SMG and pMTG; and precuneus) preponderantly support this view, although parameter top-down control α was also related to left inferior frontal cortex. Notably, associations between parameter α and hypometabolism in precuneus and especially left inferior frontal cortex were revealed in the whole-brain analysis, only. In support of the fronto-parietal disconnection hypothesis, these findings might not be as reliable as the ROI-based relationship between parameter top-down control α and metabolism in left TPJ. Taken together, executive impairments in early AD could be the consequence arising out of a partial disruption of the fronto-parietal attention network.

6.5.2. Spatial weighting and temporo-parietal hypometabolism

Across MCI and AD patients, a pathological spatial lateralization of attention w_λ towards the left visual hemifield was revealed, while in healthy elderly controls visual spatial attention was balanced. In support of these behavioral results, ^{18}FDG-PET imaging corroborated a left-hemispheric hypometabolism in prefrontal, lateral parietal cortices and precuneus compared to homologous regions in the right hemisphere across patients. Consequently, neural degeneration in AD seems to be slightly intensified in the left compared to the right hemisphere (Desgranges et al., 1998; Li et al., 2000; O'Brien et al., 1992; Thompson et al., 2003; Ueyama et al., 1994; Volkow et al., 2002).

In the patient group, the laterality parameter of attentional weighting w_λ was more directed to the left visual hemifield the lower the metabolism in the left TPJ. Parameter w_λ was neither associated with metabolism in right TPJ, other parietal regions, nor the occipital cortex. In addition, spatial lateralization of attention w_λ was not related to imbalanced metabolism between left and right primary visual cortex, which excludes primary visual-sensory deficits to be the cause of the pathological leftward spatial bias. Behavioral data complies with the PET data, revealing no significant correlation between the spatial laterality index of attentional weighting w_λ and the corresponding index of sensory effectiveness A_λ, indicating that the pathological leftward lateralization does not originate from an unilateral right- or left-sided sensory loss.

In contrast, the spatial laterality index w_λ seemed to stem from hypometabolism in left TPJ and an interhemispheric metabolic imbalance between the left and right TPJ and IPL, respectively (TPJ and IPL laterality index). The more reduced the metabolism in left TPJ and IPL compared to the right-hemispheric homologous regions, the more pronounced the leftward spatial bias. These results replicate recent findings by Meguro et al. (2001). In this SPECT study, AD patients' enhanced rightward omissions in a visual search task were correlated with

lower parietal cerebral blood flow (CBF) in the left hemisphere compared to the right, and patients with predominantly leftward omissions showed the opposite CBF pattern.

6.5.3. Parameter inter-relations

Despite the fact that both partial report parameters, top-down control α and the laterality parameter w_λ, were related to corresponding cortical regions in the left pMTG (TPJ), they were not correlated with each other in both groups, patients and controls. Hence, they were present independently from each other. The same results were revealed for all other possible TVA-based parameter inter-correlations.

Interestingly, in the clinical group, significant positive correlations were solely revealed between the laterality index of attentional weighting w_λ and both, TPJ and IPL laterality indices. Both metabolic indices were positively inter-correlated, which has been reported before (Corbetta, Patel, & Shulman, 2008; Vandenberghe & Gillebert, 2009). Consequently, direction and degree of the spatial laterality index w_λ seem to be caused by interhemispheric metabolic imbalances in both, TPJ and IPL regions. However, this relationship is independent of non-lateralized attentional mechanisms such as task-related selection (top-down control α) and processing capacity, i.e. perceptual processing speed C and VSTM storage capacity K.

According to a recent review article by Vandenberghe and Gillebert (2009), activation in intraparietal sulcus (IPS) is related to selection tasks of multiple competing stimuli, i.e. targets and distractors, such as in the TVA-based partial report task. Complemented by the computational view based on NTVA (Bundesen et al., 2005), the relationship of parameter laterality index of attentional weighting w_λ and the metabolic IPL index (IPL is adjacent to IPS) seems to correspond with the hypothesis that in IPL (and IPS, respectively) relative attentional weights are allocated and contralateral saliency maps are generated (Vandenberghe & Gillebert, 2009) in such a way that in the present sample of early AD patients, an imbalance in glu-

cose metabolism and probably also in cortical activity between left and right IPL resulted in a spatial bias.

Analogous, the relationship between parameter w_λ and the metabolic TPJ index might originate from a deficit in the appropriate *re*allocation of attentional weights (i.e. processing capacity) in this early AD sample, as attentional reallocation seems to be mediated by left and right TPJ regions (Vandenberghe & Gillebert, 2009). Both, IPL and TPJ metabolic indices, were highly inter-correlated, indicating that TPJ-mediated reallocation of attentional weights may support the instantiation of saliency maps in IPLs. Noteworthy, parameter top-down control α was in the whole-brain analysis loosely (see chapters 6.3.4.2, pp. 100 et seq. and 6.4.2, pp. 103 et seq.) associated with left TPJ and left inferior frontal lobe (apart from left precuneus). Therefore, top-down controlled reallocation of attentional weights to task-relevant target stimuli in presence of task-irrelevant distractors might be modulated by inferior frontal lobe.

In terms of the biased competition model of attentional selection proposed by Desimone and Duncan (Desimone, 1998; Desimone & Duncan, 1995; Duncan et al., 1997), which is strongly related to TVA (Bundesen, 1990), the process of attentional (re)allocation might be understood as interactions among neurons representing all stimuli which are currently present in the visual field. Competition between object representations are biased in favor of task-relevant stimuli in healthy subjects (Desimone & Duncan, 1995) but may be pathologically imbalanced in the current early AD sample. Reductions of neuronal activity in left IPL and TPJ compared to right IPL and TPJ, or vice versa, seem to cause a corresponding pathological spatial bias towards the left and right visual hemifield, respectively. In addition, decreased activity in inferior frontal lobe might underlie impairments in top-down controlled selection of neuronal representations of objects relevant to current behavior or, considered from another angle, might result in altered suppression of behaviorally irrelevant stimuli.

6.5.4. Limitations of the study

The present study has several limitations. First, this is a correlation study between resting state PET measures and cognitive performance and therefore a cautious interpretation is needed (Tulving et al., 1999). In addition, conclusions on 'activated' or relatively 'deactivated' cortical regions could be questioned, although previous studies using voxel-based mapping of correlations between cognitive performance and resting-state regional glucose metabolism have demonstrated the sensitivity of this approach in unraveling the neural substrates of cognitive impairment in AD (Bracco et al., 2007).

Second, the pattern of cognitive-metabolic correlations might vary according to disease severity (Bracco et al., 2007). Despite the fact that posterior cingulate metabolism was used as a covariate of no interest in order to control for disease severity in the analysis of parameter inter-correlations, the present findings ought to be investigated further, i.e. by opposing MCI and AD patient groups.

Third, it was not feasible to assess both, resting FDG-PET and TVA-based tasks in one single sample of healthy elderly controls. Thus, it was impossible to directly compare the relationship of the partial report parameters to patterns of metabolic correlates in both, patients and healthy controls. Therefore, this survey needs to be complemented by further studies (e.g. PET and fMRI).

6.5.5. Conclusions

The TVA-based partial report task proved to be a sensitive tool for reflecting underlying metabolic dysfunctions at an early stage of AD. Deficits in task-related selection as well as a pathological spatial bias, qualitatively distinct and quantifiable, were shown to be related to left-hemispheric hypometabolism and interhemispheric metabolic imbalances in predominantly posterior regions of the fronto-parietal attention network. These results support the hypotheses that early impairments in task-related as well as spatial weighting may be caused by a cortico-

cortical disconnection of fronto-parietal cortices on the one hand and by an imbalance in interhemispheric temporo-parietal interactions on the other hand.

As temporo-parietal hypometabolism is now considered a reliable hallmark of AD (Mosconi, 2005) and a sensitive tool for reflecting pathological interhemispheric metabolic imbalances, i.e. the TVA-based partial report paradigm, might be indicative of subjects at risk for AD.

7. General conclusions and perspectives

This dissertation intended to investigate the probable valuable contribution of the TVA-based whole and partial report of briefly presented letter arrays based on Bundesen's theory of visual attention (TVA; Bundesen, 1990, 1998; Bundesen et al., 2005) in assessing amnestic MCI and AD patients in comparison to healthy elderly control subjects.

The results of the three presented studies suggest a staging model of visual selective attentional impairments in MCI and AD (see Table 7). Deficits of pre-attentive processing (perceptual threshold t_0), task-related (top-down control α) and spatial weighting (laterality index of attentional weighting w_λ) were already detectable in MCI patients, while aspects of processing capacity (perceptual processing speed C and VSTM storage capacity K) were still intact. At a later stage of the disease, further deterioration of top-down control α and increasing lateralization of spatial weighting w_λ accompanied impairments in perceptual processing speed C and VSTM storage capacity K.

Table 7: WR-PR: Pattern of impaired and intact TVA-based attentional components in MCI and AD patients compared to healthy controls
↓: impaired attentional parameter; ↓↓: further deterioration; √: intact attentional component;

Group	Perceptual threshold t_0	Spatial weighting w_λ	Top-down control α	Processing speed C	VSTM storage capacity K
MCI	↓	↓	↓	√	√
AD	↓	↓↓	↓↓	↓	↓

It is a fact that not all subjects diagnosed with MCI will develop dementia, although the amnestic subtype bears a high prognostic value (Gauthier et al., 2006). Needless to say, this assumption merits further investigation. A longitudinal study would be required to address the question whether one or several TVA-based parameters (i.e. perceptual threshold t_0, top-down control α and the laterality index of attentional weighting w_λ) might predict which MCI patients convert to AD.

Further specific questions for future studies arise from several particular findings. Notably, perceptual processing speed *C* differed significantly between AD patients receiving acetylcholine esterase inhibitors (AChEI) and those non-medicated AD patients. Medicated AD patients exhibited higher processing speed compared to non-medicated patients, indicating that parameter *C* might bear the potential of reflecting medication effects, maybe even at the early MCI stage. Dedicated medication studies using AChEI might answer this question.

Furthermore, it would be of interest to contrast samples of AD patients with and without posterior cortical atrophy in order to investigate whether decreasing processing speed *C* might be a general factor in AD or whether it is more attributable to atrophy in specific posterior regions. Analogous to a study by Finke et al. (2007) in Huntington's disease patients showing impaired simultaneous perception, symptoms of simultanagnosia could be investigated in AD subgroups by a simultaneous perception task of visual objects presented under varying levels of difficulty. Besides a conceivable common relationship between parameter *C* and simultaneous perception of objects, both disease variants in AD might differ with regard to other TVA-based parameters and might potentially exhibit a characteristic pattern of intact and disturbed attentional aspects. In addition, these research questions should also be surveyed in MCI patients.

With regard to the pinpointed relationship between increasing leftward spatial bias and earlier disease onset in clinical carriers of the ApoE4 allele, the effect of ApoE4 genotype and disease onset on parameter w_λ should be investigated in more detail. Unfortunately, the present clinical sample or rather corresponding subgroups were not large enough to conduct an analysis of a possible Genotype x Disease onset interaction effect.

Finally, it would be desirable to further investigate the probable neuronal correlates of parameter top-down control α and the laterality index of attentional weighting w_λ, respectively, as it was not feasible to assess both partial report components together with the PET imaging data in one and the same group of healthy elderly controls. Two different control groups had to

be applied which prevented the direct comparison of cognitive-metabolic coherences in the clinical and the healthy sample. On the same subject, the influence of the level of alertness on spatial (laterality parameter of attentional weighting w_λ) and non-spatial (i.e. perceptual processing speed C) components of visual attention should be explored. Matthias et al. (2009) demonstrated the relevance of alertness to spatial attentional asymmetries, similar to those that were discovered in the present work in amnestic MCI and AD patients.

In conclusion, the TVA-based assessment of selective visual attention proved to be a sensitive diagnostic tool for revealing subtle deficits already at the stage of MCI which might exhibit the capability of an early cognitive marker for the identification of subjects at risk of AD.

8. Deutsche Zusammenfassung (German synopsis)

Die vorliegende Dissertation mit dem Titel „Erfassung visueller Aufmerksamkeitsleistungen bei Patienten mit ‚Mild Cognitive Impairment' und Alzheimer Demenz basierend auf der Theorie der visuellen Aufmerksamkeit" (englischer Originaltitel: „Visual attentional assessment in mild cognitive impairment and Alzheimer's disease based on a theory of visual attention") gliedert sich in drei Studien, welche unterschiedliche Aspekte der selektiven visuellen Aufmerksamkeit untersuchten, und zwar an Patienten mit einer amnestischen Form von ‚Mild Cognitive Impairment' (MCI; deutsch: leichte kognitive Störung) und an Patienten, die mutmaßlich an einer Alzheimerdemenz (AD) erkrankt sind.

Die Erforschung des gesunden aber v.a. auch pathologischen Alterns, bedingt durch z.B. verschiedene Formen der Demenz, nimmt mittlerweile einen hohen Stellenwert in unserer Gesellschaft ein, da mit steigender Lebenserwartung ein stetig wachsendes Risiko einhergeht, an einer neurodegenerativen Erkrankung wie der Alzheimerdemenz zu erkranken. Diese gesellschaftspolitisch relevante Entwicklung rückt immer mehr in den Fokus der Wissenschaft und der Forschung.

Die vorliegende Forschungsarbeit geht von der Annahme aus, dass bereits in einem frühen Stadium der AD-Erkrankung Defizite der selektiven visuellen Aufmerksamkeit auftreten (Foldi et al., 2002) und diese möglicherweise als erste Beeinträchtigungen (neben Gedächtnisproblemen; Perry & Hodges, 1999) im frühen Prodromalstadium MCI (Petersen et al., 1999) nachweisbar sind. Ziel dieser Dissertation war es, die Fragestellung zu untersuchen, inwiefern bestimmte Komponenten der selektiven visuellen Aufmerksamkeit v.a. im frühen MCI-Stadium bereits beeinträchtigt bzw. noch intakt sind. In diesem Zusammenhang sollte auch untersucht werden, ob sich bei MCI-Patienten bestimmte Aufmerksamkeitsfunktionen qualitativ und/ oder quantitativ von Aufmerksamkeitsleistungen bei AD-Patienten auf der einen und bei gesunden älteren Kontrollprobanden auf der anderen Seite unterscheiden.

Die Theorie der visuellen Aufmerksamkeit (TVA) von Bundesen (1990, 1998) diente hierzu als theoretische Grundlage und ermöglichte es, latente, mathematisch unabhängige und quantifizierbare Parameter zu schätzen. Diese Parameterwerte leiten sich ab von zwei sehr ähnlichen Paradigmen, dem computergestützten Ganzbericht und Teilbericht mit kurz dargebotenen visuellen Buchstabenanordnungen. Zahlreiche TVA-basierte Untersuchungen (z.B. Bublak et al., 2005; Bublak et al., 2006; Duncan et al., 1999; Duncan et al., 2003; Finke et al., 2006; Gerlach et al., 2005; Habekost & Bundesen, 2003; Habekost & Rostrup, 2006; Peers et al., 2005) konnten zeigen, dass das Ganz- und Teilberichtsverfahren als Diagnostikum für selektive Aufmerksamkeitsleistungen vier große Stärken aufweist: die Gütekriterien der Sensitivität, Spezifizität, Reliabilität und Validität sind in hohem Maße gegeben.

8.1. Studie 1

Die Amyloid-Kaskaden-Hypothese (Hardy & Selkoe, 2002) nimmt in Bezug auf die AD-Erkrankung an, dass eine Zunahme von β-Amyloid (Aβ) Plaques und Neurofibrillen durch direkte und indirekte Wirkung auf synaptische, neuronale und neuritische Funktionen langfristig zu kortikalem Zelltod (z.B. Cirrito et al., 2005) sowie fortschreitendem intellektuellem Verfall führt. Folglich könnte die Erforschung von sensitiven Biomarkern, welche die neurodegenerativen Veränderungen der AD widerspiegeln, die Möglichkeit bieten, Personen mit erhöhtem AD-Risiko möglichst früh zu diagnostizieren und somit die Chance einer wirksamen Behandlung zu eröffnen (Shah et al., 2008). Die erste Studie (Kapitel 4, S. 31 ff.) untersuchte die Fragestellung, ob kognitive Parameter zur Erfassung visueller Aufmerksamkeitskapazität diesem Anspruch gerecht werden können.

Basierend auf der TVA von Bundesen (1990, 1998) wurde die Fähigkeit zur visuellen Informationsaufnahme von 18 Patienten mit mutmaßlicher AD, 18 amnestischen MCI-Patienten und 18 gesunden älteren Kontrollprobanden untersucht. Die Gruppen waren hinsichtlich des Alters, des Geschlechts und des Bildungsniveaus vergleichbar. Alle Probanden bearbeiteten

ein Ganzberichtsverfahren, in dem möglichst viele Buchstaben benannt werden sollten, welche kurzzeitig auf einem Computerbildschirm präsentiert wurden. Ausgehend von dieser Leistung konnten vier voneinander unabhängige Parameter ermittelt werden, welche verschiedene Aspekte der visuellen Verarbeitungskapazität repräsentieren: perzeptuelle Verarbeitungsschwelle t_0, ikonisches Gedächtnis μ, perzeptuelle Verarbeitungsgeschwindigkeit *C* und visuelle Speicherkapazität des Kurzzeitgedächtnisses (KZG) *K*.

Im Gruppenvergleich wurde deutlich, dass die perzeptuelle Verarbeitungsschwelle t_0 bereits im MCI-Stadium erhöht ist, wohingegen die Verarbeitungsgeschwindigkeit *C* und die KZG-Speicherkapazität *K* nur bei den AD-Patienten signifikant reduziert vorlag. AD-Patienten, welche Acetylcholinesterasehemmer (AChEH) einnahmen, wiesen zwar eine höhere Verarbeitungsgeschwindigkeit als AD-Patienten auf, die keine AChEH erhielten, jedoch erreichten erstere nicht das Leistungsniveau der MCI-Patienten. Der Parameter perzeptuelle Verarbeitungsschwelle t_0 war signifikant mit der Krankheitsdauer korreliert, jedoch nicht mit anderen kognitiven Kennwerten. Im Gegensatz dazu wiesen die Verarbeitungsgeschwindigkeit *C* und die KZG-Speicherkapazität *K* zwar einen signifikanten Zusammenhang mit eben jenen kognitiven Maßen auf, nicht aber mit der Dauer der Erkrankung. Insbesondere zeigte sich ein Zusammenhang zwischen der KZG-Speicherkapazität *K* und neuropsychologischen Tests, die primär auf visuellem Material beruhen, wie z.B. Bildbenennung und Visuokonstruktion. Im Hinblick auf die Verarbeitungsgeschwindigkeit konnte zudem noch ein Zusammenhang mit verbalen Gedächtnismaßen belegt werden.

Diese Ergebnisse deuten darauf hin, dass im frühen MCI-Stadium Defizite der präattentiven visuellen Verarbeitung vorliegen, wohingegen bei AD-Patienten zudem die attentive Verarbeitung beeinträchtigt scheint. Eine gestufte attentionale Kapazitätsabnahme im Verlauf der AD-Erkrankung steht im Einklang mit der Amyloid-Kaskaden-Hypothese, welche besagt, dass die AD-Neuropathologie in der Frühphase vor allem durch die netzartige Anhäufung und Ablagerung von Aβ beschrieben werden kann. Dies führt zu neuronalen und neuritischen

Funktionsstörungen. Im weiteren Krankheitsverlauf bewirken der allmähliche Verlust von Neuronen und Störungen in Transmittersystemen den zunehmenden geistigen Verfall. In diesem Zusammenhang könnte die Erhöhung der perzeptuellen Wahrnehmungsschwelle als möglicher Indikator für neuronale Funktionsstörungen vor dem Zelltod in Betracht gezogen werden. Im Gegensatz dazu könnten Defizite der Verarbeitungsgeschwindigkeit und der KZG-Speicherkapazität bereits Hinweise geben auf einen massiven Verlust neuronaler Zellverbände in Verbindung mit Beeinträchtigungen in Neurotransmittersystemen.

8.2. Studie 2

Die häufigste Form von Demenz ist die AD, die zum einen als erbliche, familiär gehäufte Erkrankung auftritt, doch viel häufiger in sporadischer Form in Erscheinung tritt. Auch die sporadische Form von AD wird mit einem genetischen Risikofaktor in Verbindung gebracht: Träger des Apolipoprotein E ε4 Allels (ApoE4) haben im Vergleich zu ApoE4-negativen Personen ein 3- bis 15-fach höheres Risiko, an AD zu erkranken (Blennow et al., 2006). Finke et al. (2006) konnten mit demselben TVA-basierten Teilberichtsparadigma wie in dieser Studie bei Chorea Huntington Patienten eine enge Beziehung belegen zwischen dem Schweregrad der genetischen Pathologie der neurodegenerativen Erkrankung sowie der Ausrichtung und dem Ausmaß räumlicher Aufmerksamkeitslateralisierung. Sensitive Tests zur Messung selektiver visueller Aufmerksamkeit könnten als frühe kognitive Marker der AD zum Einsatz kommen und somit eine frühe Diagnose von Risikopersonen im MCI-Stadium ermöglichen (Shah et al., 2008), als auch von Personen mit zugrundeliegendem genetischem Risiko (ApoE4). Die Zielsetzung der zweiten Studie (Kapitel 5, S. 60 ff.) richtete sich auf die Fragestellung, ob Parameter der visuell-räumlichen und aufgabenbezogenen selektiven Aufmerksamkeit als frühe kognitive Marker in Betracht kommen.

Zur Erfassung der selektiven Aufmerksamkeitsleistungen bei 32 amnestischen MCI-Patienten, 16 AD-Patienten und 36 gesunden älteren Kontrollprobanden wurde ein TVA-

basiertes Teilberichtsverfahren (Bundesen, 1990, 1998) eingesetzt. Die Aufgabe der Probanden bestand darin, kurzzeitig präsentierte Buchstaben zu benennen. Ausgehend von dieser Leistung wurden zwei mathematisch unabhängige und quantifizierbare Parameterwerte berechnet. Der Parameter Top-down Kontrolle α ist ein Maß für die Fähigkeit, Zielreize im Gegensatz zu Distraktoren bevorzugt zu verarbeiten. Der Parameter räumliche Aufmerksamkeitsgewichtung w_λ spiegelt die Verteilung der Aufmerksamkeit über das linke und rechte visuelle Halbfeld wider.

Im Vergleich zu einer nach Alter, Geschlecht und Bildung vergleichbaren Kontrollgruppe zeigten MCI-Patienten signifikante Defizite in der Top-down Kontrolle α, die sich im AD-Stadium noch weiter verschlechterten. Zudem wiesen MCI-Patienten eine pathologische räumliche Aufmerksamkeitslateralisierung w_λ auf, die bei AD-Patienten tendenziell noch stärker ausgeprägt war. Überwiegend zeigte die Gruppe der Patienten eine Aufmerksamkeitsverschiebung w_λ zum linken Halbfeld. Träger des ApoE4 Allels in der klinischen Gruppe wiesen darüber hinaus eine linksseitige Aufmerksamkeitslateralisierung auf. Diese linksgerichtete Aufmerksamkeitsverschiebung war bei jüngeren ApoE4 Patienten bzw. ApoE4 Trägern mit früherem Krankheitsbeginn stärker ausgeprägt. ApoE4-negative Patienten konnten die Aufmerksamkeit gleichmäßig auf beide visuelle Halbfelder ausrichten.

Diese Befunde deuten darauf hin, dass Defizite in der Top-down Kontrolle α auf frühe Beeinträchtigungen in kortiko-kortikalen Faserverbindungen zwischen parietalen und frontalen Arealen zurückgeführt werden können. Zudem scheinen begleitend interhemisphärische Asymmetrien im temporo-parietalen Aufmerksamkeitsnetzwerk aufzutreten, welche einer pathologischen räumlichen Aufmerksamkeitsverschiebung w_λ zugrunde liegen können. Da die Erblichkeit von ApoE4 in Verbindung steht mit einem interhemisphärischen Ungleichgewicht in parietalen kortikalen Interaktionen, könnte eine pathologische linksseitige Aufmerksamkeitsverschiebung w_λ als früher kognitiver Marker dienen, um Personen mit erhöhtem Risiko an einer Alzheimerdemenz zu erkranken, möglichst früh zu diagnostizieren.

8.3. Studie 3

In der vorangegangenen Studie zeigte sich, dass das TVA-basierte Teilberichtsparadigma bei amnestischen MCI-Patienten als sensitives Verfahren zur frühen Diagnose von Beeinträchtigungen in der aufgabenbezogenen Selektionsfähigkeit als auch hinsichtlich eines pathologischen Ungleichgewichts in der Aufmerksamkeitsverteilung im Raum herangezogen werden kann (Kapitel 5, S. 60 ff.). Es wurden die Hypothesen aufgestellt, dass diese Beeinträchtigungen in der selektiven Aufmerksamkeit auf ein frühes Diskonnektions-Syndrom und ein interhemisphärisches Ungleichgewicht kortikaler Interaktionen im fronto-parietalen Aufmerksamkeitsnetzwerk zurückzuführen sind. In einem späteren Stadium der Krankheit kommt es dann durch ein allmähliches Absterben von Nervenzellen zu einer weiteren Verschlechterung der selektiven Aufmerksamkeitsleistungen sowie auch der geistigen Fähigkeiten.

In der dritten Studie (Kapitel 6, S. 93 ff.) wurden diese Hypothesen geprüft, indem der Zusammenhang zwischen den beiden Teilberichtsparametern, Top-down Kontrolle α und v.a. der räumlichen Aufmerksamkeitsgewichtung w_λ, und dem lokalen Glukosestoffwechsel mittels Positronen-Emissions-Tomographie (PET) in einer klinischen Gruppe mit 30 amnestischen MCI- oder AD-Patienten untersucht wurde.

Bei allen Patienten fand sich ein leicht verringerter Glukosestoffwechsel in verschiedenen Arealen der linken Hemisphäre. Interessanterweise ergab sich folgender Zusammenhang: je deutlicher der Metabolismus im linken temporo-parietalen Übergansbereich reduziert war (temporo-parietal junction, TPJ), desto schlechter war die Top-down Kontrolle α. Vergleichbare Ergebnisse zeigten sich in Bezug auf den Parameter räumlichen Aufmerksamkeitsgewichtung w_λ: ein verringerter Stoffwechsel im linken TPJ-Areal diente als Prädiktor für das Ausmaß der räumlichen Lateralisierung w_λ. Darüber hinaus korrelierte ein verringerter Glukosestoffwechsel im linken TPJ-Areal bzw. dem linken inferioren Parietallappen (IPL) im Vergleich zu rechtshemisphärischem TPJ-Areal bzw. IPL mit der Ausrichtung und der Stärke der räumlichen Aufmerksamkeitslateralisierung w_λ.

Zusammenfassend kann man schließen, dass die PET-basierten Bildgebungsdaten die eingangs aufgestellten Hypothesen untermauern. Einerseits konnte gezeigt werden, dass eine frühe Beeinträchtigung der Top-down Kontrolle α bereits auf ein fronto-parietales Diskonnektions-Syndrom im MCI-Stadium zurückgeführt werden kann. Andererseits scheint auch ein interhemisphärisches metabolisches Ungleichgewicht in homologen temporo-parietalen Arealen vorherrschend zu sein, welches einer entsprechend ausgerichteten und ausgeprägten visuell-räumlichen Aufmerksamkeitslateralisierung zugrunde liegt.

8.4. Schlussfolgerungen und Ausblick

Die vorliegende Dissertation hatte es sich zum Ziel gesetzt, den Beitrag des Ganz- und Teilberichts basierend auf Bundesen's Theorie der visuellen Aufmerksamkeit (TVA; Bundesen, 1990, 1998; Bundesen et al., 2005) als mögliches sensitives Verfahren zur Diagnostik von selektiven Aufmerksamkeitsdefiziten bei amnestischen MCI- und AD-Patienten zu untersuchen und den Aufmerksamkeitsleistungen von gesunden Kontrollprobanden gegenüberzustellen.

Die Ergebnisse der drei hier vorgestellten Studien weisen darauf hin, dass sich visuelle selektive Aufmerksamkeitsleistungen über das MCI- bis hin zum AD-Stadium graduell verschlechtern. Beeinträchtigungen in der präattentiven Verarbeitung (perzeptuelle Wahrnehmungsschwelle t_0), der aufgabenbezogenen attentionalen Gewichtung (Top-down Kontrolle α) sowie der räumlichen Gewichtung der Aufmerksamkeit (w_λ) konnten bereits bei MCI-Patienten nachgewiesen werden. Komponenten der Verarbeitungskapazität (perzeptuelle Verarbeitungsgeschwindigkeit C und KZG-Speicherkapazität K) waren hingegen im MCI-Stadium noch intakt. Im weiteren Verlauf der neurodegenerativen Erkrankung zeigte sich eine zunehmende Verschlechterungen der Top-down Kontrolle und eine stärker ausgeprägte Lateralisierung der räumlichen Aufmerksamkeit. Begleitend traten zusätzlich Defizite in der Verarbeitungsgeschwindigkeit als auch in der KZG-Speicherkapazität auf.

Die vorliegende Arbeit konnte aufzeigen, dass sich die TVA-basierte Untersuchung der selektiven visuellen Aufmerksamkeit als sensitives Diagnostikum bewährt hat, da mit diesem Verfahren schon im frühen MCI-Stadium subtile Defizite aufgedeckt werden konnten. Möglicherweise kommt dieses Aufmerksamkeitsdiagnostikum als früher kognitiver Marker in Betracht, um eine Früherkennung von MCI-Patienten mit erhöhtem Risiko, an AD zu erkranken, zu unterstützen. Längsschnittstudien müssen zeigen, ob die TVA-basierte Aufmerksamkeitsdiagnostik prognostischen Wert hat.

Supplement A: Test instructions

Test instructions were provided in written form. The experimenter made sure that every single subject understood the instruction by requesting and further verbal explanation of the task, if necessary (especially with regard to patient data assessment).

Instruction 1: Whole report instruction: German original version and English translation for healthy subjects in phase I (pre-test) and phase II (experiment)

In the pre-test the individual exposure duration was determined at which the subject could report, on average, one letter correctly (20%). This value was used as the middle exposure duration (together with a shorter and a longer presentation duration) in the main experiment (phase II). Masked and unmasked trials were balanced and were used for all participants.

„Sie sehen gleich für kurze Zeit in der Mitte des Bildschirms ein Kreuz aufleuchten. Bitte fixieren Sie dieses Kreuz. Wenig später verschwindet es wieder. Danach erscheinen für sehr kurze Zeit fünf rote oder fünf grüne Buchstaben. Ihre Aufgabe ist es, möglichst viele dieser Buchstaben zu benennen. Die Reihenfolge spielt keine Rolle. Da die Präsentationszeit sehr kurz ist, ist es völlig normal, wenn Sie nicht alle Buchstaben erkennen. Versuchen Sie einfach, die Aufgabe so gut wie möglich zu machen und nennen Sie alle Buchstaben, von denen Sie sich ziemlich sicher sind, sie erkannt zu haben. Ich werde die von Ihnen genannten Buchstaben eingeben und dann folgt ein neuer Durchgang mit neuen Buchstaben."

"Now, in a moment you will see a cross briefly presented at the middle of the screen. Please fixate this cross and keep your fixation on its position. After the cross has disappeared, five red or five green letters will appear in a column in the centre of the screen. Your task is to name, in any order you wish, as many letters as possible. As the presentation time is very short, it is absolutely normal if you are unable to recognize all of them. Just try to do your best and report only those letters of which you are quite sure you have seen them. I will type in the letters you report and then the next trial follows including a new set of letters."

Instruction 2: Whole report instruction: German original version and English translation for MCI and AD patients in phase I (pre-test) and phase II (experiment)

In the pre-test the individual exposure duration was determined at which the subject could report, on average, one letter correctly (20%). This value was used as the middle exposure duration (together with a shorter and a longer presentation duration) in the main experiment (phase II). Masked and unmasked trials were balanced and were used for all participants.

„Auf dem Bildschirm erscheint zuerst ein Kreuz. Schauen Sie dorthin, wo das Kreuz ist. Dann erscheinen fünf Buchstaben. Benennen Sie alle Buchstaben, die Sie sehen können. Die Buchstaben erscheinen nur ganz kurz. Es ist normal, dass Sie nicht alle Buchstaben erkennen werden. Nennen Sie einfach alle Buchstaben, die Sie erkannt haben."

"First you will see a cross at the screen. Fixate this cross. After the cross has disappeared, five letters will appear. Name as many letters as possible. Presentation time is very short. Therefore, it is normal that you are unable to recognize all letters. Just report all letters that you have seen."

Instruction 3: Partial report instruction: German original version and English translation for healthy subjects in phase I (pre-test) and phase II (experiment)

The pre-test was applied to determine the individual exposure duration for the experiment itself (phase II), aiming for about 80% accuracy in single letter trials and for about 20% totally correct dual target trials (based on trials with two correctly named targets, only). Masked trials were used for all participants.

„Sie sehen gleich für kurze Zeit in der Mitte des Bildschirms ein Kreuz aufleuchten. Bitte fixieren Sie dieses Kreuz. Wenig später verschwindet es wieder. Dann erscheint für sehr kurze Zeit entweder ein einzelner roter Buchstabe oder es erscheinen zwei Buchstaben: entweder zwei rote Buchstaben, oder ein roter und ein grüner Buchstabe. Ihre Aufgabe ist es, nur auf die roten Buchstaben zu achten und diese zu benennen. Die Reihenfolge spielt keine Rolle. Da die Präsentationszeit sehr kurz ist, ist es völlig normal, wenn Sie nicht alle roten Buchstaben erkennen. Versuchen Sie einfach, die Aufgabe so gut wie möglich zu machen und nennen Sie alle roten Buchstaben, von denen Sie sich ziemlich sicher sind, sie erkannt zu haben. Ich werde die von Ihnen genannten Buchstaben eingeben und dann folgt ein neuer Durchgang mit einem oder zwei neuen Buchstaben.“

“Now, in a moment you will see a cross briefly presented at the middle of the screen. Please fixate this cross and keep your fixation on its position. After the cross has disappeared, either a single red letter or two letters appear. There might be two red letters or one red letter together with one green letter. Your task is to attend to and report red letters only, whilst ignoring the green ones. As the presentation time is very short, it is absolutely normal if you are unable to recognize all the red letters. Just try to do your best and report only those red letters of which you are quite sure you have seen them. I will type in the letters you report and then the next trial follows including one or two new letters.”

Instruction 4: Partial report instruction: German original version and English translation for MCI and AD patients in phase I (pre-test) and phase II (experiment)

The pre-test was applied to determine the individual exposure duration for the experiment itself (phase II), aiming for about 80% accuracy in single letter trials and for about 20% totally correct dual target trials (based on trials with two correctly named targets, only). Masked trials were used for all participants.

„Auf dem Bildschirm erscheint zuerst ein Kreuz. Schauen Sie dorthin, wo das Kreuz ist. Danach erscheinen rote oder grüne Buchstaben. Nur die roten Buchstaben sind wichtig. Benennen Sie nur die roten Buchstaben. Die grünen Buchstaben brauchen Sie nicht zu benennen. Die Buchstaben erscheinen nur ganz kurz. Es ist normal, dass Sie nicht alle roten Buchstaben erkennen werden. Nennen Sie einfach alle roten Buchstaben, die Sie erkannt haben.“

“First you will see a cross at the screen. Fixate this cross. After the cross has disappeared, either red or green letters will appear. Name the red letters only. Only the red letters are of importance. You do not have to report the green letters. Presentation time is very short. Therefore, it is normal that you are unable to recognize all red letters. Just report all red letters that you have seen.”

Supplement B: Whole report data (study 1)

Table 8: WR: Demographic and neuropsychological data for individual MCI and AD patients

CDR: Clinical Dementia Rating Scale, global score (Morris, 1993); p: level of significance; M (SD): mean score and standard deviation; Age in years; Education in years; MMSE: Mini Mental State Examination (Folstein et al., 1975), 30-0 points, cut-off ≤ 23; CERAD: The Consortium to Establish a Registry for Alzheimer's Disease (Thalmann & Monsch, 1997), total score; CDT: Clock Drawing Test, 0-6 points, cut-off ≥ 3 (Shulman et al., 1986); CDR sum: sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4: apolipoprotein E4 genotype, positive (24, 34, 44), negative (23, 33); n.a.: not applied; AChEI: acetylcholine esterase inhibitors. All subjects were right-handers, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Nr.	Patient	Age	Gender	Education	MMSE	CERAD total score	CDT	CDR sum	Age at disease onset	Disease duration	ApoE4 genotype	Medication	
												Dementia	Depression
MCI patients													
1	KK	71.9	m	9	28	79	3	1.5	70.3	1.5	34	-	-
2	BD	75.6	f	13	28	83	2	2.0	73.5	2.2	34	-	-
3	HM	59.0	f	9	28	87	3	2.0	56.4	2.6	n.a.	-	-
4	SE	69.1	f	10	28	91	3	1.0	65.9	3.2	33	-	-
5	LE	74.7	f	10	25	79	3	3.0	73.1	1.5	34	-	-
6	TJ	61.3	m	10	28	100	1	0.5	58.1	3.2	33	-	-
7	FF	67.7	m	13	27	96	1	3.5	65.1	2.5	33	-	-
8	RB	66.4	m	13	27	112	2	2.5	63.3	3.1	33	-	-
9	BU	73.3	f	9	26	90	1	2.0	72.2	1.1	34	-	-
10	SB	71.0	f	13	27	54	3	2.0	70.5	0.5	44	-	-
11	LM	66.1	f	10	28	86	1	2.0	61.6	4.5	34	-	-
12	BW	79.0	f	9	29	80	1	1.0	76.5	2.4	34	-	-
13	MM	70.8	f	9	26	86	3	1.0	67.2	3.5	34	-	-
14	JR	68.2	m	9	27	70	3	3.0	66.8	1.4	33	-	-
15	HF	71.0	m	13	28	89	2	2.0	66.9	4.1	23	-	-
16	AW	67.5	m	13	27	79	2	3.0	63.3	4.2	44	-	-
17	NS	68.4	m	9	30	76	1	1.5	66.3	2.1	33	-	-
18	HI	74.8	f	13	26	66	4	3.0	73.7	1.1	34	-	-
	Mean (SD)	**69.8 (5.0)**	**8 m, 10 f**	**10.8 (1.9)**	**27.4 (1.2)**	**83.5 (13.0)**	**2.2 (1.0)**	**2.0 (.8)**	**67.3 (5.5)**	**2.5 (1.2)**	**10+, 7-, 1 n.a.**	**un-medicated**	**un-medicated**
AD patients													
1	OK	71.4	m	9	25	71	1	4.5	65.9	5.5	34	AChEI	-
2	VA	78.2	m	10	24	52	4	7.0	66.9	4.1	34	AChEI	-
3	SAa	80.9	m	10	24	74	3	4.0	-	-	34	-	-
4	RB	55.8	f	9	25	63	4	4.5	52.1	3.7	33	AChEI	-
5	WG	65.9	m	13	24	64	3	3.5	64.3	1.6	33	AChEI	-
6	MW	67.1	m	13	n.a.	n.a.	n.a.	5.0	59.1	8	44	AChEI	-
7	SU	60.0	f	10	23	72	4	4.0	58.3	1.8	24	AChEI	-
8	LL	79.1	f	9	25	62	3	4.0	78.0	1.1	33	-	-
9	FA	75.0	f	9	19	54	4	5.5	71.9	3.1	44	AChEI	-
10	JH	62.0	f	10	23	70	4	4.0	58.1	3.8	33	AChEI	-
11	CI	65.6	f	9	20	71	5	5.0	59.2	6.4	34	AChEI	-
12	SAb	68.2	f	9	25	84	2	3.5	66.1	2.1	34	AChEI	-
13	HJW	57.0	m	10	n.a.	n.a.	n.a.	n.a.	-	-	n.a.	-	-
14	KB	60.6	f	9	22	83	3	3.5	58.4	2.2	44	AChEI	-
15	GT	63.2	m	13	24	76	2	4.0	59.2	3.9	44	-	-
16	UB	57.1	f	9	19	58	4	5.0	55.3	1.8	44	-	-
17	GE	80.6	f	9	19	51	4	5.0	78.4	2.1	n.a.	-	-
18	EM	81.5	f	9	19	51	4	5.0	78.4	3.2	33	-	-
	Mean (SD)	**68.3 (9.0)**	**7 m, 11 f**	**9.9 (1.5)**	**22.5 (2.4)**	**66.0 (10.8)**	**3.4 (1.0)**	**4.5 (.89)**	**64.4 (8.5)**	**3.4 (1.9)**	**11+, 5-, 2 n.a.**	**11 AChEI, 7 unmedicated**	**un-medicated**

Table 9: WR: Exposure durations of individual MCI and AD patients and healthy controls
50% of the trials were masked.

Nr.	AD patients	Exposure durations (ms)			Nr.	MCI patients	Exposure durations (ms)			Nr.	Controls	Exposure durations (ms)		
1	OK	157	300	600	1	KK	157	300	600	1	ED	157	300	600
2	VA	300	600	1000	2	BD	157	300	600	2	BA	157	300	600
3	SAa	157	300	600	3	HM	86	157	300	3	SJ	157	300	600
4	RB	157	300	600	4	SE	300	600	1000	4	LA	157	300	600
5	WG	157	300	600	5	LE	157	300	600	5	SE	157	300	600
6	MW	157	300	600	6	TJ	157	300	600	6	FU	157	300	600
7	SU	157	300	600	7	FF	86	157	300	7	EA	157	300	600
8	LL	157	300	600	8	RB	200	400	700	8	SS	157	300	600
9	FA	300	600	1000	9	BU	86	157	300	9	DG	157	300	600
10	JH	200	400	700	10	SB	157	300	600	10	LK	157	300	600
11	CI	157	300	600	11	LM	100	200	400	11	SI	157	300	600
12	SAb	171	343	686	12	BW	129	257	514	12	UE	157	300	600
13	HJW	157	300	600	13	MM	186	371	700	13	RML	86	157	300
14	KB	200	400	700	14	JR	229	457	814	14	PDM	71	143	271
15	GT	157	300	600	15	HF	229	457	800	15	BE	100	186	371
16	UB	300	600	1100	16	AW	171	343	686	16	SH	157	386	786
17	GE	171	343	686	17	NS	200	400	700	17	AW	114	229	457
18	EM	343	686	957	18	HI	129	257	529	18	PD	114	229	457
	Mean (SD)	**198 (64)**	**387 (134)**	**713 (172)**		**Mean (SD)**	**162 (57)**	**317 (118)**	**597 (189)**		**Mean (SD)**	**140 (29)**	**274 (61)**	**547 (127)**

Table 10: WR: Parameters of individual MCI and AD patients and healthy controls

t_0: perceptual threshold (ms); μ: iconic memory (ms); C: perceptual processing speed (N elements/ sec); K: visual short-term memory storage capacity (N elements).

Nr.	Patient	t_0	μ	C	K
AD patients					
1	OK	118	147	17.6	2.96
2	VA	181	1	4.2	1.25
3	SAa	10	133	7.4	2.48
4	RB	120	145	11.7	2.99
5	WG	70	71	13.4	2.87
6	MW	141	47	19.3	2.96
7	SU	89	76	14.7	2.86
8	LL	131	48	11.0	1.52
9	FA	217	48	15.8	2.96
10	JH	93	196	9.6	2.51
11	CI	134	38	17.7	2.94
12	SAb	96	119	8.3	2.53
13	HJW	44	229	9.4	2.70
14	KB	152	147	9.6	2.88
15	GT	96	56	13.6	2.89
16	UB	65	133	2.6	1.37
17	GE	134	105	9.6	3.00
18	EM	178	16	3.1	1.70
	Mean (SD)	**115 (51)**	**98 (63)**	**11.0 (4.9)**	**2.52 (.61)**
MCI patients					
1	KK	126	57	24.5	3.00
2	BD	108	52	20.9	4.00
3	HM	15	127	27.9	2.94
4	SE	277	50	21.2	2.90
5	LE	31	58	9.2	2.34
6	TJ	136	141	22.3	3.00
7	FF	63	128	17.5	2.96
8	RB	127	126	12.1	2.93
9	BU	23	89	12.0	2.40
10	SB	92	123	18.5	3.00
11	LM	80	91	25.8	2.84
12	BW	30	32	15.8	1.93
13	MM	119	96	12.9	3.00
14	JR	149	107	8.2	2.95
15	HF	195	79	10.4	2.86
16	AW	114	84	22.5	3.00
17	NS	137	109	19.6	2.94
18	HI	88	98	14.5	2.32
	Mean (SD)	**106 (65)**	**92 (32)**	**17.5 (6.0)**	**2.85 (.42)**

See below for healthy control subjects.

Nr.	Patient	t_0	μ	C	K
Healthy controls					
1	ED	17	233	14.3	2.98
2	BA	92	104	19.1	2.87
3	SJ	92	95	22.1	2.93
4	LA	79	111	17.3	3.00
5	SE	107	112	25.5	3.00
6	FU	40	124	15.1	3.78
7	EA	119	96	17.1	2.98
8	SS	138	64	36.2	2.90
9	DG	112	63	32.9	3.00
10	LK	78	77	17.4	3.94
11	SI	98	90	16.0	2.81
12	UE	74	64	25.3	2.96
13	RML	52	121	12.8	2.47
14	PDM	15	80	15.1	2.92
15	BE	26	109	17.3	2.53
16	SH	127	73	14.9	2.83
17	AW	71	90	24.7	2.88
18	PD	22	141	15.0	2.64
	Mean (SD)	**76 (39)**	**103 (39)**	**19.9 (6.6)**	**2.97 (.36)**

Supplement C: Partial report data (study 2)

Table 11: PR: Demographic and neuropsychological data for individual MCI and AD patients

CDR: Clinical Dementia Rating Scale, global score (Morris, 1993); p: level of significance; M (SD): mean score and standard deviation; Age in years; Education in years; MMSE: Mini Mental State Examination (Folstein et al., 1975), 30-0 points, cut-off ≤ 23; CERAD: The Consortium to Establish a Registry for Alzheimer's Disease (Thalmann & Monsch, 1997), total score; CDT: Clock Drawing Test, 0-6 points, cut-off ≥ 3 (Shulman et al., 1986); CDR sum: sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4: apolipoprotein E4 genotype, positive (24, 34, 44), negative (23, 33); n.a.: not applied; AChEI: acetylcholine esterase inhibitors; SSRI: selective serotonin reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressant; All subjects were right-handers, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Nr.	Patient	Age	Gender	Education	MMSE	CERAD total score	CDT	CDR sum	Age at disease onset	Disease duration	ApoE4 genotype	Medication	
												Dementia	Depression
MCI patients													
1	ZF	58.5	m	13	27	85	1	1.5	54.3	4.2	34	-	-
2	KK	71.9	m	9	28	79	3	1.5	70.3	1.5	34	-	-
3	MC	78.1	m	13	27	71	1	1.5	76.0	2.1	23	-	-
4	RH	64.9	m	10	26	84	1	2.0	57.1	7.8	44	-	SSRI
5	RW	64.4	f	9	28	83	1	3.0	59.7	4.7	44	-	SSRI
6	BDa	75.6	f	13	28	83	2	2.0	73.5	2.2	34	-	-
7	RHB	65.8	m	13	29	85	2	2.0	64.1	1.7	24	-	-
8	HM	59.0	f	9	28	87	3	2.0	56.4	2.6	n.a.	-	-
9	SE	69.1	f	10	28	91	3	1.0	65.9	3.2	33	-	-
10	LE	74.7	f	10	25	79	3	3.0	73.1	1.5	34	-	-
11	FA	65.4	m	13	28	84	2	2.0	62.0	3.4	23	-	-
12	WKH	57.2	m	9	27	93	2	1.5	55.6	1.6	23	-	SSRI
13	RHH	75.4	m	13	26	79	3	2.5	74.4	1.1	34	-	-
14	KJ	66.8	m	9	25	88	3	3.0	64.6	2.3	34	-	SSRI
15	TE	58.7	f	9	29	88	2	1.0	55.9	2.8	44	-	SSRI
16	BDb	77.0	m	13	28	86	2	1.5	73.8	3.2	34	-	-
17	ZU	78.9	f	13	27	89	1	1.5	76.8	2.1	n.a.	-	SSRI
18	FF	67.7	m	13	27	96	1	3.5	65.1	2.5	33	-	-
19	PHa	45.9	m	9	26	93	2	2.5	43.6	2.4	33	-	-
20	RB	66.4	m	13	27	112	2	2.5	63.3	3.1	33	-	-
21	MR	76.2	f	9	30	86	1	1.5	72.0	4.2	33	-	SSRI
22	BU	73.3	f	9	26	90	1	2.0	72.2	1.1	34	-	-
23	SB	71.0	f	13	27	54	3	2.0	70.5	0.5	44	-	-
24	LM	66.1	f	10	28	86	1	2.0	61.6	4.5	34	-	-
25	TO	79.9	m	9	28	64	1	2.5	74.5	5.4	23	-	tricyclica
26	BW	79.0	f	9	29	80	1	1.0	76.5	2.4	34	-	-
27	MM	70.8	f	9	26	86	3	1.0	67.2	3.5	34	-	-
28	JR	68.2	m	9	27	70	3	3.0	66.8	1.4	33	-	-
29	PHb	69.9	f	9	29	81	2	2.0	68.8	1.1	n.a.	-	SSRI
30	AW	67.5	m	13	27	79	2	3.0	63.3	4.2	44	-	-
31	NS	68.4	m	9	30	76	1	1.5	66.3	2.1	33	-	-
32	HI	74.8	f	13	26	66	4	3.0	73.7	1.1	34	-	-
	Mean (SD)	**69.9 (7.6)**	**17 m, 15 f**	**10.8 (1.9)**	**27.4 (1.3)**	**82.9 (10.5)**	**2.0 (.9)**	**2.0 (.7)**	**66.2 (7.9)**	**2.7 (1.5)**	**18+, 11-, 3 n.a.**	**un-medicated**	**8 SSRI, 1 tricyclica, 23 unmedicated**

See below for AD patients.

Nr.	Patient	Age	Gender	Education	MMSE	CERAD total score	CDT	CDR sum	Age at disease onset	Disease duration	ApoE4 genotype	Medication	
												Dementia	Dementia
AD patients													
1	OK	71.4	m	9	25	71	1	4.5	65.9	5.5	34	AChEI	-
2	PA	56.1	m	9	21	71	3	5.0	53.4	2.8	44	AChEI	SSRI
3	RB	55.8	f	9	25	63	4	4.5	52.1	3.7	33	AChEI	-
4	MW	67.1	m	13	.	.	.	5.0	59.1	8.0	44	AChEI	-
5	SU	60.0	f	10	23	72	4	4.0	58.3	1.8	24	AChEI	-
6	LL	79.1	f	9	25	62	3	4.0	78.0	1.1	33	-	-
7	PM	73.0	f	10	25	60	3	5.0	70.8	2.1	34	AChEI	SSRI
8	MK	73.1	f	9	23	67	3	.	72.2	0.8	44	AChEI	NaSSA
9	JH	62.0	f	10	23	70	4	4.0	58.1	3.8	33	AChEI	-
10	CI	65.6	f	9	20	71	5	5.0	59.2	6.4	34	AChEI	-
11	SA	68.2	f	9	25	84	2	3.5	66.1	2.1	34	AChEI	-
12	HJW	57.0	m	10	.	.	.	.	.	.	n.a.	-	-
13	KB	60.6	f	9	22	83	3	3.5	58.4	2.2	44	AChEI	-
14	GT	63.2	m	13	24	76	2	4.0	59.2	3.9	44	-	-
15	GE	80.6	f	9	19	51	4	5.0	78.4	2.1	n.a.	-	-
16	EM	81.5	f	9	19	51	4	5.0	78.4	3.2	33	-	-
	Mean (SD)	**67.1 (8.6)**	**5 m, 11 f**	**9.8 (1.3)**	**22.8 (2.3)**	**68.0 (10.0)**	**3.2 (1.1)**	**4.4 (.6)**	**64.5 (9.1)**	**3.3 (2.0)**	**10+, 4-, 2 n.a.**	**11 AChEI, 5 unmedicated**	**2 SSRI, 1 NaSSA, 13 unmedicated**

Table 12: PR: Exposure durations of individual MCI and AD patients and healthy controls
All stimuli were masked.

Nr.	AD patients	Exposure durations (ms)	Nr.	MCI patients	Exposure durations (ms)	Nr.	Controls	Exposure durations (ms)
1	OK	300	1	ZF	300	1	WS	157
2	PA	300	2	KK	300	2	MS	157
3	RB	600	3	MC	157	3	ED	157
4	MW	300	4	RH	300	4	HD	157
5	SU	300	5	RW	200	5	EH	157
6	LL	600	6	BDa	300	6	RR	129
7	PM	500	7	RHB	300	7	BA	157
8	MK	500	8	HM	157	8	SJ	300
9	JH	586	9	SE	600	9	SK	300
10	CI	500	10	LE	300	10	LA	300
11	SA	400	11	FA	300	11	SE	300
12	HJW	100	12	WKH	500	12	SHa	300
13	KB	700	13	RHH	257	13	KB	71
14	GT	371	14	KJ	300	14	FU	129
15	GE	429	15	TE	300	15	EA	257
16	EM	743	16	BDb	357	16	SS	157
	Mean	**452**	17	ZU	600	17	DG	200
	(SD)	**(171)**	18	FF	300	18	WK	157
			19	PHa	143	19	LK	157
			20	RB	400	20	SI	200
			21	MR	529	21	RML	357
			22	BU	257	22	PDM	114
			23	SB	329	23	BU	157
			24	LM	271	24	BE	200
			25	TO	386	25	KC	357
			26	BW	300	26	SHb	243
			27	MM	414	27	AW	157
			28	JR	457	28	PD	157
			29	PHb	200	29	LD	186
			30	AW	343	30	WH	186
			31	NS	400	31	BH	243
			32	HI	300	32	MH	200
				Mean	**330**	33	HW	143
				(SD)	**(114)**	34	ND	186
						35	LS	229
						36	BM	200
							Mean	**200**
							(SD)	**(69)**

Table 13: PR: Parameters of individual MCI and AD patients and healthy controls

A_{left}/ A_{right}: basic sensory effectiveness in the left and right hemifield, respectively; A_λ: laterality index of sensory effectiveness; w_λ: laterality index of attentional weighting; Dev(w_λ): imbalance index of attentional weighting;

Nr.	Patient	A_{left}	A_{right}	A_λ	w_λ	Dev(w_λ)
AD patients						
1	OK	2.97	4.25	.41	.55	.05
2	PA	2.40	2.75	.47	.80	.30
3	RB	3.83	2.75	.58	.53	.03
4	MW	3.01	2.45	.55	.66	.16
5	SU	3.14	2.06	.60	.74	.24
6	LL	4.55	5.96	.43	.74	.24
7	PM	3.63	2.34	.61	.57	.07
8	MK	3.23	2.57	.56	.72	.22
9	JH	2.71	3.12	.47	.14	.36
10	CI	4.05	4.29	.49	.58	.08
11	SA	2.32	2.06	.53	.43	.07
12	HJW	2.01	2.09	.49	.61	.11
13	KB	2.26	2.84	.44	.54	.04
14	GT	4.46	3.46	.56	.64	.14
15	GE	2.51	3.37	.43	.15	.35
16	EM	2.21	2.44	.48	.59	.09
	Mean (SD)	**3.08 (.81)**	**3.05 (1.04)**	**.51 (.07)**	**.56 (.19)**	**.16 (.11)**

See below for MCI patients.

Nr.	Patient	A_{left}	A_{right}	A_{λ}	w_{λ}	Dev(w_{λ})
MCI patients						
1	ZF	2.11	2.19	.49	.51	.01
2	KK	3.10	3.57	.46	.63	.13
3	MC	1.89	1.28	.60	.66	.16
4	RH	2.24	1.91	.54	.52	.02
5	RW	1.49	1.32	.53	.57	.07
6	BDa	2.95	4.45	.40	.46	.04
7	RHB	1.68	2.20	.43	.55	.05
8	HM	9.85	3.88	.72	.43	.07
9	SE	5.21	2.64	.66	.46	.04
10	LE	2.12	3.02	.41	.57	.07
11	FA	2.06	2.95	.41	.72	.22
12	WKH	3.85	2.87	.57	.31	.19
13	RHH	2.79	2.82	.50	.37	.13
14	KJ	2.04	2.90	.41	.47	.03
15	TE	3.30	4.82	.41	.70	.20
16	BDb	1.97	2.32	.46	.44	.06
17	ZU	3.44	2.65	.56	.55	.05
18	FF	2.50	2.61	.49	.49	.01
19	PHa	2.51	2.77	.48	.49	.01
20	RB	2.67	2.56	.51	.41	.09
21	MR	2.30	2.45	.48	.34	.16
22	BU	2.42	2.19	.53	.62	.12
23	SB	3.56	2.31	.61	.46	.04
24	LM	8.00	5.34	.60	.52	.02
25	TO	2.93	3.69	.44	.68	.18
26	BW	3.78	2.52	.60	.60	.10
27	MM	2.90	2.56	.53	.79	.29
28	JR	2.15	2.30	.48	.58	.08
29	PHb	2.70	2.04	.57	.54	.04
30	AW	4.68	4.00	.54	.18	.32
31	NS	2.48	2.72	.48	.13	.37
32	HI	4.73	2.59	.65	.60	.10
	Mean (SD)	**3.20 (1.76)**	**2.83 (.91)**	**.52 (.08)**	**.51 (.14)**	**.11 (.09)**

See below for healthy control subjects.

Nr.	Patient	A_{left}	A_{right}	A_λ	w_λ	Dev(w_λ)
Healthy controls						
1	WS	2.05	1.75	.54	.41	.09
2	MS	1.66	1.70	.49	.44	.06
3	ED	3.64	3.77	.49	.53	.03
4	HD	3.17	2.87	.52	.50	.00
5	EH	1.47	1.81	.45	.45	.05
6	RR	2.98	2.81	.51	.57	.07
7	BA	1.44	1.66	.46	.51	.01
8	SJ	2.40	3.67	.40	.48	.02
9	SK	3.91	3.96	.50	.57	.07
10	LA	2.23	3.29	.40	.57	.07
11	SE	4.47	3.77	.54	.48	.02
12	SHa	3.08	2.67	.54	.38	.12
13	KB	2.20	1.93	.53	.48	.02
14	FU	2.64	2.77	.49	.60	.10
15	EA	3.23	3.15	.51	.53	.03
16	SS	2.10	2.07	.50	.57	.07
17	DG	3.54	3.06	.54	.53	.03
18	WK	2.23	1.99	.53	.51	.01
19	LK	2.74	2.56	.52	.47	.03
20	SI	4.91	3.42	.59	.47	.03
21	RML	3.22	3.75	.46	.48	.02
22	PDM	2.77	1.91	.59	.43	.07
23	BU	4.83	3.00	.62	.38	.12
24	BE	3.93	3.31	.54	.48	.02
25	KC	2.80	3.10	.47	.47	.03
26	SHb	1.95	1.97	.50	.32	.18
27	AW	2.38	3.06	.44	.54	.04
28	PD	2.56	1.85	.58	.45	.05
29	LD	4.03	5.00	.45	.55	.05
30	WH	2.16	2.47	.47	.45	.05
31	BH	2.21	1.71	.56	.50	.00
32	MH	2.18	1.95	.53	.54	.04
33	HW	3.21	2.90	.53	.45	.05
34	ND	2.79	2.54	.52	.39	.11
35	LS	1.78	1.78	.50	.54	.04
36	BM	1.53	1.45	.51	.47	.03
	Mean (SD)	**2.79 (.92)**	**2.68 (.83)**	**.51 (.05)**	**.49 (.06)**	**.05 (.04)**

Supplement D: TVA-based data and PET imaging (study 3)

Table 14: TVA+PET: Demographic and neuropsychological data for individual MCI and AD patients

CDR: Clinical Dementia Rating Scale, global score (Morris, 1993); p: level of significance; M (SD): mean score and standard deviation; Age in years; Education in years; MMSE: Mini Mental State Examination (Folstein et al., 1975), 30-0 points, cut-off ≤ 23; CERAD: The Consortium to Establish a Registry for Alzheimer's Disease (Thalmann & Monsch, 1997), total score; CDT: Clock Drawing Test, 0-6 points, cut-off ≥ 3 (Shulman et al., 1986); CDR sum: sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4: apolipoprotein E4 genotype, positive (24, 34, 44), negative (23, 33); n.a.: not applied; AChEI: acetylcholine esterase inhibitors; SSRI: selective serotonin reuptake inhibitor; All subjects were right-handers, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Nr.	Group	Patient	Age	Gender	Education	MMSE	CERAD total score	CDT	CDR sum	Age at disease onset	Disease duration	ApoE4 genotype	Medication	
													Dementia	Depression
1	MCI	RH	64.9	m	10	26	84	1	2.0	57.1	7.8	44	-	SSRI
2	MCI	RW	64.4	f	9	28	83	1	3.0	59.7	4.7	44	-	SSRI
3	MCI	BD	75.6	f	13	28	83	2	2.0	73.5	2.2	34	-	-
4	MCI	RHB	65.8	m	13	29	85	2	2.0	64.1	1.7	24	-	-
5	MCI	HM	59.0	f	9	28	87	3	2.0	56.4	2.6	n.a.	-	-
6	MCI	SE	69.1	f	10	28	91	3	1.0	65.9	3.2	33	-	-
7	MCI	LE	74.7	f	10	25	79	3	3.0	73.1	1.5	34	-	-
8	MCI	RHH	75.4	m	13	26	79	3	2.5	74.4	1.1	34	-	-
9	MCI	KJ	66.8	m	9	25	88	3	3.0	64.6	2.3	34	-	SSRI
10	MCI	TE	58.7	f	9	29	88	2	1.0	55.9	2.8	44	-	SSRI
11	MCI	ZU	78.9	f	13	27	89	1	1.5	76.8	2.1	n.a.	-	SSRI
12	MCI	FF	67.7	m	13	27	96	1	3.5	65.1	2.5	33	-	-
13	MCI	PHa	45.9	m	9	26	93	2	2.5	43.6	2.4	33	-	-
14	MCI	RB	66.4	m	13	27	112	2	2.5	63.3	3.1	33	-	-
15	MCI	MR	76.2	f	9	30	86	1	1.5	72.0	4.2	33	-	SSRI
16	MCI	BU	73.3	f	9	26	90	1	2.0	72.2	1.1	34	-	-
17	MCI	SB	71.0	f	13	27	54	3	2.0	70.5	0.5	44	-	-
18	MCI	TO	79.9	m	9	28	64	1	2.5	74.5	5.4	23	-	tricyclica
19	MCI	BW	79.0	f	9	29	80	1	1.0	76.5	2.4	34	-	-
20	MCI	MM	70.8	f	9	26	86	3	1.0	67.2	3.5	34	-	-
21	MCI	JR	68.2	m	9	27	70	3	3.0	66.8	1.4	33	-	-
22	MCI	PHb	69.9	f	9	29	81	2	2.0	68.8	1.1	n.a.	-	SSRI
23	MCI	HI	74.8	f	13	26	66	4	3.0	73.7	1.1	34	-	-
24	AD	PA	56.1	m	9	21	71	3	5.0	53.4	2.8	44	AChEI	SSRI
25	AD	RB	55.8	f	9	25	63	4	4.5	52.1	3.7	33	AChEI	-
26	AD	SU	60.0	f	10	23	72	4	4.0	58.3	1.8	24	AChEI	-
27	AD	CI	65.6	f	9	20	71	5	5.0	59.2	6.4	34	AChEI	-
28	AD	SA	68.2	f	9	25	84	2	3.5	66.1	2.1	34	AChEI	-
29	AD	KB	60.6	f	9	22	83	3	3.5	58.4	2.2	44	AChEI	-
30	AD	GT	63.2	m	13	24	76	2	4.0	59.2	3.9	44	-	-
		Mean (SD)	**67.5 (7.9)**	**11 m, 19 f**	**10.3 (1.8)**	**26.2 (2.4)**	**81.1 (11.5)**	**2.4 (1.1)**	**2.6 (1.1)**	**64.7 (8.3)**	**2.8 (1.6)**	**19+, 8-, 3 n.a.**	**6 AChEI, 24 unmedicated**	**8 SSRI, 1 tricyclica, 21 unmedicated**

Table 15: TVA+PET: Whole and partial report exposure durations of individual MCI and AD patients and healthy controls

In the whole report task, 50% of the trials were masked. In the partial report task, all stimuli were masked.

Nr.	Diagnosis	Patients	Whole report exposure durations (ms)			Partial report exposure durations (ms)	Nr.	Controls	Whole report exposure durations (ms)			Partial report exposure durations (ms)
1	MCI	RH	157	300	600	300	1	WS	157	300	600	157
2	MCI	RW	157	300	600	200	2	MS	157	300	600	157
3	MCI	BD	157	300	600	300	3	ED	157	300	600	157
4	MCI	RHB	157	300	600	300	4	HD	157	300	600	157
5	MCI	HM	86	157	300	157	5	EH	157	300	600	157
6	MCI	SE	300	600	1000	600	6	RR	157	300	600	129
7	MCI	LE	157	300	600	300	7	BA	157	300	600	157
8	MCI	RHH	157	300	600	257	8	SJ	157	300	600	300
9	MCI	KJ	157	300	600	300	9	SK	157	300	600	300
10	MCI	TE	157	300	600	300	10	LA	157	300	600	300
11	MCI	ZU	300	600	1000	600	11	SE	157	300	600	300
12	MCI	FF	86	157	300	300	12	SHa	157	300	600	300
13	MCI	PHa	43	86	157	143	13	KB	86	157	300	71
14	MCI	RB	200	400	700	400	14	FU	157	300	600	129
15	MCI	MR	300	600	1000	529	15	EA	157	300	600	257
16	MCI	BU	86	157	300	257	16	SS	157	300	600	157
17	MCI	SB	157	300	600	329	17	DG	157	300	600	200
18	MCI	TO	171	343	686	386	18	WK	86	157	300	157
19	MCI	BW	129	257	514	300	19	LK	157	300	600	157
20	MCI	MM	186	371	700	414	20	SI	157	300	600	200
21	MCI	JR	229	457	814	457	21	RML	86	157	300	357
22	MCI	PHb	186	371	743	200	22	PDM	71	129	271	114
23	MCI	HI	129	257	529	300	23	BU	114	229	457	157
24	AD	PA	157	300	600	300	24	BE	100	186	371	200
25	AD	RB	157	300	600	600	25	KC	129	257	500	357
26	AD	SU	157	300	600	300	26	SHb	157	386	786	243
27	AD	CI	157	300	600	500	27	AW	114	229	471	157
28	AD	SA	171	343	686	400	28	PD	114	229	457	157
29	AD	KB	200	400	700	700	29	LD	71	157	314	186
30	AD	GT	157	300	600	371	30	WH	114	243	486	186
		Mean	**167**	**325**	**618**	**360**	31	BH	157	300	600	243
		(SD)	**(58)**	**(120)**	**(191)**	**(138)**	32	MH	129	271	514	200
							33	HW	143	286	571	143
							34	ND	129	257	514	186
							35	LS	100	214	429	229
							36	BM	143	286	571	200
								Mean	**135**	**265**	**528**	**200**
								(SD)	**(29)**	**(58)**	**(118)**	**(69)**

Table 16: TVA+PET: Whole and partial report as well as metabolic parameters of individual MCI and AD patients

w_i: laterality index of attentional weighting; A_i: laterality index of sensory effectiveness; TPJ: temporo-parietal junction; IPL: inferior parietal lobe; $\text{TPJ laterality index} = \frac{\text{right TPJ metabolism}}{\text{right TPJ metabolism} + \text{left TPJ metabolism}}$; $\text{IPL laterality index} = \frac{\text{right IPL metabolism}}{\text{right IPL metabolism} + \text{left IPL metabolism}}$;
C: perceptual processing speed (N elements/ sec); *K*: visual short-term memory storage capacity (N elements).

Nr.	Diagnosis	Patients	w_i	A_i	TPJ laterality index	IPL laterality index	*C*	*K*
1	MCI	RH	.52	.54	.497	.509	19.1	2.94
2	MCI	RW	.57	.53	.506	.518	13.3	2.70
3	MCI	BD	.46	.40	.488	.494	20.9	4.00
4	MCI	RHB	.55	.43	.504	.510	11.0	2.48
5	MCI	HM	.43	.72	.493	.506	27.9	2.94
6	MCI	SE	.46	.66	.502	.490	21.2	2.90
7	MCI	LE	.57	.41	.495	.496	9.2	2.34
8	MCI	RHH	.37	.50	.492	.498	23.0	2.81
9	MCI	KJ	.47	.41	.506	.515	13.7	2.94
10	MCI	TE	.70	.41	.493	.489	17.7	2.83
11	MCI	ZU	.55	.56	.501	.506	6.0	2.93
12	MCI	FF	.49	.49	.498	.512	17.5	2.96
13	MCI	PHa	.49	.48	.485	.491	35.4	2.92
14	MCI	RB	.41	.51	.492	.500	12.1	2.93
15	MCI	MR	.34	.48	.498	.487	5.0	2.92
16	MCI	BU	.62	.53	.507	.506	12.0	2.40
17	MCI	SB	.46	.61	.482	.486	18.4	3.00
18	MCI	TO	.68	.44	.507	.492	8.5	2.51
19	MCI	BW	.60	.60	.516	.528	15.7	1.93
20	MCI	MM	.79	.53	.535	.541	12.9	3.00
21	MCI	JR	.58	.48	.500	.515	8.2	2.95
22	MCI	PHb	.54	.57	.496	.515	17.5	3.68
23	MCI	HI	.60	.65	.483	.495	14.5	2.32
24	AD	PA	.80	.47	.510	.493	18.2	2.98
25	AD	RB	.53	.58	.516	.496	11.7	2.99
26	AD	SU	.74	.60	.524	.528	14.7	2.86
27	AD	CI	.58	.49	.460	.479	17.7	2.94
28	AD	SA	.43	.53	.501	.489	8.3	2.53
29	AD	KB	.54	.44	.473	.474	9.6	2.88
30	AD	GT	.64	.56	.494	.497	13.5	2.89
		Mean (SD)	**.55 (.11)**	**.52 (.08)**	**.498 (.015)**	**.502 (.015)**	**15.2 (6.5)**	**2.85 (.38)**

Supplement E: Neuropsychological assessment

Test 1: The Consortium to Establish a Registry for Alzheimer's Disease: Neuropsychological test battery (CERAD-NP; Welsh et al., 1994)

Anwendungs- und Bewertungs-Manual

für die

Neuropsychologische Testbatterie CERAD

Allgemeine Instruktionen

Es muss unbedingt gewährleistet werden, dass die neuropsychologischen Daten, welche von den Testpersonen (TP) und Kontrollgruppen erhoben werden und in die CERAD-Datenbank eingehen, reliabel sind. Deshalb ist es wichtig, dass die Tests, welche die kognitiven Funktionen untersuchen, exakt gemäss den Instruktionen angewendet werden.

Alle CERAD-Aufgaben müssen in ihrer entsprechenden Reihenfolge durchgeführt werden. Ferner muss die gesamte CERAD-Batterie immer **vor** allen anderen neuropsychologischen Tests, welche an den jeweiligen klinischen Zentren verwendet werden, durchgeführt werden. Die Versuchsleiter, welche die Untersuchung mit der Testbatterie durchführen, sollen die TP dazu ermutigen die Aufgaben zu beenden, ohne aber die Testsituation noch mehr zu belasten. Sie sollen neutrale Aufforderungen zur Unterstützung der TP anbieten, wenn eine TP eine Aufgabe nicht erfüllen kann. Ein Feedback für die TP sollte positiv sein, darf aber **keine** Information über die Richtigkeit der Antwort enthalten.
Angemessene Sätze, welche verwendet werden können, sind: **"Das ist gut!"** oder **"Sie machen das ausgezeichnet!"**. Ausserdem müssen die Bewertungsblätter ausserhalb des Sichtfeldes der TP plaziert werden.

ID-Nr.: ☐☐☐☐☐

Initialen Testperson: ☐☐☐

Untersuchungsdatum: ☐☐ ☐☐ ☐☐
Tag Monat Jahr

Name, Vorname Untersucher/-in _____

CERAD

The Consortium to Establish a Registry for Alzheimer's Disease

Neuropsychologische Testbatterie

ID-Nr.: ☐☐☐☐☐ Untersuchungsdatum: ☐☐ Tag ☐☐ Monat ☐☐ Jahr

0. Zusammenfassung der Tests

	Durchgeführte Tests		Nicht durchgeführte Tests			
	Score = 0	Score = > 0	Körperliche Behinderung (Welche?)	Nicht kooperativ	Kognitiv beeinträchtigt	Andere Gründe (Welche?)
1. Verbale Flüssigkeit	0	1	2	3	4	5
2. Boston Naming Test	0	1	2	3	4	5
3. Mini-Mental Status	0	1	2	3	4	5
4. Wortliste Gedächtnis	0	1	2	3	4	5
5. Konstruktive Praxis	0	1	2	3	4	5
6. Wortliste Abrufen	0	1	2	3	4	5
7. Wortliste Wiedererkennen	0	1	2	3	4	5
8. Konstr. Praxis (Abrufen)	0	1	2	3	4	5

Kommentar: _____

1. Verbale Flüssigkeit: Kategorie 'Tiere'

Dieser Test misst einerseits Störungen in der verbalen Produktion, andererseits ist es ein Test zur Untersuchung des semantischen Gedächtnis und der Sprache.

Instruktion:

> **"Ich werde Ihnen eine Kategorie nennen und möchte, dass Sie so schnell Sie können alle Dinge aufzählen, die in diese Kategorie gehören. Wenn ich zum Beispiel 'Kleidungsstücke' sage, können Sie 'Hemd', 'Kravatte' oder 'Hut', usw. aufzählen. Können Sie mir weitere Kleidungsstücke nennen?"**

Warten Sie bis die TP **zwei** Wörter genannt hat. Gelingt es ihr, dann sagen Sie, dass die Antworten korrekt sind und fahren sie mit dem eigentlichen Test **(Kategorie 'Tiere')** fort.
Nennt die TP ein falsches Wort oder gibt eine unpassende Antwort, korrigieren sie die Antwort und wiederholen sie die Instruktion. Misslingt es der TP abermals zu antworten, wiederholen sie die Instruktion ein zweites Mal. Wenn es eindeutig wird, dass die TP die Instruktion immer noch nicht versteht, beenden sie diese Aufgabe und klären sie ab, weshalb dies so ist.

Wenn sie überzeugt sind, dass die TP die Aufgabe versteht und zwei Wörter genannt hat, die Kleidungsstücke bezeichnen, sagen Sie:

> **"Gut! Ich möchte Sie nun bitten, mir alle Dinge aufzuzählen, die zu einer anderen Kategorie gehören nämlich zur Kategorie 'Tiere'. Sie haben eine Minute Zeit. Sind Sie bereit? Bitte beginnen Sie!"**

Die Bearbeitungszeit dieses Tests ist auf 60 Sekunden beschränkt. Hört die TP vor Ablauf dieser Zeit auf, ermutigen Sie sie weitere Wörter zu finden. Nennt er/sie länger als 15 Sekunden keine Tiere, wiederholen Sie die Instruktion (**"Zählen Sie mir alle Tiere auf, die Ihnen in den Sinn kommen"**). Auch wenn die Instruktion während der Untersuchung wiederholt werden muss, wird kein Zeitzuschlag gewährt!

Bewertung:

Im Verlaufsprotokoll werden die Antworten entsprechend den vier 15-Sekunden-Intervallen notiert. Der Punktwert der TP ist die Summe der korrekten Tiernennungen aus jedem 15 Sekunden-Intervall. Korrekt als 'Tier' bewertet wird alles, was lebendig ist und weder Pflanze noch Mineral darstellt. Jeder Vertreter des Tierreiches, real oder fiktiv, jede männliche, weibliche und kindliche Tierbezeichnung, jede Tierart oder -rasse innerhalb einer Spezies wird als richtig bewertet. Ausnahmen bilden Repetitionen und Eigennamen.

Beispiele für die Bewertung:

Antworten	Punkte
Hund	1
Terrier	1
Dackel	1
Köter	1
Grosser Hund	0 - Repetition
Welpe	1
Hündin	1
Fido	0 - Eigenname
Einhorn	1
Amöbe	1
Hundebaby	0 - Repetition
Grizzly	1
Braunbär	1

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1. Verbale Flüssigkeit: Kategorie 'Tiere'

Zeitintervalle:	TIERE			
0 - 15				
16 - 30				
31 - 45				
46 - 60				

Bewertung:	Richtige
0 - 15 Sekunden	☐☐
16 - 30 Sekunden	☐☐
31 - 45 Sekunden	☐☐
46 - 60 Sekunden	☐☐
Total	☐☐

2. 15 Items des Boston Naming Test

Kaplan E, Goodglass H, Weintraub S, Segal O. (1978). Boston Naming Test. Lea & Febiger, Philadelphia.

Dieser Test untersucht die sprachliche Fähigkeit der TP Objekte, welche als Strichzeichnungen vorliegen, zu benennen. Diese Kurzform enthält 15 Items, welche dem Boston Naming Test (Kaplan et al., 1978) entnommen sind. Die Auswahl enthält 5 häufige, 5 mittelhäufige und 5 weniger häufige Items. Jeder TP werden alle 15 Items (siehe Testheft) angeboten. Die richtigen Bezeichnungen der abgebildeten Objekte befinden sich auf dem Antwortblatt.

Instruktion:

"Nun werde ich Ihnen einige Bilder zeigen. Bitte sagen Sie mir, wie diese Dinge heissen."

Fragen Sie bei jedem Bild:

"Wie ist der Name dieses Gegenstandes?" oder **"Wie heisst das?"**

Notieren Sie fortlaufend alle Antworten wörtlich. Ist die Antwort falsch, notieren Sie die Antwort der TP und fahren Sie mit dem nächsten Item fort.
Gewähren Sie pro Bild eine maximale Antwortzeit von 10 Sekunden. Ist die TP nicht in der Lage, das Bild in dieser Zeit zu benennen, ermuntern Sie die TP und gehen Sie zum nächsten Item über. Macht die TP einen Fehler und korrigiert sich selbst spontan, wird die Antwort als richtig gewertet.

Bewertung:

Die Summe aller korrekten Benennungen der häufigen, mittelhäufigen und weniger häufigen Items ergibt den Gesamtwert.

Es dürfen keine semantischen oder phonematischen Hilfen angeboten werden. Eine unspezifische Hilfe darf **nur dann** angeboten werden, wenn die Antwort zu allgemein ist. Zum Beispiel, wenn die TP für das Item 'Kanu' die Antwort 'Boot' gibt, fragen Sie dann: **"Gibt es einen anderen Namen dafür?"**, aber fragen Sie **nicht**: **"Ist dies nicht eine spezielle Art von Boot?"** Müssen Sie eine Hilfe nach einer zu allgemeinen Antwort (z.B. 'Boot') anbieten, wird nur die korrigierte Antwort (z.B. 'Kanu') bewertet. Regionale Varianten von Ausdrücken und Synonyma, falls verifiziert, werden als richtig bewertet.

Beispiele für die Bewertung:

Item	Beispiele für korrekte Antworten
Blume	Rose, Distel
Haus	Schulhaus, Spital
Maske	Larve, Halbmaske
Harmonika	Mundharmonika, Schnurengeige, Maulorgel
Kamel	Dromedar

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2. Boston Naming Test

"Nun werde ich Ihnen einige Bilder zeigen. Bitte sagen Sie mir, wie diese Dinge heissen."
(Notieren Sie alle Antworten wörtlich. Die maximale Bilddarbietungsdauer beträgt 10 Sekunden.)

Bild	Antwort	falsch	richtig
[HÄUFIG]			
Baum	_____	0	1
Bett	_____	0	1
Pfeife	_____	0	1
Blume	_____	0	1
Haus	_____	0	1
[MITTEL]			
Kanu	_____	0	1
Zahnbürste	_____	0	1
Vulkan	_____	0	1
Maske	_____	0	1
Kamel	_____	0	1
[SELTEN]			
Mundharmonika	_____	0	1
Zange	_____	0	1
Hängematte	_____	0	1
Trichter	_____	0	1
Dominosteine	_____	0	1

Richtige Antworten

[HÄUFIG] ☐

[MITTEL] ☐

[SELTEN] ☐

Total ☐☐

Seite 8

3. Mini-Mental Status

Folstein MF, Folstein SE, McHugh PR. "Mini Mental State"- A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12:189-198.

Stellen Sie die Fragen genau so, wie sie aufgeschrieben sind. Die drei Beiblätter können lose von den Untersuchungsbeilagen sein, vergewissern Sie sich aber, dass die CERAD ID-Nr. und das Datum auf jedem Blatt vermerkt sind.

Vorbemerkungen:

ad Fragen:

5) Welchen Monat haben wir? — Sowohl der Monatsname (z.B. 'Juli') als auch die entsprechende Zahl (z.B. der 'siebte' Monat) werden richtig gewertet.

7) ..... Kanton? — Gemeint ist der Kanton in welchem der Test durchgeführt wird. Fragen Sie **nicht** nach dem Heimatkanton!

10) ..... Adresse? — Fragen Sie nach dem "Namen oder der Adresse". Sowohl Name, als auch Adresse werden richtig gewertet.

12) Bewertung des rückwärts buchstabierten Wortes "**PREIS**"
- korrekte Sequenz = 5 Punkte.
- je 1 Fehler für jede Auslassung, Buchstabentranspositionen (Verwechseln benachbarter Buchstaben), Einfügungen (Einfügen eines neuen Buchstaben) oder Fehlplazierungen (Fehlplazierung der Buchstaben **P**, **R**, **E**, **I**, **S** um mehr als nur einen ihm angestammten Platz).

Beispiele: (Punktzahlen in Klammern)

Richtig = **S I E R P** (5)

	Auslassung	Transposition	Einschub	Fehlplazierung
Auslassung	S I R P (4)			
Transposition	S R I P (3)	S I R E P (4)		
Einschub	S I T R P (3)	I E P P R S (3)	S I E E R P (4)	
Fehlplazierung	I R P S (3)	I E P R S (3)	I E P R P S (3)	I E R P S (4)

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3. Mini-Mental Status

Fehler	Richtig	Nicht beurteilbar	
0	1	9	**"Nun möchte ich Ihnen einige Fragen stellen, um Ihr Gedächtnis und Ihre Konzentration zu prüfen. Einige Fragen mögen einfach, andere schwieriger sein."**
0	1	9	1) "Welches Jahr haben wir?" _____
0	1	9	2) "Welche Jahreszeit?" _____
0	1	9	3) "Den wievielten des Monates?" _____
0	1	9	4) "Welcher Wochentag ist heute?" _____
0	1	9	5) "Welcher Monat?" _____
0	1	9	6) "In welchem Land sind wir?" _____
0	1	9	7) "In welchem Kanton?" _____
0	1	9	8) "In welcher Ortschaft?" _____
0	1	9	9) "Auf welchem Stockwerk?" _____
0	1	9	10) "An welchem Ort (Name oder Adresse) befinden wir uns hier?" _____

11) "Ich werde Ihnen nun drei Wörter nennen. Nachdem ich Ihnen diese gesagt habe, möchte ich Sie bitten, sie zu wiederholen. Versuchen Sie sich diese Wörter zu merken; in einigen Minuten werde ich Sie bitten, sich wieder an diese Wörter zu erinnern."

0	1	9	"**Zitrone**"	Bitte wiederholen Sie die Wörter! (Die **erste** Wiederholung ergibt die Punktzahl [1 Punkt pro genanntes Wort]. Werden nicht alle drei Wörter im ersten Versuch nachgesprochen, wiederholen Sie die drei Begriffe bis zu 3 Mal, bis alle Wörter gelernt sind.)
0	1	9	"**Schlüssel**"	
0	1	9	"**Ball**"	

12) "Nun werde ich Ihnen ein Wort nennen und bitte Sie dieses vorwärts und rückwärts zu buchstabieren. Das Wort ist "PREIS". Können Sie es vorwärts buchstabieren? Bitte buchstabieren Sie es jetzt rückwärts!"

(Wiederholen Sie das Wort wenn nötig und helfen Sie, wenn nötig, beim Vorwärtsbuchstabieren.)

Bewertung: Anzahl richtige Buchstaben in der korrekten Reihenfolge:

☐

_____ _____ _____ _____ _____
S I E R P

(0 bis 5; 9 = nicht durchführbar).

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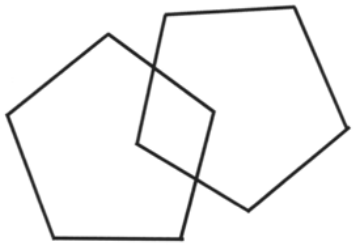
Fehler	Richtig	Nicht beurteilbar	
			"Welches sind die drei Wörter, die Sie sich merken sollten?"
0	1	9	13) " **Zitrone** " _____
0	1	9	14) " **Schlüssel** " _____
0	1	9	15) " **Ball** " _____
0	1	9	16) (Zeigen Sie der TP ihre Armbanduhr) "Was ist das?" _____
0	1	9	17) (Zeigen Sie der TP einen Bleistift) "Was ist das?" _____
0	1	9	18) "Sprechen Sie mir nach: (Der Satz lautet:) '**BITTE KEINE WENN UND ABER** '." Es ist **nur ein Versuch** erlaubt!
0	1	9	19) "Lesen Sie bitte was auf diesem Blatt steht und führen Sie es aus!" (Auf dem Blatt steht:) "**SCHLIESSEN SIE IHRE AUGEN** " **Richtig ist** , wenn die TP die Augen **schliesst** !
			20) "Ich werde Ihnen ein Blatt Papier geben. Wenn ich es Ihnen gebe, nehmen Sie es bitte mit der rechten Hand,
0	1	9	**Rechte Hand** falten Sie es mit beiden Händen und
0	1	9	**Falten** legen es dann auf Ihren Schoss!"
0	1	9	**Auf Schoss** Lesen Sie zuerst die vollständige Instruktion und reichen Sie **erst dann** der TP das Blatt mit beiden Händen. Wiederholen Sie weder die Instruktion, noch leiten Sie die TP an.
0	1	9	21) "Schreiben Sie bitte irgendeinen vollständigen Satz auf dieses Blatt Papier!"
0	1	9	22) "Hier ist eine Figur. Bitte zeichnen Sie diese Figur auf dem gleichen Blatt Papier ab!" Richtig ist, wenn die zwei sich überlappenden Fünfecke ein Viereck bilden und alle Ecken der Fünfecke vorhanden sind.

☐☐ **Total** (Summe aller Punkte der 22 Fragen, ausgeschlossen sind Scores von '9'.)

Schliessen Sie Ihre Augen



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4. Wortliste Gedächtnis

Dieser Wortlisten-Gedächtnistest mit zehn alltäglichen Begriffen dient dazu, die Fähigkeit der TP zu untersuchen, neu gelernte Information zu erinnern. Um sicher zu stellen, dass die TP mit den Wörtern vertraut ist und diese auch möglichst gut aufnimmt, wird sie gebeten, die Wörter einzeln aus dem Testheft vorzulesen. Die zehn Wörter werden in gleichmässiger Geschwindigkeit nacheinander präsentiert. Unmittelbar nach der Präsentation der Wörter bitten Sie die TP, so viele wie möglich zu erinnern. Die Reihenfolge spielt dabei keine Rolle.
(Denjenigen TPen, die aufgrund einer Sehbehinderung oder minimaler Bildung die Wörter nicht lesen können, werden die Wörter vom Testleiter vorgelesen und die TPen müssen die Wörter laut wiederholen. Allerdings ist festzuhalten, dass diese Vorgehensweise nicht dem laut lesen lassen entspricht, kommt der Originalaufgabe aber am nächsten. Auf diese Weise ist es möglich auch sehbehinderte und wenig gebildete TPen zu untersuchen, welche sonst nicht getestet werden könnten).
Es gibt **drei** Durchgänge, in jedem werden die Wörter in einer anderen Reihenfolge präsentiert.

Die **Instruktion** für den ersten Durchgang lautet:

> **"Ich werde Ihnen zehn Wörter zeigen. Lesen Sie bitte jedes Wort laut vor, wenn ich es Ihnen zeige. Danach werde ich Sie bitten, alle diese zehn Wörter aus dem Gedächtnis abzurufen."**

Zeigen Sie der TP die Wörter des ersten Durchganges im Abstand von zwei Sekunden. Sollte die TP ein Wort nicht lesen können, lesen Sie es ihr/ihm vor und vermerken Sie es auf dem Antwortblatt für das entsprechende Wort in der Spalte "Kann nicht lesen". Nachdem das letzte Wort gelesen wurde, soll die TP versuchen, möglichst viele dieser Wörter zu erinnnern. Die TP hat maximal 90 Sekunden Zeit. Verfahren Sie dann in gleicher Weise mit dem zweiten und dritten Durchgang dieser Wörter; ändern Sie Ihre Instruktion ein wenig, um die TP zu ermutigen.

Der Punktwert der TP ergibt sich aus der Summe der richtig erinnerten Wörter pro Durchgang. Vermerken Sie auch bei jedem Durchgang die Anzahl Wörter, welche die TP "erinnert", die aber nicht in der Liste enthalten sind (Intrusionen).

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4. Wortliste Gedächtnis

Instruktion:

"Ich werde Ihnen zehn Wörter zeigen. Lesen Sie bitte jedes Wort laut vor, wenn ich es Ihnen zeige. Danach werde ich Sie bitten, diese zehn Wörter aus dem Gedächtnis abzurufen."

Expositionszeit: je 1 Wort im Abstand von 2 Sekunden
Erinnerungszeit: maximum 90 Sekunden pro Durchgang

⟵ Nummerieren Sie jedes Wort so, wie es erinnert wurde ⟶

Kann nicht lesen	1. Durchgang	2. Durchgang	3. Durchgang
☐	Butter ☐	Karte ☐	Königin ☐
☐	Arm ☐	Hütte ☐	Gras ☐
☐	Strand ☐	Butter ☐	Arm ☐
☐	Brief ☐	Strand ☐	Hütte ☐
☐	Königin ☐	Motor ☐	Stange ☐
☐	Hütte ☐	Arm ☐	Strand ☐
☐	Stange ☐	Königin ☐	Butter ☐
☐	Karte ☐	Brief ☐	Motor ☐
☐	Gras ☐	Stange ☐	Karte ☐
☐	Motor ☐	Gras ☐	Brief ☐
Intrusionen:	.....	.....	.....
	.....	.....	.....
	.....	.....	.....
	.....	.....	.....
	.....	.....	.....
Total:			
☐☐ <= Kann nicht lesen			
Richtige =>	☐☐	☐☐	☐☐
Intrusionen =>	☐☐	☐☐	☐☐

5. Konstruktive Praxis

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease.
American Journal of Psychiatry 1984;11:1356-64.

Diese vier einfachen geometrischen Figuren von Rosen (1984) werden benutzt, um die konstruktive Praxis zu untersuchen, welche bei der Demenz beeinträchtigt ist. Die vier Figuren nehmen in ihrer Komplexität zu, so dass sowohl Patienten mit milderen als auch schwereren Beeinträchtigungen beurteilt werden können.

Instruktionen:
Zeigen Sie der TP das Blatt mit dem Kreis *(Figur 1)* und sagen Sie, indem Sie auf die untere leere Hälfte des Blattes zeigen:

"Hier ist ein Kreis. Bitte zeichnen Sie ihn hier direkt darunter ab!"

Die meisten TP können einen geschlossenen Kreis zeichnen.

Zeigen Sie der TP das Blatt mit dem Rhombus *(Figur 2)* und sagen Sie:

"Hier haben wir die Zeichnung eines Rhombus. Zeichnen Sie sie ebenfalls so gut es geht darunter ab."

Hat die TP diese Figur abgezeichnet, zeigen Sie ihr das Blatt mit den sich überschneidenden Rechtecken *(Figur 3)*:

"Gut! Und nun zeichnen Sie bitte auch diese dritte Figur!"

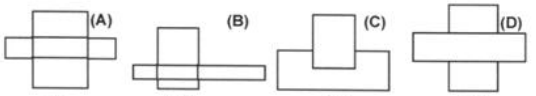
Nach der Figur der sich überschneidenden Rechtecke zeigen Sie der TP das Blatt mit dem Würfel *(Figur 4)*:

"Nun kommt die schwierigste Figur, die Sie zeichnen sollen. Lassen Sie sich Zeit!"

Lassen Sie der TP für jede zu kopierende Figur maximal 2 Minuten Zeit. Wiederholen Sie die Instruktion **einmal**, wenn die TP die Aufgabe nicht beim ersten Mal versteht. Es ist den TPen erlaubt, Fehler zu korrigieren, weshalb für diese Aufgabe ein Bleistift verwendet werden muss. Wenn die TP mehrere Male beginnt, ist dies erlaubt, ermutigen Sie sie/ihn aber **nicht** dazu. Bewertet wird der letzte Versuch oder diejenige Figur, welche von der TP als diejenige mit der Vorlage am besten übereinstimmend, angegeben wird.

Bewertung (spezielle Details):

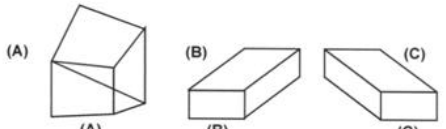
Figur 1 *(='Kreis')* **und 2** *(='Rhombus')*: zwischen den Linien einer Figur werden Lücken von 3 mm akzeptiert.
Figur 3 *(='Rechtecke')*:



1. Beide Rechtecke haben 4 Seiten (=
2. Die Überschneidung entspricht in

	(A)	(B)	(C)	(D)
	1	1	0	0
	1	1	0	1
Score	2	2	0	1

Figur 4 *(= 'Würfel')*:



* Die Frontseite kann links- oder rechtherum orientiert sein. Dies ist abhängig von der individuellen Sichtweise.

1. Dreidimensionalität (= 1 Punkt)
2. Vorderseite korrekt orientiert (= 1 Punkt)*
3. Innere Linien korrekt gezeichnet (= 1 Punkt)
4. Gegenüberliegende Seiten sind parallel (= 1 Punkt)

	(A)	(B)	(C)
	0	1	1
	1	1	1
	0	0	0
	0	1	1
Score	1	3	3

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5. Konstruktive Praxis

	Falsch	Richtig
Figur 1: 'Kreis'		
a) geschlossener Kreis (Lücken ≤ 3 Milimeter)	0	1
b) annähernd kreisförmig	0	1
Figur 2: 'Rhombus'		
a) vier Seiten vorhanden	0	1
b) geschlossene Linien (Lücken ≤ 3 Milimeter)	0	1
c) Seiten alle etwa gleich lang	0	1
Figur 3: 'Rechtecke'		
a) beide Figuren haben vier Seiten	0	1
b) überschneidende Rechtecke sehen dem Original ähnlich	0	1
Figur 4: 'Würfel'		
a) Figur ist dreidimensional	0	1
b) Frontseite korrekt orientiert (egal ob links- oder rechtsorientiert)	0	1
c) innere Linien sind korrekt gezeichnet	0	1
d) die gegenüberliegenden Seiten sind parallel (innerhalb 10°)	0	1

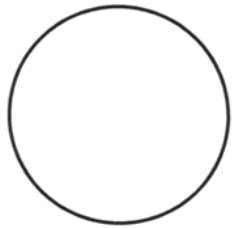
Total richtig:

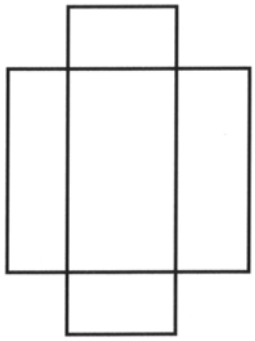
Figur 1 ('Kreis') ☐

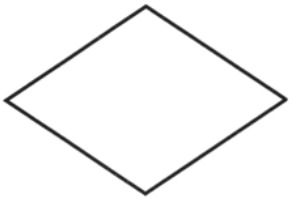
Figur 2 ('Rhombus') ☐

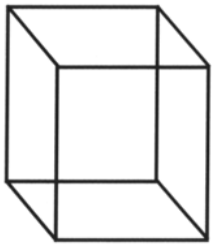
Figur 3 ('Rechtecke') ☐

Figur 4 ('Würfel') ☐









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6. Wortliste Abrufen

Das Ziel dieser Aufgabe ist es festzustellen, wie gut sich die TP noch an die Wörter von **Aufgabe 4** erinnern kann.

Die **Instruktion** für diese Erinnerungsaufgabe lautet:

> **"Vor wenigen Minuten habe ich Sie gebeten, eine Liste von 10 Wörtern zu lernen, die Sie eins nach dem anderen von verschiedenen Kärtchen vorgelesen haben. Jetzt möchte ich Sie bitten, sich an diese Wörter zu erinnern und möglichst viele dieser 10 Wörter aufzuzählen!"**

Die TP hat für diese Aufgabe 90 Sekunden Zeit. Die erinnerten Wörter werden auf dem Antwortbogen entsprechend der durch die TP reproduzierten Reihenfolge numeriert.

Bewertung:

Die Summe der richtig erinnerten Wörter ergibt den Punktwert.
Notieren und bewerten Sie ebenfalls Wörter, welche durch die TP aufgezählt werden, die aber **nicht** auf dieser Liste figurierten (= Intrusionen!).

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6. Wortliste Abrufen

Instruktion:

> **"Vor wenigen Minuten habe ich Sie gebeten, eine Liste von 10 Wörtern zu lernen, die Sie eins nach dem anderen von verschiedenen Kärtchen vorgelesen haben. Jetzt möchte ich Sie bitten, sich an diese Wörter zu erinnern und möglichst viele dieser 10 Wörter aufzuzählen!"**

Zeitlimite: 90 Sekunden

	Nummerieren Sie die Wörter entsprechend der Nennung durch die TP
Butter	☐
Arm	☐
Strand	☐
Brief	☐
Königin	☐
Hütte	☐
Stange	☐
Karte	☐
Gras	☐
Motor	☐

Intrusionen: ....
....
....
....

Total:

Richtige: ☐☐

Intrusionen: ☐☐

7. Wortliste Wiedererkennen

Die **Instruktion** für diesen Erkennungstest lautet:

> **"Als nächstes werde ich Ihnen eine Reihe von auf Kärtchen geschriebenen Wörtern zeigen. Einige davon sind Wörter, die Sie auf der früheren Liste schon gesehen haben und einige sind Wörter, die ich Ihnen noch nicht gezeigt habe. Ich möchte Sie bitten, mir diejenigen Wörter zu nennen, die Sie auf der früheren Liste bereits gesehen haben, und welche dieser Wörter neu sind."** (Zeigen Sie nun die erste Karte mit dem ersten Wort ['Kirche']). **"Ist das eines der Wörter, das sie vorher schon gesehen haben?"**

Wiederholen Sie bei jedem Wort diese letzte Frage oder sagen Sie:

> **"Und wie ist es mit diesem Wort?"**

Notieren Sie sich die Antworten der TP auf dem Antwortblatt.

Bewertung:

Die Bewertung für diesen Test berücksichtigt die richtig erkannten Wörter, die zuvor auch gesehen wurden (richtige **'Ja'**-Antworten [= 'hit']) und die Anzahl der korrekt zurückgewiesenen neuen Wörter (richtige **'Nein'**-Antworten [= 'correct rejection']).

Fordern Sie die TP dazu auf, die Frage mit **'Ja'** oder **'Nein'** zu beantworten, weil **"Ich weiss es nicht"**-Antworten nicht bewertbar sind.

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8. Konstruktive Praxis (Abrufen)

"Vor einiger Zeit habe ich Ihnen auf separaten Blättern einige Zeichnungen gezeigt. Sie mussten sie sich ansehen und dann auf dem gleichen Blatt Papier abzeichnen. Erinnern Sie sich noch an diese Figuren? Ich möchte Sie nun bitten, diese Figuren aus dem Gedächtnis auf dieses Blatt Papier zu zeichnen."

	Erinnert		Erinnert mit Cue*	
	Nein	Ja	Nein	Ja
1. "Kreis"				
a) geschlossener Kreis	0	1	0	1
b) zirkuläre Form	0	1	0	1
2. "Rhombus"				
a) vier Seiten vorhanden	0	1	0	1
b) alle Winkel geschlossen	0	1	0	1
c) alle Seiten etwa gleich lang	0	1	0	1
3. "Rechtecke"				
a) beide Figuren haben vier Seiten	0	1	0	1
b) Überschneidung entspricht in etwa dem Original	0	1	0	1
4. "Würfel"				
a) Figur ist dreidimensional	0	1	0	1
b) Frontseite korrekt orientiert	0	1	0	1
c) innere Linien sind korrekt gezeichnet	0	1	0	1
d) die gegenüberliegenden Seiten sind parallel (innerhalb 10°)	0	1	0	1

* Wird eine der obigen Figuren ausgelassen, geben Sie der TP neutrale Gedächtnisstützen, wie z.B.:
"Erinnern Sie sich noch an andere Figuren?"

Zeichnet die TP die 5-Eck-Figuren aus dem MMS, bewerten Sie sie nach untenstehender Formel.
Werden die 5-Eck-Figuren aus dem MMS nicht gezeichnet, fragen Sie die TP:
"Waren da noch andere Zeichnungen?"

5. "Fünfecke"				
a) zwei fünfseitige Figuren	0	1	0	1
b) sich überschneidend	0	1	0	1
c) der sich überschneidende Teil ist eine Figur mit vier Seiten	0	1	0	1

Total Richtig: Item 1 ☐ Item 2 ☐ Item 3 ☐ Item 4 ☐ Item 5 ☐

Zusammenfassung der CERAD-NP Resultate

Name des Zentrums: _____ Zentrum-Nr.: _____ (*)
Name d. Unters.: _____ Tel.nummer: _____
Initialen Testperson (Name/Vorname): _____ ID-Nr.: _____
Alter (in Jahren): _____ Schule u. Ausbildung (in Jahren): _____ Geschlecht (W/M): _____
Diagnose: _____
Dauer der Krankheit (in Monaten): _____ Untersuchungsdatum (Tag/Monat/Jahr): _____

(*) = bitte leer lassen

1. Verbale Flüssigkeit (Anzahl korrekte Wörter)
0 - 15 Sekunden: _____
16 - 30 Sekunden: _____
31 - 45 Sekunden: _____
46 - 60 Sekunden: _____
Total korrekt (1 Minute): _____

2. Boston Naming Test (Anzahl richtige Antworten)
"HÄUFIG": _____/ 5
"MITTEL": _____/ 5
"SELTEN": _____/ 5
Total Boston Naming Test: _____/ **15**

3. Mini-Mental Status (**total**): _____/ **30**

4. Wortliste Gedächtnis

	Durchgang 1	Durchgang 2	Durchgang 3	**Total** (1-3)
Richtige:	_____/ **10**	_____/ **10**	_____/ **10**	_____/ **30**
Intrusionen:	_____	_____	_____	_____

5. Konstruktive Praxis
'Kreis': _____/ 2
'Rhombus': _____/ 3
'Rechtecke': _____/ 2
'Würfel': _____/ 4
Total Konstruktive Praxis: _____/ **11**

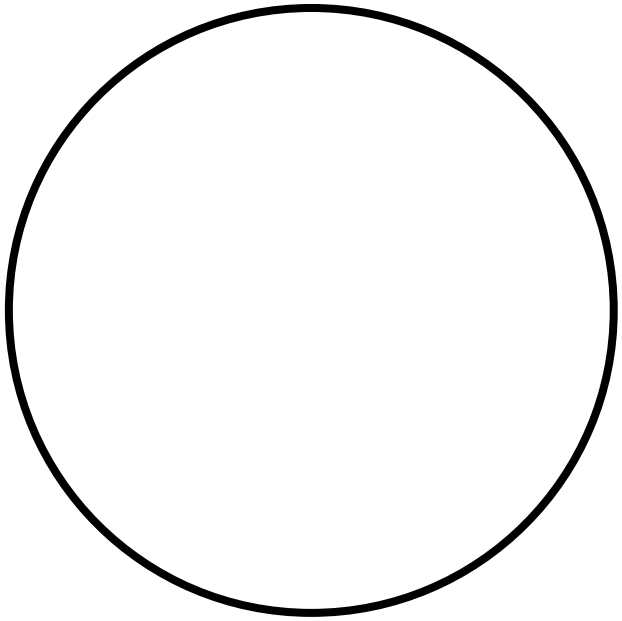
6. Wortliste Abrufen
Richtige: _____/ **10**
Intrusionen: _____

7. Wortliste Wiedererkennen
Anzahl richtige "JA" (Hits, richtig Positive): _____/ **10**
Anzahl richtige "NEIN" (Correct rejections, richtig Negative): _____/ **10**

8. Konstruktive Praxis (Abrufen)
'Kreis': _____/ 2
'Rhombus': _____/ 3
'Rechtecke': _____/ 2
'Würfel': _____/ 4
'Fünfecke': _____/ 3
Total Konstruktive Praxis (Abrufen): _____/ **14**

Bemerkungen; für Diagnose verwendete Tests: _____

Test 2: Clock Drawing Test (CDT; Shulman et al., 1993)

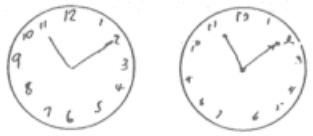
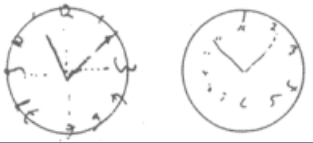
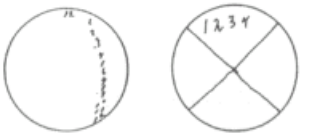


Der Uhren-Test (modifiziert nach Shulman 1993)

Anweisungen zur Durchführung:

1. Geben Sie dem Patienten ein Blatt Papier mit einem vorgezeichneten Kreis. Zeigen Sie ihm, wo oben und unten ist.
2. Geben Sie dem Patienten folgende Anweisung: „Dies soll eine Uhr sein. Ich möchte Sie bitten, in diese Uhr die fehlenden Ziffern zu schreiben. Zeichnen Sie danach die Uhrzeit ‚10 nach 11' ein."
3. Machen Sie sich Notizen zur Ausführung der gestellten Aufgabe (Reihenfolge, Korrekturen etc.).
4. Bewerten Sie die angefertigte Zeichnung gemäß der untenstehenden Kriterien. Notieren Sie den Score zusammen mit Datum und Namen des Patienten auf dem Zeichenblatt.
5. Der validierte Cut-Off zur Unterscheidung zwischen Normalbefund einerseits und kognitiver Beeinträchtigung im Sinnes einer evtl. vorliegenden Demenz andererseits liegt zwischen 2 und 3. Anders ausgedrückt: Ein Score von ≥ 3 Punkten ist als pathologisch anzusehen.

Bewertung (1 = ohne Fehler, 6 = keine Uhr erkennbar)

Score	Beschreibung	Beispiele
1	**„perfekt“** • Ziffern 1 – 12 richtig eingezeichnet • zwei Zeiger, die die richtige Uhrzeit anzeigen	
2	**leichte visuell-räumliche Fehler** • Abstände zwischen Ziffern nicht gleichmäßig • Ziffern außerhalb des Kreises • Blatt wird gedreht, so dass Ziffern auf d. Kopf stehen • Pat. verwendet Linien („Speichen") zur Orientierung	
3	**Fehlerhafte Uhrzeit bei erhaltener visuell-räumlicher Darstellung der Uhr** • nur ein Zeiger • „10 nach 11" oder ähnliches als Text eingegeben • keine Uhrzeit eingezeichnet	
4	**Mittelgradige visuell-räumliche Desorganisation, so dass ein korrektes Einzeichnen der Uhrzeit unmöglich wird** • unregelmäßige Zwischenräume • Ziffern vergessen Perserveration; wiederholt den Kreis, Ziff. jenseits der 12 • Rechts-Links-Umkehr (Ziffern gegen den Uhrzeigersinn) • Dysgraphie – keine lesbare Darstellung der Ziffern	
5	**Schwergradige visuell-räumliche Desorganisation** • wie unter (4) beschrieben, aber stärker ausgeprägt	
6	**keinerlei Darstellung einer Uhr** **(cave: Ausschluss Depression / Delir!)** kein wie auch immer gearteter Versuch, eine Uhr zu zeichnen • keine entfernte Ähnlichkeit mit einer Uhr • Pat. schreibt Wort oder Name	

Literatur:
1. Shulman, K.I., Shedletsky, R., & Silver, I.L. (1986). The challenge of time: Clock-drawing and cognitive function in the elderly. *International Journal of Geriatric Psychiatry*, 1(2), 135-140.
2. Shulman, K.I., Gold, D.P., Cohen, C.A., & Zucchero, C.A. (1993). Clock-drawing and dementia in the community: a longitudinal study. *International Journal of Geriatric Psychiatry*, 8(6), 487-496.
3. Brodaty, H., & Moore, C.M. (1997). The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. *International Journal of Geriatric Psychiatry*, 12(6), 619-627.

Test 3: Clinical Dementia Rating Scale (CDR; Morris, 1993)

Bewerten Sie nur die Verschlechterung im Vergleich zum früheren Zustand, die auf kognitive Beeinträchtigung zurückzuführen ist, nicht die Beeinträchtigung aus anderen Gründen.

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Fragebogen zur Klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zum Orientierungsvermögen an die befragte Person:

Wie oft kann er/sie Folgendes genau benennen:

1. Das Datum?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
2. Den Monat?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
3. Das Jahr?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
4. Den Wochentag?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
5. Hat er/sie Schwierigkeiten, Ereignisse zeitlich zueinander in Beziehung zu setzen?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
6. Findet er/sie sich in vertrauten Straßen zurecht?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
7. Wie oft weiß er/sie, wie man außerhalb seiner/ihrer vertrauten Umgebung von einem Ort zum anderen kommt?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht
8. Wie oft findet er/sie sich in einem vertrauten Gebäude zurecht?
   ☐Meistens ja ☐Manchmal ☐Selten ☐Weiß ich nicht

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zum Leben in der Gemeinschaft an die befragte Person:

Berufstätigkeit

1. Arbeitet der Patient/die Patientin noch? ☐Ja ☐Nein ☐Nicht zutreffend
   Wenn nicht zutreffend, machen Sie bitte weiter mit Frage 4
   Wenn ja, machen Sie bitte weiter mit Frage 3
   Wenn nein, machen Sie bitte weiter mit Frage 2
2. Haben Probleme mit dem Gedächtnis oder mit dem Denkvermögen zu dem Entschluss des Patienten/der Patientin beigetragen, in den Ruhestand zu gehen? ☐Ja ☐Nein ☐Weiß ich nicht
   (Bitte weiter mit Frage 4)
3. Hat der Patient /die Patientin deutliche Probleme bei seiner/ihrer Arbeit aufgrund von Problemen mit dem Gedächtnis oder dem Denkvermögen?
   ☐Selten oder Nie ☐Manchmal ☐Meistens ja ☐Weiß ich nicht

Soziale Eigenständigkeit

4. Ist er/sie jemals Auto gefahren? ☐Ja ☐Nein
   Fährt der Patient / die Patientin heute noch Auto? ☐Ja ☐Nein
   Wenn nein, ist dies so aufgrund von Problemen mit dem Gedächtnis oder dem Denkvermögen? ☐Ja ☐Nein
5. Wenn er/sie immer noch fährt, gibt es Probleme oder Risiken aufgrund des schlechten Denkvermögens? ☐Ja ☐Nein
6. *Kann er/sie selbständig die Dinge einkaufen, die er/sie braucht?
   ☐Selten oder Nie (muss bei jedem Einkauf begleitet werden) ☐Manchmal (geht geringe Menge an Artikeln einkaufen, kauft Artikel doppelt oder vergisst benötigte Artikel) ☐Meistens ja ☐Weiß ich nicht
7. Kann er/sie selbständig Aktivitäten außerhalb von zu Hause durchführen?
   ☐Selten oder Nie (kann im Allgemeinen ohne Hilfe keine Aktivitäten ausüben) ☐Manchmal (eingeschränkt und/oder Routine, z.B. oberflächliche Teilnahme an Kirchgängen oder Treffen; Fahrten zum Friseur) ☐Meistens ja (sinnvolle Teilnahme an Aktivitäten, z.B. zur Wahl gehen) ☐Weiß ich nicht
8. Wird er/sie zu Feiern außerhalb von zu Hause mitgenommen? ☐Ja ☐Nein
   Wenn nein, warum nicht? _____
9. Würde jemand, der das Verhalten des Patienten/der Patientin zufällig beobachtet, denken, dass er/sie krank ist? ☐Ja ☐Nein
10. Wenn in einem Pflegeheim, nimmt er/sie aktiv an Festen teil (geistig anwesend)? ☐Ja ☐Nein

WICHTIG:
Sind genug Angaben verfügbar, um zu beurteilen, inwieweit das Leben des Patienten/der Patientin in der Gemeinschaft beeinträchtigt ist?
Wenn nicht, fragen Sie bitte weiter nach.

Leben in der Gemeinschaft: Kirchgänge, Besuche bei Freunden oder Verwandten, politische Aktivitäten, Berufsorganisationen, Vereine, Hilfsorganisationen, etc.

*Bitte wenn nötig das Funktionsniveau des Patienten/der Patientin in diesem Bereich mit Kommentaren verdeutlichen.

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz (CDR)©

Dies ist ein semi-strukturiertes Interview. Bitte stellen Sie alle Fragen, ohne Ausnahme. Stellen Sie auch alle zusätzlichen Fragen, die nötig sind, um den Schweregrad der Demenz des Patienten/der Patientin festzustellen. Notieren Sie bitte alle Angaben, die Sie durch die zusätzlichen Fragen erhalten.

Fragen zum Gedächtnis an die befragte Person:

1. Hat er/sie Probleme mit dem Gedächtnis oder mit dem Denkvermögen? ☐Ja ☐Nein
1a. Wenn ja, treten diese Probleme ständig auf (nicht nur ab und zu)? ☐Ja ☐Nein
2. Kann er/sie sich an Dinge erinnern, die kürzlich passiert sind? ☐Meistens ja ☐Manchmal ☐Selten
3. Kann er/ sie eine kurze Liste mit Dingen (Einkaufsliste) im Kopf behalten? ☐Meistens ja ☐Manchmal ☐Selten
4. Ist sein/ihr Gedächtnis im letzten Jahr schlechter geworden? ☐Ja ☐Nein
5. Ist sein/ihr Gedächtnis so stark beeinträchtigt, dass es die Ausübung seiner/ihrer Alltagsaktivitäten vor ein paar Jahren (oder der Aktivitäten vor dem Ruhestand) beeinträchtigt hätte? (Meinung zusätzlicher Quellen) ☐Ja ☐Nein
6. Vergisst er/sie ein größeres Ereignis (z.B. eine kurze Reise, ein Fest, eine Hochzeit in der Familie) innerhalb von wenigen Wochen nach diesem Ereignis? ☐Meistens ja ☐Manchmal ☐Selten
7. Vergisst er/sie relevante Details dieses Ereignisses? ☐Meistens ja ☐Manchmal ☐Selten
8. Vergisst er/sie wichtige Ereignisse oder Daten aus der weiter zurückliegenden Vergangenheit vollkommen (z.B. Geburtstag, Hochzeitstag, Arbeitsplatz)? ☐Meistens ja ☐Manchmal ☐Selten
9. Bitte erzählen Sie mir von einem Ereignis aus seinem/ihrem Leben, das kürzlich stattgefunden hat und an das er/sie sich erinnern sollte. (Fragen Sie für spätere Vergleiche mit den Antworten des Patienten nach Details wie dem Ort des Ereignisses, der Tageszeit, nach Beteiligten, wie lange das Ereignis gedauert hat, wann es zuende war und wie der Patient/die Patientin oder andere Beteiligte dorthin gelangten.)
   Zeitraum innerhalb einer Woche: _____
   Zeitraum innerhalb eines Monats: _____
10. Wann wurde er/sie geboren? _____
11. Wo wurde er/sie geboren? _____
12. Welche Schule hat er/sie zuletzt besucht?
    Name _____
    Ort _____
    Klasse _____
13. Was war sein/ihr Hauptberuf (oder der des Partners/der Partnerin, falls der Patient/die Patientin nicht berufstätig war)? _____
14. Was war seine/ihre letzte hauptsächliche Anstellung/Arbeit (oder die des Partners/der Partnerin, falls der Patient/die Patientin nicht berufstätig war)? _____
15. Wann ging er/sie (oder der Partner/die Partnerin) in den Ruhestand und warum? _____

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zur Körperpflege an die befragte Person:

*Wie schätzen Sie seine/ihre Fähigkeiten in den folgenden Bereichen ein:

		Ohne Hilfe	Knöpft gelegentlich falsch zu, usw.	Falsche Reihenfolge vergisst oft Kleidungsstücke	Kann sich nicht anziehen
A.	Anziehen (The Dementia Scale of Blessed)	0	1	2	3

		Ohne Hilfe	Muss aufgefordert werden	Benötigt manchmal Hilfe	Benötigt immer oder fast immer Hilfe
B.	Waschen, Körperpflege	0	1	2	3

		Sauber; benutzt das entsprechende Besteck	Unsauber; Löffel	Einfache feste Nahrung	Muss vollständig gefüttert werden
C.	Essgewohnheiten	0	1	2	3

		Normale, vollständige Kontrolle	Nässt gelegentlich das Bett ein	Nässt häufig das Bett ein	Sowohl Harn- als auch Stuhlinkontinenz
D.	Schließmuskelkontrolle (The Dementia Scale of Blessed)	0	1	2	3

*Wenn die Körperpflege des Patienten/der Patientin im Vergleich zu früher beeinträchtigt ist, kann ein Wert von 1 in Frage kommen, auch wenn der Patient/die Patientin keine Aufforderung benötigt.

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zur Urteilsfähigkeit und Problembewältigung an die befragte Person:

1. Wenn Sie ganz allgemein seine/ihre derzeitige Fähigkeit beurteilen sollten, Probleme zu lösen, würden Sie sagen sie ist:
   - ☐ So gut wie immer
   - ☐ Gut, aber nicht so gut wie früher
   - ☐ Einigermaßen
   - ☐ Schlecht
   - ☐ Nicht vorhanden
2. Beurteilen Sie bitte seine/ihre Fähigkeit, mit kleineren Geldmengen umzugehen (z.B. die Menge des Wechselgelds richtig einzuschätzen, ein kleines Trinkgeld zu geben):
   - ☐ Nicht weniger geworden
   - ☐ Etwas weniger geworden
   - ☐ Sehr viel weniger geworden
3. Beurteilen Sie bitte seine/ihre Fähigkeit, mit komplizierten finanziellen oder geschäftlichen Vorgängen umzugehen (z.B. Kontoauszüge überprüfen, Rechnungen bezahlen):
   - ☐ Nicht weniger geworden
   - ☐ Etwas weniger geworden
   - ☐ Sehr viel weniger geworden
4. Kann er/sie mit Notfällen im Haushalt fertig werden (z.B. tropfende Wasserleitung, kleines Feuer)?
   - ☐ So gut wie früher
   - ☐ Schlechter als früher, weil er/sie Probleme mit dem Denkvermögen hat
   - ☐ Schlechter als früher, aus einem anderen Grund (warum) _____
5. Kann er/sie Situationen oder Erklärungen verstehen?
   ☐ Meistens ja ☐ Manchmal ☐ Selten ☐ Weiß ich nicht
6. Verhält* er/sie sich angemessen [d.h. so, wie er/sie sich normalerweise (vor der Krankheit) verhalten hat] in Situationen mit anderen Menschen und im Umgang mit anderen Menschen?
   ☐ Meistens ja ☐ Manchmal ☐ Selten ☐ Weiß ich nicht

*dieses Item beurteilt Verhalten und nicht die äußere Erscheinung.

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zum Orientierungsvermögen an den Patienten/die Patientin:

Bitte notieren Sie die Antwort des Patienten/der Patientin bei jeder Frage wörtlich.

1. Welches Datum haben wir heute? ☐Richtig ☐Falsch

2. Welcher Wochentag ist heute? ☐Richtig ☐Falsch

3. Welchen Monat haben wir? ☐Richtig ☐Falsch

4. Welches Jahr haben wir? ☐Richtig ☐Falsch

5. Wo sind wir hier? ☐Richtig ☐Falsch

6. In welcher Stadt sind wir hier? ☐Richtig ☐Falsch

7. Wie spät ist es? ☐Richtig ☐Falsch

8. Weiß der Patient/die Patientin, wer die befragte Person ist (nach Ihrer Einschätzung)? ☐Richtig ☐Falsch

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zu Haushalt und Hobbys an die befragte Person:

1a. Was hat sich verändert an seinen/ihren Fähigkeiten, Aufgaben im Haushalt auszuführen? _____

1b. Was kann er/sie immer noch gut? _____

2a. Was hat sich verändert an seinen/ihren Fähigkeiten, Hobbys zu betreiben? _____

2b. Was kann er/sie immer noch gut? _____

3. Wenn im Pflegeheim, was kann er/sie nicht mehr so gut (im Haushalt und bei Hobbys)? _____

Alltagsaktivitäten (The Dementia Scale of Blessed):

	Nicht weniger geworden		Sehr viel weniger geworden
4. Fähigkeit, Aufgaben im Haushalt durchzuführen	0	0.5	1

Bitte beschreiben Sie: _____

5. Ist er/sie in der Lage, Aufgaben im Haushalt wie folgt durchzuführen:
(Kreuzen Sie eine Antwort an. Die befragte Person muss nicht direkt gefragt werden).

☐ Keine Fähigkeiten von Bedeutung
(erledigt auch einfache Aufgaben, wie Betten machen, nur mit sehr viel Anleitung)

☐ Fähigkeiten nur in eingeschränkten Aktivitäten
(wäscht mit Anleitung das Geschirr, so dass es annehmbar sauber ist; deckt den Tisch)

☐ Zeigt bei einigen Aktivitäten Selbständigkeit
(benutzt Haushaltsgeräte, z.B. einen Staubsauger, bereitet einfache Mahlzeiten zu)

☐ Kann normale Aktivitäten durchführen, allerdings nicht auf normalem Niveau

☐ Normale Fähigkeiten bei normalen Aktivitäten

WICHTIG:

Sind genug Angaben verfügbar, um den Beeinträchtigungsgrad des Patienten/der Patientin im Haushalt und bei Hobbys zu beurteilen?
Wenn nicht, fragen Sie bitte weiter nach.

Aufgaben im Haushalt: z.B. Kochen, Wäsche machen, sauber machen, Lebensmittel einkaufen, Müll wegbringen, Gartenarbeit, kleinere Reparaturen im Haushalt.

Hobbys: Nähen, Malen, Handarbeiten, Lesen, Gäste haben, Photographieren, Gartenarbeit, ins Theater oder in ein Konzert gehen, Holzarbeiten, Sport.

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zum Urteilsvermögen und zur Problembewältigung an den Patienten/die Patientin:

Anleitung: Wenn die erste Antwort eine Bewertung mit 0 nicht rechtfertigt, fragen Sie nach, um zu erkennen, inwieweit der Patient/die Patientin das Problem versteht. Kreuzen Sie die zutreffendste Antwort an.

Ähnlichkeiten:

Beispiel: "Worin gleichen sich ein Bleistift und ein Kugelschreiber?" (Schreibwerkzeuge)

"Worin gleichen sich die folgenden Dinge?" — Antwort des Patienten/der Patientin

1. Möhre.... Blumenkohl
   (0 = Gemüse)
   (1 = essbare Nahrungsmittel, Pflanzen, kann man kochen, etc.)
   (2 = antwortet nicht zum Thema; Unterschiede; man kann sie kaufen)

2. Schreibtisch .... Regal
   (0 = Möbel, Büromöbel; in beide kann man Bücher stellen)
   (1 = sind aus Holz)
   (2 = nicht zum Thema, Unterschiede)

Unterschiede:

Beispiel: "Was ist der Unterschied zwischen Zucker und Essig?" (süß und sauer)

"Worin besteht der Unterschied zwischen folgenden Dingen?" — Antwort des Patienten/der Patientin

3. Lüge .... Fehler
   (0 = eins ist Absicht, eins unbeabsichtigt)
   (1 = eins ist schlecht, das andere gut; oder erklärt nur eins von beiden)
   (2 = irgend etwas anderes, Ähnlichkeiten)

4. Fluss .... Kanal
   (0 = natürlich - künstlich)
   (2 = irgend etwas anderes)

Rechnen:

5. Wieviel 5-Pfenning-Stücke sind eine Mark? ☐Richtig ☐Falsch

6. Wieviele 50-Pfennig-Stücke sind DM 15,50? ☐Richtig ☐Falsch

7. Ziehen Sie 3 von 20 ab und ziehen Sie weiter immer wieder 3 ab, bis es nicht mehr weiter geht. ☐Richtig ☐Falsch

Urteilsvermögen:

8. Sie kommen in einer fremden Stadt an und möchten herausfinden, wo ein Freund von Ihnen wohnt, den Sie sehen möchten. Was tun Sie?
   (0 = versuche es mit dem Telefonbuch, dem Adressbuch, frage in der Stadtverwaltung nach; rufe einen gemeinsamen Freund an)
   (1 = rufe die Polizei, rufe die Auskunft an (gibt normalerweise keine Adressen))
   (2 = keine klare Antwort)

9. Wie beurteilt der Patient/die Patientin seine Behinderung und seine Stellung im Leben und inwieweit versteht er/sie, warum er/sie bei dieser Untersuchung ist (Ihrer Meinung nach, auch wenn dieser Bereich bereits gefragt wurde):
   ☐Zeigt gute Einsicht ☐Zeigt teilweise Einsicht ☐Zeigt wenig Einsicht

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Fragebogen zur klinischen Einschätzung des Schweregrades einer Demenz©

Fragen zum Gedächtnis an den Patienten/die Patientin:

1. Haben Sie Probleme mit dem Gedächtnis oder mit dem Denken? ☐Ja ☐Nein

2. Vor einigen Minuten erzählte mir Ihr/e (Partner/in, etc.) von einigen Erlebnissen, die Sie kürzlich hatten. Könnten Sie mir etwas darüber erzählen? (Fragen Sie nach Details, wenn nötig, wie etwa dem Ort des Geschehens, der Tageszeit, Beteiligten, wie lange das Ereignis dauerte, wann es zu Ende war und wie der Patient/die Patientin und andere Beteiligte dorthin kamen.)

   Innerhalb einer Woche:

   1.0 -größtenteils richtig _____

   0.5 _____

   0.0 -größtenteils nicht richtig _____

   Innerhalb eines Monats:

   1.0 -größtenteils richtig _____

   0.5 _____

   0.0 -größtenteils nicht richtig _____

3. Ich möchte Sie jetzt bitten, sich einen Namen und eine Adresse für ein paar Minuten zu merken. Wiederholen Sie bitte so, wie ich es Ihnen vorspreche: (Wiederholen Sie beides, bis es richtig wiederholt wurde, oder bis zu maximal drei Versuchen.)

Elemente	1	2	3	4	5
	Hans	Müller	Am Markt	42	Hamburg
	Hans	Müller	Am Markt	42	Hamburg
	Hans	Müller	Am Markt	42	Hamburg

(Unterstreichen Sie die Elemente, die bei jedem Versuch richtig wiedergegeben wurden.)

4. Wann wurden Sie geboren? _____

5. Wo wurden Sie geboren? _____

6. Welche Schule haben Sie zuletzt besucht?

   Name _____

   Ort _____ Klasse _____

7. Was war Ihr Hauptberuf (oder der des Partners/der Partnerin, falls nicht berufstätig)? _____

8. Was war Ihre letzte hauptsächliche Anstellung/Arbeit (oder die des Partners/der Partnerin, falls nicht berufstätig)? _____

9. Wann gingen Sie (oder der Partner/die Partnerin) in den Ruhestand und warum? _____

10. Wiederholen Sie bitte den Namen und die Adresse, die Sie sich merken sollten:

Elemente	1	2	3	4	5
	Hans	Müller	Am Markt	42	Hamburg

(Unterstreichen Sie die Elemente, die richtig wiedergegeben wurden.)

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Clinical psychologist April till October 2005	Clinic for Neurology and Neurological Rehabilitation of the County Hospital in Günzburg
Seminar facilitator October 2004 till March 2005	Professional Training Center of the Bavarian Economy /Berufliches Fortbildungszentrum der Bayerischen Wirtschaft, bfz (professional rehabilitation for adults) in Munich
Research assistant May till September 2004	Department of Biological Psychology, Clinical Psychology and Neuropsychology at the Catholic University of Eichstätt-Ingolstadt

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Erklärungen (Declarations)

Erklärung in Bezugnahme auf Studie 1 (Kapitel 4, S. 31 ff.)

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Bestätigung

Es ist mir eine große Freude zu bestätigen, dass Frau Dipl.-Psych. **Petra Redel** an dem Artikel **„Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease"**, erschienen 2009 in der Zeitschrift *Neurobiology of Aging* (doi:10.1016/j.neurobiolaging.2009.07.012) einen wesentlichen Beitrag hatte. Sie war an der Konzeption und allen Phasen der Durchführung und Auswertung der Studie entscheidend beteiligt und hat auch an der Formulierung aller Abschnitte des Manuskripts prägend mitgewirkt. Ich danke ihr außerordentlich für ihre Mitarbeit, ohne die eine Publikation nicht möglich gewesen wäre.

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Persönliche eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass die Dissertation mit dem Titel „Erfassung visueller Aufmerksamkeitsleistungen bei Patienten mit ‚Mild Cognitive Impairment' und Alzheimer Demenz basierend auf der Theorie der visuellen Aufmerksamkeit" (englischer Originaltitle: „Visual attentional assessment in mild cognitive impairment and Alzheimer's disease based on a theory of visual attention") selbständig und ohne unerlaubte fremde Hilfe angefertigt und keine anderen, als die von mir angegebenen Schriften und Hilfsmittel benutzt wurden. Die den benutzten Werken wörtlich und inhaltlich entnommenen Stellen sind kenntlich gemacht.

Die Dissertation hat in gleicher oder ähnlicher Form noch keiner anderen Fakultät/ Fachbereichskommission vorgelegen. Teile der Dissertation haben nicht bereits als Teile der Magisterarbeit vorgelegen.

Petra Redel

Eichstätt, November 2009