



## Deficits of spatial and task-related attentional selection in mild cognitive impairment and Alzheimer's disease

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### Abstract

Visual selective attention was assessed with a partial-report task in patients with probable Alzheimer's disease (AD), amnesic mild cognitive impairment (MCI), and healthy elderly controls. Based on Bundesen's "theory of visual attention" (TVA), two parameters were derived: 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 the right hemifield.

Compared with controls, MCI patients showed significantly reduced top-down controlled selection, which was further deteriorated in AD subjects. Moreover, attentional weighting was significantly unbalanced across hemifields in MCI and tended to be more lateralized in AD. Across MCI and AD patients, carriers of the apolipoprotein E  $\epsilon 4$  allele (ApoE4) displayed a leftward spatial bias, which was the more pronounced the younger the ApoE4-positive patients and the earlier disease onset.

These results indicate that impaired top-down control may be linked to early dysfunction of fronto-parietal networks. An early temporo-parietal interhemispheric asymmetry might cause a pathological spatial bias which is associated with ApoE4 genotype and may therefore function as early cognitive marker of upcoming AD.

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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 et al., 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  $\epsilon 4$  allele (ApoE4) have a 3 (heterozygotes) to 15 times (homozygotes) higher risk of developing the disease, compared with non-carriers. In both variants, the neuropathological basis of AD is an accumulation of  $\beta$ -amyloid ( $A\beta$ ) either due to a lifelong overproduction (familial variant) or a failure of the clearance (sporadic form) of  $A\beta$  (Blennow et al., 2006).

Mild cognitive impairment (MCI) is considered a 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 amnesic type bears a high risk for subjects to develop

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AD (Gauthier et al., 2006). The highest risk, with an annual conversion rate to AD of up to 30%, is borne by amnesic MCI patients with multiple domains affected (Mitchell et al., 2009). Nevertheless, even amnesic MCI is considered a heterogeneous concept that also comprises nonprogressive subjects and subjects converting to forms of dementia other than the Alzheimer type (Mitchell et al., 2009; Tabert et al., 2006).

Selection of a limited number of objects (out of the multitude of stimuli being present) in a visual scene is a fundamental function of attention for the control of ongoing behavior. Selection of objects may be controlled by the task set, which specifies criteria of which stimuli are relevant targets (e.g. red letters) and which to-be-ignored distractors (e.g. green letters); this is referred to as task-related, or top-down controlled, selection. By contrast, visuospatial selection depends on the distribution of attention across the visual field, where attention might be equally distributed (e.g. healthy subjects) or biased towards one hemifield (e.g. neglect patients). 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 and 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 et al., 2002). AD patients have been shown to suffer from a reduced spatial attentional window (Rizzo et al., 2000) and to present difficulties in disengaging attention from invalidly cued locations (Tales et al., 2005). Drago et al. (2008) reported that the capacity to reallocate spatial attention was 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 hemi-spatial neglect (Bartolomeo et al., 1998; Ishiai et al., 2000; Mendez et al., 1997; Venneri et al., 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 our 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 irrele-

vant 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 mechanisms 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 et al., 2004; Minati et al., 2009). In contrast to inferences from rather indirect measures of task-related selection (e.g. inferred from dissimilar v. similar distractors), our 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, we employed a task requiring partial-report of briefly presented letters, based on Bundesen's (1990) formal "theory of visual attention" (TVA). The TVA-based approach permits parametric estimates of visual attentional selection to be derived from performance in this simple psychophysical task (see Method section 1.2), that reflect both spatial (parameter spatial attentional weighting across the visual field) and task-related aspects (parameter top-down control) of attentional processing. In this way, comparability of conditions was ensured for interpreting separable aspects of selective attention in both MCI and AD subjects. Although important insights have been gained in the field of MCI and AD based on response time (RT) measures (e.g. Gorus et al., 2008), arguably, the TVA-based approach adopted in the present study offers at least two advantages. First, the partial-report paradigm does not rely on RT-based assessment and thus eliminates a general slowing of motor performance as a potentially confounding factor. Second, by individually adjusting the stimulus presentation times, comparable levels of task difficulty can be ensured across subjects.

In a previous study, we had already, successfully, applied this approach to investigate patients with a subcortical type of dementia, Huntington's disease (Finke et al., 2006). Furthermore, a related TVA-based whole report paradigm had proved to be sensitive to revealing visual attentional capacity reductions in both MCI and AD patients (Bublak et al., 2009). Therefore, we deemed this method to be appropriate for assessing spatial and task-related aspects of attentional processing in subjects at different stages of cortical degeneration: amnesic 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) and Bundesen (1998). On this account, 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" factors (e.g. a single

red element among green ones) or intentional, “top-down” factors (e.g. a search for a known face in a crowd). In TVA, task-related selection of a visual object is synonymous with its encoding into a visual short-term memory (VSTM) store with limited capacity. This store can hold only a small number of objects, which represent what is consciously “perceived” (and, thus, reportable) at a given moment. According to TVA, all visual objects compete for encoding into VSTM, but only those processed fastest will enter the store and are, thus, consciously represented. The probability of selection is determined (i) by an object’s processing rate  $v$ , which depends on the relative attentional weight ( $w$ ) the object receives. The relative weight of an object is defined as a certain proportion of the total weight distributed across all objects within the whole visual field. Consequently, increasing the relative weight of a specific object  $x$  decreases the weights of the other objects. This biases the race for selection in favor of object  $x$ , which has, thus, a higher probability of being selected. The probability of selection is also determined (ii) by the capacity of the VSTM store. Once the store is filled to capacity, the race for selection terminates. Because of this parallel and capacity-limited processing, only a subset of the (initially) nonconsciously processed objects will be represented within VSTM. Only this subset is available for further processing and goal-directed actions, such as verbal report.

TVA provides parameters for characterizing specific aspects of attentional weighting, in particular: (i) task-related weighting for prioritizing the processing of task-relevant visual target objects at the expense of distractor objects (top-down control), and (ii) the ability to process objects from both visual hemifields equally, which is indicated by the (balanced) spatial distribution of attentional weights across the left and the right hemifield. 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 prespecified (e.g. with respect to color), while ignoring distractors.

Employing this task, the present study was designed to complement a previous TVA-based investigation of visual processing capacity in MCI and AD using a whole-report task (Bublak et al., 2009), which does not allow for selective weighting of stimuli to be examined. We applied the partial-report paradigm in patients with amnesic MCI, probable AD, and healthy control subjects. In patients, we also assessed the possible influence of genetic risk on attentional weighting 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 neurodegenerative, namely Huntington’s, disease and the direction and degree of spatial attentional weighting. Therefore, we examined whether ApoE4 carriers in our clinical groups might exhibit more pronounced deficits in

spatial and/or task-related attentional weighting than clinical non-carriers of the ApoE4 allele.

## 1. Experimental procedures

### 1.1. Subjects

Forty-eight patients with the clinical diagnosis of amnesic MCI or probable AD, respectively, were recruited from the Memory Clinic of the Department of Psychiatry, Technische Universität München, Germany. Thirty-two MCI and 16 AD patients as well as 36 healthy elderly controls took part in the study. All subjects 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) including the Mini Mental State Examination (MMSE; Folstein et al., 1975), and the Clock-Drawing Test (CDT; Shulman et al., 1986) 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), structural brain imaging (MRI), and blood tests.

All AD patients fulfilled the criteria of probable dementia (CDR global score  $\geq 1$ ) of the Alzheimer type based on the diagnostic criteria of the ICD-10 classification of mental and behavioral disorders for dementia, 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 (11 single-domain amnesic MCI patients and 21 multiple-domain amnesic MCI patients) according to Petersen (2000, 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 such as stroke or substance abuse or MRI evidence of brain lesions possibly affecting cognitive functions (e.g. vascular abnormalities).

Table 1  
Overview of biographical and clinical details

	AD ( <i>n</i> = 16, CDR $\geq$ 1)	MCI ( <i>n</i> = 32, CDR = 0.5)	Control ( <i>n</i> = 36)	<i>P</i>
Age,	67.1 (8.6)	69.0 (7.6)	67.2 (6.6)	> 0.55
M (SD), range	55.8–81.5	45.9–79.9	50.0–82.0	
Gender	5 M, 11 F	17 M, 15 F	16 M, 20 F	> 0.35
Education,	9.8 (1.3)	10.8 (1.9)	10.5 (2.1)	> 0.20
M (SD), range	9–13	9–13	7–13	
Handedness	all R	all R	all R	
MMSE,	22.8 (2.3)	27.4 (1.3)	29.0 (1.0)	< 0.01
M (SD), range	19–25	25–30	27–30	
CERAD,	68.0 (10.0)	82.9 (10.5)	n.a.	< 0.01
M (SD), range	51–84	54–112		
CDT,	3.2 (1.1)	2.0 (.9)	n.a.	< 0.01
M (SD), range	1–5	1–4		
CDR sum,	4.4 (.6)	2.0 (.7)	n.a.	< 0.01
M (SD), range	3.5–5.0	1.0–3.5		
Age at onset,	64.5 (9.1)	66.2 (7.9)	—	> 0.50
M (SD), range	52.1–78.4	43.6–76.8		
Disease duration,	3.3 (2.0)	2.7 (1.5)	—	> 0.25
M (SD), range	0.8–8.0	0.5–7.8		
ApoE4 genotype	10+/4–/2 n.a.	18+/11–/3 n.a.	n.a.	> 0.75

CDR, Clinical Dementia Rating Scale global score [2]; *p*, level of significance; M (SD), mean score and standard deviation; Age in years; M, male; F, female; Education in years; Handedness, according to the Edinburgh Handedness Inventory [3]; R, right-hander; MMSE, Mini Mental State Examination [1], 30–0 points, cut-off  $\leq$  23; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease [5], total score; n.a., not applied; CDT, Clock Drawing Test, 0–6 points, cutoff  $\geq$  3 [4]; CDR sum, sum of CDR category scores; Age at disease onset in years; Disease duration in years; ApoE4, apolipoprotein E4 genotype, positive (+), negative (–).

None of the MCI patients was medicated with antidepressants, but 11 (69%) AD patients were treated with acetylcholine esterase inhibitors (AChEI). Due to mild symptoms of depression, nine 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, nine MCI and 6 AD patients received antihypertensive medication. As can be seen in Table 1, 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 was recruited by word-of-mouth recommendation, flyers and notices. None of the control subjects reported a neurological or psychiatric history, and none were medicated. All subjects had normal or corrected-to-normal vision. MCI and AD patients as well as control 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 1. 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, see 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.

## 1.2. 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., 2005; Finke et al., 2006).

### 1.2.1. Task

In Figure 1, 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.

### 1.2.2. Procedure

First, subjects were instructed to fixate a central white cross (0.3° visual angle) presented for 300 ms (see Figure 1A). Then, after a gap of 100 ms, red and/or green letters (0.5° high  $\times$  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

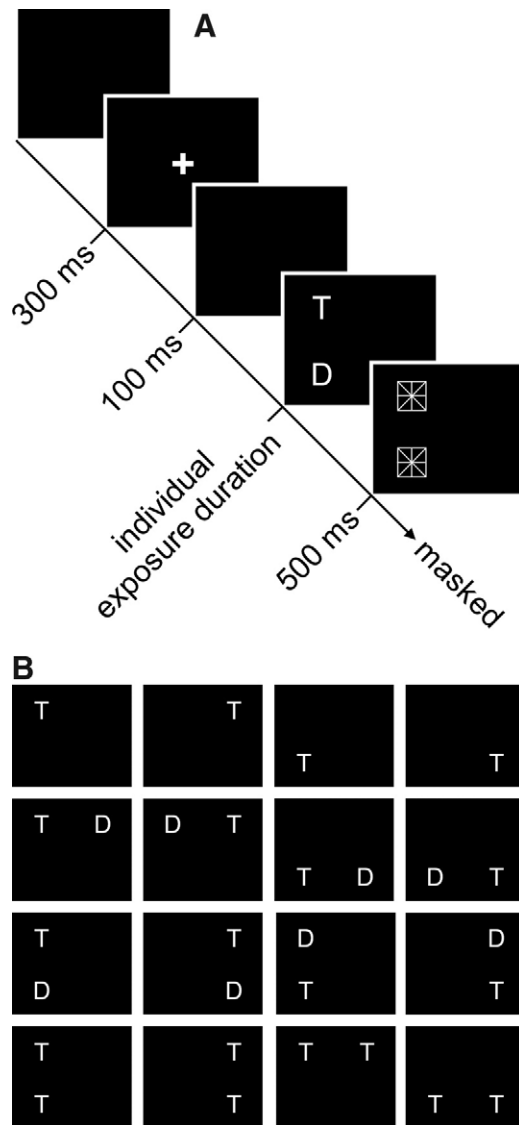


Fig. 1. (A) Partial-report paradigm with (B) 16 trial types: four single target (depicted as “T”, always red), eight target plus distractor (depicted as “D”, always green) and four dual target conditions.

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.

The total number of trials was 288, divided into blocks of 48 trials each. Within each block, the 16 different trial types were presented equally often (with 18 trials each) and in

randomized order. On each trial, a single red target, or a target plus a green distractor, or two red targets (see Figure 1B) were presented at the corners of an imaginary square with an edge length of  $5^\circ$ , 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 to avoid anticipatory responses by the subjects.

### 1.2.3. Stimuli

From the prefixed set “ABEFHJKLMNPRSTWXYZ”, the letters for a given trial were randomly chosen, 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  $0.5^\circ$  filled with a “+” and an “x”, which were presented for 500 ms at each stimulus location after stimulus presentation.

### 1.2.4. Apparatus

Stimuli were presented on a personal computer with a 17” monitor ( $1,024 \times 768$  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.

### 1.3. Estimation of theory of visual attention-based parameters

The individual assessment of performance accuracy across the different partial-report conditions (see Figure 1B) was modeled by a TVA-based algorithm using a maximum likelihood method (e.g. Ross, 2000). Detailed descriptions of the model fitting procedure and the software used, can be found in Kyllingsbæk (2006). By fitting TVA to individual raw datasets, 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 the right hemifield. Additionally, parameter estimates for basic sensory effectiveness reflecting the processing rate for each hemifield are provided to differentiate between true attentional (spatial distribution of attention) and pure sensory effects of stimulus processing (e.g. processing bias due to reduced contrast sensitivity in one eye).

The qualitative pattern of each group’s performance was quantitatively described by a TVA-based model that produced, individually for each subject, estimates of attentional weights  $w_i$  separately for each of the four display locations and separately for targets and distractors. Similarly, for each subject, estimates of basic 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  $r = 0.87$  (SD = 0.11) for controls, of  $r = 0.92$  (SD = 0.11) for MCI patients and of  $r = 0.95$  (SD = 0.04) for AD patients. The predicted values accounted for  $r^2 = 77\%$  (SD = 0.17) of the variance of the observed mean score in controls, for  $r^2 = 85\%$  (SD = 0.16) in MCI patients and  $r^2 = 91\%$  (SD = 0.07) in AD patients.

### 1.3.1. Task-related weighting

Parameter  $\alpha$ , 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  $\alpha$  values indicate more efficient top-down control. Unselective processing, by contrast, would give rise to equally weighted target and distractor processing, increasing  $\alpha$  to approach one. A value of  $\alpha$  greater than one would indicate that the subject actually prioritizes the task-irrelevant distractors.

### 1.3.2. Spatial weighting

The spatial distribution of attentional weighting,  $w_\lambda$ , is estimated from performance in conditions in which subjects have to report stimuli presented either unilaterally, on either visual hemispace, or bilaterally, in the left and the right hemifield. From the accuracy of target identification, separate attentional weights are derived for the left ( $w_{\text{left}}$ ) and the right hemifield ( $w_{\text{right}}$ ). The absolute attentional weighting has no meaning; only relative intraindividual values can be compared. Therefore, a laterality index was computed from the raw data of the  $w$  estimates: parameter  $w_\lambda$ , reflecting the laterality of the spatial distribution of attentional weights. It is defined as the ratio  $w_{\text{left}}/(w_{\text{left}} + w_{\text{right}})$ . Hence, a value of  $w_\lambda = 0.5$  indicates balanced weighting ( $w_{\text{left}} = w_{\text{right}}$ ), values of  $w_\lambda > 0.5$  indicate a leftward and values of  $w_\lambda < 0.5$  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. In AD with bilateral neurodegenerative processes, single patients might show a dysbalance to either hemifield, that reflects either predominantly right- or left-sided neural damage, rather than suffering from a systematic spatial bias to a specific hemifield. Thus, we computed the absolute deviation of  $w_\lambda$  from the optimum value 0.5 in any direction,  $\text{Dev}(w_\lambda)$ , as an index of the subject's general ability to attend equivalently to both hemifields (see also Finke et al., 2005).

### 1.3.3. Basic 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 basic sensory effectiveness ( $A$ , reflecting the processing rate) of an object (Duncan et al., 1999), which is independent of its attentional weight. 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. Concep-

tually, the estimates of  $A$  are measures of basic sensory effectiveness and thus are related to accuracy on a single element presented alone, rather than to performance losses in multielement displays.

According to TVA, a spatial bias may be caused by attentional weights being reduced for one compared with the other hemifield (Duncan et al., 1999), unbalancing the competition between objects on the 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 (Eqn. 2 of Bundesen, 1990). To decide between these possibilities (true attentional or pure sensory effects of stimulus processing), values of  $A_{\text{right}}$  and  $A_{\text{left}}$  were calculated, that is, the mean values of basic sensory effectiveness for the upper and lower positions in the left and the right hemifield, respectively. In addition, a laterality index for sensory effectiveness ( $A_\lambda$ ) was computed as the ratio  $A_{\text{left}}/(A_{\text{left}} + A_{\text{right}})$ . Thus, a laterality value above 0.5 reflects a lateralization of sensory effectiveness to the left, and a value below 0.5 a lateralization to the right visual hemifield. To test for sensory accuracy loss in either of the two hemifields, we computed the absolute deviation of  $A_\lambda$  from the balanced value 0.5 in any direction,  $\text{Dev}(A_\lambda)$ , as an index of a given subject's general degree of balance/imbalance in sensory effectiveness between the two hemifields.

## 2. Results

The Results 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 additional information about the clinical relevance of the TVA parameters, we also document their relationship with external clinical measures and cognitive tests. Furthermore, to assess whether the parameters are related to possible underlying gene-associated pathology, we examine the effect of ApoE4 genotype on the parameter values.

### 2.1. Task-related weighting

In this section, we present the findings pertaining to the ability to do 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  $\alpha$ .

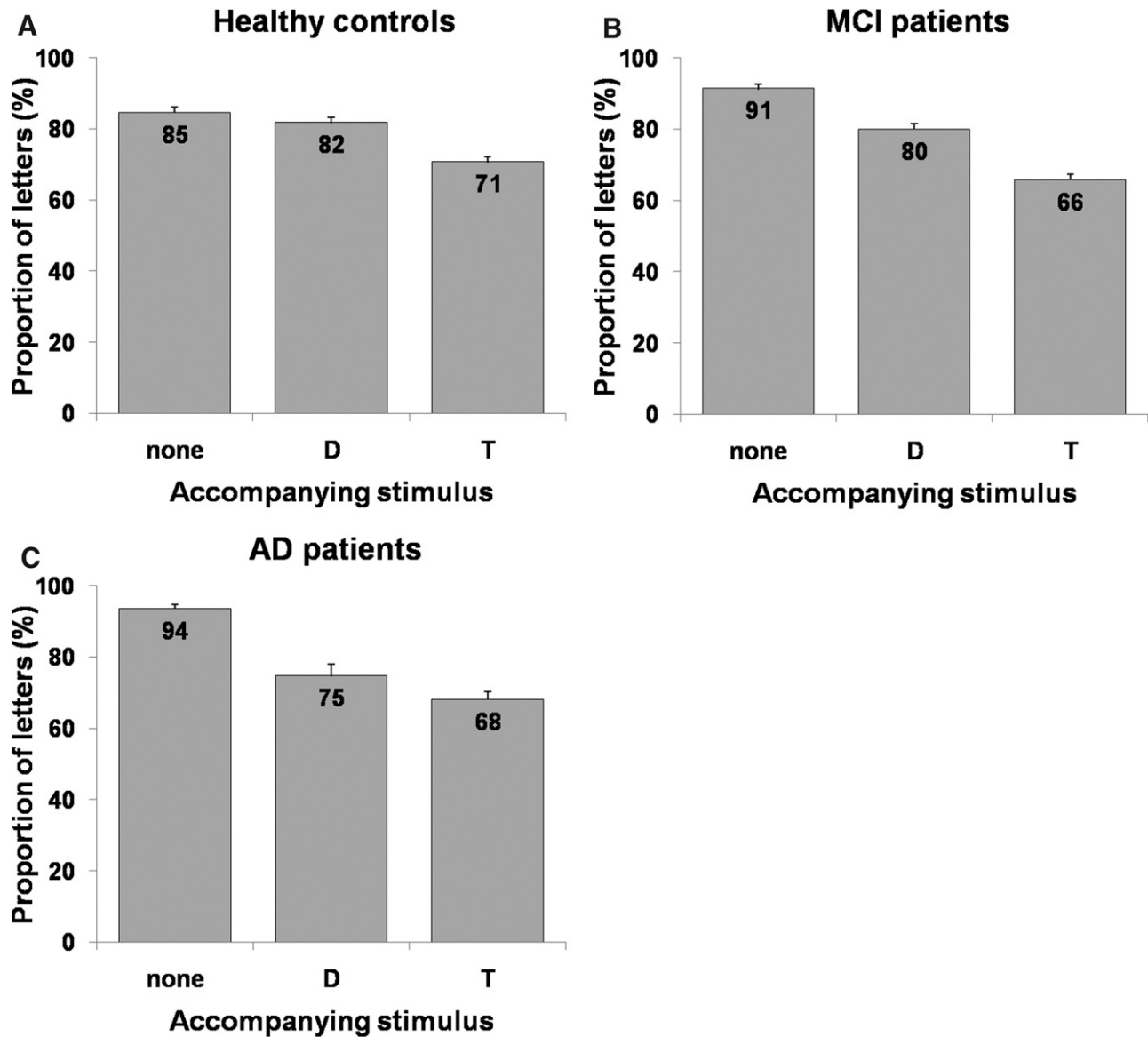


Fig. 2. Mean proportion of correctly reported letters (in %) of (A) control subjects, (B) MCI patients, and (C) AD patients in the single target (none), the target plus distractor (D), and the target plus target (T) conditions across both hemifields. Error bars show standard errors of the mean.

### 2.1.1. 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 2** shows the mean proportion of target letters correctly identified, separately for conditions with single targets, targets accompanied by distractors and by a second target. As our interest here is in a general estimate of top-down control in the whole visual field, averaged values across hemifields are presented.

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 with normal controls. In AD patients finally, accuracy in distractor conditions nearly equals that in dual target conditions (7% difference; 19% difference to the single target condition). Therefore, distractors and additional targets interfere with AD patients' performance to a comparable degree, indicative of rather nonselective processing.

As selectivity is reflected in performance on target plus distractor displays compared with the single target condition

(baseline), we calculated a raw data selectivity index 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 indexes, 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 ( $M = 0.97, SD = 0.05$ ) and MCI patients ( $M = 0.88, SD = 0.10$ ) differed significantly [ $t_{(66)} = 4.74, p < 0.01$ ], as well as MCI and AD patients ( $M = 0.80, SD = 0.14$ ) [ $t_{(46)} = 2.31, p < 0.05$ ]. 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.

### 2.1.2. Theory of visual attention parameter estimates

From the raw data of the  $w$  estimates, we calculated the parameter efficiency of top-down control  $\alpha$  and compared these estimates across subject groups. An ANOVA of the parameter top-down control  $\alpha$  with the between-subject factor Group (MCI, AD, healthy controls (HC)) and the within-subject factor horizontal Side of Visual Field (left, right) revealed a highly significant effect of Group [ $F_{2,81} = 12.37, p < 0.01$ ]. The main effect of horizontal Side [ $F_{1,81} = 0.95, p > 0.30$ ] and the Group  $\times$  horizontal Side interaction were not significant [ $F_{2,81} = 1.30, p > 0.25$ ]. Analogous results were obtained in consideration of vertical field differences (top, bottom). The main effect of Group was significant [ $F_{2,81} = 9.20, p < 0.01$ ], whereas the main effect of vertical Side [ $F_{1,81} = 0.33, p > 0.55$ ] and the Group  $\times$  vertical Side interaction were not significant [ $F_{2,81} = 0.01, p > 0.95$ ]. These results indicate that top-down control parameter  $\alpha$  is quite consistent across the whole visual field. As depicted in

F3

Figure 3A, post hoc tests revealed that top-down control was impaired in both MCI patients [ $t_{(66)} = 1.83, p < 0.05$ ] and AD patients [ $t_{(50)} = 2.97, p < 0.01$ ], compared with healthy subjects. The decline was staged, that is, values of AD patients were worse than those of MCI patients [ $t_{(46)} = 2.19, p < 0.05$ ].

### 2.2. Spatial weighting and sensory effectiveness

First, we will report on visual field differences related to the spatial laterality and imbalance indexes of attentional weighting, as well as that of sensory effectiveness across the left and the right hemifield, starting with the presentation of raw data results followed by the parameter estimates.

#### 2.2.1. Raw data

To illustrate attentional weighting and sensory effectiveness across the two hemifields, Figure 4 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)

F4

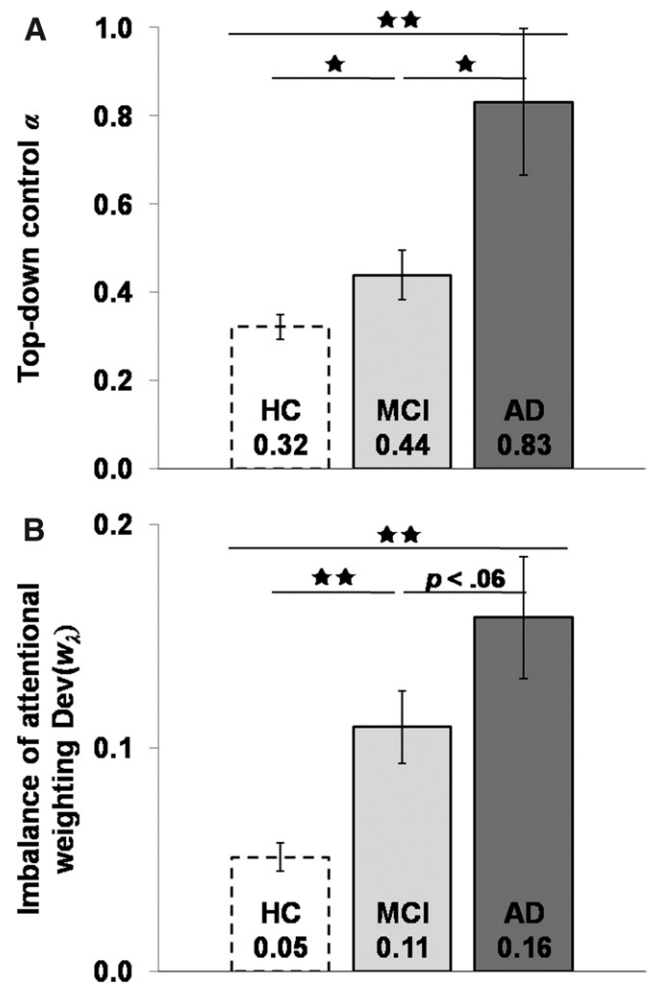


Fig. 3. Mean values of (A) parameter top-down control  $\alpha$  and (B) the imbalance index of attentional weighting  $Dev(w_i)$  for healthy controls (HC), MCI and AD patients. Error bars represent standard errors of the mean.

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, attentional weights have to be distributed across the left and the right visual hemifield, with the weight

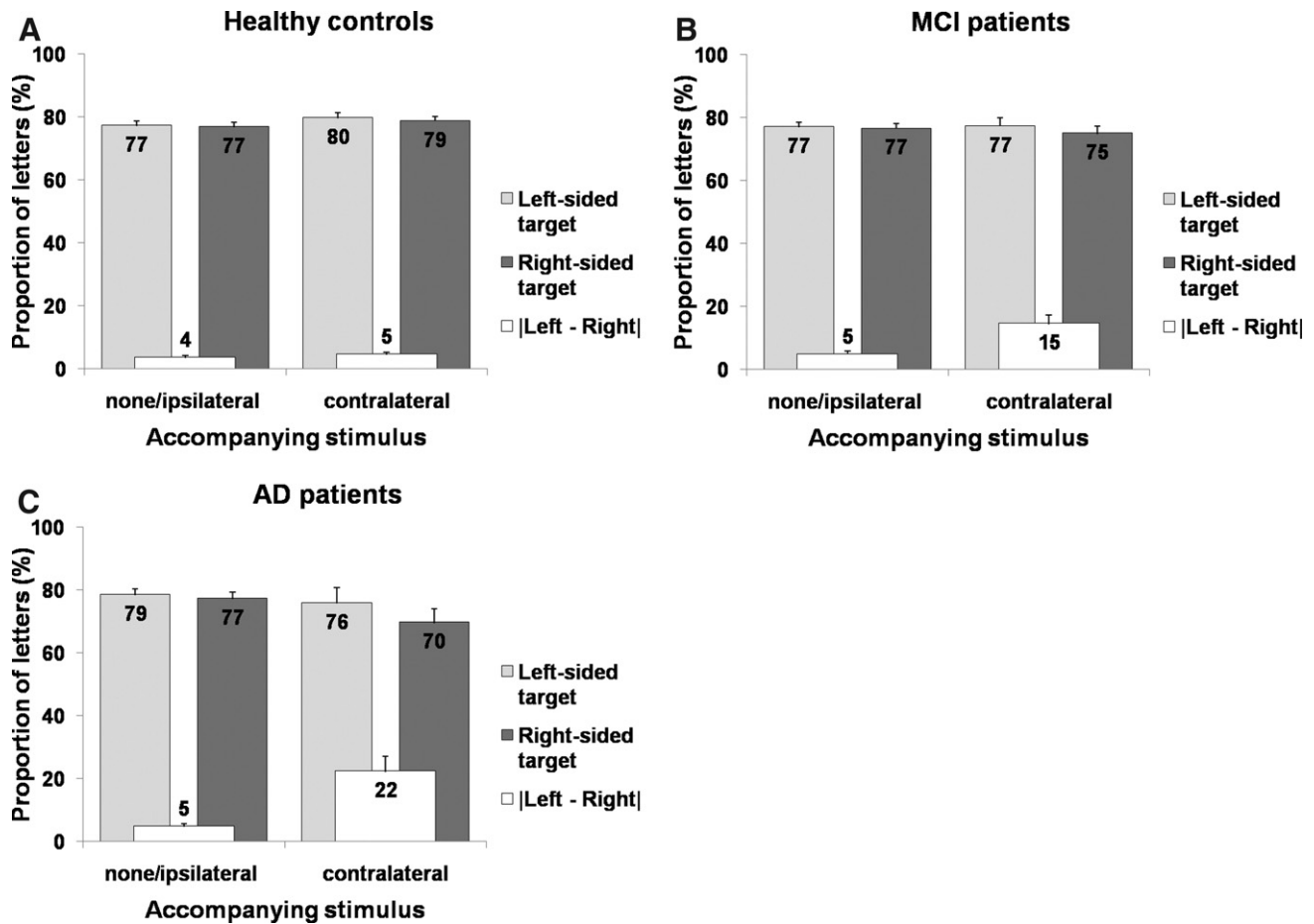


Fig. 4. Mean proportion of correctly reported letters (in %) of (A) control subjects, (B) MCI patients and (C) AD patients in unilateral stimulus conditions (accompanying stimulus: none/ipsilateral) and bilateral stimulus conditions (contralateral). The white bars indicate the averaged individual hemifield differences in the respective conditions. Error bars represent standard errors of the mean.

allocation determined by a competitive process between the two hemifields. If attentional weights are biased towards one hemifield, performance in the bilateral (compared with the unilateral) target condition will suffer more for a target presented in the hemifield with relatively low attentional weights, compared with a target in the hemifield with high weights. In bilateral presentation conditions, controls showed no obvious hemifield differences. In contrast, MCI patients showed slightly better performance in the left compared with the right hemifield, indicating that objects on the left side received higher attentional weights 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 with healthy subjects, indicating a remarkable variance in performance. To examine whether this variance reflects individually enhanced spatial attentional biases either to the left or the right hemifield, we computed the average accuracy differences between the left and the right hemifield,  $\text{accuracy}_{\text{left}} - \text{accuracy}_{\text{right}}$ .

These hemifield differences are illustrated, separately for each group and the different conditions, by the white bars in Figure 4. In unilateral conditions, no significant differences between groups were found [ $F_{2,81} = 1.11$ ;  $p > 0.30$ ]. In bilateral conditions, however, the groups differed significantly [ $F_{2,81} = 12.62$ ;  $p < 0.01$ ], with enhanced values in MCI [ $t_{(66)} = 3.82$ ;  $p < 0.01$ ] and AD patients [ $t_{(50)} = 3.66$ ;  $p < 0.01$ ] compared with controls.

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

### 2.2.2. Theory of visual attention parameter estimates

Three laterality indexes were computed from the raw data of the A and w estimates: the laterality index of sensory effectiveness  $A_{\lambda}$ , the laterality index of attentional weight-

ing  $w_\lambda$  and the imbalance index of attentional weighting  $\text{Dev}(w_\lambda)$ .

An ANOVA of sensory effectiveness parameters  $a$  (HC:  $A_{\text{left}} = 2.79$ ,  $SD = 0.92$ ;  $A_{\text{right}} = 2.68$ ,  $SD = 0.83$ ; MCI:  $A_{\text{left}} = 3.20$ ,  $SD = 1.76$ ;  $A_{\text{right}} = 2.83$ ,  $SD = 0.91$ ; AD:  $A_{\text{left}} = 3.08$ ,  $SD = 0.81$ ;  $A_{\text{right}} = 3.05$ ,  $SD = 1.04$ ) 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 [ $F_{2,81} = 0.95$ ,  $p > 0.35$ ] and Side [ $F_{1,81} = 2.00$ ,  $p > 0.15$ ], nor the Group  $\times$  Side interaction [ $F_{2,81} = 0.79$ ,  $p > 0.45$ ]. Similarly, the index for the laterality of sensory effectiveness  $A_\lambda$  (HC:  $A_\lambda = 0.51$ ,  $SD = 0.05$ ; MCI:  $A_\lambda = 0.52$ ,  $SD = 0.08$ ; AD:  $A_\lambda = 0.51$ ,  $SD = 0.07$ ) did not differ significantly between subject groups [ $F_{2,81} = 0.21$ ;  $p > 0.80$ ]. Neither the control group's nor the patients' index differed significantly from 0.5, which indicates equal sensory effectiveness on both sides (all  $p > 0.20$ ).

The parameter laterality of attentional weighting  $w_\lambda$  (HC:  $w_\lambda = 0.49$ ,  $SD = 0.06$ ; MCI:  $w_\lambda = 0.51$ ,  $SD = 0.14$ ; AD:  $w_\lambda = 0.56$ ,  $SD = 0.19$ ) did not differ among groups [ $F_{2,81} = 1.95$ ;  $p > 0.10$ ], and none of the group mean values differed significantly from the unbiased value 0.5 (all  $p > 0.15$ ). These results indicate that there was no specific bias in the sense of a general leftward or rightward preference in the patient groups. In addition, we controlled for probable imbalances regarding attentional weighting in the upper and lower hemifield. Therefore, the ratio  $w_{\text{top}}/(w_{\text{top}} + w_{\text{bottom}})$  was calculated, analogous to the laterality index of attentional weighting  $w_\lambda$  (Section 1.3.2.). The mean group values of the ratio  $w_{\text{top}}/(w_{\text{top}} + w_{\text{bottom}})$  did not differ significantly across groups [ $F_{2,81} = 1.17$ ;  $p > 0.30$ ], indicating that distributions of attentional weights across the upper and the lower hemifield can be considered constant across subject groups (HC:  $M = 0.66$ ,  $SD = 0.15$ ; MCI:  $M = 0.72$ ,  $SD = 0.19$ ; AD:  $M = 0.70$ ,  $SD = 0.17$ ).

However, we were mostly interested in a possible attentional bias towards the left or right of the visual field. Thus, we investigated this issue in more detail. A significant group effect was found for the deviation from the optimum value, that is, the imbalance index  $\text{Dev}(w_\lambda)$  (HC:  $\text{Dev}(w_\lambda) = 0.05$ ,  $SD = 0.04$ ; MCI:  $\text{Dev}(w_\lambda) = 0.11$ ,  $SD = 0.09$ ; AD:  $\text{Dev}(w_\lambda) = 0.16$ ,  $SD = 0.11$ ) [ $F_{2,81} = 11.07$ ,  $p < 0.01$ ]. As depicted in Figure 3B, post-hoc comparisons revealed highly significant differences between healthy control subjects and both MCI [ $t_{(66)} = 3.27$ ,  $p < 0.01$ ] and AD patients [ $t_{(50)} = 3.75$ ,  $p < 0.01$ ]. Furthermore, AD patients tended to show even more increased values compared with MCI patients [ $t_{(46)} = 1.60$ ,  $p < 0.06$ ] 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  $\text{Dev}(w_\lambda)$  in healthy subjects,

the 90th percentile was selected to indicate a pathological spatial imbalance ( $\text{Dev}(w_\lambda) \geq 0.11$ ) in patients. On this criterion, 12 MCI (38%; seven left, five right) and 9 AD patients (56%; seven left, two right) suffered from a pathological imbalance of attention, predominantly directed to the left visual hemifield (67%), though, to a smaller portion, also directed to the right (33%).

To rule out probable sensory confounds with the imbalance index  $\text{Dev}(w_\lambda)$ , we correlated it with the corresponding parameter indicating imbalance of sensory effectiveness  $\text{Dev}(A_\lambda)$ . Nonsignificant correlations were obtained for all subject groups (HC:  $r = -0.05$ ,  $p > 0.75$ ; MCI:  $r = -0.17$ ,  $p > 0.35$ ; AD:  $r = -0.02$ ,  $p > 0.90$ ). Thus, the pathological imbalance of spatial weighting is not attributable to a more fundamental sensory imbalance.

### 2.3. Parameter intercorrelation

No significant correlation was found between the imbalance index of attentional weighting  $\text{Dev}(w_\lambda)$  and parameter top-down control  $\alpha$  within single groups (all  $p > 0.25$ ). These results indicate that partial-report parameters are independent of each other in healthy controls as well as in both clinical groups.

### 2.4. Relationship of partial-report parameters to external clinical measures

Furthermore, we examined the relationship of both partial-report parameters, imbalance index of attentional weighting  $\text{Dev}(w_\lambda)$  and the efficiency of top-down control  $\alpha$ , with external criteria 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  $p > 0.10$ ).

### 2.5. Relationship of partial report parameters to measures of cognitive function

Across both clinical groups, 46 MCI and AD patients (clinical indexes of two AD patients were not available), we calculated Spearman correlations between the pathological imbalance of spatial attentional weighting  $\text{Dev}(w_\lambda)$  and the decreased efficiency of top-down control  $\alpha$ , 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  $\text{Dev}(w_\lambda)$  and the CERAD total score ( $r_s = -0.34$ ,  $p < 0.05$ ) 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  $\alpha$  was significantly positively related to the CDR score ( $r_s = 0.34$ ,  $p < 0.05$ ). 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 nonsignificant.

## 2.6. Effect of ApoE4 genotype

To test whether the partial report parameters are related to a possibly underlying gene-associated pathology, we analyzed the effect of ApoE4 genotype (1–2 allele carriers denoted as ApoE4<sup>+</sup> v. ApoE4<sup>-</sup>) on the parameter values.

ApoE4 status was available in 43 patients. We used the combined patient group to boost the sample size. The patients were divided into two subgroups (post hoc split), 28 ApoE4<sup>+</sup> (18 MCI, 10 AD) and 15 ApoE4<sup>-</sup> patients (11 MCI, 4 AD). ApoE4<sup>+</sup> and ApoE4<sup>-</sup> subgroups did not differ with regard to age, gender, education, diagnosis (MCI/AD), handedness, MMSE, CERAD total score, CDT, CDR sum of category scores, age at onset, disease duration and the distribution of antidementive and antidepressant medication (all  $p > 0.15$ ). A trend-level difference between ApoE4 subgroups was revealed with regard to the spatial laterality index of attention  $w_\lambda$  [ $t_{(41)} = 1.62, p < 0.06$ ]. A significant deviation from the optimal unbiased  $w_\lambda$  value 0.5 was only present in ApoE4<sup>+</sup> patients [ $w_\lambda = 0.56, SD = 0.13; t_{(27)} = 2.61, p < 0.01$ ], indicating, on a group level, a leftward spatial bias in contrast to the heterogeneous nondirected distribution of attention in ApoE4<sup>-</sup> patients [ $w_\lambda = 0.48, SD = 0.19; t_{(14)} = 0.31, p > 0.75$ ].

As can be seen from Figure 5, age and the spatial laterality index of attention  $w_\lambda$  were significantly correlated in ApoE4<sup>+</sup> patients ( $n = 27, r = -0.33, p < 0.05$ ) and a trend level correlation was found between parameter  $w_\lambda$  and disease onset ( $r = -0.30, p < 0.07$ ). These correlations indicate that ApoE4<sup>+</sup> patients with an early onset show a more pronounced leftward spatial bias. This result was revealed after the exclusion of one outlier value (three standard deviations above mean) produced by MCI patient AW ( $w_\lambda = 0.13$ ).

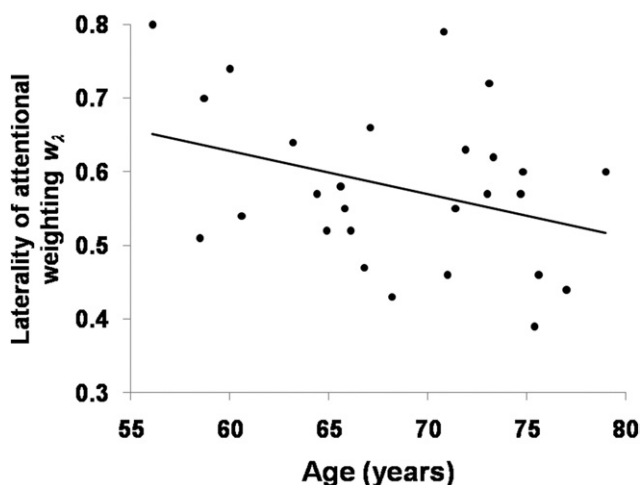


Fig. 5. Scatterplot relating the spatial laterality index of attentional weighting  $w_\lambda$  to age in ApoE4<sup>+</sup> patients.

## 3. 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 amnesic MCI and probable AD patients compared with a healthy elderly control group. The partial-report task required verbal report of briefly displayed target letters (presented among to-be-ignored distractor letters) and allowed the derivation of two independent quantitative parameter estimates from the qualitative performance pattern: task-related efficiency of top-down control  $\alpha$  and spatial imbalance of attentional weighting  $Dev(w_\lambda)$ . MCI and AD patients were impaired in both attentional functions compared with healthy controls. Early deficits in both parameters  $\alpha$  and  $Dev(w_\lambda)$  at the MCI stage further deteriorated at the stage of AD. In apolipoprotein E  $\epsilon 4$  allele (ApoE4) carriers, earlier disease onset was associated with a more pronounced leftward spatial bias  $w_\lambda$ .

Thus far, to our knowledge, there have been no reports of both spatial and task-related aspects of deficits in visual attentional weighting in MCI as well as AD patients, although it is widely accepted that early AD is marked by visuospatial (Hao et al., 2005; Parasuraman et al., 2002) and executive deficits (Perry and Hodges, 1999; Perry and Hodges, 2003). The imbalance index of attentional weighting  $Dev(w_\lambda)$  and the efficiency of top-down control  $\alpha$  were uncorrelated within each group, indicating that these indexes 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  $w_\lambda$ , while efficiency of top-down control  $\alpha$  was intact; the second patient with a superior frontal brain lesion displayed the reverse pattern, with impaired top-down control and balanced spatial weighting.

### 3.1. Impairments in task-related weighting

Frontal lobe pathology is generally not seen in the early stages of AD (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 et al., 2003; Grady et al., 2001; Sorg et al., 2007). Correspondingly, a number of studies suggest that impairment in top-down processing might even be a very early feature in the course of AD (Azari et al., 1992; Perry and Hodges, 1999; Perry and Hodges, 2003). The results of our study are in line with this assumption. The task-related selection, that is, the efficiency of top-down control  $\alpha$ , 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 tan-

gles are prevailing in associative areas, that is, the parietal and frontal lobes, and in large cortical neurons mediating corticocortical connections (Pearson et al., 1985), while neuritic plaques seem to accumulate at the ends of corticocortical tracts (De Lacoste and 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 caused predominantly 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 and Braak, 1991; Whitwell et al., 2007), which is in accordance with further deterioration of top-down control selectivity in AD compared with MCI patients. Using a similar TVA partial-report task, Peers et al. (2005) found that, in patients with frontal lobe lesions, deficits in the efficiency of top-down control  $\alpha$  were predicted by lesion volume. Consequently, the staged decline in efficiency of top-down control  $\alpha$ , as revealed in the present study, might result from early corticocortical disconnection in the fronto-parietal attention network at the MCI stage, followed by an additional loss of nerve cells in corresponding association areas at the later stage of AD.

It should be noted, however, that whether or not plaques and tangles are present in MCI appears to be relatively unclear, and there is also evidence that plaques and tangles can occur at loads suggestive of AD in completely healthy and clinically normal older adults (Ince, 2001). Therefore, the status of neurotransmitters such as acetylcholine might be of additional importance for explaining our results; however, we are unable to further examine this possibility based on the present data (but see Bublak et al., 2009).

### 3.2. Impairments in spatial weighting

In our clinical samples, we obtained a pathological deviation of spatial attention  $Dev(w_\lambda)$  to either hemifield 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  $A_\lambda$  across the left and the right visual hemifield and nonsignificant correlations be-

tween imbalance of attentional weighting  $Dev(w_\lambda)$  and the corresponding imbalance index of sensory effectiveness  $Dev(A_\lambda)$  in all subject groups. The spatial bias exhibited by our clinical groups is also not attributable to an inability to maintain central fixation during the 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  $A_\lambda$ .

Significant accuracy asymmetries in patients were present in bilateral presentation conditions only, in accord with visual extinction – a symptom mainly found in unilaterally brain-damaged patients – being at the root of the patients' visuospatial bias. 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 and Vuilleumier, 2001). In manifest neglect, patients would be completely unaware of all stimuli presented in the contralateral hemifield.

These findings are consistent with the assumption that parietal lobe degeneration in AD is bilateral (Braak et al., 1993), but probably not absolutely balanced in individual patients' brains. Neural degeneration in AD might be slightly intensified in the left compared with 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 et al., 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. Given that 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. Our TVA-based partial-report results resembled these findings even at the early stage of the disease, because a pathological spatial bias prevailed in 38% of MCI and 56% of AD patients. 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 most patients (i.e. Meguro et al., 2001). In this study, AD patients' enhanced rightward omissions were correlated with lower parietal cerebral blood flow (CBF), as measured with SPECT, in the left hemisphere compared with the right, and patients with predominantly leftward omissions showed the opposite CBF pattern. Accordingly, it is possible that in our clinical groups, the present pathological laterality of spatial attention  $w_\lambda$  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. PET) studies are necessary to investigate this issue. The staged increase in pathological spatial bias from MCI to AD patients in our 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 displayed a lateral spatial bias, which was associated with lesion volume.

### 3.3. Effect of ApoE4 genotype

One major influence on spatial attention in AD might stem from genetic influences. This is suggested by findings in several FDG-PET studies in healthy subjects (Reiman et al., 1996; Small et al., 1995b; Small et al., 2000) as well as MCI and AD patients (Mosconi et al., 2004a; Mosconi et al., 2004b; Mosconi et al., 2005), which showed that the dose of ApoE4 allele influences the typical age-related decline in parietal, temporal and posterior cingulate cerebral glucose metabolism. Healthy monozygotic ApoE4<sup>+</sup> subjects with subjective memory impairments (Small et al., 1995a) as well as homozygous ApoE4<sup>+</sup> subjects without memory complaints (Reiman et al., 1996) were found to display significantly lower parietal metabolism compared with ApoE4<sup>-</sup> 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 2 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, we could replicate the findings of Finke et al. (2006) in a combined clinical group of MCI and AD patients, suggesting a more pronounced leftward spatial bias in ApoE4<sup>+</sup> patients with earlier disease onset. Note, though, as not all MCI patients represent individuals at the prodromal stage to AD, these findings might just apply to a subgroup of our

clinical sample. However, corroborated diagnoses in the MCI sample might reveal a stronger relationship between spatial bias and disease onset in ApoE4<sup>+</sup> patients.

The correlation was lower in the present study compared to Finke et al. (2006), which is most probably related to the deeper impact of the underlying gene-associated pathology in Huntington's disease. Because interactive effects of ApoE4 genotype and (onset) age have been documented (Mosconi et al., 2004c; Mosconi et al., 2005), 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  $w_\lambda$ .

## 4. Conclusions

The TVA-based partial-report task proved to be a sensitive tool for assessing selective visual attention in amnesic MCI patients. Both deficits in task-related selection and a pathological attentional imbalance are already present at the early MCI stage, besides the 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 interhemispheric 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. Our findings point to the efficiency of top-down control and to the spatial imbalance of visual attention as potential early cognitive markers. Both attentional parameters may be taken into account as sensitive measures of neuronal dysfunction before 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 recommend the partial-report procedure as efficient diagnostic tool for early identification of subjects at risk for AD.

However, a few caveats ought to be mentioned. First, not all MCI patients will convert to AD – so the above conclusions might hold just for a subgroup of MCI subjects in the prodromal stage of AD. Given this, the present cross-sectional investigation needs to be complemented by a longitudinal study, which would allow those MCI patients really prodromal to AD to be identified and thus permit a more definitive test of these assumptions. Second, it cannot be ruled out that antidepressant medication had an influence on the partial-report parameters. However, no significant effects were found in any of the patient groups (all  $p > 0.25$ ). Likewise, it cannot be excluded that the antidepressant medication in AD patients had either a negative (i.e. Ancelin et al., 2006) or a positive effect (i.e. Bentley et al., 2004; Bublak et al., 2009) on the assessed attentional performance in the AD group (note that none of the MCI patients received antidepressives). Though, again, antidepressant med-

ication was not found to have a significant effect on any of the two attentional parameters in the AD group (both  $p > 0.50$ ). Admittedly, the sample sizes included in these analyses are relatively small and do not allow reliable conclusions with regard to antidepressant and antidementive medication.

### Disclosure statement

The authors report no actual or potential conflicts of interest.

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