Functional Imaging of Visuospatial Processing in Alzheimer’s Disease


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Alzheimer’s disease (AD) is known to cause a variety of disturbances of higher visual functions that are closely related to the neuropathological changes. Visual association areas are more affected than primary visual cortex. Additionally, there is evidence from neuropsychological and imaging studies during rest or passive visual stimulation that the occipitotemporal pathway is less affected than the parietal pathway. Our goal was to investigate functional activation patterns during active visuospatial processing in AD patients and the impact of local cerebral atrophy on the strength of functional activation. Fourteen AD patients and fourteen age-matched controls were measured with functional magnetic resonance imaging (fMRI) while they performed an angle discrimination task. Both groups revealed overlapping networks engaged in angle discrimination including the superior parietal lobule (SPL), frontal and occipitotemporal (OTC) cortical regions, primary visual cortex, basal ganglia, and thalamus. The most pronounced differences between the two groups were found in the SPL (more activity in controls) and OTC (more activity in patients). The differences in functional activation between the AD patients and controls were partly explained by the differences in individual SPL atrophy. These results indicate that parietal dysfunction in mild to moderate AD is compensated by recruitment of the ventral visual pathway. We furthermore suggest that local cerebral atrophy should be considered as a covariate in functional imaging studies of neurodegenerative disorders.

INTRODUCTION

The impairment of higher visual functions is one of the neuropsychological hallmarks of Alzheimer’s disease (AD) (Mendez et al., 1990). Visual attention and visuospatial processing, two functions related to the superior parietal lobule (SPL) (Vandenberghe et al., 2001; Linden et al., 1998; Alivisatos and Petrides, 1997), are impaired in AD (Meguro et al., 2001; Rizzo et al., 2000; Parasuraman et al., 1992; Ska et al., 1990), and affect greatly the patients’ activities of daily living.

By inducing temporary functional lesions in the SPL using repetitive transcranial magnetic stimulation (rTMS), we recently demonstrated that the activation of the SPL during an angle discrimination task is not only sufficient but also essential for successful visuospatial processing (Sack et al., 2002a). These findings are in line with the well-known reductions in resting regional glucose metabolism (Dura et al., 1986) and regional cerebral blood flow (Perani et al., 1988) in the parietal cortex of AD patients, reflecting severe functional damage to this region, that might explain the visuospatial impairments of these patients (Fujimori et al., 2000; Buck et al., 1997). This damage is also evident through a marked atrophy of the parietal gray and white matter (Baron et al., 2001; Thompson et al., 2001; Fox et al., 1996; Foundas et al., 1997; de la Monte, 1989), indicating an irreversible structural damage due to the death of neurons and degradation of dendrites and axons caused by accumulation of amyloid plaques and neurofibrillary tangles (NFTs) (Braak and Braak, 1991; DeKosky et al., 1996). These considerations lead to two important questions: (1) What is the relationship between the amount of structural damage of SPL and its functional activation during visuospatial processing in AD? (2) Are there mechanisms of functional reorganization by which the AD brain attempts to compensate for the impaired processing capacity in regions essential for visuospatial processing?

Cortical atrophy may cause some artificial decreases in measured functional signals, especially with imaging techniques with low spatial resolution, such as PET and SPECT, which are particularly vulnerable to the
partial volume effect. While many articles have addressed the influence of the partial volume effect on measures of the atrophic brain (Bokde et al., 2001; Chawluk et al., 1990; Tanna et al., 1991), the neurobiological relationship between brain atrophy in AD and functional activation has so far been formally addressed only in the study by Johnson et al. (2000). These authors found a positive correlation between atrophy and the amount of blood oxygenation level-dependent (BOLD) signal change in the inferior frontal gyrus (IFG) during a semantic task. This correlation was noted only in AD patients but not in age-matched healthy controls. Furthermore, they found this correlation only in the IFG but not in other regions activated by the task. This result implies that local atrophy may influence the amount of functional activation, and that this impact is not equal across different brain regions.

In the present study we aimed to investigate the impact of local atrophy in SPL on the amount of BOLD signal change during visuospatial processing.

A large body of studies have proved the capability of the adult (non-AD) brain for intra-and cross-modal functional reorganization as a response to peripheral or central lesions (see Chen et al., 2002). In AD, there is evidence from immunhistochemical (Arendt et al., 1998; Mikkonen et al., 1999) and imaging (Kondo et al., 1999) studies of the presence of mechanisms involved in plastic neuronal and synaptic remodeling, particularly across limbic and higher-order neocortical association areas. Recent functional activation studies indicate that the AD brain attempts to compensate for the damage to multiple functional systems by reorganizing the spatial and temporal patterns of functional circuits (Grady et al., 1993; Woodard et al., 1998; Becker et al., 1996a,b; Bookheimer et al., 2000; Smith et al., 2002).

It has been shown that not all higher visual areas are equally damaged in AD. Functions related to the dorsal visual pathway (Haxby et al., 1991) (occipital and parietal cortex) such as motion detection and visuospatial processing seem to be more impaired in AD than functions related to the ventral visual pathway (occipitotemporal cortex), such as color recognition (Mendez et al., 1990). The first functional imaging study, which measured in vivo the differential functional impairment of the dorsal visual stream in AD, was performed by Mentis et al. (1996). In their PET study, they demonstrated hypoactivation of extrastriate visual areas during passive visual stimulation only at frequencies involving the dorsal but not the ventral visual stream. However, it remained open what effect this differential damage would have on the distribution of activation across the ventral and dorsal stream during the performance of active visual tasks.

The goal of our study was to detect a functional counterpart of the unequal distribution of AD-related pathological changes across the visual system. A recent study by Pfefferbaum et al. (2001) found marked signs of functional reorganization in (non-AD) alcoholics related to visuospatial processing. In a visuospatial memory task, the patients revealed less activation in the parietal cortex, but more activation in areas of the ventral visual stream compared with healthy controls.

On the basis of these findings, we hypothesized that task-related functional activation changes in the parietal lobe would be smaller in AD patients than in controls and that this hypoactivation could be compensated for by a recruitment of ventral visual areas. To our knowledge this is the first fMRI study of cortical activation changes during active visuospatial processing in AD. It is also the first study to evaluate the impact of atrophy of visual cortical areas on the resulting fMRI signal.

**METHODS**

Subjects and Clinical Assessment

Fourteen patients (mean age, 69.2 ± 9.9; 6 women, 8 men) suffering from mild to moderate AD were recruited from our outpatient memory unit (diagnosed according to NINCDS-ADRDA (McKhann et al., 1984) and ICD-10 criteria (Braker, 1988)). The clinical diagnosis of probable AD was established by clinical workup with special attention to insidious onset of the cognitive impairment and progression over time. Relevant medical disorders (aside from AD) were excluded on the basis of the medical history, by medical and neurological examination, laboratory tests (including VDRL, vitamin B12, folate, and thyroid hormones), and cerebral MRI showing only cerebral atrophy if abnormal. Patients were included only if they were able to understand the tasks sufficiently and were not treated with any kind of psychotropic drugs.

The severity of cognitive impairment was assessed using the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (group mean score, 21.5 ± 5.6). The control group consisted of 14 healthy subjects, similar to the patient group in age (mean age 63.7 ± 4.8) and gender (7 women, 7 men). All control subjects had a score ≥ 27 points in the MMSE and no pathological changes in T1 and T2 structural cranial MR images. They had no psychiatric, neurological, or cardiovascular history and did not use psychotropic drugs. One year after the fMRI experiment, the cognitive status of the control subjects was investigated by a telephone interview. It was found that the control subjects had not developed subjective memory decline or impairments of daily living during the year following the investigation. All patients and controls were right-handed as assessed by the Edinburgh handedness inventory. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the University of Frankfurt, and all sub-
jects provided written informed consent prior to participation.

MR Imaging

The fMRI examination was carried out using a 1.5-T whole-body superconducting MR system (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) equipped with a standard head coil, an active shielded gradient coil (25 mT/m), and Echo Planar (EPI) sequences for ultrafast MR imaging.

For functional imaging, 15 slices (slice thickness = 5 mm, interslice distance = 1 mm), parallel to the anterior–posterior commissure line, were acquired using a BOLD signal-sensitive single-shot EPI sequence [echo time (TE) = 66 ms; repetition time (TR) = 4000 ms; flip angle (FA) = 90°; matrix size = 128 × 128; field of view (FOV) = 210 mm²]. Each functional time series consisted of 64 volumes and lasted 256 s. Additionally, a high-resolution three-dimensional data set covering the whole brain was collected for each subject with a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence [TE = 4 ms; TR = 9.7 ms; FA = 12°; matrix = 256 × 256; thickness = 1 mm; voxel dimensions = 1 (×) 1 (×) 1 mm].

Experimental Paradigm

The visual stimuli were generated on a personal computer using the STIM software package (Neuroscan, Inc., El Paso, TX, USA) and delivered to a high-lumiance LCD projector (EIKI LC-6000), which projected the stimuli onto a frosted screen in front of the MR scanner. Subjects were positioned in the center of the head coil and stabilized against bulk head movements using custom-made foam pads. They viewed the stimuli through a mirror mounted on the head coil. All control subjects and patients performed two tasks: In the first task, analogue clocks were presented for 800 ms every 2 s with the two clock hands configured in different angles. Subjects were asked to press a button whenever they detected a small angle (<90°). In the control condition, clocks without hands were presented with the same duration and frequency as in the previous task. Subjects had to press a button every time they observed a stimulus. This control task was intended to account for the contribution of primary visual cortex stimulation, general visual attention, visuomotor integration, and motor performance to the activation observed during the execution of the clock task. The functional scan followed a classic block design where the angle and control stimuli were presented in four blocks (of 32 each), alternating with fixation periods of 32 s. Two scans of 64 volumes were performed for each subject within one scanning session.

Data Analysis

Data analysis, registration, and visualization were performed with the fMRI software package BrainVoyager 2000 (www.brainvoyager.com). The complete functional data for each subject were transformed into Talairach space, yielding a 4D data representation (volume time course: 3 × space, 1 × time). The spatial normalization into Talairach space as implemented in the BrainVoyager software is based on the following steps: (1) The 3D MR volume is rotated into the AC–PC plane anterior commissure (AC)–posterior commissure (PC) plane. (2) The AC and PC and the anterior and posterior, upper and lower, and right and left outermost points of the cerebrum are determined. (3) On the basis of these points, 12 subvolumes of the cerebrum are determined [(left and right of the midsagittal plane × (above and below the AC–PC line) × (anterior to AC, between AC and PC, posterior to PC)]. (4) The individual brain coordinates are transformed into the coordinates of the Talairach brain (Talairach and Tournois, 1998) for each of these 12 subvolumes separately. Prior to statistical analysis, the time series of functional images were aligned to minimize the effects of head movements. Preprocessing furthermore included a gaussian spatial (FWHM = 4 mm) and temporal (FWHM = 3 volumes) smoothing of the functional data.

Atrophy Index Measurements

We calculated the cerebral atrophy in the SPL of AD patients and control subjects based on the MP-RAGE data sets obtained from each subject. We used a semi-automatic approach provided by the BrainVoyager software package. We used 3D data sets, which were only rotated in the AC–PC plane, but were not scaled into the Talairach-based coordinate system, because we considered that the scaling of 3D data sets into Talairach space might lead to undesired distortions of the cerebrospinal fluid (CSF)/brain tissue ratio. To obtain a representative part of the SPL that would be consistent across all subjects, a region was marked posterior to the corpus callosum (CC), extending 20% of the longitudinal distance between the anterior and posterior border of the CC in the midsagittal plane (Figs 1a, 1d). Its lower border was defined by the plane of the subparietal sulcus. In the next step the intracranial space was outlined along the dura mater on each coronal slice within the SPL region (Fig. 1b) (Johnson et al., 2000; Andreasen et al., 1993). Based on visual inspection, an appropriate intensity threshold was set to mark brain tissue and CSF space (Fig. 1c). Finally, the atrophy index was calculated by division of the number of voxels of brain tissue by the total number of voxels in the intracranial space within the SPL region (brain tissue + CSF space). This individually calculated atrophy index has a range between 0 and 1. It
was computed for the right and left SPL separately. Higher values of the atrophy index indicate smaller amounts of atrophy. To estimate the objectivity of this approach, 11 independent observers performed the procedure on the same data set. Additionally, 7 observers repeated the same procedure after 1 week to test the intraobserver reliability of this method. This procedure revealed high interobserver reproducibility (SD = 0.01, range = 3%) and intraobserver reliability ($r = 0.918$, $P = 0.004$).

FMRI Data Analysis

Because of theoretical considerations we used a double statistical approach to analyze the fMRI data: Regardless of the scaling into Talairach space, different levels and locations of cerebral atrophy in the AD group would lead to some spatial misalignment of functional data sets and thus to reduced averaged local levels of BOLD signal change. We therefore calculated not only group-based but also individual-based general linear model (GLM) maps to reveal focal maxima of activation. We additionally counted the number of activated voxels at different thresholds revealed by linear correlation analysis inside the total volume of a defined region of interest [SPL and fusiform gyrus (GF)]. This dual approach should benefit not only from the high specificity of focal maxima of BOLD signal change to detect activation, but also from the high sensitivity of the total count of activated voxels at different thresholds within a region of interest (Klein-schmidt et al., 1995).

BOLD signal change analysis. The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). The GLM of the experiment was computed...
FIG. 3. Relative contribution maps derived from group GLM analysis (14 AD patients, 14 control subjects) with a two-predictor set (predictor 1: angle discrimination task, predictor 2: visuomotor control task). Only voxels with an RC value above 0.7 in favor of the angle discrimination task and a BOLD correlation range of 0.45–0.8 are indicated (P < 0.05, corrected).
for each group from the individual Z-normalized volume time courses. The signal values during the angle detection and control tasks were considered the effects of interest. The corresponding predictors, obtained by convolution of an ideal boxcar response (assuming the value 1 for the time points of task presentation and the value 0 for the control task) with a linear model of the hemodynamic response (Boynton et al., 1996), were used to build the design matrix of the experiment. Three-dimensional statistical maps were generated by associating each voxel with the F value corresponding to the specified set of predictors and calculated on the basis of the least-mean-square solution of the GLM. Voxels were accepted as activated only when the corresponding regression coefficient was greater than 0.45 (P < 0.05, corrected for multiple comparisons). For significantly activated voxels, the relative contribution (RC) between two selected sets of conditions in explaining the variance of a voxel signal time course were computed (Trojano et al., 2000; Goebel et al., 2001). An RC value of 1 (green) indicates that the variance of a voxel time course is solely explained with predictor 1 (control condition), whereas an RC value of –1 (red) indicates that the variance of a voxel time course is explained solely with predictor 2 (angle discrimination task). In the contrast maps, only RC values greater than 0.7 were visualized. The peak BOLD signal change in the significantly activated areas during task condition in comparison to the control task was computed for every single subject. These values were exported to the statistical software package SPSS for Windows, Release 10.0 (SPSS Inc., Chicago, IL).

Statistical analysis of the BOLD signal change. We computed a one-factorial analysis of variance (ANOVA) of the peak values of BOLD signal change between both groups. We additionally computed a two-factorial ANOVA for repeated measurements to reveal a possible interaction between the groups (AD and control group) and BOLD signal changes within areas of the dorsal (SPL) and ventral (GF) visual stream. On the basis of previous studies and theoretical considerations (Linden et al., 1998; Sack et al., 2002a,b) we focused the analysis of BOLD signal change on bilateral SPL, PVC, and GF. Because we expected a significant contribution of individual atrophy levels to the interindividual variance of BOLD signal changes, we additionally computed two ANCOVAs with the left and right SPL atrophy index as covariates to compare the number of activated voxels between groups after statistically controlling for the influence of the individual atrophy level.

RESULTS

Behavioral Data

The AD patients performed significantly worse than the controls in the MMSE (Mann–Whitney U test: P < 0.01). The performance of the patients in the visuospatial task (reaction time: 721 ± 153 ms; error rate: 10.6 ± 9.7%) did not differ significantly from the performance of the control group (reaction time: 677 ± 106 ms; error rate: 6.7 ± 3.6%). However, although the statistical comparison of centrality differences in the visuospatial task between patients and controls was nonsignificant for both measurements (Mann–Whitney U test: reaction time: P = 0.56; error rate: P = 0.64), the variance of the patients’ error rate was significantly higher in comparison to that of the control group (F(13,13) = 6.99, P < 0.01). This significantly higher variability of the error rate in AD patients reflects the higher heterogeneity of this group in comparison to the healthy subjects and indicates that some patients performed much worse than the control subjects.
Structural Imaging: Volumetry

The local cerebral volume loss in SPL was significantly higher in patients than in controls (left SPL: t = 4.58, P < 0.01; right SPL: t = 4.44, P < 0.01) (Fig. 2). In the AD group there was a significant positive correlation between the atrophy index and MMSE score [r = 0.725, P = 0.003 (left SPL volume index); r = 0.650, p = 0.012 (right SPL volume index)]. There were no significant correlations between the atrophy index and the variables age, latency, and errors in the AD group or the control group.

BOLD Signal Change

The analysis of group RC maps for AD and controls revealed a corticosubcortical network consisting of regions located in the frontal lobe, the occipital lobe, occipitotemporal cortex, basal ganglia, thalamus, and, most pronounced, superior parietal lobule (Table 1, Fig. 3). The one-factorial ANOVA of the BOLD signal change revealed a significantly higher BOLD signal change in the control group in comparison to the patients in the SPL, bilaterally [SPL left: F(1,26) = 9.778, P = 0.004; SPL right: F(1,26) = 5.237, P = 0.03], and a significantly higher BOLD signal change in the patient group in the left GF [F(1,26) = 7.914, P = 0.009], while the PVC did not show any significant difference between the groups (Table 2, left). The difference between the groups in the SPL and GF remained significant after controlling for task performance (latency and accuracy), age, and MMSE as covariates within an ANCOVA. The number of activated voxels in PVC and GF did not differ significantly between groups. As in the ANCOVA of the amplitude of BOLD signal change, consideration of the individual atrophy index as a covariate revealed that the significant difference between groups in the left and right SPL is statistically explained by the individual atrophy index (Table 3, middle and right). The ANCOVA with the right SPL atrophy index as a covariate resulted in a nonsignificant difference in the number of activated voxels between groups for the right SPL, while the difference in the left SPL remained significant between groups (Table 3, right), indicating the specificity of the atrophy index for the respective hemisphere.

DISCUSSION

We demonstrate a network related to visuospatial processing whose outline is very similar in AD patients and controls, with circumscribed frontal, parietal, occipital, occipitotemporal, and subcortical contributions. The relative contribution of the components of this network differed between the two groups in that the AD patients showed less activation in the frontal regions, basal ganglia, thalamus, and left and right superior parietal cortex (Table 1) while they revealed...
more task-related activity in left OTC than controls. These activation patterns were obtained while the two groups did not differ significantly in their task performance. However, the AD group had a significantly higher variance of the number of errors made during the angle discrimination task, indicating that the heterogeneity of task accuracy was higher in the AD group than in the control group. We used both task accuracy and reaction time as covariates to test their influence on the differences in the amplitude of BOLD signal change and the number of activated voxels between the AD and control groups. When corrected for differences in accuracy and reaction time, the differences remained significant, indicating that these differences cannot be explained by the behavioral data. Thus, differences in brain activation between patients and controls cannot be attributed to deficits in global attention and performance, but are likely brought about by specific disease-related changes in brain physiology.

An important finding of our study is a double dissociation between patients and controls concerning their differential activation of the dorsal (SPL) and ventral visual (GF) stream. While patients showed significantly less activation in the dorsal stream, they revealed higher task-related activity (as measured by the amplitude of the BOLD signal change) in the left fusiform gyrus than controls. This shows that in AD, ventral and dorsal visual pathways are not only differently damaged at the input side as demonstrated during passive visual stimulation (Mentis et al., 1996) but these differences remain during active engagement of these regions.

Thulborn et al. (2000) reported reduced parietal cortex activation in the right hemisphere in AD patients during an eye movement task. They interpreted their finding as being a correlate of reduced spatial attention caused by AD. Our results converge with those of Thulborn et al. in that they suggest a reduced capacity of
AD patients to recruit the parietal cortex for visuospatial processing. Our covariance analysis with SPL atrophy as a cofactor revealed that this hypoactivation can at least be partly explained by local cerebral atrophy.

While their parietal activation was reduced, AD patients showed higher amplitude of BOLD signal change in the left GF during task processing than controls. This additional remote activation can be interpreted as a potential mechanism to compensate for the reduced functional capacity of the SPL in AD patients. In keeping with this interpretation, we found that the higher GF activation in AD patients can also in part be explained by SPL atrophy, indicating that the additional activation of GF is related to the structural and functional impairment of SPL. Grady et al. (1993) demonstrated that the GF, an area of the ventral visual stream that is central for face recognition, was similarly activated in AD patients and healthy control subjects during a face-matching task, indicating that cortical areas of the ventral stream retain their functional capacity at least in the early stages of AD. This is also in accord with the findings of Mentis et al. (1996), who showed in their sample of AD patients that visual

### TABLE 2
Comparison of BOLD Signal Change Amplitude between Patients and Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Group</th>
<th>One-factorial ANOVA without covariates</th>
<th>ANCOVA with left SPL volume index as covariate</th>
<th>ANCOVA with right SPL volume index as covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>F (1, 26)</td>
<td>P</td>
</tr>
<tr>
<td>SPL, right</td>
<td>Subjects</td>
<td>2.491</td>
<td>9.778</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>0.877</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPL, left</td>
<td>Subjects</td>
<td>1.949</td>
<td>5.237</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>1.093</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVC, right</td>
<td>Subjects</td>
<td>0.953</td>
<td>1.182</td>
<td>0.287</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>1.240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVC, left</td>
<td>Subjects</td>
<td>1.068</td>
<td>0.367</td>
<td>0.550</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>0.838</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GF, left</td>
<td>Subjects</td>
<td>1.281</td>
<td>7.914</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>1.923</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparison between subjects and patients with respect to mean BOLD signal change during task performance in bilateral SPL and PVC and left GF. Group differences were analyzed with a one-factorial ANOVA (left part) as well as two separate ANCOVAs with left (middle) or right (right) SPL atrophy index as covariate.*

### TABLE 3
Comparison of the Number of Activated Voxels between Patients and Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Group</th>
<th>One-factorial ANOVA without covariates</th>
<th>ANCOVA with left superior parietal cortex atrophy index as covariate</th>
<th>ANCOVA with right superior parietal cortex atrophy index as covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>F (df)</td>
<td>P</td>
</tr>
<tr>
<td>SPL, left 0.3</td>
<td>Subjects</td>
<td>6871.571</td>
<td>9.108 (1, 26)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>2415.929</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>Subjects</td>
<td>5025.786</td>
<td>7.754 (1, 26)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>1784.500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>Subjects</td>
<td>2742.857</td>
<td>5.337 (1, 26)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>1094.429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPL, right 0.3</td>
<td>Subjects</td>
<td>6788.357</td>
<td>4.737 (1, 26)</td>
<td>0.039</td>
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<tr>
<td></td>
<td>Patients</td>
<td>3094.786</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>Subjects</td>
<td>5107.876</td>
<td>3.093 (1, 26)</td>
<td>0.090</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>2595.429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>Subjects</td>
<td>2953.286</td>
<td>0.706 (1, 26)</td>
<td>0.408</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>2042.857</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparison between subjects and patients with respect to mean number of activated voxels during task performance in left and right SPL at different correlation thresholds (0.3–0.5). Group differences were analyzed with a one-factorial ANOVA (left part) as well as two separate ANCOVAs with left (middle) or right (right) SPL atrophy index as covariate.*
cortical areas with input from the ventral visual pathway responded better to passive visual stimulation than cortical areas related to the dorsal visual pathway. However, with the ventral visual areas being essential for color, object, and face processing (Haxby et al., 1991; Bartels and Zeki, 2000) it remains open how the compensatory recruitment of these regions may compensate for impaired visuospatial functions related to the dorsal visual stream. We hypothesize that AD patients might have used a different strategy in recognizing the presented angles by processing them as unique objects and not as two lines with a specific orientation. This could explain the additional activation of GF in AD patients. The fact that we found only a higher BOLD signal change amplitude in GF in the AD group but not a higher number of activated voxels would support the assumption that the compensatory recruitment of GF is rather focal and involves only a small part of the GF, perhaps owing to the specific functional properties of this subregion or to a disruption of corticocortical connection fibers within the GF that prevents a broader spread of activation along this area.

The results of the present study need to be considered in the context of the large body of neurobiological and neuroimaging literature on functional reorganization in AD. In recent fMRI studies, Smith et al. (1999, 2002) administered a verbal fluency task and revealed reduced activation of inferotemporal cortex but higher activation of left SPL in asymptomatic patients at high risk for AD in comparison to low-risk subjects. In a verbal learning paradigm, Bookheimer et al. (2000) found that activation of hippocampal, parietal, and prefrontal regions was higher among high-risk subjects than among subjects with low risk of developing AD. In contrast, Schröder et al. (2001) reported diminished activation during verbal learning in temporal, occipital, and prefrontal cortical regions in AD patients with no additional areas being activated. These heterogeneous results seem to reflect the different mechanisms involved in functional changes in AD. On the one hand, impaired processing capacities can lead to higher cognitive effort and thus to increased activation of cortical regions subsuming task processing or to the additional activation of regions initially not involved in the task. On the other hand, disruptions of intercortical signal flow and direct cortical damage may lead to reduced activity. In addition, a recent fMRI study found that compensatory effects in subjects at risk for AD are highly task-specific (Burggren et al., 2001).

The results of our study suggest that in AD compensation mechanisms within neuropathologically altered higher areas of the dorsal visual pathway are limited and that visuospatial task processing is accompanied by the recruitment of remote areas of the ventral visual stream. We also demonstrate the value of the consideration of local atrophy for the interpretation of functional imaging data in AD patients and regard our study as one step in the unraveling of the pathophysiological processes of this important neurodegenerative disease.

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