Functional Imaging During Recognition of Personally Familiar Faces and Places in Alzheimer’s Disease

Markus Donix1,2,*, Luisa Jurjanz1†, Shirin Meyer1, Eva C. Amanatidis1, Damaris Baeumler1, Thomas Huebner1,3, Katrin Poettrich1, Michael N. Smolka1,3, Vjera A. Holthoff1,2

1Department of Psychiatry and Psychotherapy, Division of Old Age Psychiatry and Cognitive Neuropsychiatry, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
2DZNE, German Center for Neurodegenerative Diseases, Dresden, Germany
3Neuroimaging Center, Technische Universität Dresden, Dresden, Germany

*Corresponding author at: Department of Psychiatry and Psychotherapy, Division of Old Age Psychiatry and Cognitive Neuropsychiatry, University Clinic Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany. Tel.: +49-351-458-4474; fax: +49-351-458-5316.
E-mail address: markus.donix@uniklinikum-dresden.de (M. Donix).

Accepted 20 September 2012

Abstract

Alzheimer’s disease (AD) patients show better everyday functioning in a familiar setting, but they have a reduced ability to access contextual details and episodes associated with a familiar person or environment. This suggests a dysfunction in the neural networks associated with stimulus identification. Using functional magnetic resonance imaging, we investigated the neural activity during the recognition of personally familiar and unfamiliar faces and places among AD patients and elderly controls. We did not find a group difference in the neural activity within brain areas important for perceptual familiarity recognition. Patients showed reduced activation for familiar stimuli in prefrontal brain areas known to be important for retrieving contextual information for a stimulus when compared with controls. These changes may contribute to how AD patients experience a personally familiar face or place.

Keywords: Alzheimer’s disease; Dementia; Everyday functioning; Neuroimaging (functional)

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia (Mount & Downton, 2006). In addition to pharmacological treatment options, non-pharmacological strategies aimed at preventing dementia onset or slowing its progression are increasingly studied. Little is known about the relationship of such interventions and the neural functioning in patients suffering from AD. Neuroimaging techniques may contribute to a better understanding of why some interventions would show good results but others would not, or why a specific subject population may benefit more than another.

Personal familiarity plays a unique role in dementia care and treatment. Dementia patients often experience disorientation in time and place, and familiar environments can make them feel safe and confident to perform everyday activities (Brittain, Corner, Robinson, & Bond, 2010). A personally familiar environment is reassuring and reduces wandering behavior in patients with dementia (Hong & Song, 2009). Liu, Gauthier, and Gauthier (1991) revealed that patients with early AD show impaired functional task performance in an unfamiliar environment, but the skills are preserved in a familiar environment. In real-world situations, the environment has distinct physical and social characteristics. It has been demonstrated that a close relationship with a familiar person is associated with greater “wellbeing” and improved problem-solving capacity (Burgener & Twigg,
A personally familiar environment supports and strengthens a demented person’s social and cognitive skills, although the person may gradually lose the ability to fully identify a familiar face, place or object (Reisberg, Ferris, de Leon, & Crook, 1982). This is in line with an observation by Giovanetti and colleagues (2006). The authors showed that patients with dementia perform significantly better in identifying personal objects versus unfamiliar analogs. However, explicit recognition of an object as one’s own was not a prerequisite for this effect (Giovanetti et al., 2006). Therefore, recognizing something as familiar, and having access to semantic and episodic information surrounding that stimulus, may reflect distinct processes contributing to stimulus representation, which are differentially affected during dementia progression. If we perceive a stimulus we were previously exposed to, we may have a feeling of knowing irrespective of context information availability. In functional magnetic resonance imaging (fMRI) studies, this “perceptually-based” familiarity (Cloutier, Kelley, & Heatherton, 2011) has been shown to activate the precuneus and the posterior cingulate cortex across different stimulus modalities (Epstein, Higgins, Jablonski, & Feiler, 2007; Gobbini & Haxby, 2006; Shah et al., 2001; Sugiura et al., 2009). Feelings of familiarity can also vary in strength. Using fMRI, several studies demonstrated increasing activity in specific brain regions, including the posterior cingulate cortex, when presenting faces or scenes differing in familiarity strength (Gobbini, Leibenluft, Santiago, & Haxby, 2004; Kosaka et al., 2003; Montaldi, Spencer, Roberts, & Mayes, 2006).

In contrast, stimulus identification based on contextual knowledge, such as facts or episodes, is associated with additional neural activity in the posterior superior temporal sulcus as well as lateral and medial frontal cortical areas, brain regions involved in episodic memory retrieval, social cognition, and self-referential processes (Adolphs, 2009; Cabeza & Nyberg, 2000; Cloutier et al., 2011; Fossati et al., 2003). Semantic knowledge and the recollection of episodic details contribute to forming a context the stimulus would exist within. On a more abstract level, perceiving a stimulus as new or known and accessing contextual knowledge for the stimulus reflect major cognitive processes, “familiarity” and “recollection”, which underlie recognition (Yonelinas, 2002). Although there is still a debate about whether familiarity and recollection represent different psychological processes and whether or not they are dependent upon another (Dunn, 2004; Yonelinas, 2002), it has been shown that they are associated with overlapping but distinct neural networks (Montaldi et al., 2006). In this context, personally familiar faces and places are interesting stimulus modalities because they elicit both familiarity and recollection processes, which might be differently affected by aging and dementia. Whereas familiarity seems to be better preserved in older age and cognitive deterioration, recollective abilities decline with age and this impairment is one of the most prominent features in early dementia and its preclinical stages (Bugaiska, Morson, Moulin, & Souchay, 2011; Castel & Craik, 2003; Rhodes, Castel, & Jacoby, 2008; Serra et al., 2010). In a previous study, we revealed that the neural network involved in the representation of personally familiar faces and places remains relatively preserved during aging (Donix, Petrowski, et al., 2010). We also demonstrated reduced frontal cortical activity among patients with amnestic mild cognitive impairment (aMCI) associated with the perception of personally familiar stimuli (Jurjanz et al., 2011). To our knowledge, the neural networks involved in personal familiarity processing have not yet been investigated in patients with AD. In this study, we therefore performed an fMRI experiment with AD patients and healthy controls. We presented personally familiar faces (spouse and children) and places (from the participants’ own homes) as well as unfamiliar faces and places during fMRI scanning. In patients with dementia, there is a well-known decline in recollective abilities and in forming contextual associations when compared with basic familiarity recognition. Since these processes are particularly associated with frontal cortical activity, we hypothesized that AD patients compared with healthy elderly people show reduced neural activity in the frontal cortex when they perceive personally familiar versus unfamiliar stimuli.

Methods

Study Participants

AD subjects, meeting NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984), were recruited through the University’s Memory Clinic, whereas control participants responded to public advertisements. The University’s Ethics Committee approved the study and written informed consent was obtained. We only recruited patients with early-stage AD (CDR Stage 1) who had the full capacity to consent. The capacity to consent was established in a clinical evaluation by an experienced and independent psychiatrist who was not involved in the study. Twelve AD subjects and 12 cognitively healthy subjects (CDR Stage 0) participated (Table 1). All study participants were right-handed, underwent medical history evaluation, neuropsychological testing, and structural brain MRI. The AD diagnoses were established by a geriatric psychiatrist, based on her own patient evaluation and detailed neuropsychological testing administered by an experienced neuropsychologist. Structural MRI and laboratory testing results complemented the diagnostic procedures to rule out conditions that would have explained the dementia syndrome otherwise. Only subjects free of white matter lesions or with focal white matter lesions only (age-related white
matter changes scale; Wahlund et al., 2001, score <2 points) and free of focal lesions in grey matter were included. Exclusion criteria were education <8 years, history of alcohol or substance abuse, head trauma, psychiatric or neurological disorder preceding AD onset, or major systemic disease affecting the brain function. AD patients were on stable acetylcholinesterase inhibitor medication and did not receive any medication (such as benzodiazepines or neuroleptics) that could modulate cognitive functioning. All control participants were also free of any psychotropic medication. The control group served as a control population in two previous studies investigating familiarity effects in healthy aging and aMCI (Donix, Petrowski, et al., 2010; Jurjanz et al., 2011). None of the AD participants were former MCI subjects investigated in previous studies.

**fMRI Stimulus Preparation**

We obtained photographs of each participant’s close relatives (spouse and children) with a digital camera. Each relative was photographed from five different angles (left side, 45° left, frontal, 45° right, and right side). The images were digitally manipulated to ensure similar head size, luminance, and background. Pictures of unfamiliar faces were obtained from family members of the clinical staff. Familiar and unfamiliar face stimuli were matched for gender and approximate age. Images of familiar places were taken of the participants’ homes. We obtained photographs of rooms rather than of single furniture. Pictures of unfamiliar places were obtained from the homes of clinical staff members and their relatives. In order to control for possible differences in the visual complexity of the place stimuli, we approximately matched the presented familiar and unfamiliar places (e.g., familiar bedroom picture and unfamiliar bedroom picture with about the same room size and layout).

**Experimental Design**

We used a blocked factorial design to investigate the neural activity associated with different stimulus modality (face/place) and personal familiarity (familiar/unfamiliar). During fMRI scanning, five stimuli of one of the four conditions (familiar face, FF; unfamiliar face, UF; familiar place, FP; unfamiliar place, UP) were blocked together (stimulus onset time 5 s). To avoid habituation effects, each block’s images showed the same stimulus but photographed from different angles. Individual stimulus images were not repeated within experimental conditions. Images were presented in a counterbalanced order across the experimental runs for both familiarity and stimulus modality. To ensure alertness and to test whether participants would correctly recognize familiar and unfamiliar stimuli, each block contained a question stimulus in response of which the subjects were
asked to press the correct button (“if the stimulus presented was familiar press the button in your left hand/if unfamiliar press the button in your right hand”). We therefore enabled the subjects to provide a familiarity judgment for all the familiar and unfamiliar persons and places throughout the experiment. Experimental conditions were separated by intervals lasting 9 s, during which the participants focused at a fixation cross. A total of three experimental runs, each consisting of eight stimulus blocks were performed using a 3T MRI scanner (Trio; Siemens AG, Erlangen, Germany). fMRI images were acquired with an echo-planar imaging (EPI) pulse sequence using blood oxygenation level dependent (BOLD) contrast: repetition time (TR) = 1.95 s, echo time (TE) = 25 ms, α = 80°. 34 transversal slices acquired in descending order, orientated axially parallel to the ac-pc line, thickness 3 mm (1 mm gap), field of view (FOV) = 220 mm, voxel size 3.44 × 3.44 × 4 mm³. We collected 547 volumes for each subject. Stimuli were presented using bi-screen goggles below the head coil (VisuaStim Digital, Resonance Technology Inc., Northridge, CA, USA). Task presentation and behavioral response recording was performed with Presentation® software (version 9.9, Neurobehavioral Systems Inc., Albany, CA, USA). High-resolution anatomic images were also acquired using a T1-weighted three-dimensional magnetization-prepared, rapid acquisition gradient echo (MPRAGE) pulse sequence: TR = 1.9 s, TE = 2.26 ms, FOV = 256 mm, 176 slices, voxel size 1 × 1 × 1 mm³.

Image Processing and Statistical Analysis

Image processing and statistical calculations were performed using MATLAB (The Mathworks Inc., Natick, MA, USA) and statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). The first five EPI images were discarded to allow the MRI signal to reach a steady state. To correct for head movement, we spatially realigned individual data to the first volume. We used a standard EPI template (Montreal Neurological Institute [MNI] brain) for normalization. After resampling to achieve 3 × 3 × 3 mm³ isotropic voxels, we smoothed functional data using an isotropic Gaussian kernel of 10 mm full width at half maximum (FWHM). At the single-subject level, we modeled all four conditions of the paradigm in the context of a general linear model. We also modeled the question stimulus, the subjects’ response (button presses) and feedback separately from the rest condition (focusing on a fixation cross). We used a flexible factorial modeling procedure for second-level analyses in a 2 × 2 × 2 factorial design, which includes an implicit subject factor to control for subject-specific variance, investigating the factors stimulus type (face/place), familiarity (familiar/unfamiliar), and group (control/AD). After examining the factors’ main effects, we investigated all two-way interactions (group × familiarity, group × stimulus type, and familiarity × stimulus type). Because of the significant age difference between our groups, we introduced age as a covariate of no interest in all fMRI group analyses. We additionally calculated the respective simple main effects (e.g., effect of familiarity in both groups). Voxels in MNI space were considered statistically significant at a voxel-level threshold of p < .001 uncorrected, corresponding to T = 3.28 when they were part of a cluster exceeding 30 voxels (the cluster level threshold of p < .05, family wise error corrected). Sociodemographic data and neuropsychological scores were compared using raw data and two-tailed t-tests. In order to prevent spurious findings among the neuropsychological test comparisons, we verified that we could establish significance in an omnibus multivariate test prior to these univariate analyses. We also ensured that using age-adjusted z-scores instead of raw values would not change the pattern of significant findings.

Voxel-Based Morphometry

We used T1-weighted MPRAGE scans for performing a voxel-based morphometric (VBM) analysis (Good et al., 2001), assessing possible brain volume differences between the participant groups. We first defined the anterior commissure in each image as the origin of the individual stereotactic space. We then manually reoriented all scans to the axial view before automatically segmenting the images into gray matter, white matter, and cerebrospinal fluid probability maps. After removing all non-brain voxels, gray and white matter maps were separately normalized to MNI space using SPM5 and a VBM toolbox (Christian Gaser, http://dbm.neuro.uni-jena.de/vbm). We normalized the individual anatomical T1 images using transformation parameters derived from normalizing individual gray matter maps to MNI templates, before averaging and smoothing to create a study-specific template. Individual images were locally deformed to the template using non-linear spatial transformations. After correcting for non-uniformities in signal intensity, the normalized images were segmented into gray and white matter and cerebrospinal fluid maps. Finally, we corrected for possible volume changes (modulation; Good et al., 2001) as a result of spatial normalization and the resulting gray and white matter maps were smoothed with a Gaussian kernel of 8 mm FWHM. In a second analysis, we also investigated the unmodulated data. Whereas modulated data reflect the absolute amount of gray matter (volume), unmodulated data reflect differences in regional gray matter concentration (Ashburner & Friston, 2000; Good et al., 2001). Voxels were considered statistically significant at a threshold of p < .05 (corrected at the cluster level) using a height threshold of p < .001 uncorrected.
Results

Neuropsychological and Behavioral Results

Control subjects performed within the normal range (age adjusted z-scores, not shown) in all neuropsychological tests. AD patients were significantly impaired in various tests across different cognitive domains (Table 1). In the familiarity judgment task during scanning, all participants were able to provide accurate judgments. As an additional approach to investigate the reliability of the familiarity judgments, the individual stimuli used during the scan were again presented on a computer screen in a post-scanning debriefing. Using a simple familiarity judgment task (“is the depicted face/place personally familiar?”—yes/no), both participant groups did not significantly differ in their ability to correctly categorize familiar and unfamiliar stimuli.

Functional MRI

We were specifically interested in examining a possible interaction between the factors group and familiarity. We detected significant main effects for familiarity and group as well as a significant interaction between both factors. Group comparison (interaction group × familiarity) revealed reduced bilateral superior frontal cortical activity among AD patients when compared with control participants for familiar versus unfamiliar stimuli ([FF + FP] − [UF + UP], Table 2, Fig. 1). We also detected reduced activity in the right middle orbital gyrus among the patients. In the right cerebellum, AD patients showed greater neural activity for unfamiliar stimuli when compared with control participants. We then calculated the effect of familiarity within both groups (simple main effect familiarity). Among control subjects, familiar compared with unfamiliar stimuli, irrespective of the stimulus type (FF + FP) − (UF + UP), elicited substantially more brain activity, primarily in medial and inferior frontal, anterior cingulate, and posterior cingulate areas bilaterally. AD patients did not show greater brain activity when perceiving familiar versus unfamiliar stimuli.

Investigating the interaction terms stimulus type × group and stimulus type × familiarity did not reveal brain regions showing significantly greater or reduced neural activity associated with one of the conditions.

Table 2. Relative increases in brain activity associated with personal familiarity

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-score</th>
<th>kE (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>L</td>
<td>−9</td>
<td>45</td>
<td>17</td>
<td>7.11</td>
<td>5553*</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>R</td>
<td>6</td>
<td>14</td>
<td>29</td>
<td>6.41</td>
<td>87</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>L</td>
<td>−12</td>
<td>−51</td>
<td>30</td>
<td>6.67</td>
<td>129</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>R</td>
<td>42</td>
<td>35</td>
<td>17</td>
<td>6.15</td>
<td>129</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>L</td>
<td>−30</td>
<td>24</td>
<td>−18</td>
<td>5.07</td>
<td>133</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>L</td>
<td>−51</td>
<td>6</td>
<td>12</td>
<td>4.62</td>
<td>174</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>L</td>
<td>−33</td>
<td>−12</td>
<td>51</td>
<td>4.62</td>
<td>219</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>L</td>
<td>−36</td>
<td>−42</td>
<td>45</td>
<td>4.25</td>
<td>108</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>33</td>
<td>−54</td>
<td>−51</td>
<td>5.58</td>
<td>130</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>R</td>
<td>51</td>
<td>−51</td>
<td>3</td>
<td>5.17</td>
<td>151</td>
</tr>
</tbody>
</table>

AD patients

No suprathreshold clusters

Group comparison (interaction group × familiarity)

Controls > AD

Superior frontal gyrus | R    | 12 | 39 | 57 | 4.25 | 507 |
Superior frontal gyrus | L    | −12 | 36 | 57 | 4.08 | 129 |
Cerebellum | R    | 15 | −78 | −27 | 3.96 | 284 |
Middle orbital gyrus | R    | 33 | 48 | −12 | 3.99 | 173 |
Inferior frontal gyrus | R    | 33 | 30 | −18 | 3.99 | 173 |

Notes: All activations are significant at p < .05, corrected for multiple comparisons at the cluster level (with a height threshold of p < .001, uncorrected at the voxel level). For each region of activation, the coordinates of the maximally activated voxels within the activation cluster are given in the standard stereotactic MNI space. FF = familiar faces; UF = unfamiliar faces; FP = familiar places; UP = unfamiliar places.

*This activation maximum is part of the same cluster.
Voxel-Based Morphometry

VBM analysis did not reveal significant local differences between the gray matter volumes of older adults and AD participants. We also performed the region of interest analyses for frontal and posterior cingulate regions based on the coordinates of our significant within and between group fMRI results. This analysis also did not reveal a significant result.

Discussion

Our aim was to investigate the neural networks associated with the recognition of personally familiar faces and places in AD patients and healthy controls. We found that the AD patients showed reduced bilateral superior frontal cortical as well as reduced right middle orbital gyrus neural activity when they perceived familiar stimuli irrespective of the stimulus type (face or place). We additionally investigated the brain activity in both groups during the baseline intervals preceding the presentation of familiar or unfamiliar stimuli. Based on this, our data suggest that AD patients did not specifically deactivate for familiar stimuli, but failed to activate in these regions. We also revealed a significant group difference in the right cerebellum when contrasting familiar and unfamiliar stimuli. The differential activity in this region was due to the unfamiliar stimuli being associated with greater brain activity in AD patients when compared with control subjects. However, we did not have a specific hypothesis for the cerebellum, but our data add to the increasing evidence of its important role for cognitive functioning (Hogan et al., 2011). We further did not find a between-group difference in brain activity among cortical regions known to be associated with perceptual familiarity, specifically the posterior cingulate cortex (Epstein et al., 2007; Gobbini & Haxby, 2006; Shah et al., 2001). There was also no significant interaction between the factors stimulus type and familiarity. This is in line with previous findings, which suggest that the neural networks associated with personal familiarity are relatively stimulus-independent (Shah et al., 2001; Sugiura et al., 2009; Sugiura, Shah, Zilles, & Fink, 2005).

Personal familiarity plays an essential role in dementia care. Greater psychosocial “wellbeing” and better everyday functioning may result from AD patients’ interactions with familiar people (Burgener & Twigg, 2002; Norton et al., 2009), objects (Giovannetti et al., 2006), and a personally familiar environment (Brittain et al., 2010; Hong & Song, 2009). Giovannetti and colleagues (2006) showed that demented people could better name and use personally familiar objects, although they may not recognize them as their own. This implies that having access to detail information surrounding a stimulus is not a prerequisite for personally familiar stimuli being represented as a unique stimulus category.
The medial frontal cortex plays an important role for familiarity processing. Previous work by others and by our own group (Cloutier et al., 2011; Donix, Petrowski, et al., 2010; Gobbini et al., 2004; Leibenluft, Gobbini, Harrison, & Haxby, 2004) as well as the data presented here suggest important contributions of medial frontal cortical subregions to the experience of personal familiarity. Activity in the medial frontal cortex is associated with explicit access to contextual information surrounding a stimulus, irrespective of whether or not the stimulus is perceptually familiar (Cloutier et al., 2011). This information, which may involve semantic facts and episodic content, contributes to stimulus identification. In our study, AD patients showed reduced familiarity-associated neural activity in the bilateral superior frontal gyrus when directly compared with normal controls. The brain area showing this group difference extends in the anterior rostral region of the medial frontal cortex. The medial frontal cortex is essential for social cognition, such as making inferences about others’ thoughts (Amodio & Frith, 2006), self-reflection (Fossati et al., 2003), and self-referential processing (Gobbini et al., 2004; Leibenluft et al., 2004). Our AD patients’ inability to activate the orbitofrontal region when they viewed personally familiar faces or places could be in line with a possible impairment in monitoring self-associated consequences in the light of a social context (Amodio & Frith, 2006).

Neuroimaging data provide evidence for frontal cortical function changes relatively early in the course of pathologic cognitive decline, although it remains controversial whether AD patients may sometimes be able to recruit frontal cortical networks during cognitive tasks as a compensatory mechanism to maintain or support task performance (Grady et al., 2003; Li, Zheng, Wang, & Gui, 2009). However, the subjects’ performance may vary depending on task modality and dementia progression, which could contribute to the variation in neuroimaging data. The results from the present study and our previous findings in aMCI patients (Jurjanz et al., 2011) suggest a frontal cortical functioning deficit in early pathologic cognitive decline. Other brain imaging studies are in line with this finding. In a positron emission tomography study, Fouquet and colleagues (2009) demonstrated a lower medial frontal glucose metabolism in MCI subjects later converting to AD. Using fMRI, Allen and colleagues (2007) revealed a functional disconnection between the medial temporal lobe and the frontal cortex in AD patients.

Both groups did not significantly differ in their ability to recognize a stimulus as familiar during scanning, and there was no difference in brain activity in the posterior cingulate cortex, a region known to be important for perceptual familiarity recognition (Cloutier et al., 2011). Various fMRI studies demonstrated the relationship of brain activity in the posterior cingulate cortex and the precuneus with perceiving familiar versus unfamiliar stimuli (Epstein et al., 2007; Gobbini & Haxby, 2006; Shah et al., 2001). Although the posterior cingulate region is known as one of the earliest sites showing functional abnormalities in MCI and AD (Nestor, Fryer, Ikeda, and Hodges, 2003; Wu et al., 2010), Ries and colleagues (2006) showed preserved posterior cingulate functioning in MCI patients associated with the retrieval and evaluation of meaningful, self-relevant information. Sperling and colleagues (2003) even found increased posterior cingulate activity in AD patients performing an encoding task during fMRI scanning, which could reflect a task-dependent compensatory process.

This study has several limitations. Our AD patient group was on acetylcholinesterase inhibitor medication, which might have influenced the results. Miettinen and colleagues (2011) showed that chronic acetylcholinesterase inhibitor treatment was associated with greater neural activity during a face recognition memory task in AD patients in several brain regions, including the right inferior frontal gyrus, the left anterior cingulate cortex, as well as the left middle frontal gyrus and the left superior frontal gyrus. We neither observed neural activity in the frontal cortex among our AD patients in the within-group analysis nor did we observe greater frontal activity in patients when directly compared with controls. Although acetylcholinesterase inhibitor medication could still have modulated our fMRI results, the Miettinen and colleagues (2011) data suggest that our results are not mainly driven by this treatment. The limited sample size reduces statistical power. However, reanalyzing the fMRI data with a less stringent height threshold did not change the general pattern of significant group differences. Although the results of our VBM analyses could indicate that brain activity patterns are not mainly driven by substantial differences in gray matter integrity between AD patients and control participants, anatomical changes may have been undetectable in our mildly impaired AD patients given the limited subject sample size. The VBM data could also suggest that our results may only be valid for patients with early AD who do not yet suffer from substantial cortical structure changes. Our subject groups differ in their mean age, with AD subjects being ~7 years older than control participants. To examine possible age effects, we introduced age as a covariate of no interest in our fMRI group analyses, which did not change our findings. Furthermore, in a previous study, we demonstrated a relatively robust neural network associated with personal familiarity of faces and places among healthy younger and older subjects (Donix, Petrowski, et al., 2010). Finally, we did not directly examine the patients’ inability to access contextual information and episodes for a stimulus they recognize as familiar on the behavioral level. We previously showed that there is a decline in the richness of details and detail specificity for familiar (autobiographical) context even in preclinical and mild stage AD (Donix, Brons, et al., 2010).

In summary, our data suggest changes in neural functioning associated with familiarity recognition among our AD patients. Their inability to recruit frontal brain regions during the perception of personally familiar stimuli could indicate reduced access to contextual knowledge and episodes surrounding a familiar stimulus, although the patients were able to perceptually
recognize familiarity. Our data support the clinical observation that familiarity associated effects in dementia care and therapy do not depend on knowledge-based stimulus identification.

Funding

The study was funded by Hirnliga e.V.

Conflict of Interest

The authors report no financial relationships with commercial interests.

References


