Brief communication

Reduced olfactory bulb and tract volume in early Alzheimer’s disease—A MRI study

Philipp A. Thomann a ∗, Vasco Dos Santos a, Pablo Toro a, Peter Schönknecht a, Marco Essig b, Johannes Schröder a

a Section of Geriatric Psychiatry, University of Heidelberg, Voßstr. 4, 69115 Heidelberg, Germany
b German Cancer Research Center, Heidelberg, Germany

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Abstract

Olfactory dysfunction has been reported to occur already in the early stages of Alzheimer’s disease (AD) and to increase with disease severity. In neuropathological research, the deposition of neurofibrillary tangles and neuritic plaques in the olfactory bulb and tract (OBT) of AD patients has been consistently demonstrated. We used high-resolution magnetic resonance imaging (MRI) to determine the volume of the OBT in 21 patients with early AD and in 21 healthy comparison subjects. The OBT was manually traced on consecutive coronal slices. When compared to healthy controls, right, left and mean OBT volumes were significantly reduced in patients with AD ( p < 0.01). In AD patients, the mean OBT volume was significantly correlated with global cognitive performance as determined by the mini-mental state examination ( r = 0.605; p = 0.004). Manual tracing on MRI images revealed OBT atrophy to be present early in the course of AD. Since the respective findings were associated with cognitive impairment, they may contribute to early recognition and diagnosis of the disease.

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1. Introduction

Alzheimer’s disease (AD) is the most frequent dementia beyond the age of 65 years, affecting an eminent and increasing part of the population. Neuropathologically, AD is characterized by neuronal loss and deposition of neurofibrillary tangles (NFTs) and amyloid plaques in the brain. Post-mortem studies demonstrated that three main stages can be differentiated during the clinical course of AD (Braak stages, Braak et al., 1993), with parahippocampal regions the earliest to be affected (Braak stages 1 and 2), before the pathological alterations spread into additional structures of the medial temporal lobe/limbic system (Braak stages 3 and 4) and then encroach major parts of the temporal, parietal, and frontal cortical areas (Braak stages 5 and 6).

Limbic structures, early involved in the course of the AD, have olfactory connections. Olfactory dysfunction in AD has consistently been reported by a number of independent research groups (Larsson et al., 1999; Mesholam et al., 1998; Murphy et al., 1990; Nordin et al., 1997). Following the results of neuropathological studies (Attens and Jellinger, 2006; Kovacs et al., 1999; Tsuboi et al., 2003) impaired olfaction in AD seems to refer to the deposition of amyloid plaques and neurofibrillary tangles in the olfactory bulb which constitutes the first synaptic relay in the olfactory pathway (e.g., Niewenhuys et al., 1988).

The majority of magnetic resonance imaging (MRI) studies investigating morphological alterations in early AD revealed – according to the above mentioned main stages of the disease – predominantly the substructures of the medial temporal lobe to undergo atrophic processes (for review see
Chetelat and Baron, 2003). Interestingly, MRI studies on potential structural changes of the olfactory bulb and tract (OBT) in AD have not been performed yet, although this structure can be reliably delineated on adequate MR images (Abolmaali et al., 2002; Rombaux et al., 2006; Turetsky et al., 2003; Yousem et al., 1998).

In the present study, we therefore ascertained the volumes of the OBT in patients with mild AD and in healthy controls by using high-resolution MRI under the hypothesis that AD patients would show significantly lower OBT volumes than healthy comparison subjects, referring to an early accumulation of NFTs and amyloid plaques in this area.

2. Materials and methods

2.1. Subjects

Twenty-one patients with mild AD (according to the NINCDS-ADRDA criteria (McKhann et al., 1984), with all patients fulfilling the criteria of probable AD) and 21 healthy controls were included in this study. Both patients and controls were consecutively recruited through the section of geriatric psychiatry at the University of Heidelberg, Germany. The clinical evaluation of all subjects included ascertainment of personal and family history as well as physical, neurological and neuropsychological examination. Global cognitive deficits were assessed using the mini-mental state examination (MMSE, Folstein et al., 1975). All investigations were approved by the local ethics committee. Written informed consent was obtained from all participants.

2.2. Image acquisition

The MRI-data were obtained at the German Cancer Research Center with a 1.5-T Magnetom Symphony MR scanner (Siemens Medical Solutions, Erlangen, Germany) by using a T1-weighted 3D magnetization prepared rapid gradient echo sequence (MP-RAGE, 126 coronal slices, image matrix = 256 × 256, voxel size = 0.98 mm × 0.98 mm × 1.8 mm, TR = 10 ms, TE = 4 ms).

2.3. Manual segmentation

Manual OBT measurement was performed using the manual segmentation function of BRAINS2 software (Magnotta et al., 2002). In coronal view, the olfactory bulb was identified at the anterior cribriform plate and traced on a mean of 24.43 ± 2.25 (mean ± standard deviation; S.D.) consecutive slices (Fig. 1); posteriorly, the olfactory tract extends to enter the brain below the rostral part of the corpus callosum. The rater (P.A.T.) was blinded to the diagnosis. Twenty randomly selected scans were retraced twice by the same as well as by a second rater (V.D.S.); intraclass correlation coefficients ranged from 0.914 to 0.937 for intraobserver, and from 0.917 to 0.929 for interobserver variation.

2.4. Statistical analysis

The SPSS for Windows version 14 was used for statistical analysis. To address inter-individual differences in head size, the OBT volumes were corrected by dividing them by each subject’s intracranial volume. The latter was estimated by the sum of gray matter, white matter and cerebrospinal fluid after segmentation of the T1-weighted data sets by applying the iterative a-prior knowledge based algorithm implemented in SPM2 software (http://www.fil.ion.ucl.ac.uk/spm). Student’s two-tailed t-test procedure was used to evaluate significant differences between AD patients and controls. In the patient group, the relationship between mean OBT volume and global cognitive performance (as determined by the MMSE score) was assessed by using Pearson’s correlation coefficient.

3. Results

According to statistical analysis there were no significant differences with respect to age, gender distribution, and level of school education. As expected, the mean MMSE
score in AD patients was significantly lower when compared to controls \((p < 0.001)\). Subject demographics and volumetric measures are reported in Table 1. Student’s two-tailed \(t\)-test yielded no significant difference for the intracranial volume, but for the right \((p = 0.001)\), left \((p = 0.003)\) and mean \((p = 0.001)\) OBT volume with lower values in AD patients.

In patients with AD, the mean OBT volume was found to be significantly associated with the MMSE score according to Pearson’s moment correlation \((r = 0.605, p = 0.004)\).

### 4. Discussion

Our study yielded two major findings: (i) in patients with mild AD, the OBT volume was significantly reduced when compared to healthy controls and (ii) in the patient’s group, the OBT volume was significantly correlated with global cognitive performance as determined by the MMSE.

Recently, neuropathological research described the OBT to undergo degenerative alterations in AD; in their study on 15 autopsy AD cases and 15 healthy controls, Kovacs et al. (1999) detected NFT pathology in the OBT in the very early Braak stages, even before an affection of the entorhinal cortex could be observed. By Tsuboi et al. (2003), NFTs were also found to be present in the OBT early in the course of AD as indicated by the fact that, in their study sample of 93 individuals, one-third of the cases with Braak stage 2 already showed tau pathology in this area. And most recently, Attems and Jellinger (2006) reported a comparable result from their examination of a large number of autopsy cases \((n = 273)\), where 36.4% of the Braak stages 2 showed olfactory tau pathology. Additionally, the latter study demonstrated a strong association between rate of NFT deposition and disease severity. Taken together, these results clearly emphasize an involvement of the OBT in AD that occurs very early in the course of the disease. Hence, we assume that our result of significantly smaller OBTs in patients with mild AD compared to cognitively unaffected control subjects reflects the degenerative processes described above.

In AD patients, smaller mean OBT volumes were significantly correlated with lower MMSE scores. This result suggests that the OBT atrophy increases with progression of the disease, likely reflecting the neuropathological finding of NFT density increasing with higher Braak stages (Attems and Jellinger, 2006; Kovacs et al., 1999; Tsuboi et al., 2003).

Further research is needed to clarify whether our finding of a significantly reduced OBT volume in patients with mild AD also applies to individuals with mild cognitive impairment, the assumed preclinical stage of AD. Moreover, future studies should also correlate OBT atrophy with olfactory function and changes of other cerebral structures to enhance our understanding of how these factors relate to each other.

### Disclosure statement

No conflicts of interest to declare by any of the authors.

### References


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Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>AD</th>
<th>(t)-value</th>
<th>d.f.</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>13 F/8 M</td>
<td>14 F/7 M</td>
<td>–</td>
<td>–</td>
<td>n.sig.(^a)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.38 ± 7.14</td>
<td>71.76 ± 4.94</td>
<td>–0.73</td>
<td>40</td>
<td>0.470</td>
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<tr>
<td>Education (years)</td>
<td>9.67 ± 1.74</td>
<td>9.81 ± 1.94</td>
<td>–0.251</td>
<td>40</td>
<td>0.803</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.05 ± 0.81</td>
<td>22.10 ± 1.87</td>
<td>15.66</td>
<td>40</td>
<td>0.000</td>
</tr>
<tr>
<td>ICV (dm(^3))</td>
<td>1.33 ± 0.10</td>
<td>1.57 ± 0.10</td>
<td>0.125</td>
<td>40</td>
<td>0.125</td>
</tr>
<tr>
<td>Right OBT (mm(^3))</td>
<td>127.41 ± 16.73</td>
<td>112.85 ± 14.01</td>
<td>3.06</td>
<td>40</td>
<td>0.004</td>
</tr>
<tr>
<td>Left OBT (mm(^3))</td>
<td>124.21 ± 13.00</td>
<td>114.10 ± 14.99</td>
<td>2.34</td>
<td>40</td>
<td>0.025</td>
</tr>
<tr>
<td>Mean OBT (mm(^3))</td>
<td>125.81 ± 14.12</td>
<td>113.47 ± 14.01</td>
<td>2.84</td>
<td>40</td>
<td>0.007</td>
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<tr>
<td>Right OBT(^b)</td>
<td>95.80 ± 13.75</td>
<td>82.91 ± 9.09</td>
<td>3.58</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Left OBT(^b)</td>
<td>93.23 ± 9.63</td>
<td>83.82 ± 9.77</td>
<td>3.15</td>
<td>40</td>
<td>0.003</td>
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<tr>
<td>Mean OBT(^b)</td>
<td>94.52 ± 11.26</td>
<td>83.36 ± 9.01</td>
<td>3.55</td>
<td>40</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mean ± S.D.; d.f., degrees of freedom; n.sig., not significant; MMSE, mini-mental state examination; ICV, intracranial volume; OBT, olfactory bulb and tract. \(^a\) \(\chi^2\)-Test. \(^b\) Corrected by intracranial volume.


