Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae

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The aetiology, pathomechanisms and anatomical correlates of transient global amnesia (TGA) still remain obscure. Recently, focal MR-signal diffusion-weighted imaging (DWI) changes in the hippocampus have been described in patients with TGA, but the exact localization, long term outcome and pathophysiological nature of these lesions still remain unknown. The topography and time course of hippocampal DWI lesions in 41 TGA patients was studied using serial 3 T high-resolution MR-imaging and correlated to clinical and neuropsychometric results. Of these, 29 patients showed 36 DWI lesions with corresponding T2 lesions in the hippocampus within a time window of 48 h after onset. Almost all lesions (94%; 34/36) were selectively found in the CA-1 sector (Sommer sector) of the hippocampal cornu ammonis. Most DWI lesions (8/10) were already detectable in the peri-acute phase <6 h after onset of symptoms. A follow-up study 4–6 months after the episode did not show evidence for residual structural sequelae of these lesions (n = 20/20). A venous MR angiography of the intracranial dural sinus showed an asymmetric venous drainage in 21/24 (88%) patients. In 11/16 (69%) patients with unilateral lesions, the asymmetry corresponded to the side of the DWI lesion. Significant episodic verbal memory deficits in the acute phase (n = 14/18) were associated with lesions of the dominant hemisphere while impairment of visuospatial memory was associated with lesions of the non-dominant hemisphere. Persistent neuropsychological sequelae were not detected 4–6 months after the episode (n = 16). This is the first prospective study combining high-resolution imaging and neuropsychometry analysing the detailed functional anatomy and outcome of hippocampal DWI/T2 lesions in TGA supporting the view the TGA being a benign transient disorder. The TGA can be considered a model for a focal transient perturbation of memory circuits in the tempororo-mesial region.

Keywords: cornu ammonis; DWI; hippocampus; memory; selective vulnerability; transient global amnesia

Abbreviations: CA = cornu ammonis; DWI = diffusion-weighted imaging; RAVLT = Rey auditory verbal learning and recognition test; RBMT = Rivermead Behavioural Memory Test; TGA = transient global amnesia

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Introduction

The transient global amnesia (TGA) is a rare amnestic syndrome that is characterized by a sudden onset of a selective antero- and retrograde amnesia and for which the time course is limited up to 24 h. The clinical and neuropsychological spectrum of this syndrome has been characterized in the past and several aetiological factors, such as migraine, focal ischaemia, venous flow abnormalities and epileptic phenomena have been suggested to be involved in the pathophysiology, although no clear picture has emerged from these findings (Olesen and Jorgensen, 1986; Lewis, 1998; Gorji, 2001).

Recent imaging data suggest an involvement of hippocampal structures as focal MR hyperintensities showing restricted diffusion (DWI lesions) in the lateral hippocampus have been described (Woolfenden et al., 1997; Ay et al., 1998; Schaefer, 2000; Greer et al., 2001; Matsui et al., 2002; Kappeller et al., 2003; Sedlaczek et al., 2004; Winbeck et al., 2005). The exact location of the DWI lesions in the...
hippocampal injury, epilepsy, psychiatric diseases). The characteristics and time course of the TGA episode was documented including events and factors precipitating the TGA episode (Table 1).

**Neuropsychometric evaluation**

Neuropsychological assessment was performed (i) in the acute episode (<24 h after onset of symptoms), if possible, otherwise on admission, (ii) during presence of DWI lesions (within 48–96 h), usually after subjective clinical remission and (iii) after 4–6 months if DWI lesions had initially been found.

The neuropsychometric test battery included the following subtasks: evaluation of orientation, working and verbal memory [forward and backward digit span, Rey auditory verbal learning and recognition test (RAVLT), Rivermead Behavioural Memory Test (RBMT)], visuoconstructive and -spatial memory [Rey–Osterrieth Complex Figure copy and delayed recall (RFC and RFR), Benton visual retention test], attention (Stroop test). Naming and conceptual knowledge was tested by means of verbal fluency (letter/category) of spontaneous speech which was evaluated with the Regensburg word fluency test. Different versions of the subtests were used in a randomized order and patients acted as their own controls during the study.

**Neuroradiological study**

Cranial MRIs were performed (i) in the acute or peri-acute phase 4–6 h after onset, if possible and (ii) in the time window of 24–72 h after onset of symptoms. Patients showing DWI lesions were again studied (iii) 10–20 days and (iv) 4–6 months after the TGA.

High-resolution (HR) MRIs were performed on a 3 T unit (Philips Intera Achieva). The following sequences were acquired:

- Dual echo standard transverse (parallel to AC–PC line), proton density- and T2-weighted (TSE, TR 3306 ms, TE 16/80 ms, field of vision [FOV] 230 mm, matrix size 400 × 512, slice thickness 4 mm).
- FLAIR sagittal (TR 1200 ms, TE 160 ms, TI 2850 ms, FOV 230 mm, matrix size 256 × 512, slice thickness 3 mm). DWI-echo planar imaging (SE-EPI) transverse oblique plane parallel to the hippocampus and coronal perpendicular to the hippocampus (TR 3319 ms, TE 71 ms, FOV 240 mm, matrix size 144 × 256, slice thickness 3 mm, isotropic, b = 1000 s/mm²) with subsequent maps of the apparent diffusion coefficient (ADC).
- T2-weighted, TSE, transverse and coronal, orientation as for DWI [TR 3000 ms, TE 80 ms, FOV 220 mm, matrix size 432 × 512, slice thickness 2 or 1 mm (follow-up)].
- T1-weighted, fast-field-echo (FFE), transverse, orientation as for DWI, pre-/post contrast media (TR 160 ms, TE 1,82 ms, FOV 150 mm, matrix size 256 × 512, slice thickness 3 mm).
- Time-of-flight MR-angiography (TOF-3D). A venous 3 T MR-angiography (PC-MRA) was performed in 24 patients and visually inspected with regard to asymmetry of flow signals and configuration of the dural venous sinus (Ayanzen et al., 2000).

The initial MRI in the first 12 patients was studied on a 1.5 T unit using comparable sequences with a conventional standard imaging protocol; the follow-up was performed on a 3 T unit.

Focal hyperintensities were considered as a hippocampal lesion in a consensus agreement if they were detectable in both diffusion sequences and T2-weighted images. Lesions were mapped with respect to the location within the different sectors of the cornu ammonis (CA) after Lorento deNo according to the anatomical reference Atlas of Duvernoy (Duvernoy, 2005; Lorente de No’o, 1934). Lesions had to be clearly distinguishable from pre-existing residual cavities of the vestigial hippocampal sulcus (Fig. 1D).
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Duration TGA (h)</th>
<th>Duration retrograde amnesia</th>
<th>Lesion hippocampus</th>
<th>Hypoplastic venous sinus</th>
<th>Cerebrovascular risk factors</th>
<th>Circumstances of onset</th>
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<tr>
<td>1</td>
<td>62</td>
<td>12</td>
<td>Weeks</td>
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<td>TIA, artHT(β)</td>
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<td>2</td>
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<td>5</td>
<td>Days (96 h)</td>
<td>Left (&lt;6 h)</td>
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<td>Post-coital</td>
<td>Breakfast</td>
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<td>3</td>
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<td>3</td>
<td>Days</td>
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<td>After consultation of a physician; 2nd TGA</td>
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<td>4</td>
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<td>&gt;1 year</td>
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<td>ArtHT(ACE), CHD(ase, art), hyperlipid(stat)</td>
<td>Gardening</td>
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<td>5</td>
<td>60</td>
<td>8</td>
<td>Weeks</td>
<td>Ø lesion (&lt;12 h)</td>
<td>ArtHT(ACE)</td>
<td>After consultation of a physician; 2nd TGA</td>
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<td>Days</td>
<td>Right (48 h)</td>
<td>ArtHT(ACE)</td>
<td>Walking; 3rd TGA; 2nd TGA 2 months before, 1st TGA 2 years before</td>
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<td>12 h</td>
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<td>Massive emotional stress</td>
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<td>After napping</td>
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<td>12 h</td>
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<td>ArtHT(β),</td>
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<td>62</td>
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<td>Years</td>
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<td>After napping; 3rd TGA</td>
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<td>Bilateral (6 h)</td>
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<td>Wood chopping/cycling</td>
<td>After doing the laundry; 2nd TGA</td>
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<td>After breakfast</td>
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<td>Right (48 h)</td>
<td>ArtHT(β), MI, CHD(asp)</td>
<td>After breakfast</td>
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<tr>
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<td>56</td>
<td>5</td>
<td>Days</td>
<td>Right (72 h)</td>
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<td>5–6 h</td>
<td>Left (48 h)</td>
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<td>Overarm drilling</td>
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<td>2 days</td>
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<td></td>
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<td>3</td>
<td>Days</td>
<td>Left (24 h)</td>
<td>ArtHT(β),</td>
<td>After breakfast</td>
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<td>Days–weeks</td>
<td>Left (&lt;6 h)</td>
<td>ArtHT(β),</td>
<td>After napping</td>
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<td>Hours</td>
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<td>Gardening</td>
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<td>4</td>
<td>Days</td>
<td>Right (72 h)</td>
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<td>Gardening</td>
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<td>31</td>
<td>67</td>
<td>8</td>
<td>12 h</td>
<td>Left (24 h)</td>
<td>ArtHT(β), hypchol, MI</td>
<td>Gardening</td>
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<td>32</td>
<td>70</td>
<td>4</td>
<td>12 h</td>
<td>Left (48 h)</td>
<td>ArtHT(β), warf, ACE, digi, TEA ICA, stenting VAR; MI</td>
<td>Gardening</td>
<td></td>
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<tr>
<td>33</td>
<td>39</td>
<td>4</td>
<td>12 h</td>
<td>Left (48 h)</td>
<td>ArtHT(β), CHD, MI, aFil, hypchol</td>
<td>Post-coital</td>
<td>Gardening/woodwork</td>
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<tr>
<td>34</td>
<td>71</td>
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<td>Days</td>
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<td>Post-coital</td>
<td>Gardening/woodwork</td>
</tr>
<tr>
<td>35</td>
<td>64</td>
<td>5</td>
<td>Days</td>
<td>Left (48 h)</td>
<td>ArtHT(β), ace, aFil, hypchol</td>
<td>Onset of travelling</td>
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<tr>
<td>36</td>
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<td>4</td>
<td>120 d</td>
<td>Ø lesion (24 and 48 h)</td>
<td>ArtHT, CHD, migraine PFO, migraine</td>
<td>After napping</td>
<td>One day after leg varicosis surgery; TGA after putting on compression hosiery 3rd TGA, during dragging logs 1st TGA during strenuous carpeting (heavy pulling) 2nd TGA after jet skiing</td>
</tr>
<tr>
<td>37</td>
<td>75</td>
<td>5</td>
<td>Days</td>
<td>Left (24 and 48 h)</td>
<td>ArtHT, CHD, migraine PFO, migraine</td>
<td>After napping</td>
<td>3rd TGA, during dragging logs 1st TGA during strenuous carpeting (heavy pulling) 2nd TGA after jet skiing</td>
</tr>
<tr>
<td>38</td>
<td>55</td>
<td>6</td>
<td>1 day</td>
<td>Right (72 h)</td>
<td>PFO</td>
<td>After napping</td>
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Table 1 Continued

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<th>Patient No.</th>
<th>Age (years)</th>
<th>Duration TGA (h)</th>
<th>Duration retrograde amnesia</th>
<th>Lesion hippocampus</th>
<th>Hypoplastic venous sinus</th>
<th>Cerebrovascular risk factors</th>
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<td>73</td>
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<td>Right (48 h)</td>
<td>Right</td>
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<td>Walking, emotional stress</td>
<td>ArtHT, after getting up</td>
</tr>
<tr>
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<td>72</td>
<td>8</td>
<td>Left (72 h)</td>
<td>None</td>
<td>ArthT</td>
<td>After giving a lecture</td>
<td>Walking, emotional stress</td>
</tr>
<tr>
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<td>64</td>
<td>4</td>
<td>Right (48 h)</td>
<td>Left</td>
<td></td>
<td></td>
<td>Walking, emotional stress</td>
</tr>
</tbody>
</table>

ArtHT = arterial hypertension; hypchol = hypercholesterolaemia; aFil = atrial fibrillation; PFO = patent foramen ovale = MI, myocardial infarction; CHD = coronary heart disease; ICA = internal carotid artery; asi = aspirin; ACE = ACE-inhibitor; β = β-blocker; nitr = nitrate; stat = statin. Timepoint given under lesions refers to the initial MRI.

Statistical analysis

Results from the psychometric subtests were compared with normative, age- and sex-matched reference values published for each subtest (Geffen et al., 1990; Spreen and Strauss, 1998; Aschenbrenner, 2000; Lezak, 2005). Statistical analysis was conducted using SPSS 13.0. Depending upon the scale of measurements, Fisher’s exact test, parametric or non-parametric tests for independent samples were used. The psychometric results from each time point of testing (T0–T2) were compared using paired t-tests. For all tests the local level of significance was set at 0.05.

Results

A total of 41 patients [20 women, 21 men, mean 65 years ± 7 (±SD), range 39–77 years] presenting with 42 TGA episodes were included in the study (Table 1). The majority of episodes occurred either in the morning (08:00 a.m.–1:00 p.m.; n = 24) or between 1:00 p.m. and 6:00 p.m. (n = 13); a minority occurred after 6:00 p.m. (n = 5). The mean duration of attacks was 312 ± 204 min (±SD), while two patients experienced an attack lasting ≤1 h and 5 patients had an attack lasting ≥10 h. Thirty attacks (71%) occurred during or directly after physical activity and exertion, after Valsalva-associated manoeuvres, after mental and emotional stress (gardening, sexual intercourse, straining, woodwork, coughing, emotional distress) including attacks that occurred directly after resting involving postural changes. The majority of patients (n = 32) had one or more cerebrovascular risk factors (1 cRF = 15, 2 cRF = 8, ≥3 cRF = 9) amongst which arterial hypertension was the most frequent (n = 29, Table 1); however a history of preceding strokes or lacunar infarction in the past medical history could not be observed. Seven patients were taking aspirin (n = 8) or warfarin (n = 2). Mild vegetative symptoms (headache, nausea) were present in eight patients during the acute phase. Four patients experienced one TGA in the past medical history while three patients had two episodes in their past medical history. One patient experienced a second TGA while enrolled in the study.

The neurological and neurovascular testing did not show any abnormalities apart from a detection of an asymptomatic stenosis (70%) of the internal carotid artery in two, a subclavian steal due to a subclavian artery stenosis in one, and a patent foramen ovale in three patients. EEG abnormalities were found in two patients showing dysrhythmic EEG patterns under hyperventilation and one intermittent dysrhythmic focus (Table 1).

MRI study

Of 41 patients presenting with a TGA, 29 patients showed a total of 36 DWI lesions (n = 5 bilateral, n = 2 > 2 lesions) and corresponding T2 lesions in the hippocampus preferentially in a time window of 48–72 h after onset (Figs 1, 2 and 3). Most patients (8/10) which could be scanned already showed detectable DWI lesions that increased its signal intensity to the following MRI in the 24–48 h interval (Fig. 3). In contrast to the DWI lesions, lesions in the T2-weighted images were not detectable in the peri-acute phase but usually later than 24 h after onset.

The size of focal hyperintense lesions ranged from 1 to 5 mm and corresponded to DWI and T2 signal changes. Lesions in the T2-weighted images showed an oedema-like configuration and were clearly distinguishable from the sharply configured pre-existing cavities of the vestigial hippocampal sulcus (Fig. 1).

A detailed analysis of the distribution of lesion showed that almost all lesions (34/36) were selectively found in the area corresponding to the CA-1 sector (Somer sector) of the hippocampal cornu ammonis, while one lesion was found in the area corresponding to the CA-3 sector (Fig. 2). Due to MR artefacts the exact location of one lesion could not adequately be determined within the cornu ammonis.

DWI or T2 lesions could not be detected in 13 attacks. The distribution of lesions did show a slight preponderance of the left hippocampus (20 versus 16; Fig. 5). Lesions were equally distributed along the anterior–posterior axis within the hippocampus thus showing no preference for the vascular territories of the supplying posterior cerebral artery or the anterior choroidal artery, the latter supplying the head of the hippocampus (Erdem et al., 1993; Ludemann et al., 2001; Urbach et al., 2001).
The number and laterality of lesions were not significantly correlated with the number of TGA’s in the past medical history, the number of vascular risk factors, the duration of the antero- and retrograde amnesia, age and sex ($P > 0.05$).

A first follow-up control 10–20 days after the TGA did not show any persistent DWI signal changes or corresponding T2 lesions (Fig. 3). A second follow-up study 4–6 months after the TGA episode in 16 patients (24 months in two patients) did not show a transition of these 20 DWI/T2 lesions into residual cavities (Fig. 3). Neither there was atrophy, loss of volume and tissue or an emergence or enlargement of subcortical hippocampal cavities on the spot of the DWI/T2 lesion. There were no signal changes corresponding to evolving gliosis.

MRI and MRA did not show abnormal contrast enhancement or any gross abnormalities apart from an incidental aneurysm of the anterior cerebral artery in one patient, which did not reach interventional significance and a frontal atrophy in one patient. One patient showed a contra-lateral hippocampal atrophy. DWI lesions outside the hippocampal cornu ammonis were not detected.

MR venography of the intracranial dural sinus in 21/24 (88%) patients showed a hypoplastic transverse sinus with a slight preponderance of the hypoplasia for the left side (left 12/right 9). Considering those patients with a unilateral lesion, in 11/16 (69%) patients the hypoplastic side corresponded to the side of the DWI lesion (left = 6/right = 5) while in 5 patients the lesion was contra-lateral (Table 1).

Neuropsychometric assessment
A total of 34 patients were tested neuropsychometrically; 18 patients were analysed during the peri-acute phase (24 h after onset while the patient was either still symptomatic or gradually recovering from the amnestic interval.

The testing in the peri-acute phase did reveal memory deficits in episodic verbal memory subtests (RAVLT, RBMT) in 14 patients. Subtests of the RAVLT (sum score list 1–5, retention, delayed recall, recognition) testing quantitative and temporal aspects of verbal memory did significantly improve over the following assessments until reaching the normal reference range at 48–96 h ($P < 0.01, n = 14$, paired $t$-test; Fig. 4).

Fig. 1 Representative 3 T MRI showing typical DWI lesions with subsequent ADC changes corresponding to lesions in T2-weighted images. Note in this case the bilateral T2 lesions in the CA-1 sector of the cornu ammonis (red arrow) extending over 4–5 mm (slice thickness 2 mm) which are clearly separated from the cavity of the pre-existing vestigial hippocampal sulcus (green arrow) located in deeper subcortical layers in the vicinity of the gyrus dentatus.
Fig. 2 (A) Anatomical template showing a representative coronary slice of the hippocampal cornu ammonis indicating the vascular distribution and the topography of the CA neuronal sectors after Lorento de No (1934). Graphical template modified after Duvernoy (2005); used with permission. (B) Synopsis of all 34 DWI/T2 lacunar lesions depicted from T2-weighted images of each patient and transferred to an anatomical template of the cornu ammonis. The topography of the lesions within the cornu ammonis was referred to the distribution of the CA sectors according to the anatomical reference *Atlas of Duvernoy* and transferred from the MR-images to a 2D graphical model (Duvernoy, 2005). (C) Representative MRI sequences showing that lesions were confined to the CA-1 cortical areas of the cornu ammonis and were clearly distinguishable from the residual cavities of the vestigial hippocampal sulcus that were found in the subcortical layers in the vicinity of the gyrus dentatus. Note the anatomical resolution of the different neuronal layers in the 3 T MR-images.
From these 14 patients, 8 patients did show an impairment of episodic verbal memory only. The majority of DWI lesions (6/8) in these patients were confined to the dominant hemisphere (Fig. 5). In these affected patients, orientation including autobiographical memory, working memory, inhibition, conceptual knowledge and verbal fluency was preserved. Six patients out of 14 did show an additional impairment of visuospatial (non-verbal) memory during the acute phase. DWI lesions in these patients were confined to the non-dominant hemisphere (5/6 patients; Fig. 5).

All patients showed retrograde amnesia during the acute TGA ranging from a few hours to several years (Table 1).

Fig. 3 Synopsis of representative DWI/T2 lesions showing the time course of lesion evolution from the acute phase of the TGA to the 6 months follow-up in identical slice positions. In almost all cases DWI changes were already detectable in the acute phase of the TGA preceding the T2 changes. No residual structural changes in the location of the acute T2 changes were detectable after 6 months after the TGA.
After 4–6 months all patients retained an amnestic interval covering at least parts of the acute TGA interval. Sixteen patients showed normal results either in the peri-acute phase (<24 h) or in the time window of 24–96 h after the episode. Patients with DWI lesions were tested again after 4–6 months ($n = 16$); however no significant difference from the reference values could be detected in this follow-up examination suggesting complete recovery (Fig. 4). Interestingly, patients, although being already in the reference range of the memory test at the second test date and subjectively normal, showed a further significant improvement in their RAVLT subtests at the test date 4–6 months after the TGA ($P = 0.041$ sum score list 1–5; 0.041 retention; 0.013 delayed recall; 0.026 recognition; paired $t$-test, $n = 8$; Fig. 4). Two patients were tested 24 months after the TGA, while two patients were tested 6 months after the TGA only.

The verbal and spatial memory deficits did not correlate with the duration of the TGA, the number, anterior–posterior distribution of lesions, educational level, age, sex, number of pre-TGAs, or the duration of the retrograde amnesia ($P > 0.05$). The average years of education was 13 years in 15 subjects and 10 years in 26 subjects.

**Discussion**

In this study, we could show that transient MRI signal changes emerging in the course of a TGA are confined to the CA-1 sector of the hippocampal cornu ammonis. These lesions are reversible and do not evolve into residual structural changes detectable with high-resolution MRI 4–6 months after the episode. The functional correlate of the CA-1 lesions consisted of an impairment of episodic memory limited to days to weeks after the TGA while long-term neuropsychological sequelae could not be detected.

Although the pathomechanisms involved in TGA are still poorly understood, recent neuropsychological and neuro-radiological findings suggest a transient functional and structural perturbation of hippocampal structures in TGA patients. A recent study shed some light on the phenotype of...
MRI signal changes as DWI lesions within a time window of 24–72 h after the acute TGA were detected in the lateral hippocampus corresponding to the Sommer sector (Sedlacek et al., 2004). However, from this MRI study it has been unclear where exactly the DWI lesions in the hippocampal formation are located.

Clinical and experimental data show that hippocampal CA-1 neurons are critically involved in the process of memory consolidation in terms of a relay function in direct and polysynaptic intrahippocampal circuits and lesions to this area are sufficient to produce a clinically significant memory impairment (Kartsonis et al., 1995; Rempel-Clower et al., 1996; Burgess et al., 2002; Squire et al., 2004).

Pathophysiologically, neurons of the CA-1 sector (Sommer sector) of the cornu ammonis are of particular interest as they show a selective vulnerability to cellular metabolic stress such as during hypoxaemia and ischaemia that leads to a glutamate and calcium induced and apoptosis-mediated ‘delayed neuronal death’ of the affected neurons 1–3 days after hypoxia (Schmidt-Kastner and Freund, 1991; Kirino, 2000; Calabresi et al., 2003; Quintana, 2006). In post-mortem studies, it has been shown that activation of glutamate receptors due to domoic acid intoxication in humans causes damage to CA-1 neurons with a subsequent amnestic state (Teitelbaum et al., 1990). Experimental evidence in animals also suggests that emotional and behavioural stress situations selectively alter CA-1 glutamatergic release and uptake (Kim et al., 1996; Yang et al., 2005).

The susceptibility of CA-1 neurons and hence a crucial component in the pathophysiological cascade leading to a TGA may additionally be determined by a particular anatomical arrangement as the upper and lower hippocampal artery form an internal anastomosis within the CA-1 sector (Sommer Sector) (Heiman, 1937–1938; Sommer, 1880). Similar lesions in hypoxia-susceptible regions outside the hippocampus such as the striatum have not been observed in TGA patients.

The nature of the observed MRI changes and hence the pathophysiological mechanisms during TGA are still unclear. Several pathogenic mechanisms have been suggested, such as migraine, cortical spreading depression, ischaemia, venous flow abnormalities and seizure activity that may lead to impairment of cellular diffusion with subsequent DWI changes (Le Bihan, 1995; Gorji, 2001; Bradley et al., 2002; Sander and Sander, 2005; Parmar et al., 2006).

DWI/ADC signal changes were seen as early as 6 h after the onset of the TGA episode indicating substantial neuronal metabolic stress. The complete and uniform reversibility and lack of any structural sequelae within 4–6 months post lesion does not resemble the time course and evolution of an ischaemic lesion from an initial cytotoxic (DWI/ADC) to a vasogenic (T2) lesion and further resulting in gliotic sequelae. This time course observed contrasts the time course of hippocampal ‘delayed neuronal death’ that has been described as a typical response of CA-1 neurons to ischaemia (Dirnagl et al., 1999; Calabresi et al., 2003; Back et al., 2004).

In a recent retrospective, post hoc study an increased number of hippocampal cavities in patients with TGA compared with controls was described (Nakada et al., 2005). Thus, it has been suggested that episodes of TGA may lead to neuronal loss in the vicinity of the Sommer sector, although the cavities described were located subcortically within the vestigial hippocampal sulcus outside the Sommer sector (Nakada et al., 2005). Lesions in the CA-1 sector of the cornu ammonis in our study could clearly be differentiated from the vestigial hippocampal sulcus and do not evolve into cavities (Duvernay, 2005). A converging hypothesis could be that a higher ‘load’ of pre-existing cavities contributes to the susceptibility of hippocampal CA-1 neurons to metabolic and vascular stress.

Recent studies suggested the possibility of an increased venous pressure leading to hippocampal venous congestion and ischaemia contributing to the aetiology of a TGA as a substantial amount of patients performed a precipitating Valsalva-associated manoeuvre shortly before the onset of the TGA (Lewis, 1998; Akkawi et al., 2001). Subsequently, a higher rate of retrograde flow patterns in the jugular vein during Valsalva in combination with a higher rate of insufficient jugular-vein valves was described (Akkawi et al., 2002).
hemisphere mediating non-verbal memory (Golby et al., 2001; Coleshill et al., 2004).

Conclusions
Considering the MRI phenomenology, clinical and epidemiological data we suggest a multifactorial, non-vascular aetiology leading to a common pathophysiological pathway in terms of a transient disturbance of hippocampal CA-1 neurons without structural and neuropsychological sequelae.

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References
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Our data are in line with previous neuropsychological studies characterizing the antero- and retrograde verbal episodic memory impairment of TGA patients with a largely preserved visuospatial and working memory (Kritchevsky et al., 1988; Hodges and Ward, 1989; Zeman, 1999; Quinette et al., 2003; Guillery-Girard et al., 2004). Furthermore, our data show that a mild amnestic deficit persisted for some days after the initial symptoms and suggests an even longer subtle persistence before complete recovery after 4–6 months (Hodges and Ward, 1989; Hodges and Oxbury, 1990; Gallassi et al., 1993; Kritchevsky et al., 1997; Borroni et al., 2004). The dissociation between the time course of the subclinical neuropsychological symptomatology and the MR-signal changes indicates a persistent functional impairment of CA-1 neurons. This may be determined by the critical relay function of CA-1 neurons in terms of the particular cellular arrangement within regulatory and compensatory allocortical circuits (Eichenbaum, 2004; Morris, 2006).

Our results show also that a selective lesion in the hippocampal CA-1 area is sufficient to result in a transient impairment of episodic memory. Previous studies investigating a memory impairment due to CA-1 lesions as a result of hypoxic states or seizures could not rule out collateral impairment of the other memory-relevant structures of the hippocampal formation (Kartsounis et al., 1995; Rempel-Clower et al., 1996). Furthermore, judging from the constellation of the memory impairment in TGA patients, it has been suggested that the structural damage must involve more than the CA-1 region (Kritchevsky and Squire, 1989).

The finding of lateralized memory impairment corroborates a functional organization of temporo-mesial structures in terms of a dissociation between the dominant hemisphere mediating verbal memory and the non-dominant
Hippocampal CA-I neurons and TGA


