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# Transient epileptic amnesia is significantly associated with discrete CA1-located hippocampal calcifications but not with atrophic changes on brain imaging

Running title: Brain imaging in transient epileptic amnesia.

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## 1 Abstract

2 *Background:* The exact etiology of transient epileptic amnesia (TEA) is currently unknown. In older  
3 individuals, common neurodegenerative dementias and small-vessel diseases (SVDs) could be major  
4 contributors. We examined these hypotheses on the basis of imaging analysis.

5 *Methods:* In total, 36 TEA patients were compared with 25 healthy controls for (1) cortical atrophic  
6 changes (in the mesial temporal, frontal, anterior temporal, and parietal regions) using four  
7 established MRI-based visual rating scales, and for (2) SVD evidence using two MRI-based visual  
8 rating scales (Fazekas and MARS scores). In 24 TEAs cases, there were also brain CT scans available  
9 that were compared with 57 controls for the presence of hippocampal calcifications (HCs).

10 *Results:* We did not find significant differences in cortical atrophy between TEAs and controls, nor did  
11 we observe a different SVD brain load on MRI. However, TEAs were significantly associated ( $p < 0.01$ )  
12 with uni- or bilateral CA1-located HCs in half of the patients compared with the controls (less than  
13 20%).

14 *Conclusions:* This study argues in favor of a hippocampal-restricted SVD (as indicated by HCs) as one  
15 of the major etiologies of TEA, while neurodegenerative dementias are probably minor causes. It  
16 furthermore highlights the pivotal role of the CA1 hippocampal subfield in the pathophysiology of  
17 this syndrome.

18

## 19 Introduction

20 Transient epileptic amnesia (TEA) has now been thoroughly characterized based on  
21 publications dating back to the 1990s [1,2] supplemented by two important articles in the 2000s and  
22 2010s [3,4]. It has been established that this syndrome of late-onset temporal lobe epilepsy  
23 (commonly starting after the age of 50 years) manifests both by transient, repeated acute memory  
24 disturbances (amnesic seizures strictly speaking) and by interictal and therefore chronic memory  
25 disorders (i.e., accelerated forgetting, autobiographical amnesia, and topographical amnesia). The  
26 latter suggest permanent mesial temporal dysfunction, predominating in the hippocampus [5]. In  
27 fact, volumetric studies have shown decreased volume in both hippocampi of TEA patients,  
28 correlated with performance on standard memory tests but not with accelerated forgetting or with  
29 autobiographical memory evaluations and therefore with subjective complaints [6]. The major  
30 etiology of TEA is unknown, but all conditions involving the mesial temporal lobe regions – in  
31 particular the hippocampus – are potential causes, which include neurodegenerative diseases.  
32 Several case reports consistently showed that Alzheimer's disease [7], frontotemporal dementia [8],  
33 and even Lewy body disease [9] may trigger TEA. Yet, they are probably not representative because  
34 this epilepsy syndrome has a low risk of conversion to dementia, contrary to the natural history of  
35 neurodegenerative disorders [10,11]. Moreover, the vascular origin – especially the involvement of  
36 cerebral small-vessel diseases (SVDs) – has been suspected since the publication by Zeman *et al.* [2]  
37 but was not confirmed in a subsequent study [12]. This may be due to the use of inappropriate SVD  
38 imaging markers (Fazekas or Wahlund scores measuring white matter changes), since they are  
39 measured outside the mesial temporal lobe regions that are central to TEA pathophysiology [13]. By  
40 contrast, CT scan-visible hippocampal calcifications (HCs) open up an interesting perspective: they  
41 most likely indicate a specific SVD of the hippocampus because their vascular origin is  
42 neuropathologically proven [14], since they are linked to the presence of vascular risk factors such as  
43 diabetes and smoking [15] as well as to mild-to-moderate cognitive impairment [16-18]. HCs could  
44 therefore be a relevant SVD feature in TEA. In view of the scarce data in the literature regarding

45 potential neurodegeneration and/or SVD-related TEAs, we examined whether there was evidence for  
46 such etiologies on imaging (including HCs) in a retrospective cohort.

## 47 Patients and methods

### 48 Selection of patients and TEA characterization

49 *Patient selection.* In January 2018, we searched the database of the Memory Clinic  
50 (Strasbourg University Hospital) for patients who had been diagnosed with transient amnesic  
51 syndromes from 2012 to 2016 ( $n=320$ ). Among these patients, we then searched for patients who  
52 had been diagnosed with TEA according to current criteria [2]: (1) recurrent, witnessed episodes of  
53 unprovoked transient amnesia (at least two as defined by the current epilepsy guidelines); (2)  
54 cognitive functions other than memory judged to be intact by a reliable witness during the attack; (3)  
55 evidence for a diagnosis of epilepsy based on one or more of: epileptiform EEG abnormalities, co-  
56 occurrence of other clinical features of epilepsy (e.g., automatisms, olfactory hallucinations), and a  
57 clear-cut response to antiseizure medications (ASMs). For patients who had only one occurrence of  
58 clinically typical TEA (i.e., short duration, upon waking), epileptiform discharges and/or  
59 accompanying epileptic features were mandatory for the diagnosis (supplemental table 1). A total of  
60 67 individuals met the TEA criteria. The mandatory inclusion criteria for this study were: (1) having  
61 undergone a brain MRI within 1 year of diagnosis, or before (since seizure onset), which (2) included  
62 at least longitudinal FLAIR, coronal T1-weighted reconstructions, and longitudinal T2-weighted  
63 gradient-echo and/or susceptibility-weighted imaging (SWI) acquisitions (Figure 1). The exclusion  
64 criteria were: a clinical dementia rating scale score  $> 0.5$ ; insufficient clinical and/or EEG  
65 documentation at baseline; insufficient follow-up to ensure seizure response to ASM ( $< 2$  years);  
66 loss follow-up ; incomplete/unavailable MRI data or MRI performed more than 1 year after the  
67 diagnosis; or a prior history of epileptic seizures, alcohol or drug abuse, Korsakoff syndrome,  
68 uncontrolled severe medical disease (including extraneurologic primitive cancers, HIV or Lyme  
69 infection, congestive heart failure, uremia, hypercalcemia, hyponatremia), untreated endocrinal  
70 disturbances or B-vitamin deficiency, multiple sclerosis or other demyelinating diseases, cortical

71 stroke, brain tumors, neurosurgery or severe traumatic brain injury with cerebral contusion and/or  
72 hematoma. Finally, 36 individuals were included in the study, six of whom (16.7%) had only one  
73 occurrence of TEA. In the end, we identified 24 patients with available brain CT scans that were  
74 carried out before being referred to our Memory Clinic. Examinations were performed within the  
75 year of diagnosis or before, since the onset of seizures, for the diagnostic work-up of unexplained  
76 transient amnesia(s).

77 \*\* Insert figure 1 \*\*

78 *TEA characterization.* The age at epilepsy diagnosis was retained as the age of ASM  
79 prescription or, if not, as the age of the epileptiform EEG recording. The characteristics of the TEAs  
80 were taken from structured interviews with the patients themselves and their caregiver(s): age of  
81 first occurrence, precipitants, occurrence on waking, number of iterations with their duration in  
82 minutes and their frequency, accompanying ictal signs (i.e., brief contact loss, automatisms, olfactory  
83 hallucinations, etc.), repetitive questioning, anterograde and/or retrograde amnesia during spells,  
84 and partial recall of the amnestic attack.

85 *Electroencephalogram (EEG).* Standard and/or video-electroencephalography was performed  
86 for each patient, with the international 10–20 system for scalp electrodes in a session lasting at least  
87 30 min. On EEGs, epileptic foci were defined as the regions of maximum electronegativity.  
88 Nonepileptiform recordings included background slowing in the theta and/or delta range.  
89 Epileptiform recordings were defined by seizures and/or interictal epileptiform discharges (IEDs;  
90 sharp waves and/or spikes and/or spike waves). No sleep-deprived EEGs were performed.

91 *Antiseizure medications.* All patients were proposed an ASM when the diagnosis of epilepsy  
92 was retained, based on clinical ± electrical features. All but two (5.5%) patients accepted it. The  
93 choice of the drug was made by the patient's referring physician. We recorded the drug type and the  
94 daily dosage of the prescribed ASM. The clinical response was measured in the patient's and  
95 caregiver's diary. Seizure response was defined as a reduction in seizure frequency of > 50%.

96           *Clinical and paraclinical measures.* All patients underwent Mini-Mental State Exam (MMSE)  
97 scoring at baseline. The other medical features were obtained from patients and caregivers:  
98 demographics, education and professional occupation, personal and family medical history, age of  
99 onset, and type of cognitive changes (with special attention paid to accelerated forgetting,  
100 topographical amnesia, and autobiographical memory deficits). All patients underwent physical  
101 examination as well as dementia blood screening (including B<sub>12</sub> and folates).

## 102 Selection of controls

103           *MRI healthy controls.* Healthy volunteers for brain MRI protocols were recruited via  
104 advertisements in local community newsletters in Strasbourg (they contacted our Memory Clinic  
105 after reading the announcements that we were seeking controls for clinical studies) and via the  
106 listing of controls at the local clinical investigation center (*Centre d'Investigation Clinique*) in charge  
107 of all types of medical research conducted at the Strasbourg University Hospital. All enrolled  
108 participants were verified as being cognitively healthy on the basis of normal neuropsychological test  
109 results (global CDR score = 0, MMSE score > 24, Frontal assessment battery score ≥ 16, normal results  
110 on subtests exploring memory, executive functions, verbal fluencies, gestural praxic abilities,  
111 attentional and visuoconstructive abilities) and were judged to be neurologically healthy on the basis  
112 of normal clinical examination and normal scale scores (UPDRS III score ≤ 3, fluctuations scale score =  
113 0). Twenty-five healthy controls matching our patients for age and gender were included. MRI  
114 sequences included longitudinal FLAIR, longitudinal T2-weighted gradient-echo and longitudinal  
115 millimetric MPRAGE. The latter provides a 3D reconstruction for the rating of the different atrophy  
116 scores used in this study (see below). The results of the MRI scans were registered in the database of  
117 the IMIS-ICube Laboratory initially created for the alpha-Lewy-MA study [19].

118           *CT scan control group.* Patients were identified from the database of the Neuroradiology  
119 Department of the Strasbourg University Hospital. The list of all the consecutive patients who had  
120 undergone a brain CT between December 2019 and June 2020 was extracted. We excluded patients  
121 with abnormal brain CT scans and, if normal, patients with a prior or ongoing chronic neurological



122 condition according to the medical records (including dementing diseases). Patients matching the  
123 TEA individuals for age and gender were then selected ( $n=57$ ). Indications for CT were, in descending  
124 order: head trauma (44 [77.2%]), iatrogenic confusion (7 [12.3%]), headache (5 [8.8%]), fall while on  
125 a vitamin K antagonist (1 [1.7%]).

## 126 Imaging ratings

127 On MRI, six quantitative visual rating scales were used. They explored atrophic changes (on  
128 coronal reconstructions) and SVDs (on longitudinal appropriate sequences). First, mesial temporal  
129 lobe atrophy (reflecting hippocampal volume) was staged with the Scheltens visual scale ranging  
130 from 0 (no atrophy) to 4 (maximum atrophy) [20]. Second and third, frontal and anterior temporal  
131 lobe atrophy was assessed with the Kipps visual scale, ranging from 0 (no atrophy) to 4 (maximum  
132 atrophy) [21]. Fourth, parietal atrophy was staged with the Koedam visual scale, ranging from 0 (no  
133 atrophy) to 3 (maximum atrophy) [22]. Fifth and sixth, white matter hyperintensities were staged  
134 with the Fazekas visual scale, ranging from 0 (no hyperintensities) to 3 (confluent extensive  
135 hyperintensities) [23]; and microbleeds with the MARS score, reflecting the sum of lesions seen in  
136 anterior and posterior fossa [24]. On available CT scans, three qualitative measurements were given  
137 for hippocampal calcifications (HCs): no visually detectable HCs, unilateral (right or left) HCs, or  
138 bilateral (right and left) HCs. The MRIs and CT-scans of patients and controls were independently  
139 rated by two trained neurologists (rater #1 = AB, rater #2 = BC). They were not blinded to the  
140 diagnosis (patient vs. control) but were not aware of the other rater's ratings. After completion of  
141 their independent report, they compared their results. Each rater had a total of 216 MRI-based  
142 scores for patients (i.e., six different scores established on 36 available MRIs) vs. 150 for controls (i.e.,  
143  $6 \times 25$ ), and a total of 72 CT-based scores for patients (i.e.,  $3 \times 24$ ) vs. 171 for controls ( $3 \times 57$ ).

## 144 Statistical analysis

145 Quantitative variables are described using standard position and dispersion statistics,  
146 namely, mean, median, variance, minimum, maximum, and quantiles. Qualitative variables are  
147 described with the numbers and proportions of each category. Cumulative proportions were also

148 calculated for variables with more than two categories. The Gaussian character of the quantitative  
149 variables was evaluated using the Shapiro–Wilk test. We used the nonparametric Mann–Whitney *U*  
150 test, or Student *t* test as appropriate, to test differences in means (or other quantitative variables)  
151 between groups, and Fischer's exact test, or the chi-square test as appropriate, to compare two  
152 sample proportions (%). Rater agreement on imaging was determined using the Spearman coefficient  
153 for quantitative scores (i.e., measurements of cortical atrophy, white matter hyperintensities, and  
154 microbleeds) and using Cohen's kappa for qualitative measurements (i.e., presence or absence of  
155 hippocampal calcifications). All analyses were performed using the R software version 3.1 (R  
156 development Core Team, 2008), via the Strasbourg University Hospitals' GMRC Shiny Stats software  
157 (2017).

#### 158 [Standard protocol approval, registration, and patient consent](#)

159 All retrospective study procedures were performed following protocols approved by the  
160 Institutional Review Board (*Direction de la Recherche Clinique et de l'Innovation*) at our center.  
161 Written informed consent was obtained from all research participants recruited. The study was  
162 conducted in accordance with the Declaration of Helsinki.

#### 163 [Data availability](#)

164 Data that support the findings of this study are available from the corresponding author upon  
165 reasonable request.

## 166 [Results](#)

### 167 [Clinical characteristics of TEA patients](#)

168 The main clinical features of the 36 patients are displayed in **Table 1**. The complaint of  
169 amnesia was very common, mainly consisting in accelerated forgetting. It started at a mean age of 66  
170 years, which was usually concomitant with seizure onset or soon after (within less than 1 year).

171 **Table 1: Clinical features of the cohort**

TEA ( <i>n</i> =36)	
<b>Demographics</b>	

Women, <i>n</i> (%)	26 (72)
Education, years, mean ( $\pm$ SD)	11.2 (2.3)
Handedness (R/L), %	97.2/2.8
Age at cognitive complaints, years, mean ( $\pm$ SD)	66.0 (9.0)
Age at MRI acquisition, years, mean ( $\pm$ SD)	70.4 (8.4)
Age at CT scan acquisition, years, mean ( $\pm$ SD)	71.8 (7.5)
<b>Cognitive complaints, <i>n</i> (%)</b>	
Accelerated forgetting	31 (87)
Autobiographical amnesia	11 (30)
Topographical amnesia	17 (47)
<b>Baseline MMSE score, mean (<math>\pm</math> SD)</b>	26.9 (2.5)
<b>Cardiovascular risk factors, <i>n</i> (%)</b>	
Hypertension	17 (47.2)
Diabetes mellitus	3 (8.3)
Dyslipidemia	14 (38.9)
Smoking (active or discontinued)	6 (16.6)
Alcohol consumption	3 (16.6)
Cardiac disease	9 (25)

172

### 173 [Epileptological features of TEA patients](#)

174       The epileptological features of the TEA patients are summarized in **Table 2**. The mean age at  
175 onset of amnesic seizures was 65.2 years, while the mean age at diagnosis was 69.1 years. Prior to  
176 the diagnosis, patients had a median 4.5 acute amnesic episodes, commonly lasting between 12 and  
177 60 min; **but 6 (16.7%) had only one occurrence of TEA (Supplemental Table 1)**. 34 were treated with  
178 ASM monotherapy, including 29 (85.3%) with lamotrigine (mean daily dose = 164 mg  $\pm$  114). Of the  
179 treated patients, 64.7% were seizure-free (no relapse of acute amnesia) and 35.3% were not seizure-  
180 free but responders (decrease in seizure frequency  $\geq$  50%). Only one (2.9%) did not respond.  
181 Regarding interictal chronic memory complaints, 17 (50%) reported subjective relief under ASM  
182 therapy.

183 **Table 2: Epileptological features of the cohort**

	TEA ( <i>n</i> =36)
<b>Age at first seizure, years, mean (<math>\pm</math> SD)</b>	65.3 (8.6)
<b>Age at epilepsy diagnosis, years, mean (<math>\pm</math> SD)</b>	69.1 (9.3)
<b>Seizure semiology</b>	

Iterations, median (min–max)	4.5 (1–200)
Maximum duration, min, median (min–max)	60 (3–1440)
Minimum duration, min, median (min–max)	12.5 (0.5–1440)
Ictal anterograde amnesia, <i>n</i> (%)	30 (83)
Ictal retrograde amnesia, <i>n</i> (%)	31 (87)
Repetitive questioning, <i>n</i> (%)	12 (33)
Upon waking, <i>n</i> (%)	7 (19)
Accompanying epileptic signs, <i>n</i> (%)	30 (83)
<b>EEG features, <i>n</i> (%)</b>	
First standard EEG	Normal: 22 (65) Slowing: 9 (26.5) Right: 3 (8.8) Left: 5 (14.7) Bilateral: 1 (3) IEDs: 3 (9) Left: 2 (6) Bilateral: 1 (3) Seizure: 0 Not done: 2 (6)
Video-EEG	Normal: 7 (25) Slowing: 8 (28.5) Left: 4 (14.25) Bilateral: 4 (14.25) IEDs: 11 (39) Right: 1 (4) Left: 4 (14) Bilateral: 6 (21) Seizure: 2 (7) Left: 2 (7) Not done: 8 (22)

184

### 185 Atrophy scores and small-vessel disease evidence on brain MRI

186 The mean scores, calculated from the pooled results of both raters, for TEA patients and for  
187 MRI controls, are presented in **Table 3**. There was no statistically significant difference between TEA  
188 patients and controls for atrophy or SVD brain load (as evidenced by the Fazekas and MARS scores).  
189 HCs were not visible on MRI using T2-weighted gradient-echo or SWI acquisitions because of  
190 technical limitations (thick slices). The MRI control participants were significantly more educated and  
191 had a higher MMSE score than the TEA patients ( $p = 0.02$  and  $0.01$ , respectively).

192 **Table 3: Mean scores of atrophic and vascular changes of patients and healthy controls**

	TEA ( <i>n</i> =36)	MRI controls ( <i>n</i> =25)	<i>p</i>
Female, <i>n</i> (%)	26 (72)	14 (63.6)	0.4
Education, years, mean ( $\pm$ SD)	11.4 (2.4)	12.8 (2.7)	<b>0.02</b>

<b>MMSE score</b>	26.9 (2.5)	28.8 (0.9)	<b>0.01</b>
<b>Age at MRI acquisition, years, mean (<math>\pm</math> SD)</b>	70.4 (8.8)	67.2 (8.5)	0.4
<b>Right MTA, mean (<math>\pm</math> SD)</b>	1.2 (0.8)	1.2 (1)	0.9
<b>Left MTA, mean (<math>\pm</math> SD)</b>	1.2 (0.8)	1.2 (0.9)	0.8
<b>Right frontal lobe atrophy, mean (<math>\pm</math> SD)</b>	0.8 (0.7)	0.7 (0.8)	0.6
<b>Left frontal lobe atrophy, mean (<math>\pm</math> SD)</b>	0.8 (0.7)	0.75 (0.8)	0.7
<b>Right anterior temporal lobe atrophy, mean (<math>\pm</math> SD)</b>	0.7 (0.7)	0.5 (0.5)	0.3
<b>Left anterior temporal lobe atrophy, mean (<math>\pm</math> SD)</b>	0.8 (0.7)	0.7 (0.6)	0.3
<b>Right parietal lobe atrophy, mean (<math>\pm</math> SD)</b>	1.0 (0.8)	1.2 (0.9)	0.3
<b>Left parietal lobe atrophy, mean (<math>\pm</math> SD)</b>	1.0 (0.8)	1.3 (0.9)	0.1
<b>Fazekas score, mean (<math>\pm</math> SD)</b>	1.2 (0.9)	1.0 (0.7)	0.3
<b>MARS lobar score, mean (<math>\pm</math> SD)</b>	0.3 (0.7)	0.1 (0.4)	0.1
<b>MARS deep score, mean (<math>\pm</math> SD)</b>	0.4 (1.1)	0.3 (0.5)	0.4

193 Note: The posterior temporal lobe atrophy scores were not measured because the anterior temporal lobe atrophy scores were preferred  
194 given their relevance for TDP-43-related neurodegenerative changes mainly affecting the temporal poles; the MARS score for the  
195 infratentorial structures and the cerebellum was not measured given these structures' low relevance for epilepsy, which involves distant  
196 cortical structures; MTA, mesial temporal lobe atrophy.

#### 197 Hippocampal calcifications on CT scans

198 The separate comparisons between TEAs and CT controls of rater #1 and #2 are presented in  
199 **Table 4**. They both found a significant association of HCs, uni- or bilateral, with TEAs ( $p < 0.01$  or  $p <$   
200  $0.001$  for rater #1 and #2, respectively). There was a clear predominance of HCs on the right  
201 hemisphere. All patients with HCs were right-handed. The comparison between HC-positive and HC-  
202 negative patients was made for each rater: No significant difference was found for demographic,  
203 clinical (including cardiovascular risk factors), epileptological, cognitive, and radiological data (not  
204 shown). This includes the progression of the cognitive complaint under ASM (e.g., for rater #2, the  
205 cognitive complaint was improved for 7/12 [58.3%] of the HC-negative and for 5/12 [41.7%] of the  
206 HC-positive patients,  $p = 0.41$ ). Right or left HCs did not correlate with a specific cognitive complaint  
207 **nor they did with the epileptic focus on EEG** (not shown). Examples of bilateral HCs are given in  
208 Figure 2.

209

210 **Table 4: Compared prevalence of HCs in TEA patients and controls according to both raters.**

		TEA (n=24)	CT scans controls (n = 57)	p (TEA vs. controls)
<b>Female, n (%)</b>	-	26 (72)	40 (70.2)	0.8
<b>Education, years, mean (± SD)</b>	-	11.4 (2.4)	NA	-
<b>MMSE score</b>	-	26.9 (2.5)	NA	-
<b>Age at CT scan acquisition, years, mean (± SD)</b>	-	71.8 (7.5)	69.2 (5.2)	0.1
<b>Age at diagnosis in patients with available CT scan</b>		72.5 (7.8)	-	-
<b>Right hippocampal calcifications, n (%)</b>	Rater #1	11 (45.8)	5 (8.8)	< <b>0.001</b>
	Rater #2	12 (50)	6 (10.5)	< <b>0.001</b>
	Interrater agreement	$\kappa = 0.9^\dagger$	$\kappa = 0.5^\dagger$	-
<b>Left hippocampal calcifications, n (%)</b>	Rater #1	6 (25)	7 (12.3)	0.2
	Rater #2	6 (25)	4 (7.0)	0.06
	Interrater agreement	$\kappa = 1^\dagger$	$\kappa = 0.7^\dagger$	-
<b>Right and/or left hippocampal calcifications, n (%)</b>	Rater #1	12 (50)	10 (17.5)	<b>0.01</b>
	Rater #2	12 (50)	7 (12.3)	< <b>0.001</b>
	Interrater agreement	$\kappa = 1^\dagger$	$\kappa = 0.7^\dagger$	-

211 Note: Rater # 1 = AB, rater #2 = BC; † =  $p < 0.001$  for agreement between rater #1 and rater #2 according to Cohen's kappa coefficient

212 \*\* Insert Figure 2 \*\*

### 213 Rater agreement

214 Qualitative measures of HCs were significantly correlated with Cohen's kappa, ranging from  
 215 0.5 to 0.9 for right HCs ( $p < 0.001$ ) and from 0.7 to 1.0 for left HCs ( $p < 0.001$ ) (Table 3), with a  
 216 moderate ( $\kappa = 0.5$ ) to strong ( $\kappa = 1$ ) agreement according to Landis and Koch. Interrater agreement  
 217 was good for quantitative atrophy scores with a statistically significant correlation coefficient  
 218 between raters for all measurements (Spearman rho,  $p < 0.01$ ), ranging from 0.7 to 1.0 for mesial  
 219 temporal lobe atrophy scores, from 0.6 to 0.8 for both frontal atrophy and anterior temporal lobe  
 220 atrophy, and from 0.5 to 0.8 for parietal atrophy (Supplemental Table 2). MRI evidence of SVD was  
 221 also significantly correlated between the two raters, with rho ranging from 0.75 to 0.9 for the  
 222 Fazekas score ( $p < 0.001$ ), from 0.7 to 0.9 for the lobar MARS score ( $p < 0.001$ ), and 0.9 for the deep  
 223 MARS score ( $p < 0.001$ ) (Supplemental Table 2).

## 224 Discussion

### 225 A large and representative cohort of TEA patients

226 This work describes the clinical, electrical, and radiological characteristics of 36 patients with  
227 TEA: **they replicate the prior reported clinical and paraclinical features of TEA (except in terms of the**  
228 **female overrepresentation)**. It is one of the largest published cohorts since the studies reported by  
229 Butler *et al.* [3] and Mosbah *et al.* [4], which included 50 and 30 cases of TEAs, respectively. The  
230 other published studies were indeed smaller, including 19 [25], 15 [26], and 11 patients [27], as was  
231 the princeps case study by Zeman *et al.* ( $n = 10$ ) [2].

### 232 The interictal cognitive complaints facilitate faster recognition of TEA

233 The present study highlights that the diagnosis of TEA is still delayed for several years (here  
234 nearly 4 years on average, similar to other studies) [4,25], **but it can also be diagnosed on the first**  
235 **isolated amnesic transient, as it was the case in 6 (16.7%) patients based on electro-clinical features**  
236 **that were not consistent with the diagnosis of TGA and that moreover fitted with the ILAE definition**  
237 **of epilepsy (see Supplemental table 1) [26-28]**. Amnesic attacks are in fact poorly understood during  
238 their initial management [3,4,26]. There are frequent relapses (mean,  $18 \pm 35$  occurrences here), as  
239 Butler *et al.* reported ( $18 \pm 17$  occurrences), but the median total number of attacks for our patients  
240 was significantly lower than that published by the same authors (4.5 vs. 10 total iterations) [3]. This  
241 indicates that TEAs are currently being recognized more quickly, probably because specific interictal  
242 memory deficits are now taken into account [4,25,30,31]. Anterograde memory complaints were  
243 indeed more frequent in this study than in others: For example, 21% of patients complained of  
244 accelerated forgetting in one study [25], 44% in another [3], and 87% in the present cohort. This can  
245 be explained by two factors: (1) the recruitment procedures in a Memory Center, which are not  
246 exclusively based on transient acute amnesic spells (i.e., TEAs) but on chronic cognitive impairment  
247 as well; (2) the fact that we are especially attentive to patients' cognitive complaints for the diagnosis  
248 of TEA, particularly in the case of a first amnesic attack [30]. We believe that both these factors  
249 shortened the time to diagnosis. However, a retrospective bias is not excluded: patients who

250 initiated treatment and continued follow-up in our Memory Center were possibly more concerned  
251 about their memory than others, thus increasing the present prevalence of memory complaints.

#### 252 [No evidence of neurodegenerative or classic small-vessel disease on MRI in TEA cases](#)

253 This study is the first to investigate the yield of MRI-based atrophy visual rating scales in TEA,  
254 while other imaging methods have already been addressed (i.e., volumetric MRI and PET scans)  
255 [4,6,25,32]. These scales have all been validated by appropriate studies and published in  
256 international scientific journals. They provide easy, quick, and reproducible measurements of  
257 atrophy in neurodegeneration-sensitive key regions of the brain [33]. They thus make it possible to  
258 argue for underlying incipient dementia in TEA, in particular when persistent cognitive complaints are  
259 present [7-9]. The good interrater agreement obtained here is in line with previous publications [20-  
260 22,33] and confirms the applicability of such scales to late-onset epilepsy syndrome. This study did  
261 not find any significant lobar atrophic changes in patients compared with healthy controls. This  
262 indirectly suggests that neurodegenerative dementias are infrequent in TEA, consistent with a  
263 previous publication [10]. Furthermore, this study did not find evidence of significant vascular  
264 changes in TEA based on MRI scores [13], confirming the findings of an earlier report [12]. However,  
265 the Fazekas and MARS scales are probably not relevant to this late-onset temporal lobe epilepsy, as  
266 stated in the Introduction, because they are measured in anatomical sites distant from the region of  
267 interest in TEA (i.e., the hippocampus) [4,6,25,34,35].

#### 268 [Hippocampal calcifications indicate a hippocampal restricted SVD in a substantial 269 proportion of TEA patients](#)

270 HCs are easily identified on CT scans (because of thin slices and high contrast), which is  
271 confirmed in the present study by the strong interrater agreement regarding their detection in TEA  
272 patients and controls. They are likely a marker of microvascular damage to the hippocampus given  
273 their intraparietal location in the hippocampal capillaries as well as in the hippocampal pre-capillaries  
274 and arterioles [14]. In addition, they correlate with cognition [15-17]. We show here that HCs and  
275 TEAs are significantly associated in comparison with controls. Uni- or bilateral HCs were present in  
276 half of the cases in this study ( $p < 0.01$ ) but were not combined with evidence of diffuse cerebral SVD



277 (see section above). In fact, if all of the unavailable CT scans ( $n = 12$ ) were normal, HCs would still  
278 affect one third of the patients (12/36); on the contrary, if they were all abnormal, HCs would be  
279 present in two thirds of TEA (24/36). As a consequence, HCs most probably indicate that a specific  
280 and limited hippocampal SVD is one of the major causes of TEA. This result is in accordance with  
281 previously published neuropathological TEA reports that showed intrahippocampal capillary  
282 calcifications [38,39]. It is also in line with numerous studies in older individuals indicating that  
283 vascular pathology is a major cause of epilepsy [36]. This includes cerebral SVD [37]. Furthermore,  
284 such limited hippocampal SVD would explain why TEA carries a low risk of conversion to dementia  
285 (including vascular dementia) [10].

#### 286 Hippocampal calcifications probably play a role in the pathogenesis of ictal and 287 interictal features of affected TEA patients

288 Beyond their etiological value, HCs also add pathophysiological information. When present,  
289 they are very likely to be involved in the pathogenesis of the clinical picture of affected TEA patients,  
290 whether in their transient amnesic attacks or in their interictal memory deficits. With regard to  
291 iterative acute transient amnesias, it should be noted first that SVDs are recognized as epileptogenic:  
292 by blood–brain barrier breakdown [40] and, in the case of HCs, by a probable loss of normal  
293 astrocyte function as well. The latter results from an ectopic osteogenic environment [41]. Second,  
294 HCs are preferentially located in the CA1 field of Ammon’s horn [14]. The disorganization of this  
295 hippocampal subfield is crucial for the production of transient amnesia. This is demonstrated by the  
296 association of a CA1-located punctuate cytotoxic edema with the onset of benign transient global  
297 amnesia (TGA), which clinically resembles TEA but lasts longer [42]. In this perspective, very focal  
298 seizures arising in the immediate vicinity of the HCs – in the CA1 subfield – could explain an isolated  
299 (or predominant) ictal amnesic presentation even in the case of rapid spread to both hippocampal  
300 structures [34,43]. In addition, due to their preferential right hippocampal location (i.e., the  
301 nondominant hemisphere for all the HC-positive patients in this study), the HCs could cause seizures  
302 restricted to the nondominant temporal lobe regions, which are more frequently manifested by brief

303 auras followed by automatisms with preserved consciousness [44], i.e., causing seizures with clinical  
304 semiology similar to the TEA described in the literature and herein [1-4,25, 26, 29]. Such hypothesis  
305 cannot yet be affirmed given the lack of correlation between HCs lateralization and EEG foci. Further  
306 studies are needed on this point, with stronger statistical power (i.e. more patients with recorded  
307 epileptiform EEGs and more available CT-scans). Regarding the interictal chronic memory deficits,  
308 CA1-located HCs may again be explanatory. They may disrupt the mnemonic encoding and storage  
309 processes involving this part of the cornu ammonis [42,45] and consequently explain the chronic  
310 memory complaints of patients regarding episodic memory deficits (i.e., accelerated forgetting or  
311 autobiographical amnesia, which are probably interrelated) [46]. It is noteworthy that the key role  
312 played by CA1 in autobiographical memory has been demonstrated in patients with TGA as well [47].  
313 Furthermore, the topographical amnesia reported by patients may also be based on disturbed CA1-  
314 located place cells [48]. Due to the design of the present study – lacking appropriate and  
315 comprehensive testing of accelerated forgetting, topographical and autobiographical amnesia – we  
316 cannot provide confirmatory correlations of HCs with such specific cognitive deficits. If present, they  
317 would have reinforced this discussion. Finally, HCs could also explain why patients on effective ASM  
318 therapy persistently complain of memory problems even though seizures and IEDs no longer appear  
319 on EEG recordings.

320 [HC-negative TEA patients do not differ from HC-positives: a specific CA1 disturbance in](#)  
321 [all TEA patients?](#)

322 Interestingly, we did not find statistical differences between HC-positive and HC-negative  
323 TEAs, nor we did find a significant effect of the lateralization of HCs on specific cognitive complaints.  
324 These results have limited relevance due to the small number of HC-positive patients. Nevertheless,  
325 they point to the chronic disturbance of bilateral CA1 subfields in all TEA cases, with or without  
326 colocalized HCs. Neuronal loss and gliosis have been described in neuropathological cases: They  
327 affected the CA1 subfield of the hippocampus and the other parts as well (CA1-4) [38,39,49,50].  
328 Moreover, these changes have been previously linked to accelerated forgetting and autobiographical

329 amnesia in a case with pathological verification [39]. They may explain occasional MRI-apparent  
330 hippocampal atrophy or sclerosis [29]. CA1 chronic impairment therefore convincingly explains the  
331 ictal and interictal amnesic features, as well as the persisting memory deficits despite a well-  
332 conducted ASM therapy in patients with TEA. In other words, persistent bilateral CA1 disruption may  
333 be the common thread of the full-blown clinical picture. **We now need to establish if it explains the**  
334 **subtle loss of hippocampal volume seen in TEA cases, with better correlations with cognition [6,32,**  
335 **39], and to understand the etiology of TEAs in HC-negative individuals.**

### 336 Study limitations

337 One of the major biases of this study is that the raters were not blinded to the diagnosis  
338 when analyzing MRI and CT acquisitions of patients and controls. They carried out their ratings  
339 independently, and they were well correlated, but a diagnostic bias may explain the agreement.  
340 Nevertheless, they both retrieved a proportion of HCs in controls similar to the general population  
341 [17,18]. This indirectly indicates that their estimation was quite accurate. In addition, our  
342 retrospective design entails missing data (in particular for CT scans, not systematically carried out at  
343 seizure onset) and probably accounts for the overrepresentation of women in this study, whereas  
344 TEA usually affects slightly more men than women [3,4]. Yet, a cohort with predominantly female  
345 representation has already been reported [26]. The present study also suffers from recruitment  
346 biases. First, the MRI controls were recruited via advertisements. This led to a selection bias that  
347 resulted in significantly higher educational levels and MMSE scores in healthy individuals. However,  
348 the difference in MMSE scores is not clinically relevant because patients and controls both had mean  
349 scores above the pathological cut-off ( $MMSE \geq 24$ ). Second, the CT scan controls were recruited only  
350 on the basis of their medical record without clinical verification of normal cognition and neurological  
351 status. The representativeness of the CT control group is therefore altered. The frequency of HCs in  
352 our control group was similar, however, to that found in the general population [17,18]. Finally, this  
353 study also has design limitations. Neurodegeneration was assessed using MRI atrophy scores, which  
354 correspond to the "N" marker in the A/T/N classification proposed by Jack *et al.* [51]. A more in-

355 depth evaluation of neurodegeneration in TEA should also take into account the A ( $\beta$ -amyloid) and T  
356 (Tau) markers of the same classification. In other words, studies examining the yield of CSF or  
357 molecular scintigraphy tracers (amyloid and/or Tau-PET scans) would better document a possible  
358 underlying incipient neurodegenerative disorder. In a similar perspective, SVD evidence on imaging  
359 may be explored not only with white matter hyperintensities and microbleeds but with subcortical  
360 lacunes, subcortical and cortical microinfarcts, and Virchow–Robin space enlargement [13].

## 361 Conclusion

362 This study of representative TEAs did not show the involvement of brain atrophic changes: It  
363 therefore seems reasonable to consider dementias as minor etiologies of TEA [10]. By contrast, our  
364 results argue for SVD being a major cause of TEA as reflected by HCs on brain CT scans (present in at  
365 least one third of the patients, but their exact prevalence now needs to be determined). HCs most  
366 likely reflect vascular damage restricted to the hippocampus. By extension, HCs indicate that the TEA  
367 features, whether ictal or interictal, are related to limited alterations in Ammon’s horn (i.e., CA1  
368 subfield at least). This postulate needs to be confirmed by further studies, at least exploring  
369 correlations of HCs with detailed and specific cognitive paradigms. Specific MRI protocols (7T,  
370 quantitative susceptibility mapping, spectroscopy) may also be contributive.

## 371 Author contributions

372 BC and AB contributed to the study design. AB, BC, NP, FB and FS contributed in the production of  
373 the main text of the manuscript. BC supervised data acquisition, and revised the manuscript. BC and  
374 AB performed statistical analysis.

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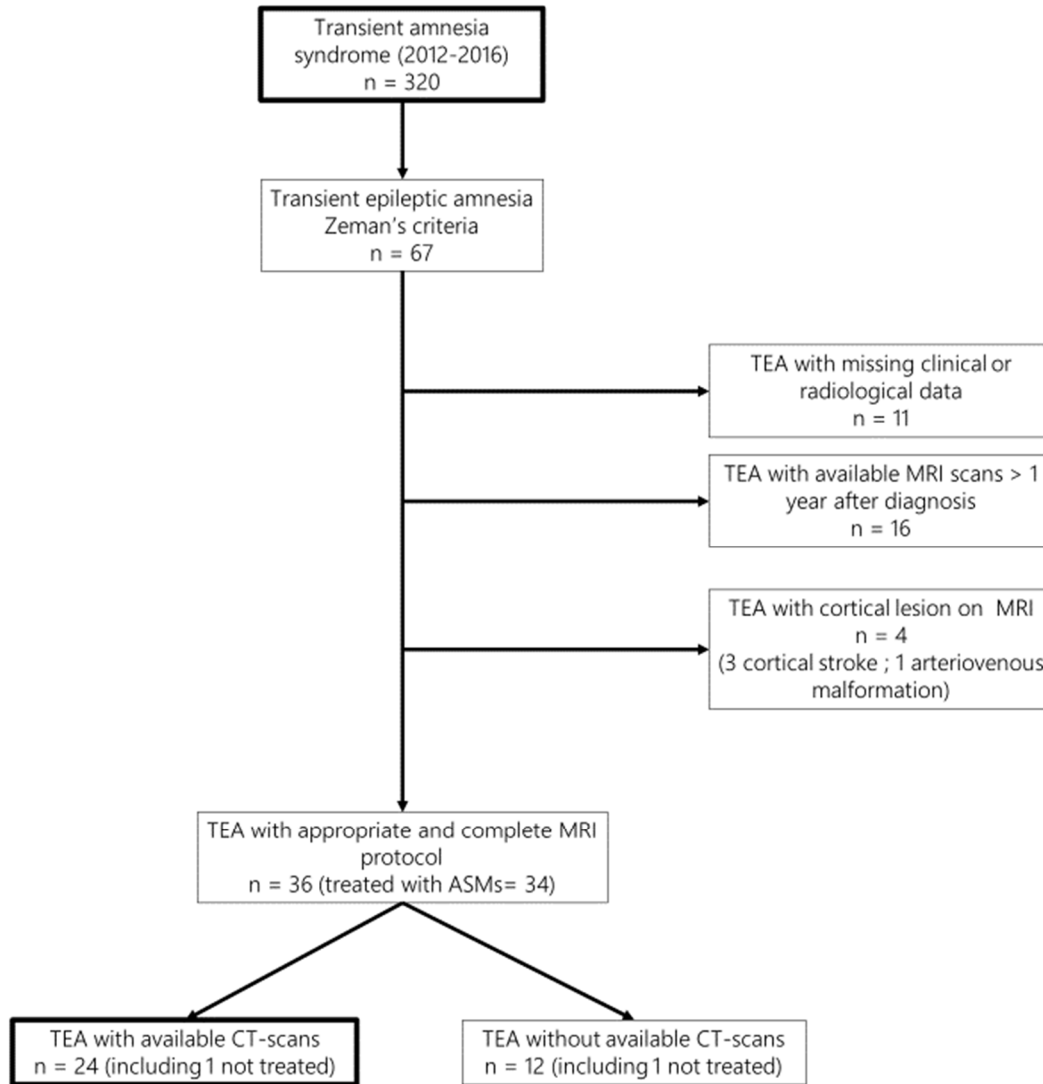
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## 557 Figures

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559 **Figure 1: Study flow-chart**

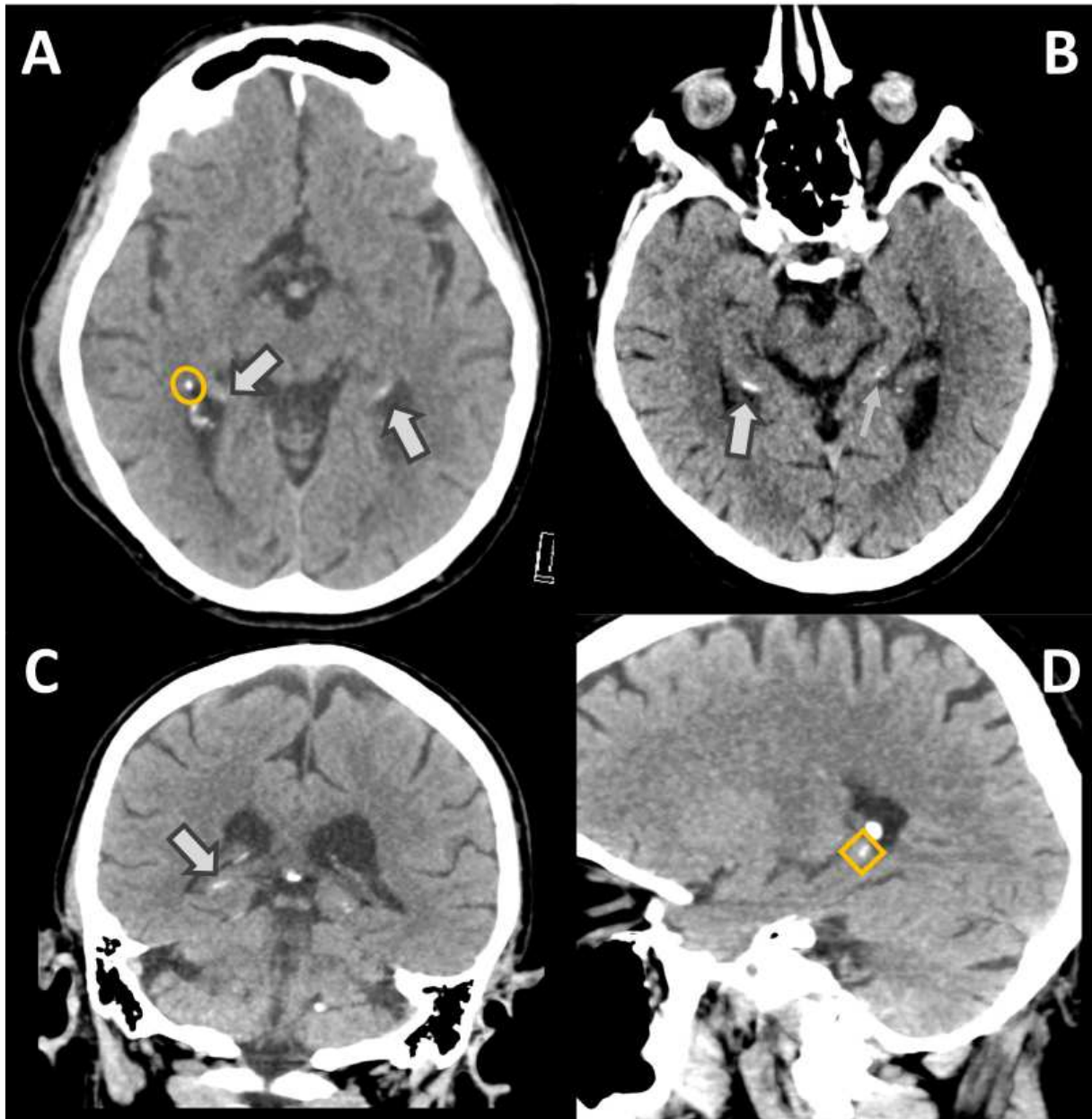




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565 Note: 2A: patient #4, bilateral subtle HCs (thick arrows), not to be confused with choroidal calcifications (orange circle); 2B, C: bilateral HCs  
566 of patient #9 (arrows), predominating on the right side (thick arrows); 2D: right HCs of patient #9, located in the CA1 region of the tail of  
567 the hippocampus (orange square).

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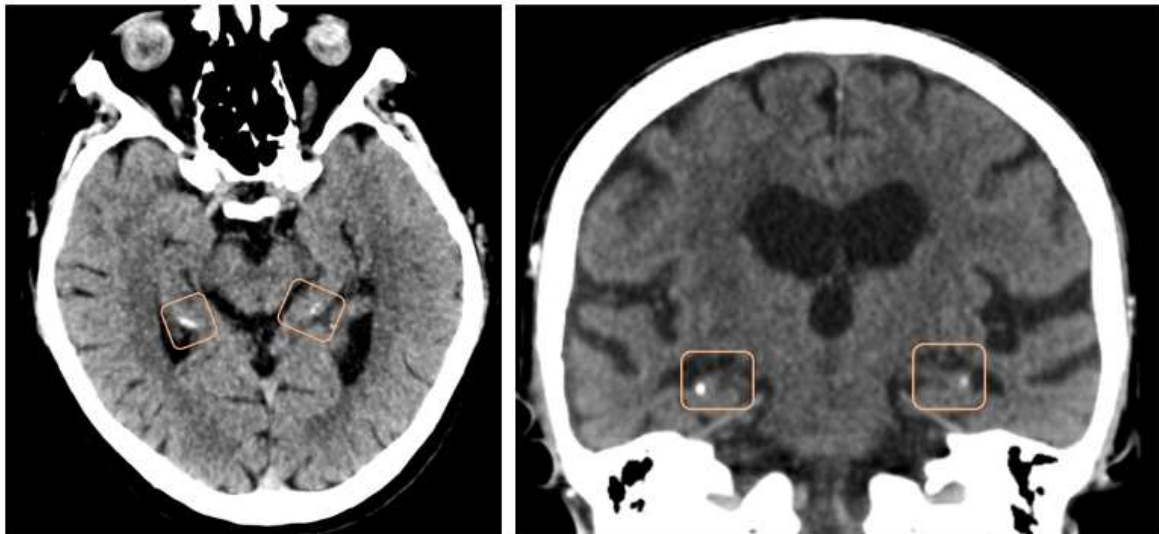
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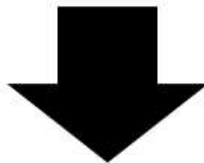
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BILATERAL OR RIGHT PREDOMINANT CA1-LOCATED HIPPOCAMPAL CALCIFICATIONS ARE PRESENT IN 1/3 TO 2/3 OF TEA PATIENTS



CA1 disruption potentially explains the clinical features of TEA:

- ⇒ Interictal memory complaints ± objective deficits on tests
- ⇒ Iterative short paroxysmal amnesias resembling TGA
- ⇒ Persistent memory complaints despite seizure cessation