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Preserved anterograde and remote memory in drug-responsive temporal lobe epileptic patients

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ABSTRACT

Purpose: To investigate cognition, particularly anterograde and remote memory, in patients suffering from unilateral drug-responsive mesial temporal lobe epilepsy (mTLE) patients and to compare their performance with that observed in drug-resistant mTLE patients.
Methods: Sixteen drug-responsive mTLE patients, with only infrequent seizures in their lifetime, were matched for demographic and clinical variables to 18 patients suffering from drug-resistant unilateral mTLE. A comprehensive neuropsychological examination, including baseline, anterograde memory tasks, and a large range of remote memory tests was carried out.
Results: Patients with drug-responsive epilepsy obtained average scores on every anterograde memory test. Although in general, they obtained lower scores than the healthy controls on remote memory tests, the differences failed to reach significance. Moreover, the drug-responsive group performed significantly better than the drug-resistant group on anterograde recall tests and an episodic autobiographical memory test. Performance was not significantly different between the patient groups in personal semantics or memory for public events.
Conclusion: Our results show that a mild clinical course of mTLE with no cognitive deficits can occur notwithstanding hippocampal sclerosis. The differences in cognitive function between the two groups are likely due to distinct pathophysiology of the underlying cause of epilepsy. Drug-resistant seizures and cognitive deficits may be the consequence of a more severe underlying cerebral process. Better understanding of the variety of pathogenesis of mTLE could help to answer this open question.

1. Introduction

Despite the availability of various newly developed antiepileptic drugs (AEDs), about 75% of patients suffering from mesial temporal lobe epilepsy (mTLE) are still considered to have drug-resistant epilepsy (Serrano-Castro et al., 2012). This percentage is even higher (up to 89%) when hippocampal sclerosis (HS) is present (Semah et al., 1998).

By contrast with the proliferation of investigations in patients candidates for surgery, only little attention has been directed towards patients showing the drug-responsive mTLE variants. An Italian research team (Aguglia et al., 1998) has addressed various issues related to what they termed "benign" (Labate et al., 2006, 2011) or "mild" mTLE (Gambardella et al., 2005; Labate et al., 2008). The entity thus described includes patients who were seizure free, or had either occasional auras or not more than two disabling (complex focal or secondarily generalised) seizures per year for at least two years with or without appropriate medication.

Consensual results in surgical series point out that 70–80% of more than 1000 patients with drug-resistant mTLE were found to show impairment of either verbal or figural anterograde memory

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(Helmstaedter, 2005). Gambardella et al. (2005) reported verbal learning deficits in only 25% of patients presenting with "mild" mTLE. In the same vein, Alessio et al. (2004a) demonstrated that patients with "benign" familial mTLE patients performed better on memory tests than patients with drug-resistant familial mTLE. On the contrary, Özkara et al. (2004) compared performance on anterograde memory tests in drug-responsive and drug-resistant patients with HS and showed that both groups were similarly impaired on verbal and nonverbal memory performance. Comparable results were found by Pacagnella et al. (2014).

Regarding remote memory, to the best of our knowledge, it has never been investigated in a group of drug-responsive mTLE patients. This issue is all the more interesting that drug-resistant mTLE showed impaired performance for both autobiographical events and memory for public events, i.e. news-related events and famous people (e.g. Lah et al., 2006; Voltzenlogel et al., 2006) and that patients with monthly seizures performed better than those with weekly seizures on autobiographical incidents and news-events memory (Voltzenlogel et al., 2014). Only Tramoni et al. (2011) examined autobiographical memory in five selected drug-responsive mTLE patients presenting an "unusual complaint of gradual forgetting personal episodes" (p. 817) with one of these patients suffering from acute episodes of isolated memory loss as depicted in transient epileptic amnesia (Zeman et al., 1998).

Research in drug-responsive mTLE patients' cognitive profile might has an important clinical value since the risk of memory impairment is present even in the context of a better cognitive outcome relatively to drug-resistant mTLE patients. Moreover, drug-responsive mTLE patients constitute a subgroup, whose specificities could help to improve our understanding on memory deficits in mTLE. The present study aims at characterising anterograde and remote memory on a carefully selected homogeneous group of patients with drug-responsive mTLE with at most markedly infrequent seizures in their lifetime and to compare their cognitive performance with those of drug-resistant mTLE patients.

2. Material and methods

2.1. Participants

Sixteen patients presenting with drug-responsive unilateral mTLE were recruited in three French hospitals (Strasbourg, Nancy and Toulouse). Inclusion criteria were the following: diagnosis of mTLE (made by the treating neurologists, EH, JPV or LV, on the basis of a range of clinical seizure semiology, typical temporal auras and EEG findings that are considered to be reliable indicators of mTLE); seizure freedom (i.e. no reported aura and no seizures of any type) for at least 12 months in accordance with drug-responsiveness definition (Kwan et al., 2010); lifelong infrequent seizures (generally only yearly seizures); no diagnosis of transient epileptic amnesia (as defined by Zeman et al., 1998); no previous status epilepticus; no bilateral abnormalities or abnormalities extending on others regions than the mesial temporal lobe on MRI; no psychiatric or neurologic comorbidities; aged 18 or older; native French speakers; and finally no mental retardation and preserved naming ability on visual confrontation (two criteria in view of the ulterior administration of remote memory tests). The recruited patients who met the aforementioned criteria were seizure-free for at mean 2.56 years (SD: 2.30; range: 12 months–8 years), but remained under anti-epileptic medication. They were matched for age, education level and clinical variables (age at onset, etiologic factors, lateralisation and type of MRI abnormalities) to 18 patients suffering from drug-resistant (as defined by Kwan et al., 2010) unilateral mTLE, drawn from our previous recent study (Voltzenlogel et al., 2014). In the present work, 8 drug-resistant patients experienced monthly focal seizures with alteration of consciousness and/or automatisms, 7 weekly seizures and 3 daily seizures. Usual seizure frequency was recorded retrospectively from medical files. We estimated the mean seizure frequency reported in the five years preceding the assessment.

Patients' seizure-related characteristics are summarised in Table 1. Not surprisingly, number of anti-epileptic drugs (AEDs) differs significantly between the two patient groups (see Table 1). Twenty control subjects matched for age and education level also selected from our previous study (Voltzenlogel et al., 2014) were included for the remote memory tests that have no normative data. All participants provided informed consent for participation in this study. We complied with the APA ethical standards, and the research was approved by the University Hospitals from Strasbourg, Nancy and Toulouse. General demographic data for both patient groups and control subjects are shown in Table 1.

2.2. Neuropsychological assessment

Patients underwent a comprehensive neuropsychological assessment (see below). All the tests were administered on the same day and followed the same order of presentation for all the participants. All patients were taking anti-epileptic treatment with fixed doses at the time of assessment.

2.2.1. Baseline tests

Verbal IQ was estimated with a short form of the Wechsler Adult Intelligence Scale-R (Warrington et al., 1986). **Nonverbal**

Table 1
Clinical data of the two patient groups.

	Drug-resistant mTLE patients	Drug-responsive mTLE patients	Healthy controls	Statistical analyses
N	18	16	20	–
Demographic data of patient groups and controls				
	Ratio	*Ratio*	*Ratio*	
Gender (male/female)	4/14	9/7	8/12	$Chi^2 = 4.14$, $p = .13$
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	
Age (in years)	36.72 (7.44)	41.19 (11.07)	37.20 (8.33)	$H = 2.08$, $p = .35$
Education level (in years)	11.89 (1.91)	13.06 (2.59)	12.6 (2.16)	$H = 2.00$, $p = .37$
Clinical data of patient groups				
	Ratio	*Ratio*		
mTLE lateralisation (right/left)	6/12	5/11		$Chi^2 = 0.02$, $p = .90$
MRI (HS/TMCD/normal)	13/0/5	10/1/5		$Chi^2 = 1.28$, $p = .53$
Initial precipitating injury (FS/meningitis/none)	5/1/12	6/1/9		$Chi^2 = 0.40$, $p = .82$
	Mean (SD)	*Mean (SD)*		
Age at onset (in years)	20.17 (5.68)	26.31 (13.99)		$U = 103.00$, $p = .16$
Number of AED	2.28 (0.57)	1.13 (0.34)		$U = 20.00$, $p < .001$

Abbreviations: mTLE: medial temporal lobe epilepsy; HS: hippocampus sclerosis; TMCD: temporo-mesial cortical dysplasia; FS: febrile seizures; AED: antiepileptic drugs.

Table 2
Baseline tests scores of the two patient groups.

	Drug-resistant mTLE patients	Drug-responsive mTLE patients	Statistical analyses
General intellectual abilities			
- Verbal IQ[a]	92.50 (11.41)	97.56 (11.13)	$U = 100.50$, $p = .13$
- Raven's matrices[b] (percentiles)	55.22 (27.55)	74.10 (22.81)	$U = 90.50$, $p = .06$
Executive functions			
- Phonological verbal fluency (raw)[c]	8.72 (2.76)	15.06 (4.19)	$U = 31.00$, $p < .001$
- Months backwards[c]			
- Time (s)	16.55 (9.01)	11.56 (4.68)	$U = 78.50$, $p = .02$
- Nb of errors (median [range])	0 [0–1]	0	
Attention			
- Digit cancellation test[d]			
- Time (s)	53.05 (14.59)	50.38 (13.41)	$U = 131.00$, $p = .65$
- Nb of omissions (median [range])	0 [0–2]	0 [0–1]	

Standard deviations are in parentheses.
[a] Wechsler Adult Intelligence Scale-Revised (Wechsler, 1989); short form (Warrington et al., 1986).
[b] Advanced Progressive Matrices, Set 1 (Raven et al., 1998).
[c] National Hospital, London.
[d] Digit cancellation test (Wade et al., 1988).

reasoning was examined with the Advanced Progressive Matrices, Set 1 (Raven et al., 1998). **Executive functions** were assessed using phonological fluency tests (National Hospital, London) and enumeration of months backwards (National Hospital, London). *Attention* was probed by digit-cancellation test (Wade et al., 1988).

2.2.2. Anterograde memory

Verbal memory was assessed using the *Recognition Memory Test for Words* (RMTW, Warrington, 1984), immediate and 30-min delayed *Story Recall* from the Adult Memory Information Processing Battery (AMIPB, Coughlan and Hollows, 1985). **Nonverbal memory** tests comprised the *Recognition Memory Test for Faces* (RMTF, Warrington, 1984) and immediate and 30-min delayed *Figure Recall* from the AMIPB (Coughlan and Hollows, 1985). Each patient's performance on anterograde memory tests was converted into percentile scores on the basis of normative reference data provided in test manuals.

2.2.3. Remote memory

Personal facts (i.e. home addresses, names of friends or teachers, etc.) were assessed using the semantic section of the *Autobiographical Memory Interview* (AMI, Kopelman et al., 1989).

Personal events were examined by means of the *shortened version of the Modified Crovitz Test* (Crovitz and Schiffman, 1974; Graham and Hodges, 1997). Six cue words (such as 'train' or 'surprise') were given to the patient with the instruction to retrieve past personal memories using those items. Each word was given four times to cover different life periods corresponding to the ages 0–9, 10–19, 20–(patient's age – 1), patient's age. Presentation of words and time periods was randomised. The patient was encouraged to provide as much detail as possible. Scores were obtained using a 0–5-point scale (from 'don't know' to detailed specific single event; see Graham and Hodges, 1997).

Public events assessment included the *Public Events Test* (adapted from Thomas-Antérion and Puel, 2006; with permission) and the *Famous Faces Test* (Denkova and Manning, unpublished). The first test consists of 15 written questions about public events that were in the public eye for a circumscribed period of time related to politics, sport, social events, scandals or catastrophes. The items are presented one by one in random order. We asked for spontaneous evocation of the event (scored 0–2) and independently of the response, recognition of the event presented together with two distractors (scored 0 or 1). The second test comprises twenty photographs of celebrities (from the 1960s onwards) were presented to the patient. Correct identification of the famous person was scored either if the patient named spontaneously the person or gave a sufficiently detailed and correct description (with relevant characteristic such as occupation, political party) of the celebrity. The participants' performance on remote memory tests was expressed as percentages, due to the lack of normative reference data.

2.3. Statistical analyses

We investigated between group differences in different clinical variables, by means of the chi-squared tests. Since preliminary analyses revealed that normality and homoscedasticity assumptions were not met (Shapiro–Wilk test and Levene test respectively), between group differences were examined using non parametric statistics. For baseline tests and anterograde memory tests, differences between patient's groups were analysed using a series of Mann–Whitney rank sum tests. For each remote memory test, intergroup differences were carried out with Kruskal–Wallis one-way analyses of variance of ranks, using groups as an independent factor (i.e., patients with drug-responsive mTLE, patients with drug-resistant mTLE and control subjects), and Mann–Whitney tests for pair-wise multiple comparisons with Bonferroni correction. The Bonferroni correction set the threshold for significance at 0.017.

Additionally, since gender ratios in the two patient groups are substantially different, statistical analyses taking into account this variable were performed. They revealed no significant differences due to gender. Due to the difficulty to recruit patients with drug-responsive mTLE, the size of our groups was too small to allow analysis of effect of right vs left mTLE or presence vs absence of hippocampal sclerosis.

3. Results

3.1. General cognitive performance

As can be seen in Table 2, statistical analysis indicated that the drug-responsive group performed significantly better than the drug-resistant group on the two executive function tasks. Drug-responsive patients tended to obtain better scores on a nonverbal reasoning test. The two patients' groups did not differ on verbal IQ or a digit cancellation test tackling attention.

3.2. Anterograde memory

Anterograde memory test scores are presented for both patient groups in Fig. 1.

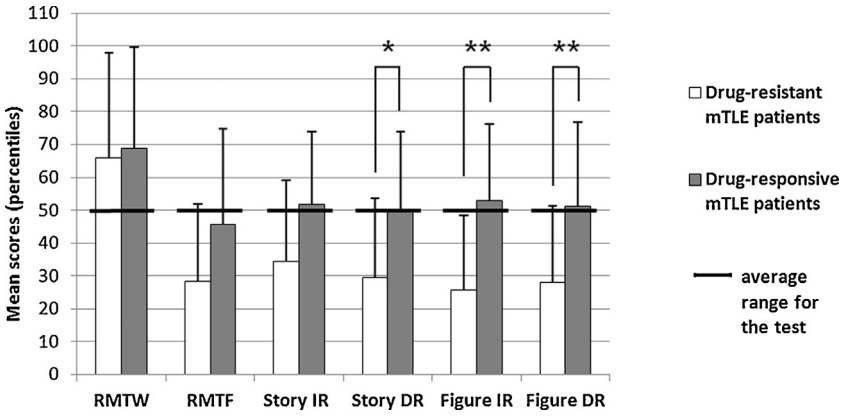

Fig. 1. Mean scores in percentiles for drug-resistant and drug-responsive mTLE patients on anterograde memory tests. Bars indicate the standard deviation of the mean. Abbreviations: RMTW: Recognition Memory Test for Words; RMTF: Recognition Memory Test for Faces; IR: immediate recall; DR: delayed recall. $^{**}p < .01$; $^{*}p < .05$.

Mann–Whitney U tests indicated that drug-resistant patient showed significantly lower scores than drug-responsive patients on delayed Story Recall ($U = 80.00$; $p = .03$) and immediate and delayed Figure Recall ($U = 52.00$; $p = .002$ and $U = 64.00$; $p = .006$, respectively). They tend to obtain lower performance on RMTF ($U = 90.00$; $p = .06$), immediate Story Recall ($U = 91.50$, $p = .07$). The two patient groups obtained similar scores on RMTW ($U = 139.00$; $p = .88$).

3.3. Remote memory

The results of each **remote memory** test for both patient groups and healthy subjects are shown in Fig. 2. Patient groups and controls exhibited similar performance for personal semantics ($H = 4.68$; $p = .10$). By contrast, a significant group effect on the scores was found for the Modified Crovitz Test ($H = 24.32$; $p < .001$), the Public Events Test, in both spontaneous evocation and recognition conditions ($H = 12.92$; $p = .002$ and $H = 6.73$; $p = .03$, respectively) and the Famous Faces Test ($H = 8.49$; $p = .01$). With use of an α significance level of <0.017 to account for multiple comparisons, Mann–Whitney tests failed to highlight significant differences between drug-responsive patients' performance and healthy controls' performance on remote memory tests ($p > .08$ in all cases). Statistical analysis revealed that drug-responsive patients performed significantly better than drug-resistant patients on the Modified Crovitz Test ($p = .00006$) and tend to obtain better scores on spontaneous evocation of the Public Events Test ($p = .03$). Both patient groups obtained similar scores on the recognition of the Public Events Test ($p = .09$) the Famous Faces Test ($p = .41$). As expected, the drug-resistant group obtained significantly inferior scores than did the healthy subjects on all remote memory tests ($p < .017$ in all cases).

4. Discussion

We have documented, for the first time to the best of our knowledge, the cognitive profile of a homogeneous group of mTLE patients presenting a characteristically infrequent drug-responsiveness. Our results show that the drug-responsive patients' scores were normal, based on normative data, in all the **anterograde memory** tests presented in this study. The hippocampal abnormalities in 62.5% of the patients (see Table 1) seemed insufficient to impair anterograde memory performance. These findings are consistent with those obtained by Alessio et al. (2004a), who reported relatively preserved verbal and visual memory in nearly all asymptomatic individuals with unilateral hippocampal atrophy. Moreover, normal retention over standard 30-min delay had already been observed in mTLE patients, even in presence of hippocampal abnormalities (e.g. Lah et al., 2014). By contrast, Özkara et al. (2004) and Pacagnella et al. (2014) reported both verbal and visual memory impairment in their patient group with less than four seizures per year. Pacagnella et al. (2014) classified patients considering seizure occurrence over the last year. However, fluctuations over time in seizure frequency being common, and drug responsiveness being rather a dynamic process than a fixed state (Kwan et al., 2010), it is conceivable that Pacagnella et al.'s patients might have suffered from more frequent seizures

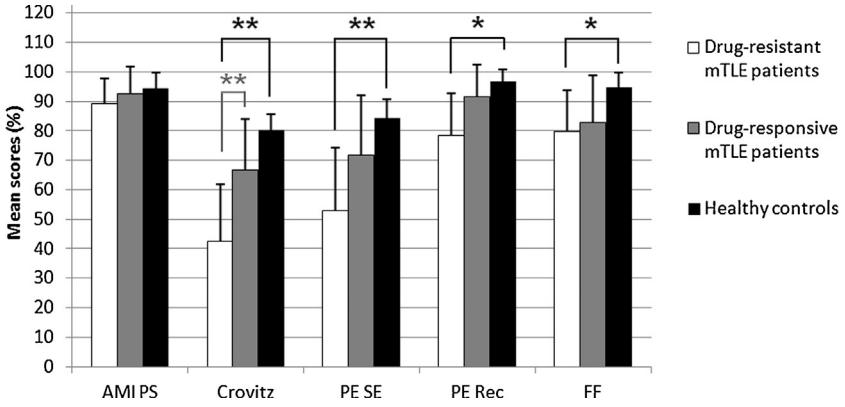

Fig. 2. Mean scores in percentages for drug-resistant and drug-responsive mTLE patients and healthy controls on remote memory tests. Bars indicate the standard deviation of the mean. Abbreviations: AMIPS: Autobiographical Memory Interview, Personal Semantics; PE: Public Events Test; SE: spontaneous evocation; Rec: recognition; FF: Famous Faces Test. $^{**}p < .003$ (Bonferroni corrected threshold for multiple comparisons).

in their lifetime. Along these lines, Helmstaedter (2005) stated that seizures could have an irreversible negative influence on development, by causing irrecoverable retardation even when seizures are under control. Moreover, more than half of Pacagnella et al.'s sample had an estimated IQ <70 that could have contributed to the floor effects on memory tests observed by the authors. Regarding Özkara et al.'s (2004) results, we tentatively suggest that the discrepancy with our results could be due, at least partially, to the earlier average age at onset of epilepsy in their 18 "good responder" patients (5.85 years, SD: 6.05).

Better verbal and nonverbal anterograde memory performance were observed in our drug-responsive patients relatively to drug-resistant patients, especially in recall tasks, all the more so that the drug-resistant patients' scores were below the average but within the normal range. Again, our findings neither agree with Özkara et al.'s (2004) nor with Pacagnella et al.'s (2014), who found comparable memory performance between drug-responsive and drug-resistant patients. Regarding Pacagnella et al.'s results, complementarily to the aforementioned likely reason, we note that some patients with lifelong drug-resistant epilepsy may become drug-responsive upon receiving a new AED (Kwan et al., 2010). In those cases, a similar memory profile to that often observed in drug-resistant patients, at the time of the memory examination, can be expected. Comparing memory performance in patients with drug-resistant familial mTLE, with patients with "benign" familial mTLE and asymptomatic first-degree relatives, who had hippocampal atrophy, Alessio et al. (2004a) demonstrated that the interactions between hippocampal atrophy and drug-resistant epilepsy were associated with the poorest anterograde memory scores. Likewise, we recently reported in patients suffering from drug-resistant unilateral mTLE (Voltzenlogel et al., 2014), that the low seizure-frequency group performed significantly better than the high seizure-frequency group on anterograde memory tests (see also Alessio et al., 2004b; Hendriks et al., 2004; Wang et al., 2001). On a retrospective analysis of data from patients who had undergone a cognitive assessment on two occasions at an interval of more than 10 years, Thompson and Duncan (2005) demonstrated that complex focal seizures were associated with memory decline. For their part, Özkara et al. (2004) observed stable memory performance over a retest interval of two years in their drug-responsive group. Finally, some studies reporting neuropsychological improvement in patients rendered seizure-free by surgery endorsed the assumption that seizure control has a positive impact on cognition (Després et al., 2011; Wachi et al., 2001).

Turning to **remote memory**, the drug-responsive patients' performance on autobiographical episode recall, public-events and Famous Faces Tests, although slightly below the healthy controls' scores, did not differ significantly. We therefore suggest, though with caution due to our small sample size, that remote memory can be relatively preserved despite unilateral hippocampal abnormalities and that long-term memory consolidation process could be preserved in the context of very rare occurrence of seizures. Three observations corroborate indirectly these results. Firstly, in an earlier study in patients who had undergone surgery for relief of drug-resistant mTLE and were free from recurrent seizures, we demonstrated that the relative integrity of the left hemisphere together with residual right hemisphere structures seemed to be sufficient to sustain postoperative autobiographical memories (Voltzenlogel et al., 2007). Secondly, some studies suggest that seizures occurring during the retention interval of newly acquired information could hinder the consolidation process (Mameniskiene et al., 2006; Wilkinson et al., 2012). Lastly, elimination of epileptic activity via epilepsy surgery improves very long-term memory consolidation (Evans et al., 2014; Gallassi et al., 2011).

The results obtained by Tramoni et al. (2011) seem inconsistent with ours since they reported autobiographical memory impairment and altered long term consolidation for contextually bound memory tasks, despite normal performance after short delays in their five drug-responsive mTLE patients. However, contrary to ours, their patients were selected on the basis of vivid memory complaints, which had been observed one to five years before the epilepsy diagnosis.

Likewise, although drug-responsive patients performed better than drug-resistant patients on strongly episodic tasks, autobiographical incidents and news-events memory, knowledge about famous people seemed to be uninfluenced by seizure frequency (Manning et al., 2013; Voltzenlogel et al., 2014). We surmise that remote memory deficits in drug-resistant mTLE patients could be influenced by poorer scores on anterograde memory compared with drug-responsive patients' scores (Bergin et al., 2000; Lah et al., 2006), together with disrupted long-term consolidation process due to frequent recurrent seizures (e.g. Lah et al., 2014). It could be noticed that the drug-resistant group did not significantly differ from the drug-responsive group in verbal immediate recognition and recall, but was impaired in delayed verbal recall, suggesting accelerated forgetting (see Blake et al., 2000). Indeed, consolidation process is bound to be more vulnerable in patients in whom interactions between structural damage and recurrent epileptic activity occur. Our results are consistent with our previous study (Voltzenlogel et al., 2014), which recorded a worsening effect of high seizure frequency for remote episodic memory, and with those of Wang et al.'s (2001), who reported that seizure frequency predicted scores of news events memory.

As it was expected, compared with healthy controls, patients with uncontrolled seizures were impaired in all domains of remote memory, except personal semantics (Voltzenlogel et al., 2006).

Concerning the **baseline tests**, although drug-responsive patients performed better than drug-resistant patients on general ability tests, the differences failed to reach statistical significance. Fluid intelligence has been related to frontal functioning that might be affected by spread epileptic discharges through the white matter tracts connecting the temporal with the frontal lobes, whereas "crystallised intelligence" depends on educational achievement. In this perspective, Wang et al. (2001) documented that verbal IQ score was significantly predicted by seizure frequency. Likewise, Alessio et al. (2004a) reported that patients with "benign" familial mTLE tended to obtain higher full scale IQ than those with uncontrolled seizures. On the contrary, Pacagnella et al. (2014) observed no difference between their frequent and infrequent seizure groups, both with low estimated IQ (see above, a likely explanation for this discrepancy). Our drug-responsive and drug-resistant mTLE groups also differed significantly in verbal fluency scores; with the latter obtaining a mean score below the cut-off. This result is coherent with investigations showing that TLE could lead to executive function deficits and that seizure frequency is a significant predictor of the level of executive functioning (Black et al., 2010; Wang et al., 2001). The two patient groups obtained similar scores on a visual selective attention task (digit cancellation). These results suggest that different degrees of coexisting cognitive deficits play a part on the poorer memory performance in drug-resistant patients.

Moreover, we could not rule out that earlier onset and use of larger numbers of AEDs also contribute to the memory impairments observed in drug-resistant patients. Indeed, Wang et al. (2001) demonstrated that age at seizure onset was the strongest predictor of intellectual impairment and that number of AEDs predicts anterograde memory impairment. Lah et al. (2006) highlighted a negative correlation between number of AEDs and remote episodic memory performance. These confounding variables are difficult to control as mild mTLE seizures usually start much later than refractory seizures, at approximately the age of 30 years and are typically well controlled by monotherapy (Gambardella et al., 2005). Patients

with drug-resistant epilepsy had earlier seizure onset and more AEDs than patients with "benign" epilepsy in Alessio et al.'s study. It can be noticed that the two patient groups in Özkara et al. (2004) and Pacagnella et al. (2014) did not differ in age at onset with an age of approximately six years for the drug-responsive group in the first and 17 in the second study. Furthermore, patients achieving 24-months seizure freedom had significantly lower occurrence of febrile seizures and hippocampal sclerosis (Aguglia et al., 1998). In the present study, occurrence of febrile seizures and hippocampal sclerosis were not significantly different in the patient groups.

The small sample size in the present study, which can be seen as a limitation, is due to the fact that drug-responsive patients, presenting with the stringent clinical characteristic we took as inclusion criteria (lifelong infrequent seizures), are remarkably rare. Another limitation was that no quantitative volumetric measurements were used in order to compare both patients' groups. The presence or otherwise of mesial temporal abnormalities was based on visual analysis of epilepsy-tailored clinical MRI sequences (T1-weighted, T2-weighted, FLAIR) made by experimented neuroradiologists. In this perspective, it is important to remind that some studies found no differences in hippocampal volumes (Andrade-Valença et al., 2003; Pacagnella et al., 2014) or in whole-brain grey matter (Labate et al., 2010) between patients with good and poor seizure control.

5. Conclusions

A mild clinical course of mTLE with no cognitive deficits has been observed, notwithstanding the presence of hippocampal abnormalities. Hippocampal sclerosis itself does not necessarily imply drug-resistant epilepsy and poor cognitive outcome. Nevertheless, more research is needed to tease apart the cause of cognitive impairment. Both drug-resistant seizures and cognitive deficits may be the consequence of a more severe underlying cerebral process (Cendes et al., 2014). MTLE is not a single entity, but a group of different conditions that share common clinical and neurophysiologic characteristics, with different underlying causes (Semah et al., 1998; Coan et al., 2015). The variety of pathogenesis may explain the multitude of clinical presentations, the different responses to anti-epileptic treatment and the different cognitive outcome. Following Pacagnella et al. (2014), we wonder whether "benign mTLE is a different syndrome or whether it is part of the spectrum of mTLE" (p. 2) with in one end, patients with good response to antiepileptic drug treatment, or even rare seizures in life, and in the other end of the spectrum patients who do not respond to medication and need surgical treatment. Finally, research in this area might be hampered to some extent, by the lack of consensual definition of "benign/mild" mTLE, approved by the International League Against Epilepsy, rendering it difficult to compare findings across studies. Further researches in larger samples are necessary to confirm our findings and to take into account other factors like hippocampal volume or lateralisation of mTLE.

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